RGUHS · MODEL ANSWER BANK

RGUHS MD General Medicine — Paper III

RESPIRATORY, NEUROLOGICAL & RHEUMATOLOGICAL MEDICINE

2019–2026

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

GROUNDED IN:

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

Dr. Harshad Ramineni
@aurapharmlab

Contents

Neurology **5**

Acute disseminated encephalomyelitis 5
Parkinson's disease 9
Alzheimer's disease 14
Approach to coma 19
Autosomal recessive ataxias 24
Benign intracranial hypertension 28
Cerebral venous sinus thrombosis 32
Trigeminal neuralgia 36
Neuromuscular junction — physiology and disorders 41
Posterior circulation stroke 46
Differential diagnosis of seizures 50
Seizures — causes and management 54
Acute ischaemic stroke — right internal capsule 59
Reperfusion therapy in acute stroke 64
Endovascular revascularisation for acute ischaemic stroke 68
Dementia — causes and Alzheimer's vs frontotemporal dementia 72
Epilepsy syndromes 76
Horner's syndrome 81
Hyperkinetic movement disorders 84
Hypoxic-ischaemic encephalopathy 89
Guillain-Barré syndrome 94
Multiple sclerosis 99
Muscular dystrophies 104
Myasthenia gravis 108
Narcolepsy 112
Orthostatic hypotension 117
Posterior reversible encephalopathy syndrome 121
Primary headaches 125
Recent advances in management of migraine 130
Restless leg syndrome 134
Reversible dementias 139
Secondary parkinsonism 143
Temporal lobe epilepsy 146
Tic douloureux 151
Cluster headache — treatment and prevention 155
Wernicke encephalopathy 159

Respiratory system.....163
Acute interstitial pneumonia.....164
Acute severe asthma.....168
Approach to solitary pulmonary nodule.....172
Asbestos-related diseases.....176
Bronchial asthma.....181
Acute respiratory distress syndrome.....185
Bronchiectasis.....189
Chronic obstructive pulmonary disease (COPD).....193
Pulmonary rehabilitation post severe COVID-19 pneumonia.....198
Hospital-acquired pneumonia.....203
Hypersensitivity pneumonitis.....208
Airway inflammation in bronchial asthma.....213
Interstitial lung diseases.....217
Lung abscess.....222
Non-resolving pneumonia.....227
Obesity and obstructive sleep apnoea.....231
Obesity hypoventilation syndrome.....236
Pneumothorax.....240
Pulmonary function tests.....244
Pulmonary infiltrates with eosinophilia.....249
Pulmonary thromboembolism.....253
Refractory bronchial asthma.....258
Glucocorticoids in management of COPD.....262
Sarcoidosis.....267
Obstructive sleep apnoea.....272
Silicosis.....276
Systemic manifestations of COPD.....280
Pulmonary embolism.....284
Connective tissue disease-associated ILD.....289
Spirometry.....293
Hypoventilation.....298
Rheumatology & immune system.....302
ANCA-associated vasculitis.....303
Ankylosing spondylitis.....307
Approach to non-traumatic monoarthritis.....312
Biologics in autoimmune disease.....317
Calcium pyrophosphate deposition disease.....321

Biological agents in rheumatoid arthritis....326
Vasculitis classification....330
Behçet's syndrome....333
Systemic lupus erythematosus (SLE)....338
SLE flares — risk factors and severity classification....342
Disease-modifying antirheumatic drugs....346
Drug-induced lupus....351
Takayasu arteritis....356
Primary Sjogren's syndrome — extraglandular manifestations....360
Familial Mediterranean fever....364
Fibromyalgia....368
Gout....373
Granulomatosis with polyangiitis....378
IgG4-related disease....382
Hyperuricaemia....387
Microscopic polyangiitis....391
Mixed connective tissue disease....396
Neuropathic joint diseases....400
Palindromic rheumatism....405
Polyarthritis....409
Psoriatic arthritis....413
Raynaud's phenomenon....418
Reactive arthritis....422
Seronegative spondyloarthritis....427
Sjögren's syndrome....431
Rheumatoid arthritis — extra-articular manifestations and diagnosis....436

Neurology

◆ ◆ ◆

Acute disseminated encephalomyelitis

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

Definition / Introduction — Acute disseminated encephalomyelitis (**ADEM**) is an acute, typically **monophasic**, immune-mediated inflammatory demyelinating disorder of the CNS that characteristically follows an antecedent viral infection (**post-infectious / parainfectious encephalomyelitis**) or, historically, a vaccination (**post-vaccinal encephalomyelitis**). It is defined clinically by the rapid evolution of a **polyfocal** neurological deficit accompanied by **encephalopathy**, and pathologically by widely scattered foci of **perivenular** inflammation and demyelination. ADEM is far commoner in children than adults; its hyperacute, haemorrhagic variant is *acute haemorrhagic leukoencephalitis (AHL)* of *Weston Hurst*.

Etiology and triggers

- **Post-infectious (parainfectious) ADEM** — the great majority of cases; the neurological syndrome typically begins *late* in the viral illness, as the exanthem is fading.
  - **Measles** is the classic and historically commonest antecedent — complicates roughly **1 in 1000** cases (Bradley: ~1 in 400 to 1 in 1000); live measles vaccination has dramatically reduced this worldwide.
  - In developed countries **varicella (chickenpox)** is now the most frequent trigger (**1 in 4000–10,000** cases); chickenpox-associated ADEM is notable for conspicuous **cerebellar** involvement.
  - Other agents: **rubella, mumps, influenza, parainfluenza, Epstein–Barr virus, human herpesvirus-6, HIV, dengue, Zika, herpes simplex/zoster, Mycoplasma pneumoniae**, Borrelia, Leptospira, and **SARS-CoV-2**.
- **Post-vaccinal ADEM** — of mainly historical importance: the original *"neuroparalytic accidents"* of the *Pasteur* rabies vaccine (rabbit spinal-cord–derived) and the *Jenner* smallpox vaccine; later reports with pertussis, rubella, diphtheria and the swine-influenza vaccine.
  - **Modern vaccines pose no meaningful risk:** the *Vaccine Safety Datalink* study of 24 vaccines in >9 million individuals (64 million doses) found no excess ADEM risk — the only possible signal was Tdap, estimated at <1 case per million doses.
- **Idiopathic** — a non-specific upper respiratory illness or no identifiable trigger in a proportion of cases. Rare drug associations: sulfonamides, para-aminosalicylic acid/streptomycin.

Form	Typical antecedent	Note
Parainfectious	Measles, varicella, rubella, mumps, EBV, Mycoplasma, SARS-CoV-2	Commonest; begins as exanthem fades
Post-vaccinal	Rabies (Pasteur), smallpox (Jenner), pertussis	Now of historical importance only
Idiopathic	None / non-specific URI	No identifiable trigger

Form	Typical antecedent	Note
AHL (Hurst)	Usually preceding URI	Hyperacute, haemorrhagic, often fatal

Pathogenesis and pathology

- **Mechanism** — a **cross-reactive (molecular-mimicry) autoimmune response** to the infectious agent triggers an inflammatory demyelinating attack on CNS myelin. Autoantibodies to **myelin basic protein (MBP)** and other myelin antigens are found in the CSF of some patients; cases with serum or CSF antibodies to **myelin oligodendrocyte glycoprotein (MOG)** are now reclassified as **MOGAD** (see below).
- **Hallmark histology** — *widely scattered foci of perivenular (perivascular) inflammation with surrounding demyelination*, involving **both white and grey matter**; vessel necrosis is frequent and meningeal reaction may be seen. This contrasts with the larger, confluent white-matter plaques of MS.
- **Acute haemorrhagic leukoencephalitis (AHL / Hurst disease)** — the most explosive form; lesions are **vasculitic and haemorrhagic** with a **necrotising vasculitis of venules and capillaries** and perivascular accumulation of polymorphonuclear cells and red blood cells. Antecedent is usually an upper respiratory infection; course is fulminant and frequently fatal.

Clinical features

- **Onset** — abrupt, with rapid progression over hours to a few days; peak deficit within days. A **prodrome** of fever, malaise and myalgia may precede the CNS syndrome.
- **Encephalopathy is the defining feature** — ranging from lethargy/irritability through stupor to coma; its presence (with multifocal signs) is the single most useful clinical discriminator from a first MS attack.
- **Polyfocal / disseminated signs** reflecting simultaneous cerebral, brainstem, cerebellar and spinal-cord involvement: hemiparesis or quadriparesis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, ataxia and movement disorders.
- **Seizures** are common; **meningismus** and headache frequent (fever often reappears as the exanthem fades).
- **Optic and spinal patterns** — when present, optic neuritis tends to be **bilateral** and any transverse myelopathy **complete** (cf. usually unilateral/partial in MS).
- **Course and prognosis** — recovery begins within days and resolves over weeks to months; the illness is **monophasic** by definition. Poor prognosis correlates with severity and abruptness of onset; measles-associated ADEM carries a worse outcome than vaccine-associated disease. Adult case-series report **mortality of 5–20%**, with permanent sequelae in many survivors.

Investigations

- **CSF** — normal/raised opening pressure; **lymphocytic pleocytosis (generally ≥200 cells/µL in ~80%)**, occasionally a mixed polymorphonuclear–lymphocytic picture in the first days; **protein modestly elevated (0.5–1.5 g/L; 50–150 mg/dL)**. **Oligoclonal bands (OCB) are transient and uncommon** — their persistence favours MS.

- **MRI (investigation of choice)** — *extensive, large, poorly-demarcated, relatively symmetric* **T2/FLAIR hyperintensities** in cerebral and cerebellar white matter, brainstem and spinal cord; characteristic involvement of **deep grey matter (thalamus, basal ganglia)** and cortex. A key feature is that the **great majority of lesions enhance with gadolinium simultaneously** (all of similar/recent age) — consistent with a single monophasic event — and they show partial resolution *without new lesions* on follow-up. (Contrast MS: lesions of differing ages, *Dawson fingers*, T1 black holes.)
- **Antibody serology** — test serum (and CSF if seronegative) **MOG-IgG** by cell-based assay and **AQP4-IgG** to identify MOGAD/NMOSD; **autoimmune/paraneoplastic encephalitis panel** where relevant.
- **Diagnostic criteria (paediatric ADEM, IPMSSG)** — a first **polyfocal** clinical CNS event of presumed inflammatory demyelinating cause **plus encephalopathy not explained by fever**, abnormal brain MRI in the acute phase, and **no new clinical or MRI events ≥3 months** after onset.

ADEM versus multiple sclerosis versus MOGAD

Feature	ADEM	Multiple sclerosis	MOGAD
Typical age	Children > adults	15–50 yr	Children and adults
Course	**Monophasic**	Relapsing/progressive	Monophasic or relapsing
Encephalopathy /seizures	Characteristic	Rare	Possible (ADEM-like in children)
Antecedent infection/vaccine	Usual	Not typical	Often
Optic neuritis	Bilateral, transient	Usually unilateral	Bilateral, longitudinally extensive, papillitis
MRI lesions	Large, symmetric, deep grey matter; **all enhance together**	Ovoid, periventricular, Dawson fingers; lesions of varying age	Fluffy ill-defined lesions; longitudinally extensive cord, conus, "H sign"
CSF OCB	Transient, uncommon	Persistent in majority	Uncommon (~6–13%)
Antibody	MBP (non-specific)	—	**MOG-IgG (cell-based assay)**

- *Caveat:* ~30% of adults initially labelled ADEM relapse within 3 years and are reclassified as **MS**; others prove to be **MOGAD, NMOSD or GFAP astrocytopathy** — hence **surveillance imaging after recovery is mandatory**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Axial brain MRI (FLAIR) schematic of ADEM** — label: *bilateral, large, poorly-demarcated, relatively symmetric subcortical/deep white-matter hyperintensities*; *thalamic and basal-ganglia (deep grey matter) lesions*; *brainstem lesion*; *all lesions enhancing simultaneously with gadolinium*. Add a contrasting small panel for MS (*periventricular Dawson fingers, lesions of differing ages*).
- **Histology of the perivenular lesion** — label: *central venule*; *perivascular cuff of lymphocytes/monocytes*; *surrounding "sleeve" of demyelination with preserved axons*; *(AHL variant: necrotising vasculitis, perivascular neutrophils and red cells, petechial haemorrhage)*.

Clinical / Diagnostic significance

- **Treatment is empirical (no controlled trials):** first-line is **high-dose IV glucocorticoids** (e.g., IV methylprednisolone) followed by an oral prednisone taper that may need to continue up to **8 weeks** to prevent rebound.
- **Refractory / steroid-unresponsive disease** (no response within a few days): escalate to **plasma exchange (plasmapheresis)** or **IV immunoglobulin**; immunosuppressants such as **cyclophosphamide** have been used in fulminant cases.
- **AHL** demands aggressive immunotherapy and neuro-critical care for raised intracranial pressure; prognosis remains poor.
- **Mandatory exclusions before committing to ADEM:** infective (herpes simplex/viral) encephalitis (treat empirically with **aciclovir** until excluded), bacterial meningoencephalitis, antiphospholipid syndrome, autoimmune/paraneoplastic (limbic) encephalitis, CNS vasculitis, neurosarcoidosis, primary CNS lymphoma and metastatic disease.
- **Key triage rule:** *simultaneous onset of disseminated signs, meningismus, encephalopathy and seizures favours ADEM over a first MS attack* — but distinction may be impossible acutely in adults, so follow up clinically and radiologically.

High-yield exam pointers

- ADEM = **monophasic, post-infectious/post-vaccinal, immune-mediated demyelination** with **encephalopathy + polyfocal deficit**.
- **Encephalopathy** is the cardinal discriminator from MS; **seizures and meningismus** also favour ADEM.
- Commonest antecedent historically = **measles (≈1 in 1000)**; now **varicella (1 in 4000–10,000)**, the latter with **cerebellar** signs.
- **Hallmark pathology = perivenular inflammation + demyelination**, white *and* grey matter.
- **AHL (Weston Hurst)** = hyperacute, haemorrhagic, necrotising-vasculitic, often fatal variant.
- MRI: **large, symmetric, deep-grey-matter lesions that all enhance simultaneously**; **OCBs transient/uncommon** (persistent OCB → think MS).
- Many "ADEM" cases with **MOG-IgG are now reclassified as MOGAD**; ~30% of adults later prove to be **MS** — *do surveillance MRI after recovery*.

- Treatment: **high-dose IV steroids → taper (up to 8 weeks); PLEX or IVIG if refractory**; adult mortality **5–20%**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Neuromyelitis Optica" (chapter covering MOGAD and Acute Disseminated Encephalomyelitis) and "Multiple Sclerosis" (Table: Disorders that can mimic MS).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the CNS" (ADEM, post-vaccinal and parainfectious forms, acute haemorrhagic leukoencephalitis).
- **CMDT 2026** — "Nervous System Disorders" (demyelinating disease differential; supportive management).
- *Coverage note:* The corpus covers ADEM well within Harrison's NMO/MOGAD chapter and Bradley, despite the spec flagging it as thin. The **formal IPMSSG (International Paediatric MS Study Group) consensus ADEM criteria** quoted under Investigations are universally accepted paediatric-neurology consensus but are not stated verbatim in the indexed corpus; all other specifics (epidemiological ratios, CSF/MRI values, mortality, Vaccine Safety Datalink data, treatment) are taken directly from Harrison 22e and Bradley 8e.

◆ ◆ ◆

Parkinson's disease

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

Definition / Introduction — Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer's disease, first described by *James Parkinson* (1817). It is a **synucleinopathy** characterised pathologically by degeneration of dopaminergic neurons in the **substantia nigra pars compacta (SNc)**, striatal dopamine depletion, and intraneuronal **α-synuclein** inclusions (*Lewy bodies* and *Lewy neurites*). Clinically it presents with the cardinal motor tetrad of **bradykinesia, rest tremor, rigidity and postural instability**, accompanied by a broad spectrum of non-motor features. Mean age of onset is ~60 years; lifetime risk is ~3% (men) and ~2% (women).

Aetiology

- **Sporadic / idiopathic** — the majority of cases occur sporadically and are of **unknown cause**; gene mutations are the only proven causes and may be found even in apparently sporadic cases.
- **Genetic (~15% familial)** — monogenic forms account for ~5% of cases, rising to ~15% when *GBA1* variants are included.
  - *Dominant*: **SNCA** (α-synuclein — first gene linked; even duplication/triplication of wild-type gene causes PD), **LRRK2** (~3% of sporadic cases; *p.G2019S* commonest, founder effect in Ashkenazi Jews & North African Berber Arabs; incomplete penetrance), **VPS35**, **RAB32**.
  - *Recessive (early-onset)*: **PRKN** (*Parkin* — commonest cause of autosomal-recessive juvenile PD, onset <20 yr, dystonia common, dementia rare), **PINK1**, **PARK7/DJ-1**.

  - **GBA1** (glucocerebrosidase) — the **strongest known genetic risk factor**; present in ~10% of PD and ~25% of Ashkenazi PD; associated with faster progression and cognitive decline.
- **Environmental** — the **MPTP** story (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, a contaminant of illicit heroin synthesis) produced parkinsonism in Californian addicts in the 1980s, proving an exogenous toxin can selectively kill dopamine neurons. Epidemiological associations (inconsistent): **pesticides, solvents, rural living, farming, well-water**. *Possible protective factors*: caffeine, cigarette smoking, NSAIDs, calcium-channel blockers.
- **"Double-hit" hypothesis** — interaction of a genetic susceptibility with an environmental toxin; neither alone is sufficient (unproven).
- **Secondary parkinsonism** — drug-induced (dopamine blockers — neuroleptics, **metoclopramide**; also tetrabenazine, **flunarizine/cinnarizine**, amiodarone, lithium), vascular, tumour, infection, normal-pressure hydrocephalus, trauma, and toxins (carbon monoxide, manganese).

Pathology and pathogenesis

- **Hallmark pathology** — loss of pigmented dopaminergic SNc neurons (depigmentation of the nigra), reduced striatal dopamine, and **α-synuclein-positive Lewy bodies/neurites**. *Non-dopaminergic* degeneration also affects cholinergic *nucleus basalis of Meynert*, noradrenergic *locus coeruleus*, serotonergic *raphe nuclei*, olfactory and peripheral autonomic systems — explaining the non-motor features.
- **Braak staging / spread** — Lewy pathology may begin in the peripheral autonomic nervous system, gut, olfactory bulb or **dorsal motor nucleus of the vagus** and ascend in a predictable sequence to the SNc and cortex, giving rise to the **"body-first" vs "brain-first"** concept. Premotor features (constipation, anosmia, REM sleep behaviour disorder, cardiac denervation) may precede motor onset by years to decades.
- **α-Synuclein "prion-like" hypothesis** — misfolded α-synuclein forms β-sheet-rich toxic oligomers and aggregates that **template** misfolding of native protein and **spread** trans-synaptically (supported by Lewy pathology developing in grafted healthy embryonic neurons, and by the **gut-brain axis** via the vagus).
- **GBA1–lysosome vicious cycle** — reduced glucocerebrosidase (GCase) activity impairs lysosomal clearance → α-synuclein accumulation; accumulated α-synuclein further inhibits GCase trafficking — a self-amplifying loop also operative in sporadic PD.
- **Final common pathways of cell death** — oxidative stress, neuroinflammation (microglial activation, HLA-DRB1 association, autoreactive T cells), excitotoxicity, **mitochondrial dysfunction** (complex I defect; *Parkin/PINK1* impair mitophagy), and lysosomal/proteasomal failure converge on a signal-mediated **apoptotic** process (interacting network — Olanow model).

Pathophysiology — basal ganglia circuitry

- The **striatum** (putamen + caudate) is the input region; **GPi/SNr** are the inhibitory (GABAergic) output regions projecting to thalamus and brainstem. Striatum and output nuclei are linked by the **direct (D1, facilitatory)** and **indirect (D2, inhibitory)** pathways, modulated by SNc dopamine.

- In PD, **dopamine denervation** → reduced inhibition of the indirect pathway → **increased firing of the STN and GPi** → excessive inhibition of the thalamus → reduced cortical motor activation → **parkinsonism**.
- This model is the rationale for surgically **lesioning or stimulating the STN/GPi**. Levodopa-induced **dyskinesia** relates not merely to reduced output firing *frequency* but to altered firing *patterns* (pauses, bursts) transmitting "misinformation" to cortex.

Clinical features and diagnosis

- **Cardinal motor features** — *Bradykinesia* (slowness, decrement); *Rest tremor* (4–6 Hz, "pill-rolling", asymmetric, re-emergent on posture); *Rigidity* (lead-pipe; **cogwheel** when tremor is superimposed — *Negro's sign*); *Postural instability* (late).
- **Other motor** — micrographia, masked facies (*hypomimia*), reduced blinking, hypophonia, drooling, dysphagia, stooped posture, **festinating shuffling gait**, freezing, falls; *Myerson's sign* (non-fatiguing glabellar tap reflex).
- **Non-motor** — anosmia, **REM sleep behaviour disorder**, constipation, orthostatic hypotension, urinary/sexual dysfunction, depression/anxiety/apathy, psychosis (visual hallucinations), and cognitive impairment/dementia.
- **Diagnosis is clinical** — historically "2 of 3" cardinal signs (24% post-mortem error). The **UK Brain Bank Criteria** (asymmetry, rest tremor, good levodopa response) raise accuracy to >90%; the **MDS Clinical Diagnostic Criteria** add supportive criteria, absolute exclusions and red flags, defining *clinically established* and *clinically probable* PD.
- **Investigations (selective)** — **DAT-SPECT / PET** shows reduced asymmetric striatal uptake (posterior putamen, caudate spared) — useful when diagnosis is uncertain; **α-synuclein seed amplification assay (SAA)** in CSF/skin (high sensitivity/specificity); MRI to exclude atypical/secondary causes; genetic testing in young-onset/familial cases. **Excellent levodopa response** strongly supports PD.

Differential diagnosis and staging

Category	Examples	Distinguishing clue
Atypical parkinsonism	MSA (MSA-p / MSA-c), PSP, corticobasal syndrome	Early speech/gait, falls, no rest tremor, symmetry, poor levodopa response
MSA	Glial cytoplasmic α-synuclein inclusions	Autonomic failure, cerebellar signs, pontine *"hot-cross-bun"* sign
PSP	Tauopathy	Vertical gaze palsy, *"hummingbird"* midbrain sign, retrocollis, early falls
Secondary	Drug-induced, vascular, NPH, toxins	History of neuroleptics; symmetrical; CO/Mn → globus pallidus
Other neurodegenerative	Wilson's disease, Huntington (Westphal), SCA, DLB	Age <40, *exclude Wilson's* (treatable)

- **Hoehn & Yahr staging** (severity): **I** — unilateral; **II** — bilateral/midline, balance intact; **III** — impaired righting reflex, mild–moderate disability; **IV** — severe disability but still walks/stands unaided; **V** — wheelchair/bedbound unless aided.

Management

- **General principle** — no current therapy is disease-modifying; treatment is **symptomatic and individualised**, using **low doses and polypharmacy** to minimise the levodopa dose and delay motor complications. Exercise, physiotherapy, speech/occupational therapy, education and caregiver support apply throughout.
- **Levodopa** (with peripheral decarboxylase inhibitor **carbidopa** or **benserazide**) — the **gold standard / most effective** drug; 200–1000 mg/day, start ≤400 mg/day (e.g. Sinemet 25/100 tds). Failure to respond should question the diagnosis. Forms: standard, CR, **Rytary/Crexont** (immediate+extended beads), Stalevo (with entacapone), intestinal gel (Duopa/Duodopa), inhaled (**Inbrija**).
  - *Motor complications* (dose- and duration-related, worse in young/female/severe disease): **wearing-off**, unpredictable **on–off**, **peak-dose (choreiform) dyskinesia**, **diphasic dyskinesia**, delayed-/no-on; behavioural — dopamine dysregulation syndrome, *punding*.
- **Dopamine agonists** — non-ergot **pramipexole, ropinirole, rotigotine patch** (less dyskinesia; favoured in younger patients); **apomorphine** (SC/sublingual — rescue for "off"). Beware sudden sleep attacks and **impulse-control disorders** (gambling, hypersexuality, shopping).
- **MAO-B inhibitors** — **selegiline, rasagiline (1 mg/day), safinamide** — mild monotherapy benefit and adjunctive reduction of "off" time; rasagiline of interest for possible disease-modification (*ADAGIO*, *DATATOP*).
- **COMT inhibitors** — **entacapone** (with each levodopa dose), **opicapone** (once daily), **tolcapone** (needs LFT monitoring — hepatotoxicity) — prolong "on" time.
- **A2A antagonist** — **istradefylline** (20–40 mg/day) reduces "off" time.
- **Amantadine** (NMDA antagonist) — the only oral agent that reduces **dyskinesia** without worsening parkinsonism.
- **Anticholinergics** — **trihexyphenidyl, benztropine** — mainly for **tremor**; avoid in elderly/cognitively impaired.
- **Advanced disease** — **continuous dopaminergic delivery** (intestinal levodopa-carbidopa gel; SC foslevodopa-foscarbidopa or apomorphine) and **on-demand therapies** (inhaled levodopa, SC/sublingual apomorphine) for refractory fluctuations.
- **Surgery** — **deep brain stimulation (DBS)** of the **STN or GPi** for disabling tremor or medically refractory motor complications (reversible, allows bilateral procedures); historical **pallidotomy / VIM thalamotomy** (tremor); **MRI-guided focused ultrasound** as a non-incisional alternative. DBS improves dopaminergic features but not non-dopaminergic disability.
- **Non-motor management** — depression/anxiety (SSRIs/benzodiazepines; pramipexole); **psychosis** (reduce offending drugs, then low-dose **quetiapine/clozapine** or **pimavanserin** — *avoid typical neuroleptics*); dementia (**rivastigmine**); orthostatic hypotension (salt, head-up tilt, **fludrocortisone, midodrine, droxidopa**); RBD (**clonazepam 0.5–1 mg / melatonin**); constipation, urinary and sexual dysfunction addressed symptomatically.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Basal ganglia direct/indirect pathway circuit (normal vs PD):** label *Cortex, Putamen (striatum), D1 (direct) pathway, D2 (indirect) pathway, SNc (dopamine), GPe, STN, GPi/SNr, Thalamus (VL), PPN* — with arrows showing in PD: ↓dopamine → ↑STN & ↑GPi firing → ↑thalamic inhibition → parkinsonism.
- **SNc pathology / Lewy body:** label *depigmented substantia nigra, melanised dopaminergic neuron, α-synuclein-positive Lewy body (with halo), Lewy neurite*.

Clinical / Diagnostic significance

- A **brisk, sustained response to levodopa** is both diagnostic and therapeutic; poor response is a *red flag* for atypical/secondary parkinsonism.
- **Premotor markers** (anosmia, RBD, constipation, DAT/SAA positivity) may permit diagnosis before motor onset — important for future disease-modifying trials.
- Always **exclude treatable mimics**: drug-induced parkinsonism (stop offending agent) and **Wilson's disease** (copper chelation prevents progression).
- Striatal dopamine terminal loss may be near-complete within ~4 years of diagnosis — relevant to the timing of any neuroprotective therapy.

High-yield exam pointers

- **Cardinal tetrad:** bradykinesia + rest tremor (4–6 Hz, pill-rolling) + rigidity (cogwheel) + postural instability; tremor is **asymmetric** at onset.
- **Pathology:** SNc dopaminergic loss + **α-synuclein Lewy bodies**; PD is a **synucleinopathy** (cf. PSP/CBS = tauopathies).
- **Genetics:** *SNCA* first linked; *LRRK2 G2019S* commonest dominant; ***GBA1* strongest risk factor**; *PRKN* commonest early-onset recessive.
- **MPTP → MPP^+** = mitochondrial complex I toxin — proof of principle for toxic dopaminergic injury.
- **Levodopa = gold standard**; combine with carbidopa/benserazide; start ≤400 mg/day; motor complications are **dose/duration-related**.
- **Amantadine** = best oral drug for **dyskinesia**; **anticholinergics** for tremor; **DBS of STN/GPi** for refractory fluctuations.
- **Avoid typical neuroleptics** in PD psychosis — use **quetiapine/clozapine/pimavanserin**.
- **Hoehn & Yahr** stages I–V; **UK Brain Bank** & **MDS** diagnostic criteria; **DAT-SPECT** + **α-synuclein SAA** as supportive tests.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Parkinson's Disease" (aetiology, genetics, pathogenesis, basal-ganglia pathophysiology, full pharmacological/surgical management) and "Dementia with Lewy Bodies".
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Parkinson Disease and Other Movement Disorders" & "Diagnosis and Assessment of Parkinson Disease" (epidemiology, clinical features, **Hoehn & Yahr staging**).
- **DeJong's The Neurologic Examination** — clinical signs (cogwheel/lead-pipe rigidity, *Negro's* and *Myerson's* signs, micrographia, masked facies).
- **CMDT 2026** — "Nervous System Disorders / Parkinsonism" (current drug regimens, doses, surgical and supportive management).

◆ ◆ ◆

Alzheimer's disease

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

Definition / Introduction — Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder and the commonest cause of dementia, contributing an estimated **60–70%** of all dementia (≈55 million people worldwide). It is characterised pathologically by extracellular **neuritic plaques** of amyloid-β (Aβ) and intraneuronal **neurofibrillary tangles (NFTs)** of hyperphosphorylated tau, with cholinergic neuronal loss in the nucleus basalis of Meynert. Clinically it presents most often with insidious-onset, progressive loss of **episodic memory** that slowly engulfs other cognitive domains and, ultimately, function and independence. Typical symptomatic duration is **8–10 years** (range 1–25).

Epidemiology & risk factors

- **Age** is the dominant risk factor: ~10% of those >65 have AD — 3% at 65–74, 17% at 75–84, and **32% at ≥85** years.
- **Genetic / family history:** the **ApoE ε4** allele on chromosome 19 is the major susceptibility gene — one ε4 allele raises risk ~2–3-fold (more in women), two alleles **10–15-fold**; each ε4 allele lowers age of onset by ~10 years. Autosomal-dominant familial AD (1–2%) is caused by mutations in **APP (chr 21)**, **Presenilin-1 (PSEN-1, chr 14)** and **Presenilin-2 (PSEN-2, chr 1)**; PSEN-1 is the commonest cause of early-onset FAD. Adults with **trisomy 21 (Down syndrome)** invariably develop AD pathology after age 40.
- **Female sex** is an independent risk factor; **TREM2** and >40 GWAS variants (CLU, PICALM, CR1) add small effects.
- **Modifiable / vascular:** mid-life hypertension, diabetes (≈3-fold risk), obesity, dyslipidaemia, smoking, hearing loss, traumatic brain injury, physical inactivity, low education, depression and air pollution. SPRINT-MIND showed intensive BP control (SBP <120) reduced incident MCI.

Pathology & neurochemistry

- Earliest and most severe degeneration begins in the **medial temporal lobe** (entorhinal cortex, hippocampus) and **nucleus basalis of Meynert**, spreading to temporoparietal then frontal neocortex.
- **Aβ** (39–42 aa) is cleaved from **amyloid precursor protein (APP)** by **β- and γ-secretases**; soluble Aβ oligomers and Aβ42 are the toxic species, polymerising into plaques. Vascular Aβ deposition = **cerebral amyloid angiopathy (CAA)**.
- **NFTs** = paired helical filaments of hyperphosphorylated **tau**, which detaches from microtubules and spreads in a prion-like, stereotyped pattern (**Braak staging**).
- **Neurochemistry:** loss of cortical **acetylcholine** and choline acetyltransferase (basis of cholinesterase-inhibitor therapy), with noradrenergic (locus coeruleus) and serotonergic (dorsal raphe) depletion.

Clinical features

AD evolves through a recognised continuum — **preclinical → MCI/early symptomatic → dementia (mild → moderate → severe)**.

- **Preclinical AD:** biomarker evidence of amyloid (± tau) pathology *without* symptoms; may precede symptoms by ≥20 years.
- **Mild cognitive impairment (MCI) / early symptomatic AD:** memory loss noticeable to patient and family and confirmed on testing, but daily function preserved. ~50% of MCI (≈12%/year) progress to dementia over 4 years.
- **Typical (amnestic) presentation:** insidious loss of **episodic memory** — repeating questions, forgetting recent conversations and appointments — reflecting hippocampal pathology. Disorientation to time/place, getting lost on familiar routes, and impaired complex tasks (finances, work, driving) follow.
- **Mild dementia:** memory + word-finding difficulty (circumlocution), early visuospatial and executive decline; depression, anxiety, social withdrawal and apathy are common and may be a **prodrome**.
- **Moderate dementia:** unable to work, easily lost, needs daily supervision. Progressive **language** failure (naming → comprehension → fluency), **apraxia** (using utensils/appliances), **visuospatial deficits** (dressing, copying figures), and acalculia/clock difficulties. **Delusions** (theft, infidelity, misidentification), agitation, wandering, disinhibition and disrupted sleep–wake cycle appear.
- **Severe (late) dementia:** patient becomes rigid, mute, incontinent, bedridden and totally dependent; **myoclonus**, hyperreflexia, parkinsonian gait and **seizures** may occur. Death is usually from **aspiration**, infection, malnutrition or pulmonary embolism.
- **Atypical variants (~20%, often younger): posterior cortical atrophy** (progressive visual processing failure), **logopenic primary progressive aphasia** (impaired naming and repetition), **dysexecutive/behavioural ("frontal") variant**, and a **corticobasal (akinetic-rigid-dystonic)** syndrome. Anosognosia (unawareness) may occur, but most retain insight early.

Diagnosis & investigations

- **Clinical diagnosis** rests on slowly progressive amnestic decline with normal systemic labs and posterior-predominant cortical + hippocampal atrophy; it is confirmed at autopsy in ~**70–80%**.
- **Cognitive screening:** MMSE (Folstein), **MoCA**, Mini-Cog — quick but insensitive to MCI; formal neuropsychometry for atypical cases.
- **Exclude reversible/secondary dementia (mandatory work-up):** serum **vitamin B12**, **TSH/free T4**, electrolytes, calcium, RPR/VDRL, HIV; LP where indicated. Treat the "treatable" differentials — B12 deficiency, hypothyroidism, normal-pressure hydrocephalus, neurosyphilis, depression (pseudodementia), chronic drug intoxication.
- **Structural MRI/CT:** medial temporal (hippocampal) and posterior-predominant cortical atrophy; chiefly excludes tumour, vascular disease, subdural haematoma and NPH.
- **Functional/molecular imaging: FDG-PET** shows temporoparietal hypometabolism (and distinguishes AD from FTD); **amyloid PET** ([18F]florbetapir/florbetaben/flutemetamol) confirms plaque burden; **tau PET** ([18F]flortaucipir) maps NFTs.
- **Fluid biomarkers:** CSF shows **low Aβ42**, reduced **Aβ42/Aβ40 ratio** and raised **phospho-tau (p-Tau181/p-Tau217)**. **Plasma p-Tau217** (and Aβ42/40) now offer scalable, blood-based confirmation.
- **Criteria:** evolution from **NINCDS-ADRDA (1984)** → **NIA-AA (2011)** clinical-biomarker criteria → **2018 ATN research framework** (Amyloid, Tau, Neurodegeneration) and the **2024 Revised Criteria** defining AD *biologically* by "core 1" biomarkers (amyloid PET, CSF/plasma Aβ and p-Tau). **ApoE genotyping** is recommended *before* anti-amyloid therapy to assess ARIA risk.

Management

AD requires a **multidomain approach**: symptomatic neurotransmitter therapy, disease-modifying anti-amyloid antibodies, treatment of neuropsychiatric symptoms, and patient/caregiver support.

1. Neurotransmitter-based (symptomatic) therapy

Drug	Mechanism	Dosing	Approved stage
Donepezil	Cholinesterase inhibitor	Start 5 mg OD ×4 wk → **10 mg OD** (23 mg for mod–severe)	Mild–severe
Rivastigmine	Cholinesterase inhibitor	1.5 mg BID, titrate to **3–6 mg BID**; or **9.5 mg/24h patch**	Mild–severe
Galantamine	Cholinesterase inhibitor	4 mg BID → **8–12 mg BID** (24 mg/day ER)	Mild–severe
Memantine	NMDA-receptor antagonist	5 mg OD, ↑5 mg/wk → **10 mg BID**	Moderate–severe

- Dose-escalate over **4–6 weeks**. Cholinesterase inhibitors modestly slow decline (MMSE maintained ~1 year vs 2–3 point fall on placebo); main side effects are **GI (nausea, diarrhoea, cramps)**, vivid dreams, bradycardia/syncope (obtain ECG in cardiac patients). A common strategy: start a cholinesterase inhibitor in mild AD and **add memantine** in moderate–severe

disease. Memantine side effects: constipation, dizziness, headache, somnolence. Cholinesterase inhibitors are **avoided in frontotemporal dementia** (worsen behaviour).

2. Disease-modifying anti-amyloid monoclonal antibodies (first DMTs for AD)

- **Lecanemab** (anti-Aβ **protofibril**): 10 mg/kg IV every 2 weeks — **Clarity-AD** showed **27% slowing** of CDR-SB decline at 18 months.
- **Donanemab** (anti-**pyroglutamate Aβ**): 700 mg IV q4w ×3 then 1400 mg q4w — **TRAILBLAZER-ALZ2** showed 22% slowing on iADRS and 28% on CDR-SB; greatest benefit in low–medium tau-PET patients.
- *Aducanumab* received accelerated approval but was withdrawn (ambiguous efficacy).
- **Restricted to MCI or mild AD dementia with biomarker-confirmed amyloid (PET/CSF).** Key toxicity = **ARIA** — ARIA-E (oedema/effusion on FLAIR) and ARIA-H (microbleeds/siderosis on GRE/SWI); ~75% asymptomatic, but seizures, stroke-like episodes and rare death occur. Risk rises with each ε4 allele (**box warning for ε4 homozygotes**). Requires serial surveillance MRI; **contraindicated** with extensive CAA (>4 microbleeds/cortical siderosis), uncontrolled hypertension, anticoagulation, and concurrent **thrombolysis** for acute stroke.

3. Neuropsychiatric / behavioural symptoms

- **Depression/anxiety:** SSRIs with low anticholinergic burden (e.g., **escitalopram** 5–10 mg).
- **Agitation/psychosis:** non-pharmacological behavioural measures first; low-dose atypical antipsychotics (risperidone, quetiapine, olanzapine) carry an **FDA black-box warning** (increased mortality in elderly dementia). **Brexpiprazole** is the only agent FDA-approved for **agitation in AD**.
- **Seizures:** levetiracetam. **Avoid strong anticholinergics** (diphenhydramine, oxybutynin) which worsen cognition.

4. Non-pharmacological & caregiver support

- Memory aids (notebooks, posted reminders), home safety, eventual cessation of driving.
- Lifestyle: physical/cognitive/social activity, vascular risk-factor control, sleep hygiene, **Mediterranean/DASH diet**.
- Address **caregiver burnout** with respite care, adult day-care and support groups (Alzheimer's Association). *(Estrogen, statins, vitamin E and ginkgo have not shown benefit in RCTs.)*

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **APP processing pathway:** membrane-spanning **APP** cleaved by **β-secretase (BACE)** then **γ-secretase** → toxic **Aβ42** (amyloidogenic) vs non-amyloidogenic **α-secretase** → **Aβ40/P3**. Label: *APP, α/β/γ-secretase, Aβ42 (toxic plaque), Aβ40, cell membrane*.
- **Brain atrophy / pathology schematic:** coronal section showing **hippocampal + medial temporal lobe atrophy** with dilated temporal horns and posterior cortical atrophy; inset labelling **extracellular neuritic (amyloid) plaque** and **intraneuronal neurofibrillary tangle**, and the **nucleus basalis of Meynert** (cholinergic loss).

Clinical / Diagnostic significance

- **Episodic memory loss + medial temporal atrophy + temporoparietal hypometabolism** is the classic triad pointing to AD.
- Always **exclude reversible dementias** (B12, thyroid, NPH, neurosyphilis, depression, drugs) before labelling AD.
- **Distinguishing clues:** early gait disturbance with mild memory loss → vascular dementia/NPH; resting tremor, fluctuations and visual hallucinations → DLB; rapid decline with myoclonus → Creutzfeldt-Jakob disease; behavioural change with anterior atrophy → frontotemporal dementia.
- Biomarker confirmation is now **mandatory before disease-modifying therapy**, and **ApoE genotyping** stratifies ARIA risk.

High-yield exam pointers

- Commonest dementia (60–70%); hallmark = **amyloid plaques + tau NFTs**; cholinergic deficit (nucleus basalis of Meynert).
- **ApoE ε4** = major risk gene (2–3× heterozygote, 10–15× homozygote); FAD genes = **APP, PSEN-1, PSEN-2**; Down syndrome → early AD.
- Earliest clinical feature = **episodic (anterograde) memory loss**; atypical variants = posterior cortical atrophy, logopenic aphasia, frontal/dysexecutive.
- **CSF:** ↓Aβ42, ↓Aβ42/40 ratio, ↑p-Tau181/217; **plasma p-Tau217** emerging. **FDG-PET** = temporoparietal hypometabolism.
- Symptomatic drugs: **cholinesterase inhibitors** (donepezil, rivastigmine, galantamine) ± **memantine** (NMDA antagonist, moderate–severe).
- Disease-modifying: **lecanemab & donanemab** (anti-amyloid mAbs) for early AD; major risk = **ARIA-E/ARIA-H**; check ApoE before starting.
- **Brexpiprazole** = only drug FDA-approved for agitation in AD; antipsychotics carry a mortality **black-box warning**.
- Death usually from **aspiration pneumonia**, infection or malnutrition.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Alzheimer's Disease" (clinical manifestations, pathology, genetics, biomarkers, treatment including anti-amyloid antibodies, ARIA) and "Dementia."
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Alzheimer Disease and Other Dementias" (MCI continuum, NINCDS-ADRDA/NIA-AA/2018 ATN diagnostic frameworks, structural/functional/amyloid–tau imaging).
- **CMDT 2026** — "Nervous System Disorders" (current drug dosing, anti-amyloid therapy regimens and cautions, diagnostic work-up).

◆ ◆ ◆

Approach to coma

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

Definition / Introduction — *Coma* is a deep sleep-like state of unarousable unresponsiveness, with the eyes closed, from which the patient cannot be roused even by vigorous stimuli. It lies at the severe end of a continuum of impaired alertness (drowsiness → stupor → coma) and is one of the commonest neurological emergencies in internal medicine. Consciousness has two components — **arousal/wakefulness** (brainstem reticular activating system, RAS) and **awareness/content** (cerebral cortex); coma reflects failure of one or both. An *organised, time-critical bedside approach* — simultaneous resuscitation, structured history, and a focused neurological examination to localise the lesion — is essential, because metabolic-toxic causes (far commoner than structural ones) are frequently reversible.

Spectrum of impaired consciousness and coma mimics

State	Arousal	Awareness	Key features
Drowsiness	↓ (easily roused)	Largely intact	Simulates light sleep
Stupor	Roused only by vigorous/repeated stimuli	Impaired	Withdraws from noxious stimuli
Coma	Absent	Absent	Eyes closed, unarousable
Vegetative state	Present (eyes open, sleep–wake cycles)	Absent	"Awake but unaware"; autonomic/respiratory function retained; *persistent* if >4 weeks
Minimally conscious state	Present	Inconsistent/ minimal	Reproducible command-following, visual tracking; better prognosis than VS
Akinetic mutism / abulia	Awake	Partly preserved	Immobile, mute; medial frontal/medial thalamic damage
Catatonia	Variable	Preserved	Psychiatric; waxy flexibility, responds to *lorazepam*

State	Arousal	Awareness	Key features
Locked-in syndrome	Awake	**Fully preserved**	Ventral pontine lesion (basilar thrombosis); quadriplegic, anarthric, but **vertical gaze + lid elevation retained**, pupils reactive

- These mimics must be distinguished from true coma at the bedside; asking the patient to look up/down and blink unmasks the *locked-in state*, and *catatonia* may reverse transiently with IV lorazepam.

Anatomical–physiological basis and causes

- Coma arises from either **(1) widespread bilateral cerebral hemispheric dysfunction** or **(2) failure of the brainstem–thalamic RAS** (upper pons, midbrain, thalamus). A unilateral hemispheric mass causes coma only by compressing the brainstem.
- Neurons depend on continuous cerebral blood flow: **glucose stores last ~2 min and oxygen stores only 8–10 s** after circulatory arrest — hence the urgency.
- **Three diagnostic categories** (Harrison):
- **No focal/lateralising signs (CT often normal)** — intoxications (alcohol, sedatives, opioids), metabolic (hypo-/hyperglycaemia, hypoxia, hyponatraemia, uraemia, hepatic coma, hypercapnia, hypercalcaemia, Addisonian/myxoedema crisis), severe systemic infection/sepsis, status/non-convulsive status epilepticus and post-ictal states, hypertensive encephalopathy/eclampsia/PRES, severe hypo-/hyperthermia.
- **Focal brainstem or lateralising signs (CT usually abnormal)** — intracerebral (basal ganglionic, thalamic, cerebellar, pontine) haemorrhage, large MCA infarct with mass effect, basilar artery thrombosis, abscess, tumour with oedema, subdural/epidural haematoma.
- **Meningeal syndromes (fever/stiff neck, CSF pleocytosis)** — bacterial meningitis/meningoencephalitis, subarachnoid haemorrhage, autoimmune/paraneoplastic encephalitis.
- **Threshold values** worth recalling: serum Na^+ <125 mmol/L → confusion, <119 mmol/L (acute) → coma/convulsions; hyperosmolar coma when osmolarity >350 mosmol/L; coma from hypothermia when core <31°C.

Herniation syndromes (structural deterioration)

- **Uncal (lateral) transtentorial** — medial temporal uncus impacts CN III → *ipsilateral fixed dilated pupil* (earliest sign; peripheral parasympathetic fibres affected first), then contralateral hemiparesis; compression of the opposite peduncle gives ipsilateral hemiparesis = ***Kernohan-Woltman notch sign*** (a false-localising sign).
- **Central transtentorial** — symmetric downward thalamic displacement; heralded by *small pupils and drowsiness*, with orderly rostro-caudal (midbrain → pons → medulla) deterioration.
- **Transfalcine (subfalcine/cingulate)** — cingulate gyrus under the falx.
- **Foraminal (tonsillar)** — cerebellar tonsils into foramen magnum → early medullary compression, apnoea, sudden death.

Step 1 — Resuscitation, history and general examination

- **Airway–Breathing–Circulation first**: protect airway/intubate if GCS ≤8, apnoea, or aspiration risk; support BP; immobilise the cervical spine if trauma is possible.
- **"Coma cocktail" without delay** (CMDT): **thiamine 100 mg IV** (before glucose, to avert Wernicke's), then **dextrose 50% 25 g IV**, and **naloxone 0.4–1.2 mg IV** for possible opioid overdose; check a bedside capillary glucose immediately.
- **History (collateral)** from family/paramedics: rapidity of onset (abrupt → SAH, brainstem stroke, ICH; gradual → mass/metabolic), antecedent headache/fever/seizures/trauma, drug/alcohol use, and chronic liver/renal/cardiac/lung disease.
- **General examination**: vital signs, fundoscopy (papilloedema, subhyaloid haemorrhage of SAH), nuchal rigidity, skin (petechiae → meningococcaemia/TTP; cherry-red → CO), breath (fetor hepaticus, ketones), and a trauma survey. *Fever* → infection/heatstroke/NMS; *hypothermia* → sedative/alcohol/myxoedema; **hypertension + bradycardia + irregular respiration = Cushing response of raised ICP**.

Step 2 — Neurological examination: grading and localisation

A. Depth of coma — scoring scales

Glasgow Coma Scale	Best response	Score
Eye opening (E)	Spontaneous / To speech / To pain / Nil	4 / 3 / 2 / 1
Verbal (V)	Oriented / Confused / Inappropriate words / Incomprehensible sounds / Nil	5 / 4 / 3 / 2 / 1
Motor (M)	Obeys / Localises / Withdraws / Abnormal flexion / Extension / Nil	6 / 5 / 4 / 3 / 2 / 1

- GCS ranges **3–15**; validated chiefly for *traumatic* coma. Limitation: cannot score V in intubated patients and omits brainstem reflexes — hence the **FOUR score** (*Full Outline of UnResponsiveness*; Wijdicks), which grades **Eye, Motor, Brainstem reflexes (pupillary, corneal, cough) and Respiration** (each 0–4, total 0–16) and is usable in the intubated patient.

B. Brainstem reflexes (localise the level — see Fig. 30-3 analogue):

- **Pupils** — reactive midsize (2.5–5 mm) excludes upper-midbrain damage; **unilateral fixed dilated >6 mm** = CN III/uncal compression; **bilateral fixed midposition** = midbrain; **pinpoint (<1 mm) reactive** = pontine haemorrhage *or* opioids (give naloxone); **small reactive (1–2.5 mm)** = metabolic/diencephalic. Pupillary reactivity is typically *preserved in metabolic coma* — a key discriminator.
- **Ocular position/movement** — *"the eyes look toward a hemispheral lesion and away from a brainstem lesion"*; roving conjugate movements exclude brainstem damage; **ocular bobbing** = bilateral pontine lesion (basilar thrombosis); **ocular dipping** = diffuse anoxic cortical damage.
- **Oculocephalic ("doll's eye")** — turn the head (only after excluding cervical injury); intact brainstem → eyes move opposite to head turn. **Oculovestibular (cold caloric)** — irrigate the canal with ice water → tonic deviation *toward* the cold ear; mnemonic **COWS** (Cold-Opposite, Warm-

Same, naming the fast phase). Both are preserved in metabolic coma and lost with structural brainstem damage.

- **Corneal reflex** — afferent CN V, efferent CN VII; tests pontine integrity.

C. Respiratory patterns (localising value, see Fig. 5.1 analogue):

- *Cheyne-Stokes* (cyclical crescendo–decrescendo with apnoea) → bihemispheric/diencephalic or metabolic; *central neurogenic hyperventilation* → upper pontine/midbrain tegmentum; *apneustic* (inspiratory pause) → mid/caudal pons; *cluster/ataxic (Biot)* → medulla (pre-terminal); *Kussmaul* (deep regular) → metabolic acidosis.

D. Motor responses & posturing:

- **Decorticate** posturing (flexion of elbows/wrists, supination; legs extended) → lesion *rostral to the midbrain*; **decerebrate** posturing (extension/pronation of arms, leg extension) → lesion in/caudal to the *midbrain–upper pons*. Purposeful withdrawal implies intact corticospinal tracts; *multifocal myoclonus and asterixis* suggest a metabolic cause.

Step 3 — Investigations

- **Bedside/blood**: capillary then lab glucose, electrolytes, calcium, magnesium, osmolarity, renal and hepatic function (with **NH_3**), ABG, full blood count, **toxicology screen**, cultures if febrile.
- **Imaging**: urgent **non-contrast CT head** for haemorrhage/herniation/hydrocephalus; add **CT/MR angiography** if posterior-circulation/basilar occlusion is suspected. A normal CT does not exclude early infarction, encephalitis, diffuse axonal injury, or isodense subdural.
- **EEG**: essential to detect **non-convulsive status epilepticus**; shows triphasic/δ slowing in metabolic coma, "alpha coma" (poor prognosis), and *extreme delta brush* in anti-NMDA-receptor encephalitis.
- **Lumbar puncture** (after CT excludes a mass): mandatory when meningitis/encephalitis or CT-negative SAH is suspected — give blood cultures + empirical antibiotics *first* if meningitis is likely.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **Brainstem-reflex localisation diagram (Harrison Fig. 30-3 style):** sagittal brainstem with labels — *Midbrain (CN III / pupillary light reflex)*, *Pons (CN V–CN VII corneal reflex; MLF; reflex conjugate eye movements; CN VI, VIII)*, *Medulla (respiratory neurons; gag/cough)*; arrows for *oculocephalic* and *oculovestibular (caloric)* pathways.
> - **Pupils-in-coma chart (Plum & Posner style):** label each — *Metabolic = small reactive*, *Diencephalic = small reactive*, *Tectal = large "fixed", hippus*, *CN III/uncal = dilated fixed*, *Pontine = pinpoint*, *Midbrain (nuclear) = midposition fixed*.

Clinical / Diagnostic significance

- The pattern of pupils + eye movements + respiration + posturing **localises** the lesion to hemisphere vs diencephalon vs midbrain vs pons vs medulla and distinguishes *structural* from *metabolic* coma (preserved pupillary and reflex eye movements favour metabolic).

- **Brain death** = irreversible cessation of all cerebral and brainstem function: prerequisites — established irreversible cause, exclusion of confounders (hypothermia <32–35°C, sedatives/paralytics, severe metabolic/endocrine derangement); findings — deep coma, **absent pupillary, corneal, oculocephalic, oculovestibular, cough/gag reflexes**, and a **positive apnoea test** (no respiratory effort with $PaCO_2$ ≥60 mmHg or a ≥20 mmHg rise above baseline, pH <7.30). Spinal reflexes may persist. Ancillary tests (cerebral angiography/radionuclide flow study) used when clinical testing is incomplete.
- **Prognosis**: metabolic coma fares far better than anoxic/traumatic coma. After cardiac arrest, *bilaterally absent pupillary light reflexes at 24 h*, and *absent corneal reflexes / absent–extensor motor responses and bilaterally absent SSEP cortical responses at 72 h*, predict poor outcome — but therapeutic hypothermia delays reliable prognostication, mandating *multimodal* assessment.

High-yield exam pointers

- Consciousness = **arousal (RAS) + awareness (cortex)**; coma needs bilateral hemispheric or brainstem RAS failure.
- **Metabolic > structural** as a cause; *reactive pupils + intact reflex eye movements* point to metabolic coma.
- **First-line drugs**: thiamine → dextrose → naloxone; intubate if GCS ≤8.
- **Uncal herniation** → ipsilateral blown pupil first; **Kernohan-Woltman** = false-localising ipsilateral hemiparesis.
- **GCS 3–15** (E4 V5 M6); **FOUR score** adds brainstem reflexes + respiration and works in intubated patients.
- **COWS** for cold-caloric fast phase; **ocular bobbing = pons**, **dipping = anoxic cortex**.
- **Decorticate = above midbrain; decerebrate = midbrain/pons** (worse).
- **Cushing response** (hypertension + bradycardia + irregular breathing) signals raised ICP/impending herniation.
- Always do **EEG** in unexplained coma to exclude **non-convulsive status epilepticus**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Coma" (Josephson, Ropper, Hauser): definitions, RAS physiology, herniation syndromes, brainstem-reflex examination, differential diagnosis (Table 30-1), brain death and prognosis.
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Stupor and Coma": Glasgow Coma Scale (Table 5.6) and FOUR score, pupillary pathways/Plum-Posner pupil chart, respiratory-pattern localisation, oculocephalic/caloric tables, posturing.
- **CMDT 2026** — "Nervous System Disorders / Coma & Stupor": emergency workup, coma cocktail doses, rostro-caudal deterioration, brain-death apnoea-test thresholds, vegetative/minimally conscious states (amantadine).

◆ ◆ ◆

Autosomal recessive ataxias

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — The **autosomal recessive cerebellar ataxias (ARCAs)** are a clinically and genetically heterogeneous group of inherited disorders in which degeneration of the **cerebellum and its afferent/efferent pathways (spinocerebellar tracts, dorsal columns, dorsal root ganglia, peripheral nerves)** produces progressive gait and limb incoordination, dysarthria and oculomotor disturbance, typically with **onset in childhood, adolescence or early adulthood**. ARCAs characteristically affect siblings while parents are asymptomatic heterozygous carriers, and they are frequently accompanied by non-cerebellar neurological and systemic features (neuropathy, pyramidal signs, cardiomyopathy, telangiectasia, skeletal deformity). With whole-exome/whole-genome sequencing the number of recognised ARCAs now exceeds **90**, but *Friedreich's ataxia* remains by far the commonest, accounting for about half of all hereditary ataxias.

Classification — a mechanism-based scheme

A genomic/pathway classification has largely superseded the older purely clinical one. ARCAs are usefully grouped by the **biological pathway disrupted** (Synofzik), which also predicts the diagnostic biomarker and potential therapy:

Pathogenic pathway	Representative ARCAs (gene → protein)	Diagnostic biomarker / clue
Mitochondrial dysfunction	Friedreich ataxia (*FXN* → frataxin); ARSACS (*SACS* → sacsin); SPG7 (*SPG7* → paraplegin); POLG/ataxia-neuropathy spectrum (*POLG1*); AVED (*TTPA* → α-tocopherol transfer protein)	Low serum vitamin E (AVED)
Defective DNA repair	Ataxia-telangiectasia (*ATM*); ataxia-telangiectasia-like disorder (*MRE11*); AOA1 (*APTX* → aprataxin); AOA2 (*SETX* → senataxin)	↑α-fetoprotein (AT, ATLD, AOA2); ↓albumin + ↑cholesterol (AOA1)
Complex lipid metabolism	Abetalipoproteinaemia (*MTTP*); Niemann-Pick type C (*NPC1/NPC2*); cerebrotendinous xanthomatosis (*CYP27A1*)	↑plasma cholestanol (CTX); oxysterols/bile acids (NPC)
Cytoskeletal / structural & repeat-expansion	SYNE1 ataxia (*SYNE1* → nesprin-1); **RFC1**-related CANVAS (biallelic *AAGGG* intronic expansion)	Cerebellar atrophy + sensory neuronopathy (CANVAS)

After Friedreich's ataxia and RFC1/CANVAS, the next commonest ARCAs are SPG7, ARSACS, AOA2, SYNE1, ataxia-telangiectasia, AOA1 and POLG-ataxia (each ≥2%).

Friedreich's Ataxia (FRDA) — the prototype ARCA

Clinical features

- Presents **before 25 years** of age with progressive staggering gait, frequent falls and *titubation*; the **lower limbs are more severely affected** than the upper.
- Examination: **nystagmus, loss of fast saccades, dysarthria, dysmetria, truncal/limb ataxia**; **areflexia** (absent ankle and knee jerks) with **extensor plantar responses** (the classic combination

of areflexia + Babinski sign in a young patient); **loss of vibration and joint-position sense** (large-fibre sensory/spinocerebellar involvement); distal weakness.

- **Systemic: hypertrophic cardiomyopathy in ~90%** (cardiomegaly, symmetrical hypertrophy, conduction defects/arrhythmias — the **commonest cause of death**); **diabetes mellitus in ~20%** (insulin resistance + β-cell dysfunction); skeletal deformities — **pes cavus, pes equinovarus and scoliosis**; optic atrophy and sensorineural deafness may occur. Median age at death ~35 years; women have a better prognosis than men.

Genetics & pathogenesis

- The **only known autosomal recessive trinucleotide-repeat disease**, caused by an unstable **GAA triplet-repeat expansion in intron 1 of the *FXN* (frataxin) gene on chromosome 9 (9q13–q21.1)**.
- **>95% are homozygous** for the GAA expansion; normal alleles carry **7–22 repeats**, patients **200–900 repeats** — *larger repeats correlate with earlier onset and greater severity*. **Compound heterozygotes** (one GAA expansion + one point mutation) give atypical/milder phenotypes (e.g. late-onset FRDA, FRDA with retained reflexes).
- **Frataxin** is a **mitochondrial protein of iron homeostasis**; its deficiency causes **mitochondrial iron accumulation, loss of iron-sulphur (Fe-S) cluster enzymes, reduced ATP production and oxidative cell injury**, with iron deposition in the heart.

Pathology: degeneration of **dorsal root ganglia, dorsal (posterior) columns, dorsal/ventral spinocerebellar tracts, lateral corticospinal tracts and the dentate nucleus**; MRI shows **spinal cord atrophy** (cerebellar atrophy is relatively mild).

Other important autosomal recessive ataxias

- **Ataxia-telangiectasia (AT):** first decade; cerebellar ataxia with **oculocutaneous telangiectasia (conjunctival)**, oculomotor apraxia, choreoathetosis, myoclonus; **recurrent sinopulmonary infections, IgA/IgG2 immunodeficiency**, marked **radiosensitivity** and high risk of **lymphoma, leukaemia and breast cancer**. *ATM* gene (11q22–23) encodes a PI3-kinase-like serine/threonine kinase activated by DNA double-strand breaks. Markers: **elevated α-fetoprotein** and immunoglobulin deficiency.
- **Ataxia with vitamin E deficiency (AVED):** *TTPA* mutation (α-tocopherol transfer protein); juvenile onset, **phenotype mimics Friedreich's** (ataxia, proprioceptive loss, areflexia, Babinski) with **low serum vitamin E but normal lipoproteins** — *treatable with vitamin E.*
- **Abetalipoproteinaemia (Bassen-Kornzweig syndrome):** *MTTP* (microsomal triglyceride transfer protein) defect impairing VLDL formation → fat-soluble vitamin (E) malabsorption; spinocerebellar degeneration with **acanthocytosis, retinitis pigmentosa, steatorrhoea** — responds to high-dose vitamin E.
- **ARSACS** (autosomal recessive spastic ataxia of Charlevoix-Saguenay, *SACS*/sacsin; Québec founder effect): triad of **cerebellar ataxia + lower-limb spasticity + sensorimotor neuropathy**; MRI shows **pontine T2-hypointense stripes and thickened middle cerebellar peduncles**.
- **RFC1-related CANVAS:** late-onset; **C**erebellar **A**taxia + **N**europathy (sensory neuronopathy) + **V**estibular **A**reflexia **S**yndrome, frequently preceded by a **chronic dry cough** and autonomic features; biallelic intronic *AAGGG* expansion.

- **AOA1 (*APTX*/aprataxin)** — ataxia + oculomotor apraxia + neuropathy with **hypoalbuminaemia and hypercholesterolaemia**; **AOA2 (*SETX*/senataxin)** — similar, with **raised α-fetoprotein**.
- **Cerebrotendinous xanthomatosis (CTX, *CYP27A1*):** ataxia, dementia, epilepsy, neuropathy with **tendon xanthomas and juvenile cataracts**; **raised plasma cholestanol** — treatable with chenodeoxycholic acid.
- **Niemann-Pick type C (*NPC1/NPC2*):** ataxia with **vertical supranuclear gaze palsy**, organomegaly and psychiatric features; **miglustat** slows progression. **POLG**-related ataxia-neuropathy spectrum (MIRAS/SANDO) — ataxia, neuropathy, seizures, ophthalmoplegia.

Diagnostic approach & biomarkers

- **Pattern recognition:** age at onset, family tree (affected siblings, consanguinity), and the *spinocerebellar/sensory* versus *pure cerebellar* phenotype.
- **Targeted serum biomarkers** (cheap, high-yield first-line): **vitamin E** (AVED, abetalipoproteinaemia), **α-fetoprotein** (AT, AOA2), **albumin + cholesterol** (AOA1), **plasma cholestanol** (CTX), **lipoprotein electrophoresis/blood film for acanthocytes** (abetalipoproteinaemia), lactate (mitochondrial).
- **Genetic testing:** repeat-primed PCR for *FXN* GAA and *RFC1* AAGGG expansions first; then a **recessive-ataxia NGS panel / WES** if negative.
- **Ancillary:** nerve conduction (absent sensory action potentials with near-normal motor velocities in FRDA), MRI brain/spine (spinal-cord atrophy in FRDA; cerebellar atrophy in others), ECG/echocardiography (FRDA cardiomyopathy), audiometry, OGTT.

Treatment

- **Identify the treatable ARCAs** — *vitamin E* for AVED/abetalipoproteinaemia, *chenodeoxycholic acid* for CTX, *miglustat* for Niemann-Pick C, *coenzyme Q10* for CoQ10-deficient ataxia; correct B1/B12/thyroid deficiencies that mimic inherited ataxia.
- **Friedreich's ataxia: omaveloxolone, an NRF2 agonist**, is the **first and only FDA-approved drug** (patients **≥16 years**), improving function in randomised trials by targeting mitochondrial energy failure. **Iron chelators and antioxidants are potentially harmful** (may aggravate myocardial injury). Otherwise supportive — physiotherapy, surveillance and management of cardiomyopathy, diabetes and scoliosis.
- **Ataxia-telangiectasia:** immunoglobulin (IVIG) replacement for immunodeficiency, infection control, avoidance of unnecessary ionising radiation, malignancy surveillance; glucocorticoids may transiently improve neurological function.
- **Genetic counselling** (1-in-4 recurrence risk, carrier testing, prenatal diagnosis) is integral to management.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spinal-cord cross-section in Friedreich's ataxia** — label and shade the degenerating tracts: *dorsal (posterior) columns (gracilis & cuneatus)*, *dorsal and ventral spinocerebellar tracts*, *lateral corticospinal tracts*, with *dorsal root ganglion* and *Clarke's column* marked as primary sites of neuronal loss; show *dentate nucleus* of the cerebellum.
- **Classification tree of inherited ataxias** — branches: *Autosomal dominant (SCAs, DRPLA, episodic ataxia)* | **Autosomal recessive (Friedreich's, AVED, abetalipoproteinaemia, AT, ARSACS, AOA1/2, CANVAS, CTX, NPC)** | *X-linked (FXTAS)* | *Mitochondrial*, with the recessive branch sub-grouped into **mitochondrial / DNA-repair / lipid-metabolism** pathways.

Clinical / Diagnostic significance

- The triad of a **young patient with areflexia, extensor plantar responses and loss of position/vibration sense** should trigger an FXN GAA test — FRDA is the single commonest inherited ataxia worldwide.
- **Cardiomyopathy drives mortality in FRDA**, so every patient needs ECG/echo surveillance — a neurological diagnosis with a cardiological endpoint.
- Recognising the **treatable mimics** (AVED, abetalipoproteinaemia, CTX, NPC, CoQ10 deficiency) is the highest-value clinical act, since timely metabolic therapy can arrest progression.
- **α-fetoprotein and cholestanol** are simple serum tests that rapidly narrow a wide genetic differential before expensive sequencing.

High-yield exam pointers

- **Friedreich's ataxia = commonest hereditary ataxia (~50%)**; *FXN/frataxin*, chromosome 9, **GAA intron-1 expansion**, only AR trinucleotide-repeat disease; normal 7–22, disease 200–900 repeats; **frataxin = mitochondrial iron-handling/Fe-S protein**.
- FRDA signs: **areflexia + Babinski + impaired proprioception**, pes cavus, scoliosis, **hypertrophic cardiomyopathy (90%, top cause of death)**, diabetes (20%).
- **Omaveloxolone (NRF2 agonist)** — only FDA-approved FRDA drug (≥16 yr); **avoid iron chelators/antioxidants**.
- **Ataxia-telangiectasia:** *ATM* gene, **↑AFP**, immunodeficiency, radiosensitivity, malignancy (lymphoma/leukaemia).
- **AVED (*TTPA*) and abetalipoproteinaemia (*MTTP*)** are **treatable with vitamin E**; abetalipoproteinaemia shows **acanthocytes + retinitis pigmentosa**.
- **CANVAS** = RFC1 *AAGGG* expansion; ataxia + sensory neuronopathy + vestibular areflexia + **chronic cough**.
- Biomarker shortcuts: **↑AFP → AT/AOA2; ↓albumin+↑cholesterol → AOA1; ↑cholestanol → CTX; ↓vitamin E → AVED/abetalipoproteinaemia.**
- ARSACS triad = **ataxia + spasticity + neuropathy** (Charlevoix-Saguenay, *SACS*/sacsin).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Ataxic Disorders" (Autosomal Recessive Ataxias: Friedreich's ataxia, RFC1-CANVAS, ataxia-telangiectasia; treatment incl. omaveloxolone).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Cerebellar Ataxia" (ARCA classification Table 23.7 by pathogenic pathway — mitochondrial/DNA-repair/lipid; gene-protein-biomarker correlations; ARSACS, AOA1/2, CTX, NPC, POLG, AVED).
- **CMDT 2026** — "Nervous System Disorders" (Friedreich ataxia clinical/genetic summary and omaveloxolone) and vitamin E deficiency.

◆ ◆ ◆

Benign intracranial hypertension

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

Definition / Introduction — *Benign intracranial hypertension*, now preferentially termed **idiopathic intracranial hypertension (IIH)** or *pseudotumor cerebri*, is a syndrome of raised intracranial pressure (ICP) — manifesting with headache and papilledema — occurring in the **absence of an intracranial mass, hydrocephalus, venous sinus thrombosis or abnormal CSF constituents**. The label "benign" is a misnomer because untreated disease causes **progressive optic atrophy and irreversible blindness**; "idiopathic" is preferred. Diagnosis is one of *exclusion* and rests on the modified Dandy (Friedman) criteria, with the cardinal goal of therapy being preservation of vision.

Terminology & epidemiology

- **Historical names:** *otitic hydrocephalus* (papilledema with otitis media), *pseudotumor cerebri* (pneumoencephalography era), *benign intracranial hypertension* — all unsatisfactory; **IIH** is the current descriptive term, though "pseudotumor cerebri" persists for the *secondary* causes.
- Overwhelmingly a disease of **obese young women of childbearing age**. In the landmark **Idiopathic Intracranial Hypertension Treatment Trial (IIHTT)** the mean age was **29 years, 97.6% were women, and mean BMI 39.9 kg/m^2**.
- Associations: obesity, recent weight gain, menstrual irregularity; with modern imaging IIH is now the **commonest cause of papilledema** in the developed world.

Pathophysiology

- The fundamental abnormality is **raised CSF pressure** with otherwise normal brain parenchyma and ventricles.
- **Venous outflow / venous sinus stenosis hypothesis** (dominant current model): bilateral distal **transverse sinus stenoses** (or stenosis of a dominant transverse sinus) → reduced cerebral venous drainage → **cerebral venous hypertension** → impaired passive CSF resorption at arachnoid granulations → rising CSF pressure → external compression of the transverse sinus → a self-perpetuating *vicious cycle*. Whether the stenosis is cause or consequence remains debated (stenoses also occur in normals).

- Elevated venous pressure has been documented in the superior sagittal and proximal transverse sinuses; raised right-atrial filling pressure can be transmitted to the sinuses.
- A contribution from cerebral interstitial **white-matter (brain) edema** has been proposed on MRI diffusion studies but remains *without consensus*.

Clinical features

- **Headache** — most frequent presenting symptom (≈84% in IIHTT); often worse on straining/coughing, may wake the patient in the early morning; phenotype is **migraine-like in ~52%** and **tension-type in ~22%**.
- **Transient visual obscurations (TVOs)** — brief (seconds) mono- or binocular greying/blacking of vision, precipitated by postural change or Valsalva; reflect transient hypoperfusion of the swollen optic nerve head (≈68%).
- **Pulse-synchronous (pulsatile) tinnitus** (~52%) and **back pain** (~53%).
- **Diplopia** from **unilateral or bilateral sixth (abducens) nerve palsy** — a classic *false localizing sign* (the long intracranial course/Dorello's canal makes CN VI vulnerable to pressure).
- **Visual loss** — only ~32% report it at onset, but it is the *feared* outcome; vision is typically preserved until late, when chronic papilledema encroaches on the macula. Visual fields show an **enlarged blind spot**, then nasal/sector scotomas.
- **Papilledema** is the cardinal sign; the patient otherwise looks well with a normal neurological exam (except CN VI).

Diagnostic criteria (modified Dandy / Friedman 2013)

Criterion	Requirement for IIH
A. Papilledema	Present
B. Neurological exam	Normal **except** cranial nerve VI palsy
C. Neuroimaging	Normal brain parenchyma; **venous sinus thrombosis excluded**
D. CSF constituents	Normal (normal/low protein, normal glucose, no cells)
E. Opening pressure	**Elevated LP pressure >250 mm CSF (>25 cm) in adults**

- **IIH without papilledema (IIHWOP):** criteria B–E **plus** a unilateral/bilateral sixth-nerve palsy.
- Normal CSF opening pressure upper limit is ~**180–200 mm H_2O**; in IIH it usually exceeds 200 and may reach >500 mm. **Measure in the lateral decubitus position** with legs extended and neck straight — *sitting and prone (fluoroscopy) readings overestimate and are invalid.*

Investigations & differentiation

- **MRI brain with contrast + MR venography (MRV)** are *mandatory before LP* to exclude a mass, hydrocephalus, and **cerebral venous sinus thrombosis (CVST)** — the key IIH mimic. Supportive (non-specific) MRI signs: **empty sella, posterior scleral flattening, optic nerve sheath distension, vertical tortuosity of the optic nerve, optic nerve head enhancement, and transverse sinus stenosis**.

- **Lumbar puncture** with manometry confirms raised opening pressure and documents normal CSF; CSF removal transiently relieves headache and obscurations.
- **Papilledema vs papillitis:** in *papilledema* (raised ICP) acuity is preserved early and pupillary reactions are normal; in *papillitis* (optic neuritis) central vision is lost early with a relative afferent pupillary defect. Distinguish true papilledema from **pseudopapilledema** (optic disc drusen) — an ophthalmologist should confirm.
- **Formal perimetry (visual fields)** and serial fundoscopy/OCT monitor the threat to vision.

Secondary "pseudotumor cerebri" — causes to exclude

- **Cerebral venous abnormalities:** venous sinus / bilateral jugular thrombosis or ligation, middle-ear/mastoid infection, raised right-heart pressure, SVC syndrome, AV fistula, hypercoagulable states.
- **Drugs/exposures:** tetracyclines (tetracycline, **minocycline, doxycycline**), nalidixic acid, sulfonamides/cotrimoxazole, nitrofurantoin; **vitamin A excess / retinoids (isotretinoin, all-trans retinoic acid)**; growth hormone, thyroxine (children), levonorgestrel, anabolic steroids; **withdrawal from chronic corticosteroids**; lithium.
- **Medical conditions:** Addison disease, hypoparathyroidism, hypothyroidism, hypercapnia, **obstructive sleep apnea / Pickwickian syndrome**, anemia, renal failure/uremia, Turner and Down syndromes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Fundus in papilledema (label):** hyperemic *elevated* optic disc, **blurred/obliterated disc margins**, filled-in physiologic cup, **engorged tortuous retinal veins**, **peripapillary flame-shaped hemorrhages**, **cotton-wool spots (NFL infarcts)**, loss of spontaneous venous pulsations; chronic stage "*champagne-cork*" disc; end-stage secondary optic atrophy.
- **Pathophysiology loop (label):** transverse sinus stenosis → ↓venous outflow → cerebral venous hypertension → ↓CSF resorption → ↑ICP → external sinus compression (vicious cycle); annotate MRI signs — empty sella, posterior scleral flattening, optic nerve sheath distension, optic nerve tortuosity.

Management

- **Goal:** prevent permanent visual field loss; treat any identifiable secondary cause (stop offending drug, gradually re-taper steroids, correct endocrinopathy/anemia, treat OSA).
- **Weight loss** is disease-modifying — up to ~15% loss can induce remission; some authors regard it as important as drug therapy.
- **Acetazolamide** (carbonic anhydrase inhibitor; lowers CSF production): start **500 mg twice daily**, titrate as tolerated up to **4 g/day**; the IIHTT supported acetazolamide ≤4 g/day **with weight loss** for mild visual loss, improving papilledema, ICP and quality of life. Monitor for metabolic acidosis, paresthesias (~25%), hypokalemia.
- **Topiramate** — also a carbonic anhydrase inhibitor, with the bonus of weight loss; alternative when acetazolamide is not tolerated. **Furosemide** 20–40 mg/day as adjunct.

- **Corticosteroids** — reserved for **fulminant** disease with rapidly progressive visual loss; avoided for maintenance because of weight gain and relapse on withdrawal.
- **Serial therapeutic LPs** — temporizing measure only.
- **Bariatric surgery** — consider for BMI ≥35 (RCT showed reduction in ICP and weight at 2 years).
- **Surgical / interventional** (failed medical therapy or threatened vision): **optic nerve sheath fenestration** (best for vision-threatening papilledema with preserved headache control), **CSF diversion shunt** (ventriculoperitoneal preferred over lumboperitoneal for patency), and **venous sinus stenting** in selected patients with a documented pressure gradient across a transverse sinus stenosis (still considered investigational).
- **Fulminant IIH:** rare, urgent — high-dose steroids + acetazolamide + early surgical decompression; despite treatment ~50% may remain legally blind, underscoring that the condition is *not* benign.

Clinical / Diagnostic significance

- IIH must be actively sought in *every* young obese woman with chronic daily headache — fundoscopy for papilledema is the screening pivot.
- The diagnosis is by **exclusion**: imaging (MRI/MRV) precedes LP to rule out mass and CVST; a sixth-nerve palsy is a non-localizing sign of raised ICP.
- Vision, not headache, dictates urgency and the threshold for surgery; serial perimetry and OCT are essential.
- Headache may persist after ICP normalizes (coexistent migraine/medication-overuse headache in a large fraction of IIHTT patients) and is then treated by its phenotype.

High-yield exam pointers

- Triad concept: **raised ICP + papilledema + normal neuroimaging/CSF** = IIH; "benign" is a misnomer (blindness risk).
- **Demographic:** obese woman of reproductive age (IIHTT: mean age 29, 97.6% female, BMI 39.9).
- **Modified Dandy/Friedman criteria** — opening pressure **>250 mm CSF**, measured in lateral decubitus.
- **CN VI palsy = false localizing sign**; commonest symptom is headache, most feared is visual loss.
- MRI signs mnemonic: **empty sella, posterior scleral flattening, optic nerve sheath distension/tortuosity, transverse sinus stenosis**.
- Secondary causes: **tetracyclines, vitamin A/retinoids, steroid withdrawal, OSA, venous sinus thrombosis**.
- First-line therapy: **weight loss + acetazolamide (up to 4 g/day)**; topiramate as alternative; **optic nerve sheath fenestration / CSF shunt / venous sinus stenting** for refractory vision-threatening disease.
- Always **exclude CVST with MRV** before labelling as idiopathic.

SOURCE & COVERAGE

- **Bradley & Daroff's Neurology in Clinical Practice 8e** — "Brain Edema and Disorders of Cerebrospinal Fluid Circulation" (Idiopathic Intracranial Hypertension: clinical features, CSF criteria, treatment) and "Headache and Other Craniofacial Pain" (IIHTT data, IIH diagnostic criteria Table 102.1, secondary pseudotumor causes Table 102.2).
- **DeJong's The Neurologic Examination** — "The Optic Nerve" (stages of papilledema, papilledema vs pseudopapilledema, transient visual obscurations).
- **CMDT 2026** — "Nervous System Disorders" (Idiopathic Intracranial Hypertension: essentials of diagnosis, imaging, drug regimens, surgical options).
- **Harrison's Principles of Internal Medicine 22e** — neurologic history/disorders of the eye (vitamin A–associated pseudotumor cerebri; corroborating detail).

Coverage note: Harrison 22e covers IIH only sparsely and scattered (no dedicated section), as flagged in the spec; the substantive depth here is drawn from Bradley & Daroff, DeJong and CMDT 2026. A formal Frisén papilledema grading scale was not present in the searched corpus, so the four descriptive stages (early, fully developed, chronic, atrophic) from DeJong are used instead.

◆ ◆ ◆

Cerebral venous sinus thrombosis

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

Definition / Introduction — Cerebral venous sinus thrombosis (CVST) is thrombotic occlusion of the dural venous sinuses and/or the cerebral veins, causing impaired venous drainage, raised intracranial pressure (ICP), venous congestion and frequently haemorrhagic venous infarction. It is an uncommon but eminently treatable cause of stroke (~0.5–1% of all strokes), distinguished from arterial stroke by its predilection for **young adults and women**, its **subacute, multi-symptom evolution**, and its excellent prognosis when anticoagulated early. Because lesions do not respect arterial territories and seizures and headache dominate the picture, a high index of suspicion is essential.

Applied anatomy of the cerebral venous system

- **Superficial (cortical) system:** cortical veins → **superior sagittal sinus (SSS)** along the falx; the *vein of Trolard* (superior anastomotic) and *vein of Labbé* (inferior anastomotic to transverse sinus) are key cortical channels.
- **Deep system:** internal cerebral veins + basal vein of *Rosenthal* → **great vein of Galen** → **straight sinus**.
- **Confluence and outflow:** SSS + straight sinus + inferior sagittal sinus meet at the **confluence of sinuses (torcular Herophili)** → paired **transverse (lateral) sinuses** → **sigmoid sinuses** → **internal jugular veins**.
- **Cavernous sinuses** flank the sella, transmitting the internal carotid artery and cranial nerves **III, IV, VI and V1/V2**; they drain via superior/inferior petrosal sinuses.

- **Commonest thrombosis sites:** superior sagittal sinus and transverse sinuses (often combined); deep venous and cavernous sinus thromboses are less common but distinctive.

Etiology and risk factors (Virchow's triad)

Multiple causes coexist in up to half of patients; an underlying prothrombotic state should always be sought.

Category	Examples
Hereditary thrombophilia	Factor V Leiden, prothrombin G20210A, protein C/S deficiency, antithrombin deficiency, hyperhomocysteinaemia
Acquired prothrombotic	Antiphospholipid syndrome, nephrotic syndrome, malignancy, paroxysmal nocturnal haemoglobinuria, myeloproliferative disease (JAK2 V617F)
Hormonal / obstetric	**Pregnancy and puerperium**, oral contraceptives, hormone replacement therapy
Infective (septic)	Otitis media / mastoiditis (transverse–sigmoid; "otitic hydrocephalus"), sinusitis, meningitis, facial/orbital sepsis (**cavernous sinus thrombosis**, classically *Staphylococcus aureus*)
Inflammatory / systemic	Behçet disease, SLE, inflammatory bowel disease, sarcoidosis, dehydration
Mechanical / iatrogenic	Head trauma, neurosurgery, jugular catheterisation, lumbar puncture
Drug / vaccine-related	Adenoviral-vector COVID-19 vaccines causing **VITT** (vaccine-induced immune thrombotic thrombocytopenia, anti-PF4 antibodies); COVID-19 infection itself

Pathophysiology

- **Two parallel mechanisms** produce symptoms: (1) sinus occlusion → impaired CSF absorption at arachnoid granulations → **raised ICP**; (2) cortical/deep vein occlusion → venous congestion → vasogenic and cytotoxic oedema → **venous (often haemorrhagic) infarction**.
- Venous infarcts characteristically **cross arterial boundaries**, are frequently bilateral/parasagittal (SSS) and have a **high propensity to haemorrhage** — a crucial point, since this haemorrhage does *not* contraindicate anticoagulation.
- **Deep venous (galenic/straight sinus) thrombosis** causes bilateral **thalamic and basal ganglia** oedema, presenting as encephalopathy or coma.

Clinical features — four classic presentations

Onset is usually **subacute (days–weeks)**; **headache is the commonest and earliest symptom** (~90%), often diffuse, progressive and worse on recumbency or Valsalva; *thunderclap* onset can occur.

Syndrome	Key features
Isolated intracranial hypertension	Headache, papilloedema, visual obscurations, **6th-nerve palsy**, pulsatile tinnitus (mimics idiopathic intracranial hypertension)
Focal syndrome	Focal deficits (hemiparesis, aphasia) and **seizures** — far commoner than in arterial stroke (~40%), often focal with secondary generalisation

Syndrome	Key features
Encephalopathy	Altered consciousness, multifocal signs, coma — typical of **deep cerebral venous thrombosis** (bilateral thalami)
Cavernous sinus syndrome	Painful ophthalmoplegia, **proptosis, chemosis, ptosis**, CN III/IV/VI palsies, V1–V2 sensory loss; frequently septic and may become bilateral

Investigations

- **D-dimer:** usually elevated and supportive, but a normal value does **not** exclude CVST (especially isolated headache or long-standing presentation).
- **Non-contrast CT:** often normal; may show a **hyperdense thrombosed sinus** ("dense triangle"/"cord sign") and parenchymal venous infarct/haemorrhage not conforming to an arterial territory.
- **Contrast CT / CT venography:** the **"empty delta sign"** — enhancing dural walls surrounding a non-enhancing central thrombus in the SSS; CTV demonstrates the filling defect.
- **MRI + MR venography (MRV):** investigation of **choice** — directly shows absent venous flow and the evolving thrombus signal, plus parenchymal oedema/haemorrhage; gradient-echo/SWI sequences highlight the clot.
- **Digital subtraction angiography (venous phase):** reserved for equivocal cases or planned endovascular therapy.
- **Lumbar puncture:** raised opening pressure; may show elevated protein, red cells and pleocytosis — useful chiefly to relieve pressure and to exclude meningitis (defer if a large mass lesion risks herniation).
- **Etiological workup:** thrombophilia screen, antiphospholipid antibodies, autoimmune and malignancy screen; in suspected VITT — platelet count, anti-PF4 ELISA, fibrinogen.

Management

- **Anticoagulation is the cornerstone**, given even in the presence of haemorrhagic venous infarction:
  - **Acute:** therapeutic **low-molecular-weight heparin** (e.g., enoxaparin 1 mg/kg SC 12-hourly), preferred over dose-adjusted unfractionated heparin (UFH reserved when rapid reversal or renal failure is a concern).
  - **Maintenance:** transition to **oral anticoagulation** — warfarin (target **INR 2–3**) or a **DOAC** (dabigatran 150 mg BD shown non-inferior in the RE-SPECT CVT trial).
  - **Duration:** provoked/transient cause **3–6 months**; unprovoked **6–12 months**; recurrent VTE or strong thrombophilia → **indefinite**.
- **Endovascular thrombolysis/thrombectomy:** considered for clinical deterioration despite adequate anticoagulation (routine use not supported — TO-ACT trial neutral).
- **Raised ICP / mass effect:** head-end elevation, **acetazolamide**, therapeutic LP for refractory hypertension; **decompressive hemicraniectomy** is life-saving for impending herniation from a large venous infarct/haemorrhage.

- **Seizures:** antiseizure medication for clinical seizures (and considered prophylactically with a supratentorial parenchymal lesion).
- **Treat the cause:** antibiotics ± surgical drainage for septic CVST/cavernous sinus thrombosis; correct dehydration; manage malignancy/thrombophilia.
- **VITT-associated CVST:** use **non-heparin anticoagulants** (argatroban, fondaparinux, or a DOAC) plus **IVIG**; **avoid heparin and platelet transfusion**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Dural venous sinus map (superolateral/midsagittal view):** label *Superior sagittal sinus, Inferior sagittal sinus, Straight sinus, Great vein of Galen, Internal cerebral vein, Vein of Labbé, Vein of Trolard, Confluence of sinuses (torcular Herophili), Transverse sinus, Sigmoid sinus, Internal jugular vein, Cavernous sinus.*
- **Diagram 2 — "Empty delta sign":** triangular cross-section of the superior sagittal sinus with *enhancing dural wall* (outer rim) and *central non-enhancing thrombus*; label both.

Clinical / Diagnostic significance

- Consider CVST in any **young patient with new persistent headache, papilloedema, seizures, or a haemorrhagic infarct crossing arterial boundaries** — especially peripartum women or those on oral contraceptives.
- It is a key differential of **idiopathic intracranial hypertension** and of arterial stroke in the young; **MRV/CTV** is decisive.
- **Bilateral thalamic** signal change suggests deep venous thrombosis; **proptosis with ophthalmoplegia** suggests cavernous sinus thrombosis.
- **Prognosis is favourable** (~80% recover well; mortality ~5–10%). Poor predictors: **coma/depressed consciousness, deep venous or posterior fossa involvement, intracranial haemorrhage, malignancy, CNS infection, male sex and older age**.

High-yield exam pointers

- CVST = stroke of the **young**, **women > men**, classic triggers **pregnancy/puerperium and OCPs**.
- **Headache** is the commonest symptom; **seizures** are much commoner than in arterial stroke.
- **Superior sagittal** and **transverse** sinuses are the most frequent sites.
- Imaging signs: **dense cord/triangle sign** (NCCT), **empty delta sign** (CECT/CTV); **MRV is the investigation of choice**.
- **Anticoagulate even when there is haemorrhagic venous infarction** — the single most important management pearl.
- **DOAC (dabigatran)** is a validated alternative to warfarin (RE-SPECT CVT).
- **Cavernous sinus thrombosis** is usually **septic** (*S. aureus*) — proptosis, chemosis, CN III/IV/VI + V1–V2 involvement, may become bilateral.
- **VITT-related CVST:** non-heparin anticoagulation + IVIG; avoid heparin and platelets.
- **Decompressive hemicraniectomy** is the rescue for impending herniation.

SOURCE & COVERAGE

Harrison 22e — Ch 437 "Introduction to Cerebrovascular Diseases" (Smith & Hemphill). **Coverage note:** The provided Ch 437 text covers arterial ischaemic stroke anatomy, hemorrhage and general cerebrovascular evaluation, but does **not** substantively cover cerebral venous sinus thrombosis — it mentions only DVT prophylaxis (Fig. 437-1) and cross-references raised intracranial pressure (Ch 439). Harrison's primary CVST coverage lies in the Ischemic Stroke chapter (Ch 438), which was not supplied. Accordingly, this answer is grounded in **universally accepted standard internal-medicine** content; the disease framework, imaging signs (empty delta/cord sign), anticoagulation principle (including in haemorrhagic infarction), RE-SPECT CVT/TO-ACT trial data and VITT management are standard textbook/guideline material and were stated only where confidently accurate. No specifics were drawn unverified from Ch 437.

◆ ◆ ◆

Trigeminal neuralgia

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Trigeminal neuralgia* (**tic douloureux**) is a chronic facial pain disorder characterised by recurrent paroxysms of excruciating, electric shock-like or stabbing pain confined to one or more divisions of the fifth cranial nerve, classically provoked by innocuous tactile stimuli to cutaneous **trigger zones** and, by definition, *without demonstrable sensory loss* on examination. It must be sharply distinguished from **trigeminal neuropathy**, in which structural disease of the nerve produces objective sensory deficit and/or motor (masticatory) weakness. The estimated annual incidence is **4–8 per 100,000**; it affects middle-aged and elderly persons, with **~60% of cases in women**.

Pathophysiology

- **Ectopic impulse generation:** Pain arises from ectopic generation of action potentials in pain-sensitive afferent fibres of the trigeminal root *just before it enters the lateral surface of the pons* (the **root entry zone**).
- **Demyelination & ephaptic transmission:** Compression/pathology causes **focal demyelination of large myelinated (Aβ touch) fibres** that do not themselves carry pain. These become hyperexcitable and **electrically (ephaptically) coupled** to adjacent small unmyelinated/poorly myelinated nociceptive fibres — explaining why a light tactile stimulus, conveyed by large fibres, can ignite a paroxysm of pain.
- **Vulnerable myelin zone:** CN V is ensheathed by **oligodendrocyte-derived central myelin for up to 7 mm** after leaving the brainstem (vs a few mm for other nerves); demyelination occurs at this central–peripheral myelin **transition (Obersteiner–Redlich) zone**, accounting for the link with multiple sclerosis (a disorder of oligodendrocyte myelin).
- **Neurovascular compression (classic TN):** A tortuous artery — most often the **superior cerebellar artery**, occasionally the **anterior inferior cerebellar artery** or a vein — compresses/indents the root, causing axonal loss and demyelination. *Vascular contact alone is*

insufficient (it is common in asymptomatic controls/cadavers); **morphological indentation/atrophy** of the root is required.

- **Ageing substrate:** Age-related brain sagging and increased vascular thickness/tortuosity explain the prevalence in later life.

Clinical features

- **Character:** Paroxysms of *excruciating*, superficial, stabbing/lancinating "electric-shock" pain; so intense the patient winces — hence *tic*.
- **Duration & periodicity:** Each jab lasts seconds to a minute or two; single jabs or clusters recur frequently **day and night for weeks–months**, then remit spontaneously. Remissions may be long but the disorder usually ultimately recurs.
- **Distribution:** Strictly **unilateral**, confined to trigeminal territory — most often **V2 (maxillary) and V3 (mandibular)**; the **ophthalmic (V1) division is involved in <5%** of cases.
- **Trigger zones / triggers:** Tactile stimulation of trigger points on the face, lips or tongue provokes attacks — *washing the face, brushing teeth, shaving, chewing, speaking, smiling, or a draught of cold air*. Patients hold the face still and avoid eating/talking.
- **Examination:** *No objective sensory loss and no motor weakness* — an **essential diagnostic feature**. (A dull background ache may persist between jabs in long-standing/"concomitant continuous pain" cases.)

Classification (ICHD-based) & differential diagnosis

Type	Mechanism	Clue
Classic TN	Neurovascular compression with morphological root change (SCA/AICA)	Older age, normal exam, vessel-nerve contact on MR angiography
Secondary (symptomatic) TN	MS plaque at root entry zone, cerebellopontine-angle tumour (acoustic schwannoma, meningioma), aneurysm, neurofibroma, chronic meningitis	**Young/bilateral patient, subtle sensory loss** → suspect MS or mass
Idiopathic TN	No cause found despite imaging	Diagnosis of exclusion

- **Differentiate from other facial pains:** Migraine/cluster pain is *deep, steady* (not superficial-stabbing); rarely cluster coexists (*cluster-tic*). **SUNCT/SUNA** and paroxysmal hemicrania are distinguished by attack frequency/duration and prominent cranial autonomic features (V1 territory). **Giant cell (temporal) arteritis** gives non-shocklike facial pain with myalgia and ↑ESR/CRP. Also exclude dental, jaw and sinus disease.
- **Red flags for a secondary cause:** onset **<40 years**, **bilateral** symptoms, V1 involvement, any objective sensory loss, or other cranial-nerve signs → mandates imaging.

Investigations

- **High-resolution contrast-enhanced brain MRI** in all: to exclude secondary causes (MS plaque, tumour, aneurysm) and demonstrate neurovascular compression. **MR angiography** delineates the nerve–vessel relationship and is used pre-operatively to plan decompression.

- **ESR/CRP** if temporal arteritis is suspected.
- Younger/atypical patients: evaluate for **MS** (a demyelinating plaque near the pontine root entry zone is the typical lesion).

Management

A. Medical therapy (first line):

- **Carbamazepine** — drug of choice, effective in **~50–75%**. Start **100 mg once daily with food**, increase by 100 mg/day in divided doses every 1–2 days to >50% relief; usual maintenance **200 mg four times daily**; doses **>1200 mg/day give no added benefit**. Monitor for dizziness, ataxia, sedation, hyponatraemia and rare **agranulocytosis** (serial blood counts + LFTs). If effective, continue ~1 month then taper.
- **Oxcarbazepine 300–1200 mg bid** — equally efficacious, less marrow toxicity (preferred by many).
- **Second-line / add-on:** phenytoin **300–400 mg/day**; **lamotrigine 400 mg/day**; **baclofen 10–20 mg tid**; **topiramate 50 mg bid**; **gabapentin up to 3600 mg/day** (useful in MS-related TN).

B. Surgical / interventional therapy (drug failure or intolerance): initial relief in ≥80%.

Procedure	Mechanism	Outcome / caveat
Microvascular decompression (MVD) — Jannetta	Suboccipital craniotomy; pad/separate offending vessel from root	**>70% efficacy, ~75% long-term relief**, low recurrence; *no sensory loss*; best for classic lancinating pain; major surgery
Stereotactic (Gamma-knife) radiosurgery	Radiation lesion of root	Complete relief (often delayed) in ~½ (~45%); recurrence in ⅓ over 2–3 yr; few serious complications
Radiofrequency thermal rhizotomy	Heat lesion of ganglion/nerve	>95% short-term, ~60% long-term; common facial numbness, masseter weakness, **corneal denervation/keratitis** (V1)
Percutaneous balloon compression	Mechanical ganglion injury (under GA)	~67% relief; ipsilateral facial numbness common

- **MS-related TN:** open surgical exploration is inappropriate; less-invasive ablative techniques may help. Glossopharyngeal neuralgia (a close mimic in the throat/ear) responds to the same drugs and MVD.

Trigeminal neuralgia vs trigeminal neuropathy

Feature	Trigeminal neuralgia	Trigeminal neuropathy
Nature of pain	Paroxysmal, brief (sec–min), shock-like/stabbing	Constant numbness/paraesthesia, burning, or no pain
Trigger zones	Present (tactile triggers)	Absent
Sensory loss	**Absent** (cardinal rule)	**Present** — objective facial numbness, ↓corneal reflex

Feature	Trigeminal neuralgia	Trigeminal neuropathy
Motor (masticatory) deficit	Absent	May be present — **jaw deviates to the weak side** (pterygoids)
Divisions	V2/V3 mainly; V1 <5%	Any; chin (mental) or cheek numbness may signal malignancy
Mechanism	Neurovascular compression / demyelination at root	Structural disease of nucleus, ganglion or nerve
Typical causes	Vascular loop; MS (secondary)	**Sjögren's, SLE, scleroderma, MCTD; herpes zoster; leprosy; tumours (schwannoma, meningioma, nasopharyngeal Ca, perineural spread); GBS; sarcoidosis; trauma; drugs (stilbamidine, trichloroethylene); idiopathic**
Examination dictum	Normal exam	"Diagnosed by the company they keep" — long-tract/other CN signs

- **Idiopathic trigeminal neuropathy:** numbness/paraesthesiae (sometimes bilateral) with sensory loss but *no jaw weakness*; gradual recovery is the rule.
- **Numb chin (mental neuropathy)** or **numb cheek syndrome:** isolated chin/cheek numbness may be the *sole presenting sign of systemic malignancy* (breast, lung, prostate, lymphoma) — never ignore.
- **Trigeminal trophic syndrome:** anaesthesia → self-induced ulceration of the **ala nasi** following ganglion damage/rhizotomy or central tract lesions.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Trigeminal nerve and its sensory territory on the face** — label: *Pons (root entry zone), Trigeminal (gasserian/semilunar) ganglion in Meckel's cave, Ophthalmic V1, Maxillary V2, Mandibular V3*, and the corresponding facial dermatomal zones; mark the **trigger zone** on the cheek/lip.
- **Neurovascular compression schematic** — label: *Trigeminal root, Superior cerebellar artery (compressing vessel), Central (oligodendrocyte) myelin segment, Central–peripheral myelin transition (Obersteiner–Redlich) zone, focal demyelination with ephaptic coupling.*

Clinical / Diagnostic significance

- A **strictly paroxysmal pain with trigger zones and a completely normal neurological examination** is virtually diagnostic of TN; *any* sensory/motor deficit reclassifies the patient as trigeminal **neuropathy** and demands a search for structural disease.
- **Bilateral TN, onset <40 years, or V1 involvement** strongly suggests **MS or a posterior-fossa mass** — image early.
- MRI/MRA is both **diagnostic** (excludes secondary causes) and **therapeutic-planning** (defines the offending vessel before MVD).

- Carbamazepine response is itself **supportive of the diagnosis**; failure or need for escalating surgery should prompt re-imaging.

High-yield exam pointers

- *Tic douloureux* = paroxysmal, unilateral, shock-like V2/V3 pain with **trigger zones** and **NO sensory loss**.
- Incidence **4–8/100,000**; **~60% women**; middle-aged/elderly.
- Pathology = **demyelination + ephaptic coupling** at the root entry zone; **superior cerebellar artery** is the commonest compressing vessel.
- **V1 involved in <5%**; if young/bilateral/V1 → think **MS** (plaque at pontine root entry zone).
- **Carbamazepine** is first-line (50–75% response); oxcarbazepine an equal alternative; max CBZ benefit ≤1200 mg/day.
- Surgery of choice = **microvascular decompression (Jannetta), >70% durable relief, no numbness**; ablative procedures cause facial numbness.
- **Neuropathy ≠ neuralgia:** neuropathy has **objective sensory loss ± jaw weakness (deviation to weak side)** and signals Sjögren's/zoster/leprosy/tumour/perineural spread.
- **Numb chin sign** = mental neuropathy = possible occult malignancy.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders" (clinical features, pathophysiology, drug doses, surgical options, Table of trigeminal nerve disorders).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Cranial Neuropathies" and "Cranial and Facial Pain" (classic vs symptomatic TN, neurovascular compression at central–peripheral myelin transition, SCA/AICA, <5% V1, numb-chin/cheek syndromes).
- **Brazis — Localization in Clinical Neurology** — "Cranial Nerve V: The Trigeminal Nerve" (trigeminal trophic syndrome, nuclear vs peripheral localization, "company they keep").
- **CMDT 2026** — "Nervous System Disorders" (current diagnostic criteria, MRI rule for secondary causes <40 yr/bilateral, surgical success rates: MVD ~75%, RF rhizotomy 60%, balloon 67%, radiosurgery 45%).

◆ ◆ ◆

Neuromuscular junction — physiology and disorders

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

Definition / Introduction — The **neuromuscular junction (NMJ)** is the specialised cholinergic synapse where a motor axon terminal makes functional contact with a skeletal muscle fibre, converting a nerve action potential into a muscle fibre action potential and hence contraction. It is uniquely vulnerable to disease because it lies *outside the blood–nerve barrier*, depends on a finely tuned excess of acetylcholine (ACh) release over demand (the **safety factor**), and is built from many distinct presynaptic and postsynaptic molecules, each of which can be targeted by autoantibodies, genetic mutation or toxins. Failure of transmission at any of these sites produces the cardinal NMJ sign — **fatigable, fluctuating weakness without sensory loss**.

Physiological anatomy — three functional compartments

The NMJ is organised into a presynaptic motor nerve terminal, the synaptic cleft and the postsynaptic muscle end-plate.

Compartment	Key structures	Function
Presynaptic terminal	Synaptic vesicles each storing one *quantum* (~5000–10,000 ACh molecules); **active zones** (release sites) apposed to postsynaptic folds; **voltage-gated (P/Q-type) Ca^{2+} channels**; **voltage-gated Na^+/K^+ channels**; SNARE fusion proteins — *syntaxin-1, SNAP-25, synaptobrevin, synaptotagmin*	ACh is synthesised from acetate + choline by **choline acetyltransferase (ChAT)**, packaged into vesicles, and released by Ca^{2+}-triggered exocytosis
Synaptic cleft	~50 nm gap; **synaptic basal lamina**; **acetylcholinesterase (AChE)** anchored to the basal lamina by its collagenic tail (**COLQ**); **agrin**	ACh diffuses across; rapidly hydrolysed by AChE, terminating signal
Postsynaptic membrane	Deeply infolded **junctional (postsynaptic) folds**; **acetylcholine receptors (AChRs)** densely packed at the *crests* of folds; **voltage-gated Na^+ channels** in the depths of folds; clustering scaffold — **MuSK, LRP4, Dok-7, rapsyn, dystroglycan**	High-density AChR + Na^+ channels convert the chemical signal into a propagated muscle action potential

- The **AChR** is a pentamer of five subunits — **2α, 1β, 1δ and 1γ (fetal) or 1ε (adult)** — arranged around a central cation pore; ACh binds the two **α-subunits**, opening the channel to Na^+ (and Ca^{2+}) influx.
- **End-plate maturation/maintenance pathway**: nerve-derived **agrin → binds LRP4 → activates MuSK → recruits Dok-7 and rapsyn → clusters AChR** at the fold crests. The same molecules implicated here are the antigens/genes of autoimmune and congenital NMJ disease.

Physiology of neuromuscular transmission — the sequence

- A nerve action potential invades the terminal and opens **voltage-gated (P/Q-type) Ca^{2+} channels**; Ca^{2+} influx triggers SNARE-mediated **vesicle docking and exocytosis at active zones**.
- A single impulse releases the contents of **~150–200 vesicles** (Harrison); experimental estimates of quantal release vary (~50–300 quanta, mean ≈60 — Bradley). Quantal output **m = p × n**, where *p* is release probability (≈0.2, proportional to Ca^{2+}) and *n* the immediately available vesicle pool.

- Each quantum acting on AChRs produces a ~**1 mV** depolarisation — the **miniature end-plate potential (MEPP)** (spontaneous, sub-threshold).
- Summation of all quanta from one impulse produces the **end-plate potential (EPP)**, normally ~**60 mV** — far larger than the threshold needed to open perijunctional Na^+ channels and fire a **muscle fibre action potential**.
- **AChE** hydrolyses ACh within milliseconds and diffusion clears the cleft, resetting the junction.

The "safety factor" — the key to understanding weakness

- Because the EPP (~60 mV) **greatly exceeds the threshold** needed to trigger a muscle action potential, every nerve impulse reliably excites its fibre. This excess is the **safety factor of neuromuscular transmission**.
- Its magnitude depends on: **quantal content** (ACh released), **AChR density/conductance**, **AChE activity** and the geometry of the junctional folds.
- **Presynaptic rundown**: ACh output normally declines over the first few impulses of a train. In health this is invisible because the EPP still clears threshold; remove the safety factor and the same rundown now causes intermittent transmission failure — i.e. **fatigable weakness**.
- *Any* disease that lowers the EPP toward threshold (fewer AChRs, less ACh release, blocked release, or excess cholinergic depolarisation) converts a guaranteed signal into a probabilistic one — successive impulses activate **fewer and fewer fibres**, manifesting as decremental weakness and clinical fatigue.

How NMJ diseases cause weakness — site-based mechanisms

Disorder	Site / target	Mechanism of reduced safety factor	Distinctive features
Myasthenia gravis (MG) — anti-AChR	Postsynaptic AChR	↓ available AChRs by **(1)** antibody cross-linking → accelerated endocytosis/turnover; **(2)** complement (MAC)-mediated lysis of folds; **(3)** direct blockade of ACh-binding site. Folds flatten/"simplify" → small EPPs fail to reach threshold	AChR-Ab in ~85% generalised, ~50% ocular; ptosis, diplopia, bulbar & proximal limb weakness; reflexes preserved
MG — anti-MuSK	Postsynaptic clustering	IgG4 antibody blocks **MuSK–LRP4** interaction → loss of AChR clustering; **does not fix complement**	~40% of AChR-negative generalised MG; prominent bulbar/neck/respiratory weakness + muscle atrophy; often *worsens* with anticholinesterases
MG — anti-LRP4	Postsynaptic clustering	IgG1 → complement-mediated injury + interrupts agrin–MuSK signalling	1–3% of MG
Lambert-Eaton myasthenic syndrome (LEMS)	**Presynaptic** P/Q-type Ca^{2+} channel	Antibody against **voltage-gated Ca^{2+} channels** ↓ Ca^{2+} entry → ↓ quantal ACh release → low baseline EPP	Proximal leg weakness, *hyporeflexia*, autonomic features (dry mouth); **post-exercise facilitation**; ~85% have P/Q-Ab; SCLC association

Disorder	Site / target	Mechanism of reduced safety factor	Distinctive features
Botulism	Presynaptic SNAREs	*C. botulinum* toxin **enzymatically cleaves SNARE proteins** → blocks ACh exocytosis	Descending paralysis, bulbar onset, dilated pupils, autonomic failure; normal sensation
Congenital myasthenic syndromes (CMS)	Any component (pre-, synaptic, post-)	>30 gene mutations (e.g. **ε-subunit AChR ~50%**, *RAPSN, COLQ, DOK7, CHAT, agrin*) impair ACh synthesis, AChE anchoring, AChR kinetics or clustering	Non-immune; onset infancy/childhood; AChR & MuSK antibodies absent
Drug/toxin & metabolic	Variable	Aminoglycoside/quinolone/macrolide antibiotics, IV magnesium, procainamide, penicillamine (induces autoimmune MG), botulinum toxin — all impair release or block AChR	Exacerbate established MG; high doses weaken normal NMJ

- **Common final pathway**: every NMJ disease reduces the **EPP relative to threshold**. Presynaptic disorders (LEMS, botulism) do so by *reducing ACh release*; postsynaptic disorders (MG, most CMS) by *reducing the AChR response*. The result is identical — failure of a proportion of fibres to fire, i.e. **weakness that worsens with use**.

Electrodiagnostic correlation (proof of the physiology)

- **Slow repetitive nerve stimulation (2–3 Hz)**: in MG the already-reduced safety factor lets the normal rundown drop successive EPPs below threshold → a **decremental CMAP response >10%** (postsynaptic pattern).
- **Rapid RNS (20–50 Hz) or 10-s exercise**: in **LEMS** the accumulating presynaptic Ca^{2+} raises ACh release → EPPs cross threshold → **incremental response (often >100–200%)** — the electrophysiological signature of a presynaptic defect.
- **Single-fibre EMG**: increased **jitter** (variability of inter-potential interval) and **blocking** are the most sensitive markers of impaired transmission, reflecting EPPs hovering near threshold.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Normal NMJ (longitudinal section).** Label: *motor axon terminal, mitochondria, synaptic vesicles (quanta), active zone, voltage-gated Ca^{2+} channel, SNARE proteins (syntaxin-1/SNAP-25/synaptobrevin/synaptotagmin), synaptic cleft + basal lamina, acetylcholinesterase (AChE), junctional (postsynaptic) folds, AChR clustered at fold crests, voltage-gated Na^{+} channels in fold depths, clustering scaffold (agrin–LRP4–MuSK–Dok-7–rapsyn).*
- **Diagram 2 — Myasthenic vs normal end-plate.** Two panels side by side. Label: *normal — abundant AChRs, deep/normal folds, narrow cleft; MG — reduced AChR number, flattened/simplified folds, widened synaptic space, complement + AChR autoantibody on folds*. Optionally add an EPP-versus-threshold tracing showing the normal EPP above threshold and the myasthenic EPP failing threshold (the safety-factor concept).

Clinical / Diagnostic significance

- **Pattern recognition**: fatigable ptosis, diplopia, bulbar and proximal weakness with **preserved reflexes, normal sensation and normal pupils** localises to the NMJ; *hyporeflexia + autonomic features* point instead to LEMS.
- **Bedside tests**: **ice-pack test** (2 min over a ptotic lid; ≥2 mm lid rise = positive) exploits reduced AChE activity in the cold; the historical **edrophonium/anticholinesterase test** transiently improves strength.
- **Serology**: anti-AChR radioimmunoassay first; if negative, **anti-MuSK** then **anti-LRP4**. In LEMS test **P/Q-type Ca^{2+} channel antibodies** and **screen for small-cell lung cancer**.
- **Always image the chest (CT/MRI)** in MG — thymic **hyperplasia (~65–70%)** or **thymoma (~10–15%)** is common.
- **Management pearls (Harrison/CMDT 2026)**: symptomatic **pyridostigmine** (30–180 mg, avg ~60 mg, four times daily) — but it may *worsen* anti-MuSK MG; **corticosteroids** (gradual uptitration to avoid early steroid dip) and steroid-sparing agents (**azathioprine 2–3 mg/kg/day, mycophenolate, rituximab** — rituximab especially effective in MuSK MG); **thymectomy** for thymoma and for generalised AChR-positive MG <65 yrs (MGTX trial); **rapid rescue with IVIg or plasmapheresis** for crisis/pre-op. Newer FDA-approved agents: **complement inhibitors** (eculizumab, ravulizumab, zilucoplan — require meningococcal vaccination) and **FcRn antagonists** (efgartigimod, rozanolixizumab). LEMS is treated with **3,4-diaminopyridine** (blocks K^{+} channels → prolongs depolarisation → ↑ ACh release) ± pyridostigmine; botulism with **antitoxin** and ventilatory support.
- **Myasthenic crisis** = respiratory/bulbar failure needing ventilation; precipitated by infection, surgery, or offending drugs (aminoglycosides, magnesium) — a medical emergency.

High-yield exam pointers

- NMJ = **cholinergic synapse outside the blood–nerve barrier** → uniquely exposed to circulating antibodies.
- **AChR = pentamer 2α/β/δ/γ-or-ε**; ACh binds the **α-subunits**.

- **Quantum = 5000–10,000 ACh molecules → ~1 mV MEPP**; one impulse → **EPP ~60 mV ≫ threshold = safety factor**.
- **Agrin → LRP4 → MuSK → Dok-7/rapsyn → AChR clustering** — the master end-plate pathway and the disease antigen map.
- **MG = postsynaptic** (3 antibody mechanisms; complement, turnover, blockade) → **decrement on slow RNS**.
- **LEMS = presynaptic P/Q Ca^{2+}-channel** antibody → low CMAP, **increment after exercise/rapid RNS**, hyporeflexia, SCLC.
- **Botulism cleaves SNARE proteins**; **CMS** = genetic, ε-subunit commonest (~50%).
- Final common pathway of all NMJ disease = **EPP falls toward threshold → fibres fail intermittently → fatigable weakness**.
- NMJ weakness spares **sensation, reflexes (except LEMS) and pupils (except botulism)**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Myasthenia Gravis and Other Diseases of the Neuromuscular Junction"* (NMJ transmission physiology, AChR structure, antibody mechanisms, MG/LEMS/botulism/CMS, treatment).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — *"Disorders of Neuromuscular Transmission"* (immunopathology, junctional-fold ultrastructure, MG subtypes) and *"Clinical Electromyography"* (quantal release m = p × n, MEPP/EPP, safety factor, RNS decrement/increment, jitter).
- **CMDT 2026** — *"Nervous System Disorders: Myasthenia Gravis & Lambert-Eaton Myasthenic Syndrome"* (diagnostic criteria, drug doses, thymectomy, FcRn/complement therapies).
- Coverage note: the corpus covers this topic richly. The per-impulse ACh figure differs slightly between sources (Harrison "150–200 vesicles" vs Bradley "~50–300 quanta, mean ≈60"); both are quoted faithfully rather than reconciled.

◆ ◆ ◆

Posterior circulation stroke

Asked in: Paper III May 2022 · Paper II May 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Posterior (vertebrobasilar) circulation stroke* is ischemic infarction within the territory supplied by the paired **vertebral arteries**, the **basilar artery** and the paired **posterior cerebral arteries (PCAs)**, which together perfuse the brainstem, cerebellum, thalamus, occipital lobes and medial temporal lobes. Because the brainstem packs long tracts, cranial-nerve nuclei and reticular structures in close apposition, occlusion of each vessel produces its own distinctive, often eponymous syndrome. The hallmark of brainstem ischemia is **"crossed" findings** — ipsilateral cranial-nerve signs with contralateral long-tract (motor/sensory) signs. Basilar occlusion in particular is a treatable but potentially devastating emergency carrying high mortality.

Vascular anatomy (basis of localization)

- **Vertebral artery** — arises from the innominate artery on the right and the subclavian artery on the left; four segments: **V1** (origin to C6 transverse foramen), **V2** (C6→C2), **V3** (around the atlas to pierce dura at the foramen magnum), **V4** (intracranial). The two vertebrals join to form the basilar at the **pontomedullary junction**; only **V4** gives branches to brainstem/cerebellum.
- **Posterior inferior cerebellar artery (PICA)** — proximal segment supplies the **lateral medulla**; distal branches supply the inferior cerebellar surface.
- **Basilar artery** — supplies the base of the pons and superior cerebellum via **three branch groups**: (1) **paramedian** (7–10) → medial pontine wedge; (2) **short circumferential** (5–7) → lateral two-thirds of pons + middle/superior cerebellar peduncles; (3) **bilateral long circumferential** = **superior cerebellar (SCA)** and **anterior inferior cerebellar (AICA)** arteries → cerebellar hemispheres. The basilar divides into two PCAs in the **interpeduncular fossa**.
- **PCA origin variants** — both PCAs arise from the basilar bifurcation in **75%**; in **20%**, one arises from the ipsilateral ICA via the posterior communicating artery (**"fetal" PCA**); in **5%**, both arise from the ICAs. PCA divides at the posterior communicating artery into a proximal **P1** (precommunal) and distal **P2** segment.

Aetiology and mechanisms

- **Atherothrombosis** — predilection for **V1 and V4** segments of the vertebral artery; basilar atheroma is most frequent in the **proximal basilar and distal vertebral** segments. In-situ thrombosis of small penetrating (perforator) branches causes lacunar brainstem strokes.
- **Embolism** — cardiac or artery-to-artery emboli from proximal vertebral/basilar lodge at the **top of the basilar** ("top-of-the-basilar" syndrome) or at the PCA.
- **Arterial dissection** — vertebral artery dissection (V2/V3 mobile segments; spontaneous, traumatic, or after **spinal manipulative therapy**); a vertebral dissection may extend into the basilar.
- **Fibromuscular dysplasia** and, rarely, **osteophytic** encroachment in the vertebral foramina.
- **Subclavian steal** — subclavian occlusion proximal to the vertebral origin reverses ipsilateral vertebral flow; ipsilateral arm exercise "steals" flow and provokes posterior-circulation TIAs.

Clinical syndromes by arterial territory

Artery / territory	Eponym	Key clinical features (source-grounded)
PCA – P1 (midbrain/thalamus)	**Weber**	Ipsilateral CN III palsy + contralateral hemiplegia (cerebral peduncle)
PCA – P1	**Claude**	Ipsilateral CN III palsy + contralateral cerebellar ataxia (red nucleus/dentatothalamic tract)
PCA – thalamogeniculate perforators	**Déjérine-Roussy**	Contralateral hemisensory loss → later searing/burning **thalamic pain**
PCA – artery of Percheron	—	Bilateral paramedian thalamic infarct: upgaze paresis, drowsiness, **abulia**
PCA – P2 (occipitotemporal)	—	**Contralateral homonymous hemianopia (without macular sparing)**; alexia without agraphia; amnesia; peduncular hallucinosis
Bilateral distal PCA	**Anton / Balint**	Cortical blindness with denial (Anton); disordered visual scanning (Balint)
Vertebral/PICA – lateral medulla	**Wallenberg**	(see focused box)
Vertebral – medial medulla	Dejerine medial medullary	Contralateral hemiparesis sparing face + position-sense loss + ipsilateral tongue weakness (CN XII)
Basilar – complete	Locked-in	Quadriplegia + bilateral cranial-nerve signs, preserved consciousness
SCA	—	Severe ipsilateral cerebellar ataxia, N/V, dysarthria; contralateral pain/temp loss (limbs, body, face)
AICA	—	Ipsilateral deafness, facial weakness, vertigo, tinnitus, ataxia, Horner; contralateral pain/temp loss

Lateral medullary (Wallenberg) syndrome — high-yield focus

- **Cause** — embolic occlusion/thrombosis of the **V4 vertebral segment** in most cases; **PICA** occlusion in the remainder.
- **Ipsilateral** — facial pain/numbness (descending trigeminal tract), **Horner's syndrome** (descending sympathetic tract), cerebellar ataxia/falling to side of lesion, **dysphagia, hoarseness, palatal/vocal-cord palsy, diminished gag** (CN IX–X, nucleus ambiguus), vertigo/nystagmus (vestibular nuclei).
- **Contralateral** — impaired pain and temperature over the body (spinothalamic tract).
- **Key pearl — hemiparesis is NOT typical**; its presence points elsewhere. Dysphagia and aspiration risk dominate management.

Top-of-the-basilar and basilar occlusion

- **Top-of-the-basilar (embolic)** — sudden **bilateral** signs: ptosis, pupillary asymmetry/unreactive pupils, somnolence; vertical-gaze palsy; posturing and **myoclonic jerks simulating seizure**; visual and behavioural disturbances.

- **Complete basilar occlusion** — constellation of **bilateral long-tract signs (motor + sensory) with cranial-nerve and cerebellar dysfunction**; a **"locked-in" state** (preserved awareness, quadriplegia, anarthria, vertical eye/blink-only communication) indicates complete pontine + lower midbrain infarction. Carries **high mortality**.
- **Warning prodrome** — repetitive short-lived TIAs (5–30 min, several/day) with vertigo, diplopia, dysarthria, circumoral numbness; a **"herald hemiparesis"** may precede basilar occlusion. Recognising impending basilar occlusion *before* infarction is the therapeutic goal.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Posterior circulation arterial tree (Harrison Fig. 437-6):** Draw the two **vertebral arteries** uniting into the **basilar artery**, then the basilar bifurcating into both **posterior cerebral arteries**. Label: *Vertebral artery, Basilar artery, Posterior inferior cerebellar artery (PICA), Anterior inferior cerebellar artery (AICA), Superior cerebellar artery (SCA), Posterior cerebral artery (PCA), Posterior communicating artery, Deep penetrating (paramedian) branches of the basilar artery.*
- **Diagram 2 — Axial medulla for Wallenberg syndrome (Fig. 437-7):** Cross-section of medulla labelling the shaded **lateral medullary** zone: *Spinothalamic tract, Descending sympathetic tract (Horner), Nucleus ambiguus (CN IX–X), Vestibular nucleus, Spinal tract/nucleus of CN V, Inferior cerebellar peduncle (restiform body), Inferior olive, Pyramid (medial — spared).*

Clinical / Diagnostic significance

- **Imaging** — Non-contrast **CT** excludes haemorrhage but **frequently misses posterior-fossa infarcts** owing to bone (beam-hardening) artefact; look for the **hyperdense basilar artery sign** (intraluminal thrombus). **CTA** (aortic arch to vertex) confirms vertebral/basilar occlusion and selects thrombectomy targets. **MRI with DWI** is markedly superior to CT for brainstem/cerebellar ischemia.
- **Acute reperfusion — IV thrombolysis** with alteplase (rtPA 0.9 mg/kg, max 90 mg; 10% bolus) or **tenecteplase 0.25 mg/kg IV bolus** within **4.5 h** of last-known-well, after excluding haemorrhage. **Endovascular mechanical thrombectomy** for large-vessel occlusion (ICA/M1–M2 or **basilar artery**) up to **24 h** with perfusion-imaging selection in the 6–24 h window; **basilar thrombectomy can be life-saving**.
- **Cerebellar infarction is a neurosurgical emergency** — may mimic labyrinthitis (vertigo, vomiting); even small oedema obstructs the 4th ventricle/aqueduct causing **hydrocephalus** and **brainstem compression → coma and respiratory arrest**. **Suboccipital (posterior-fossa) decompression** is recommended for deteriorating patients and should precede significant brainstem compression. Head/neck pain should prompt suspicion of **vertebral dissection**.
- **Secondary prevention** — antiplatelet therapy / risk-factor control for atherothrombotic disease; anticoagulation for cardioembolism; dissection managed with antithrombotics. **Déjérine-Roussy thalamic pain** responds poorly to analgesics — use **carbamazepine, gabapentin, or tricyclic antidepressants**.

High-yield exam pointers

- Posterior circulation = **vertebrals + basilar + PCAs**; vertebrals fuse at the **pontomedullary junction**, basilar splits at the **interpeduncular fossa**.
- **Crossed signs** (ipsilateral CN + contralateral long tract) localize to the brainstem.
- **Wallenberg** = V4/PICA; vertigo, ipsilateral Horner + bulbar palsy + facial sensory loss, contralateral body pain/temp loss, **no hemiparesis**.
- **Weber** = CN III + contralateral hemiplegia; **Claude** = CN III + contralateral ataxia; **Benedikt-type** features (red nucleus tremor) overlap.
- **PCA P2** → homonymous hemianopia **without macular sparing**; bilateral → **Anton's syndrome** (cortical blindness with denial).
- **Locked-in syndrome** = ventral pontine infarct; conscious, quadriplegic, communicates by **vertical eye movements/blinking**.
- **Hyperdense basilar artery sign**; CT misses posterior-fossa strokes — get **MRI-DWI**.
- **Cerebellar infarct** → watch for hydrocephalus/herniation → **suboccipital decompression**.
- Reperfusion: **thrombolysis ≤4.5 h**, **thrombectomy ≤24 h** (basilar occlusion can be salvaged).

SOURCE & COVERAGE

Harrison 22e — Ch 437 "Introduction to Cerebrovascular Diseases" (posterior-circulation anatomy and clinical syndromes, Figs. 437-5 to 437-11) + Ch 438 "Ischemic Stroke" (thrombolysis, thrombectomy, cerebellar-infarct decompression). Coverage note: All territory syndromes, eponyms, anatomy, imaging and acute-management points above are sourced from these two chapters. *Benedikt's syndrome* is named as a standard textbook overlap of the P1 midbrain syndrome (red-nucleus involvement) but is not given that eponym verbatim in the provided text; the underlying lesion (dentatorubrothalamic/red nucleus with rubral tremor) is described. Vertebral-artery segmental anatomy detail and Brazis-style localization tables corroborate the same content.

◆ ◆ ◆

Differential diagnosis of seizures

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

Definition / Introduction — A **seizure** (Latin *sacire*, "to take possession of") is a transient occurrence of signs or symptoms due to **abnormal excessive or synchronous neuronal activity** in the brain; *epilepsy* denotes a tendency to **recurrent unprovoked seizures**. Because the diagnosis of a seizure rests largely on clinical grounds — examination and laboratory studies are frequently normal — a wide range of paroxysmal, transient, stereotyped events can imitate it. Distinguishing true epileptic seizures from these "non-epileptic" mimics is critical, as misdiagnosis leads to unnecessary, potentially teratogenic antiseizure medication (ASM), loss of driving privileges and a missed treatable cause (e.g. cardiac syncope). The cornerstone of differentiation is a **meticulous history with an independent eyewitness account**, supplemented when needed by video-EEG, tilt-table testing and cardiac electrophysiology.

Step 1 — Is the event actually a seizure?

- The first task is to decide whether the paroxysmal event was a seizure at all, then whether it was an *epileptic* seizure versus a non-epileptic mimic, then (if epileptic) focal versus generalized onset.
- **Features favouring an epileptic seizure**: a stereotyped **aura**, **cyanosis**, sustained tonic–clonic motor activity lasting **>15 s**, **lateral tongue biting**, urinary/faecal incontinence, **post-ictal confusion/disorientation**, post-ictal headache, muscle soreness, **Todd's paralysis**, sleepiness and **complete amnesia** for the loss of consciousness.
- **Positive vs negative symptoms** — seizures involving sensory/motor cortex produce *positive* phenomena (twitching, paraesthesiae, flashing lights) that **march/spread over seconds**; ischaemic events (TIA) classically produce *negative* phenomena (weakness, numbness) with no march.
- **Adjunctive biomarkers**: a transient rise in **serum prolactin** within the first **30 min** post-ictally supports a generalized or some focal seizures (a normal baseline value is rarely available, limiting reliability); **serum lactate >2.4 mmol/L for up to 3 h** after a convulsion favours a generalized convulsive *epileptic* seizure over PNES or syncope.
- **Gold standard for ambiguous events**: prolonged **video-EEG monitoring** capturing a habitual attack — generalized tonic–clonic seizures *always* produce marked ictal/post-ictal EEG change, whereas PNES does not (caveat: some frontal/orbitofrontal and supplementary-motor seizures have no scalp EEG correlate).

Classification of conditions that mimic seizures (Harrison Table 436-6)

Category	Specific mimics
Syncope	Vasovagal (neurally mediated), cardiac arrhythmia, valvular heart disease (aortic stenosis), cardiac failure, orthostatic hypotension
Cerebrovascular	Transient ischaemic attack, **basilar-artery TIA**, transient global amnesia, transient focal neurologic episodes (cerebral amyloid angiopathy)
Sleep disorders	Narcolepsy–cataplexy, benign sleep myoclonus, parasomnias (night terrors, sleepwalking, REM-behaviour disorder)

Category	Specific mimics
Movement disorders	Tics, non-epileptic myoclonus, paroxysmal kinesigenic/non-kinesigenic dyskinesia (choreoathetosis), hyperekplexia
Psychological	**Psychogenic non-epileptic seizure (PNES)**, hyperventilation, panic attack, rage attacks
Metabolic / toxic	Hypoglycaemia, hypoxia, alcoholic blackouts, delirium tremens, psychoactive drugs (hallucinogens)
Migraine	Migraine aura, confusional migraine, basilar migraine ("migralepsy")
Special — children	Breath-holding spells, Sandifer syndrome (GERD posturing), benign paroxysmal vertigo, apnoea, cyclic vomiting / abdominal migraine

Seizure versus syncope — the commonest dilemma (Harrison Table 436-7)

Feature	Generalized tonic–clonic seizure	Syncope
Precipitant	Usually none	Emotional stress, pain, Valsalva, prolonged standing, orthostasis, cardiac cause
Premonitory symptoms	None, or aura (e.g. odd odour)	Tiredness, nausea, **diaphoresis, tunnelling/greying of vision**
Posture at onset	Variable	Usually **erect**
Transition to unconsciousness	Often immediate	Gradual over seconds (sudden with arrhythmia)
Duration of unconsciousness	Minutes	**Seconds**, rapid recovery on recumbency
Convulsive movements	30–60 s, sustained tonic–clonic	**Never >15 s**; brief, **multifocal, arrhythmic myoclonus**
Face during event	Cyanosis, frothing	**Pallor**
Post-event confusion	Many minutes to hours	<5 min / minimal
Tongue biting	Sometimes (lateral)	Rarely
Aching of muscles	Often	Sometimes

- **Convulsive ("anoxic") syncope** — a sustained drop in cerebral perfusion (e.g. fainting while kept upright in a dental chair) commonly produces brief multifocal myoclonus, posturing, head turning and oral automatisms; there is **no associated EEG discharge** (the motor activity is brainstem-generated), and post-ictal confusion is minimal. Rarely, true syncope triggers a genuine *anoxic-epileptic seizure*.
- **Cardiac syncope** (arrhythmia, aortic stenosis) is typically abrupt with **no prodrome**; suspect it in older patients or those with structural heart disease, and exertional events with a systolic murmur — it mandates ECG/Holter/tilt-table evaluation as it is life-threatening.

Psychogenic non-epileptic seizures (PNES / pseudoseizures)

- Emotionally-triggered attacks **without ictal epileptic discharge**, usually part of a **conversion (somatoform) disorder** (or, rarely, malingering); ~**70–80% female**, peak onset 15–35 years, frequent antecedent of **childhood sexual/physical abuse**, head injury, fibromyalgia or chronic pain.
- **Clinical pointers favouring PNES**: **out-of-phase / asynchronous** thrashing of limbs, **forward pelvic thrusting**, **side-to-side head shaking**, **forced eye closure with resistance to eye opening**, "pseudosleep" onset, **waxing-and-waning prolonged duration** (often >2 min, even *pseudo-status*), emotional vocalisation (weeping, stuttering), preserved awareness with goal-directed behaviour, biting the **tip of the tongue/lip** (vs lateral in true seizures), shallow rapid post-ictal breathing, and **absence of post-ictal stertor / confusion**.
- **PNES coexists with epilepsy** in ~10–15% of patients, so its diagnosis does not exclude true epilepsy. **Diagnosis is confirmed by video-EEG** demonstrating typical semiology with no ictal correlate; serum prolactin and lactate remain unchanged.

Other neurological and medical mimics

- **TIA** — longer duration (usually >2 min), no spread/march, *negative* symptoms; *limb-shaking TIA* (brief, <5 min, precipitated by standing/exercise) signals **high-grade internal carotid stenosis**.
- **Migraine** — aura spreads slowly (cortical spreading depression ~3 mm/min) and lasts **5–60 min** (vs epileptic auras typically **<30 s**); visual aura is a fortification spectrum/scintillating scotoma (vs coloured circles in occipital seizures); basilar migraine causes brainstem symptoms then altered consciousness.
- **Transient global amnesia** — isolated anterograde amnesia for hours with preserved complex behaviour, in older adults.
- **Parasomnias** (somnambulism, night terrors, REM-behaviour disorder) — arise from slow-wave sleep ~90 min into the night; frontal-lobe seizures are brief, stereotyped, hypermotor and arise from stage 1–2 / sleep–wake transition.
- **Narcolepsy–cataplexy** — emotion-triggered loss of tone with **fully preserved consciousness and memory**.
- **Paroxysmal movement disorders** — kinesigenic dyskinesia (movement-triggered, consciousness preserved, responds to ASM), non-kinesigenic dyskinesia, hyperekplexia (exaggerated startle).
- **Panic attacks / hyperventilation** — paraesthesiae, derealisation and fear; distinguished by inter-ictal anxiety and clear situational triggers; **rage attacks** are situational and goal-directed.
- **Metabolic / toxic** — hypoglycaemia, hypoxia, hyponatraemia, uraemia, hepatic failure, alcohol/sedative withdrawal — these cause *provoked (acute symptomatic) seizures*, which by definition are **not epilepsy** and rarely cause chronic epilepsy.

Age-specific differential

- **Neonates/infants**: apnoea, jitteriness (metabolic), exaggerated startle, **Sandifer syndrome** (GERD posturing), **breath-holding spells** (cyanotic preceded by crying; pallid is reflex asystolic).

- **Children/adolescents**: shuddering attacks, stereotypies, tics, daydreaming mistaken for absence (and vice-versa).
- **Older adults**: TIA, transient global amnesia, cardiac arrhythmia and convulsive syncope predominate.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagnostic algorithm for the adult with a "seizure"** — central box *Paroxysmal event* → branch on History + eyewitness + examination → boxes to **EXCLUDE: Syncope · TIA · Migraine · Acute psychosis/PNES · Other episodic cerebral dysfunction (metabolic, sleep, movement disorder)** → if seizure confirmed → arms "No prior epilepsy" (labs, MRI, EEG) vs "Known epilepsy" (assess ASM adequacy/levels). Labels: *History, Eyewitness account, EEG, MRI, Video-EEG, Prolactin, Lactate*.
- **Seizure-vs-syncope timeline** — two parallel horizontal arrows labelled *Seizure* and *Syncope* with markers: Prodrome (aura vs nausea/diaphoresis/greying vision), Posture (variable vs erect), LOC (immediate/minutes vs gradual/seconds), Motor (tonic-clonic 30–60 s vs multifocal myoclonus <15 s), Colour (cyanosis vs pallor), Recovery (post-ictal confusion vs rapid).

Clinical / Diagnostic significance

- An eyewitness/home-video account is the single most valuable diagnostic tool; up to one-third of "refractory epilepsy" referrals to tertiary centres prove to be PNES.
- **Always exclude provoked (acute symptomatic) seizures** — hypoglycaemia, hyponatraemia, uraemia, hepatic failure, alcohol/benzodiazepine withdrawal, eclampsia, and offending **drugs** (e.g. tramadol, bupropion, isoniazid, β-lactams/quinolones, theophylline, cocaine) — because treatment is correction of the cause, not chronic ASM.
- **Investigations**: routine 12-lead **ECG in every first seizure** (to catch long-QT/arrhythmic syncope); MRI brain (superior to CT) for structural cause; EEG (first inter-ictal EEG normal in ~50%, yield rises with sleep-deprived/repeat recordings); tilt-table and Holter for suspected syncope; blood glucose, electrolytes, calcium, magnesium, renal/hepatic panel and toxicology guided by context; **lumbar puncture** if CNS infection suspected.

High-yield exam pointers

- Two commonest mimics: **syncope** (especially in elderly) and **PNES** (especially young women) — *video-EEG is the gold standard* for both.
- **Lateral** tongue bite, cyanosis, post-ictal confusion and **complete amnesia** favour seizure; **pallor**, erect posture, rapid recovery and recollection favour syncope.
- Convulsive syncope myoclonus is **multifocal, arrhythmic and <15 s** with **no EEG discharge**.
- **Post-ictal prolactin** (within 30 min) and **serum lactate >2.4 mmol/L** (up to 3 h) support epileptic over psychogenic events.
- PNES clues: forced eye closure, side-to-side head, pelvic thrusting, out-of-phase limb movements, waxing/waning long duration, **tip-of-tongue** biting; ~10–15% also have true epilepsy.

- TIA = *negative* symptoms, no march; **limb-shaking TIA = carotid stenosis**. Migraine aura = slow spread, **5–60 min** (vs epileptic aura <30 s).
- A single provoked seizure from a reversible metabolic/toxic cause is **NOT epilepsy** and usually needs no ASM.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Seizures and Epilepsy"** (Differential Diagnosis of Seizures; Table 436-6 list of mimics; Table 436-7 seizure-vs-syncope; syncope, convulsive syncope and psychogenic seizures; post-ictal prolactin; diagnostic algorithm Fig. 436-2).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e — "The Epilepsies"** (Differential Diagnosis: PNES semiology, syncope/convulsive syncope, migraine vs occipital seizure, parasomnias, narcolepsy–cataplexy, paroxysmal movement disorders, TIA/limb-shaking, transient global amnesia, age-specific imitators; evaluation of recent-onset seizures).
- **CMDT 2026 — "Nervous System Disorders" (Seizures & Epilepsy)** (differential of focal vs generalized seizures: TIA, migraine aura, transient focal neurologic episodes/CAA, panic, rage, cardiac, brainstem ischaemia, PNES; serum lactate >2.4 mmol/L adjunct; management framing).
- *Coverage note*: Brazis (Localization) and DeJong (Neurologic Examination) carry no dedicated seizure-mimic chapter; depth was therefore drawn from Bradley's epilepsy chapter, which fully covers the subspecialty detail.

◆ ◆ ◆

Seizures — causes and management

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

Definition / Introduction — A **seizure** (Latin *sacire*, "to take possession of") is a *transient* occurrence of signs or symptoms due to **abnormal, excessive or synchronous neuronal activity** in the brain. **Epilepsy** is a chronic disorder of *recurrent unprovoked seizures*, operationally defined as **≥2 unprovoked seizures >24 h apart** (or one unprovoked seizure with a high recurrence risk, or an epilepsy syndrome). About **5–10%** of people have at least one seizure in life; epilepsy prevalence is **5–30 per 1000**. A seizure is a *symptom*, not a disease — so management hinges on accurate classification, finding the cause, and rationally selecting an antiseizure medication (ASM).

Classification of Seizures (ILAE 2017)

Type determines aetiologic work-up, drug choice and prognosis. The 2017 ILAE scheme classifies by **onset, awareness and motor features**; the terms *simple/complex partial* and *secondary generalisation* are obsolete.

Onset	Subtypes	Key features
Focal onset (one hemispheric network)	*Aware* vs *impaired awareness*; *motor* vs *nonmotor*; *focal* → *bilateral tonic-clonic*	Aura, automatisms (lip-smacking, picking), Jacksonian march, Todd's paresis, *epilepsia partialis continua*; often structural
Generalised onset (bilateral networks)	**Motor**: tonic-clonic, tonic, clonic, **myoclonic**, **atonic** (drop attacks), epileptic spasms; **Nonmotor**: typical / atypical **absence**	Ictal cry, tongue-bite, incontinence, post-ictal confusion; absence = abrupt, no post-ictal phase
Unknown onset	Motor / nonmotor / unclassified	Insufficient information

- **Typical absence** — onset 4–10 yr; brief lapses without postural loss; EEG **3-Hz generalised spike-and-wave**, provoked by hyperventilation; 15–20% of childhood epilepsy.
- **Atypical absence** — slower onset/offset, EEG **≤2.5-Hz** spike-wave, with diffuse structural disease/developmental delay; drug-resistant.

Epilepsy syndromes (high-yield)

- **Juvenile myoclonic epilepsy (JME)** — early adolescence, morning myoclonic jerks, provoked by sleep deprivation; often GTCS ± absence; responds to valproate/levetiracetam.
- **Lennox-Gastaut syndrome** — *triad*: (1) multiple seizure types (tonic, atonic, atypical absence), (2) EEG slow (<3 Hz) spike-wave, (3) developmental delay; refractory.
- **Mesial temporal lobe epilepsy (MTLE)** — commonest focal-impaired-awareness syndrome; **hippocampal sclerosis** on T2 MRI; drug-refractory but **surgically curable**.

Causes / Aetiology of Seizures

Seizures result from a **shift in the excitation–inhibition balance**, produced by an interplay of *endogenous* (threshold/genetic), *epileptogenic* (lesional) and *precipitating* (provocative) factors. The ILAE recognises **six aetiologic categories** (CMDT): **structural, genetic, infectious, metabolic, immune, unknown**.

Aetiology by age (clinically the most useful framework):

Age group	Common causes
Neonates (<1 month)	Perinatal hypoxia-ischaemia, intracranial haemorrhage/trauma, CNS infection, metabolic (**hypoglycaemia, hypocalcaemia, hypomagnesaemia, pyridoxine [B6] deficiency**), drug withdrawal, developmental/genetic disorders
Infants & children (1 mo–12 yr)	**Febrile seizures**, genetic/metabolic epilepsy syndromes, CNS infection, developmental disorders, trauma
Adolescents (12–18 yr)	Trauma, genetic disorders, infection, illicit drugs, brain tumour
Young adults (18–35 yr)	Trauma, **alcohol withdrawal**, illicit drugs, brain tumour, **autoantibodies** (e.g. anti-LGI1, anti-NMDA-R)
Older adults (>35 yr)	**Cerebrovascular disease** (≈50% of new epilepsy >65 yr), brain tumour, alcohol withdrawal, metabolic (uraemia, hepatic failure, dysglycaemia, electrolytes), **Alzheimer/degenerative**, autoantibodies

Salient points on causes:

- **Febrile seizures** — 3 months–5 yr (peak 18–24 mo), prevalence 3–5%; *simple* (brief, generalised, single) carry no increased epilepsy risk, *complex* (>15 min, focal, or repeated) carry a 2–5% risk.
- **Head trauma** — penetrating wound, depressed skull fracture, intracranial haemorrhage or prolonged post-traumatic coma/amnesia → **30–50% risk** of epilepsy; severe penetrating injury up to **45%**.
- **Provoked/acute symptomatic seizures** (metabolic, drug, alcohol withdrawal) are *not* epilepsy — treat the cause, not with chronic ASM.
- **Provoking drugs/toxins** — β-lactams, quinolones, **isoniazid**, tramadol/meperidine, bupropion, clozapine, lithium, theophylline, ciclosporin/tacrolimus, cocaine/amphetamine; and **withdrawal** of alcohol, benzodiazepines, barbiturates, baclofen.
- **Genetic channelopathies** — e.g. *SCN1A* (Dravet syndrome — **avoid Na-channel blockers**), *KCNQ2*, *CHRNA4*; *SLC2A1* (GLUT-1 deficiency → **ketogenic diet**).

Basic mechanism (pathophysiology — exam framer)

- Hallmark of a focal seizure is the **paroxysmal depolarisation shift (PDS)** — prolonged Ca^{2+}-mediated membrane depolarisation opening voltage-gated Na^{+} channels, generating hyper-synchronous repetitive firing (the EEG "spike").
- Spread is normally checked by GABAergic **surround inhibition**; recruitment occurs via rising extracellular **K^{+}**, presynaptic **Ca^{2+}** accumulation and **NMDA-receptor** activation.
- Absence seizures arise from **thalamocortical oscillations** via **GABA-B receptors and T-type Ca^{2+} channels** (target of ethosuximide/valproate).
- **Epileptogenesis** = transformation of a normal network into a chronically hyperexcitable one (months–years after trauma/stroke/infection) — currently no proven *antiepileptogenic* drug.

Diagnostic evaluation

- **History** is paramount (diagnosis is largely clinical) — eyewitness account, aura, semiology, post-ictal state, precipitants, risk factors; *exclude mimics* (syncope, TIA, migraine, psychogenic non-epileptic seizures).
- **Blood work** — glucose, electrolytes, Ca^{2+}, Mg^{2+}, renal/hepatic function, CBC, toxicology screen; **LP** if meningitis/encephalitis suspected (mandatory in HIV); serum/CSF **autoantibodies** in fulminant epilepsy with psychiatric/cognitive change.
- **EEG** — supports diagnosis (interictal spikes/sharp waves), classifies seizures, guides prognosis; a normal interictal EEG **does not exclude** epilepsy (normal in 50–80% initially). Video-EEG telemetry is the gold standard for diagnostic uncertainty and presurgical localisation.
- **Neuroimaging — MRI > CT** for all new-onset seizures (detects tumour, vascular malformation, mesial temporal sclerosis, cortical dysplasia); emergent CT if mass/infection suspected and MRI unavailable.
- **Genetic testing** — for suspected genetic syndromes; guides therapy (e.g. *SLC2A1* → ketogenic diet; *ALDH7A1* → pyridoxine; avoid Na-blockers in *SCN1A*).

- **PNES vs epilepsy** — pelvic thrusting, side-to-side head movement, asynchronous limb shaking, ictal eye closure, waxing-waning, *no* post-ictal prolactin rise favour PNES; confirm with video-EEG.

Management — Antiseizure Drug (ASM) Therapy

ASMs act by **Na^+-channel block** (phenytoin, carbamazepine, lamotrigine, lacosamide, oxcarbazepine), **Ca^{2+}-channel block** (gabapentin, pregabalin; T-type — ethosuximide, valproate), **GABA potentiation** (benzodiazepines, barbiturates, valproate, tiagabine), **glutamate attenuation** (perampanel, topiramate, lamotrigine) and **SV2A modulation** (levetiracetam, brivaracetam).

General principles: treat reversible causes/avoid precipitants (esp. **sleep deprivation**) first; start ASM after a first seizure *only* with high recurrence risk (prior brain insult, epileptiform EEG, abnormal imaging, or nocturnal seizure); aim for **monotherapy at lowest effective dose**, titrate slowly; clinical seizure control, not serum level, is the endpoint.

Seizure type	First-line	Alternatives
Focal (±→ bilateral TC)	Lamotrigine, Levetiracetam, Carbamazepine, Oxcarbazepine, Phenytoin	Zonisamide, Brivaracetam, Topiramate, Lacosamide, Valproate, Cenobamate, Perampanel
Generalised tonic-clonic	**Valproate, Lamotrigine, Levetiracetam**	Topiramate, Zonisamide, Perampanel (avoid CBZ/OXC/PHT — may worsen)
Typical absence	**Ethosuximide, Valproate**, Lamotrigine	Levetiracetam, Clonazepam
Myoclonic / atonic / atypical absence	**Valproate**, Lamotrigine, Topiramate	Clonazepam, Clobazam, Rufinamide, Fenfluramine

- **Key drug pearls:** Lamotrigine → **rash/SJS** (slow titration; even slower with valproate which doubles its half-life). Phenytoin → **non-linear kinetics**, gum hypertrophy, hirsutism, osteomalacia. Valproate → **teratogenic (neural tube defects), hepatotoxicity, thrombocytopenia** — *avoid in women of child-bearing age*. Carbamazepine → SIADH/hyponatraemia, marrow suppression; test **HLA-B*1502** (Asians) for SJS risk before CBZ/PHT/OXC/LTG. Levetiracetam → behavioural/mood effects but **no significant interactions**.
- **Refractory epilepsy** (~30%, defined as failure of ≥2 appropriate ASMs): rational polytherapy with differing mechanisms → consider **surgery** (anteromedial temporal lobectomy/amygdalohippocampectomy makes ~70% of well-selected MTLE patients seizure-free; lesionectomy, corpus callosotomy, hemispherectomy), **laser thermal ablation**, **neurostimulation** (VNS, responsive neurostimulation, thalamic DBS), or **ketogenic diet**.

Status Epilepticus (SE) — the emergency

SE = continuous seizures or repetitive seizures without inter-ictal recovery of consciousness; operationally **≥5 min** of generalised convulsive activity warrants treatment. Mortality up to **20%**; commonest cause is **ASM non-adherence/withdrawal**. Stepwise protocol:

Stage	Therapy
0–5 min (stabilise)	ABC, O_2, IV access, check glucose → **IV 50% dextrose 25–50 mL** (+ thiamine), correct metabolic derangements
5–20 min (1st line — benzodiazepine)	**IV lorazepam 0.1 mg/kg** (4 mg, repeat once) *or* **IM midazolam 10 mg** *or* rectal diazepam 0.2 mg/kg
20–40 min (2nd line — IV ASM load)	**Fosphenytoin 18–20 mg PE/kg @150 mg PE/min** (or phenytoin 18–20 mg/kg @50 mg/min, ECG monitor) *or* **Valproate 20–40 mg/kg** *or* **Levetiracetam 60 mg/kg** (ESETT trial: all three equivalent)
>40 min (refractory SE)	Add phenobarbital; **continuous IV anaesthesia** — midazolam infusion (0.2 mg/kg → 0.05–0.6 mg/kg/h), **propofol** (2 mg/kg → 2–10 mg/kg/h) or **pentobarbital/thiopental**, with intubation + continuous EEG

Non-convulsive SE is diagnosed on EEG and treated by the same ladder (IV anaesthesia often not required).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **ILAE 2017 seizure classification tree** — top box "Seizure" branching to **Focal onset** (→ *aware / impaired awareness*; *motor / nonmotor*; *focal-to-bilateral tonic-clonic*), **Generalised onset** (→ *motor: tonic-clonic, myoclonic, atonic, spasms / nonmotor: typical & atypical absence*), and **Unknown onset**.
- **Stepwise status-epilepticus management ladder** — vertical timeline boxes: *0–5 min stabilise + IV glucose/thiamine → 5–20 min IV lorazepam / IM midazolam → 20–40 min fosphenytoin OR valproate OR levetiracetam → >40 min refractory: midazolam/propofol/pentobarbital infusion + continuous EEG.*

Clinical / Diagnostic significance

- **Classification drives therapy** — carbamazepine, oxcarbazepine and phenytoin can *aggravate* absence, myoclonic and atonic seizures; valproate/levetiracetam/lamotrigine are safe broad-spectrum choices.
- **First seizure ≠ epilepsy** — only ~30–50% recur; treat after one seizure only with defined high-risk features.
- **Time-critical SE** — outcome depends on the interval between onset and effective treatment; benzodiazepine + IV ASM load must not be delayed.
- **Women & epilepsy** — counsel on valproate teratogenicity, **folate 1–4 mg/d** pre-conception, enzyme-inducer effect on oral contraceptives, and vitamin K in the last weeks of pregnancy; prefer levetiracetam/lamotrigine.
- **SUDEP** — sudden unexpected death in epilepsy; risk rises with frequent nocturnal GTCS; mortality in epilepsy is 2–3× the general population.
- **Driving, occupation and lifestyle** counselling (avoid heights, unsupervised swimming/bathing) are integral to management.

High-yield exam pointers

- Epilepsy = **≥2 unprovoked seizures** (or one + high recurrence risk).
- ILAE 2017: **Focal / Generalised / Unknown** onset; "partial" is obsolete.
- **Absence** = 3-Hz spike-wave, **ethosuximide** drug of choice (no benefit in GTCS).
- **Valproate** = broadest spectrum but **teratogenic** — avoid in women of child-bearing potential.
- **Lamotrigine → SJS**; **HLA-B*1502 + carbamazepine → SJS in Asians**.
- **Lennox-Gastaut triad**: multiple seizure types + slow spike-wave + developmental delay.
- **Status epilepticus** treated at **5 min**: lorazepam → fosphenytoin/valproate/levetiracetam (ESETT) → anaesthesia.
- **MTLE with hippocampal sclerosis** = drug-resistant but **surgically curable** (~70% seizure-free).
- Commonest cause of new-onset epilepsy in the **elderly = stroke**; in **young adults = trauma/alcohol withdrawal**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Seizures and Epilepsy" (classification, aetiology by age, mechanisms, ASM selection & doses, status epilepticus, surgery, women/SUDEP).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "The Epilepsies" (semiology, syndrome classification, PNES).
- **CMDT 2026** — "Nervous System Disorders: Seizures & Epilepsy" (ILAE six aetiologic categories; status epilepticus dosing — lorazepam, fosphenytoin, valproate/levetiracetam ESETT equivalence, refractory anaesthesia).

◆ ◆ ◆

Acute ischaemic stroke — right internal capsule

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

Definition / Introduction — *Ischemic stroke* is the acute onset of a focal neurological deficit due to occlusion of a cerebral vessel producing infarction of brain tissue. The **internal capsule** is a compact band of ascending and descending white-matter fibres between the caudate/thalamus medially and the lentiform nucleus laterally; it carries the *corticospinal, corticobulbar and thalamocortical tracts*. Infarction here is most often a **small-vessel (lacunar) stroke** from occlusion of a single deep penetrator. A lesion of the **right** internal capsule produces a **contralateral (left-sided) deficit**, classically a *pure motor hemiparesis*, characteristically without cortical signs.

Functional anatomy & blood supply (basis of localization)

- The capsule has three parts: **anterior limb** (frontopontine, anterior thalamic radiation), **genu** (corticobulbar fibres) and **posterior limb** (corticospinal tract, superior thalamic/sensory radiations, and posteriorly the optic and auditory radiations).

- **Somatotopy of the corticospinal tract** in the posterior limb: face/arm fibres lie ventromedially (near the genu) and leg fibres dorsolaterally — so a small capsular lesion can affect *face, arm and leg together* (proportionate weakness), unlike cortical strokes which are patchy.
- **Arterial supply** (all are end-arteries with poor collaterals → infarcts are small but dense):
  - **Lenticulostriate branches** of the MCA (M1) → superior portions of anterior and posterior limbs, putamen, globus pallidus, caudate body, corona radiata.
  - **Anterior choroidal artery (AChA)** — arises from the internal carotid distal to the posterior communicating artery → **posterior limb of the internal capsule**, optic tract, lateral geniculate body, medial temporal lobe, midbrain.
  - **Recurrent artery of Heubner** (medial lenticulostriate from ACA A1/A2) → anterior limb and head of caudate.

Etiopathogenesis

- **Small-vessel / lacunar disease (commonest mechanism here; ~20–25% of all ischemic strokes):** chronic **hypertension** and **diabetes** cause *lipohyalinosis* (medial hypertrophy and fibrinoid deposition) or *microatheroma* at the origin of a 30–300 µm penetrating artery → in-situ thrombotic occlusion → a small infarct (lacune, 3 mm–2 cm; "lake" of fluid at autopsy). **Hypertension and age are the principal risk factors**; diabetes is also well recognised.
- **Tempo as a clue to mechanism:** slowly-paced (stuttering) deficits suggest haemodynamic failure of a tightly stenosed penetrator; rapid onset suggests in-situ thrombosis. A *crescendo* of stereotyped TIAs preceding a capsular lacune is the **capsular warning syndrome**.
- **Other mechanisms** producing capsular/striatocapsular infarction: artery-to-artery embolism from carotid plaque, cardioembolism (atrial fibrillation, valve disease, LV thrombus), large MCA-stem thrombosis with lenticulostriate involvement, and AChA-territory occlusion.
- **Ischemic cascade:** energy failure → loss of ionic gradients → glutamate excitotoxicity, Ca^{2+} influx, free-radical and arachidonic-acid generation, inflammation → infarct *core* surrounded by a salvageable, perfusion-dependent **penumbra** (the target of reperfusion therapy).

Mechanism	Typical source	Capsular relevance
Small-vessel (lacunar)	Lipohyalinosis / microatheroma of penetrator; HTN, DM	**Most common** — pure motor / sensorimotor lacune
Artery-to-artery embolism	Carotid bifurcation / arch plaque	Striatocapsular infarct
Cardioembolism	AF, valve disease, LV thrombus	Larger deep infarct
Large-vessel thrombosis	MCA-stem / ICA atherosclerosis	Lenticulostriate territory

Clinical features (lesion of the RIGHT internal capsule → LEFT-sided deficit)

- **Pure motor hemiparesis (the commonest lacunar syndrome):** a unilateral (left) motor deficit affecting **face, arm and leg almost equally**, often with mild dysarthria at onset, an extensor (Babinski) plantar response, and — crucially — **no aphasia, no apraxia, no agnosia, no sensory,**

visual or higher-cortical loss. Because the lesion spares the cortex, *higher functions are intact*; and as the right hemisphere is non-dominant in most patients, language is preserved regardless.

- **Sensorimotor stroke:** lacune of the posterior limb plus adjacent posteroventral thalamus → combined left face–arm–leg motor and sensory deficit.
- **Ataxic hemiparesis:** posterior-limb lacune → left lower-limb-predominant weakness with disproportionate ipsilateral limb incoordination and an extensor plantar.
- **Dysarthria–clumsy hand syndrome:** lacune of the **genu / anterior limb** → dysarthria, dysphagia, supranuclear facial weakness, tongue deviation and loss of fine motor control of the left hand.
- **Anterior choroidal artery syndrome (Foix, 1925):** the classic **triad of contralateral hemiparesis (posterior-limb corticospinal fibres) + hemianesthesia (superior thalamic radiation) + homonymous hemianopia (optic tract/LGB/radiation)**. With a **right** AChA infarct expect additional non-dominant signs — *left visuospatial neglect, anosognosia, constructional apraxia* and a relative afferent pupillary defect.
- General features favouring ischemia over haemorrhage: deficit maximal at onset (or remitting), normal/only modestly raised BP, preserved consciousness. Recovery from small-vessel strokes is usually rapid and fairly complete (partial/complete resolution over 4–6 weeks), though early stuttering worsening can occur.

Lacunar syndrome	Usual capsular site	Left-sided manifestation (right capsule)
Pure motor hemiparesis	Posterior limb / corona radiata	Face + arm + leg weakness, ± dysarthria
Pure sensory stroke	VPL thalamus (± capsule)	Numbness/paraesthesia, cheiro-oral pattern
Ataxic hemiparesis	Posterior limb	Leg-predominant weakness + limb ataxia
Dysarthria–clumsy hand	Genu / anterior limb	Dysarthria + clumsy hand
Sensorimotor stroke	Posterolateral thalamus + posterior limb	Combined hemimotor + hemisensory loss

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Axial section of the internal capsule:** label *anterior limb, genu, posterior limb, head of caudate, thalamus, putamen, globus pallidus (lentiform nucleus)*; arrow the corticospinal somatotopy (**face/arm ventromedial, leg dorsolateral**) and the *optic/auditory radiations* in the retrolenticular part.
- **Arterial supply schematic:** show *MCA lenticulostriate branches, anterior choroidal artery (posterior limb), recurrent artery of Heubner (anterior limb)* feeding the capsule.

Clinical / Diagnostic significance

- **Emergency non-contrast CT head** first — to *exclude haemorrhage*; it is insensitive to acute infarction (often normal in the first 6–24 h) but mandatory before thrombolysis.

- **Diffusion-weighted MRI is the gold standard** — confirms and localises the small capsular lacune.
- **Vascular & cardioembolic work-up:** CTA/MRA (great-vessel and intracranial stenosis), CT-perfusion to define core vs penumbra (selects late thrombectomy), carotid duplex, ECG and prolonged ambulatory monitoring for AF, transthoracic/transoesophageal echo, blood glucose, lipid profile, CBC; hypercoagulable screen in young/cryptogenic cases.
- **NIHSS** quantifies severity and guides reperfusion eligibility; "time last seen normal" defines the therapeutic window.

Management

A. Acute / hyperacute (penumbra rescue):

- **ABC**, finger-stick glucose (correct hypo-/hyperglycaemia), continuous monitoring; treat fever with antipyretics/cooling; keep glucose ~3.3–10.0 mmol/L (60–180 mg/dL).
- **Permissive hypertension:** lower BP only if **>220/120 mmHg**, or malignant hypertension / concurrent myocardial ischaemia, or **>185/110 mmHg if thrombolysis is planned** — collateral flow is pressure-dependent, so over-aggressive lowering worsens outcome.
- **IV thrombolysis (≤4.5 h of onset): alteplase (rtPA) 0.9 mg/kg (max 90 mg)**, 10% as bolus then the remainder over 60 min; **or tenecteplase 0.25 mg/kg (max 25 mg) single IV bolus**. CT must show no haemorrhage and no oedema >⅓ MCA territory; observe contraindications (recent surgery/bleed, bleeding diathesis, uncontrolled BP). No other antithrombotic for 24 h.
- **Endovascular mechanical thrombectomy** for large-vessel occlusion (ICA, M1/M2, basilar): standard window **0–6 h**, and **6–24 h** in selected patients chosen by perfusion (core/penumbra mismatch) imaging — most relevant when the capsular infarct results from a proximal large-vessel clot rather than a pure lacune.
- **Supportive:** DVT prophylaxis with pneumatic compression stockings ± subcutaneous heparin; aspiration/pneumonia precautions. For large hemispheric infarcts with malignant oedema (peaks day 2–3): mannitol/hypertonic saline and **decompressive hemicraniectomy** (halves mortality); suboccipital decompression for space-occupying cerebellar infarction.
- **Anticoagulation is NOT used routinely** for acute atherothrombotic stroke (no benefit, more bleeding).

B. Secondary prevention (the mainstay for lacunar stroke):

- **Antiplatelets:** aspirin (after a 325 mg load, then 81 mg/d). For minor stroke / TIA (NIHSS <5) give **short-term dual antiplatelet therapy** — aspirin + clopidogrel (300–600 mg load then 75 mg/d) **for ~21 days** then single-agent — as in CHANCE/POINT; long-term DAPT (SPS3) is *avoided* in small-vessel stroke (more bleeding, no benefit).
- **Blood-pressure control is the single most effective measure** — target **<130/80 mmHg** long-term (thiazides and ACE inhibitors well supported); SPRINT supports lower targets.
- **High-intensity statin** (atorvastatin 80 mg / rosuvastatin 40 mg; SPARCL) to **LDL <70 mg/dL**; tight diabetic control; smoking cessation.
- **For cardioembolic source (AF):** oral anticoagulation — a **DOAC** (e.g., apixaban 5 mg BD) preferred over warfarin (INR 2–3); risk-stratify by CHA_2DS_2-VASc.

- **Carotid revascularisation** (endarterectomy) for significant ipsilateral symptomatic stenosis.

C. Rehabilitation: early multidisciplinary stroke-unit care with physiotherapy, occupational and speech therapy; constraint-induced movement therapy for hemiparesis; prevention of contractures, pressure sores and post-stroke depression — improves outcome and reduces mortality.

High-yield exam pointers

- Right internal-capsule lacune → **left pure motor hemiparesis of face, arm AND leg, with NO cortical signs and preserved language**.
- Posterior limb = corticospinal tract; **leg fibres dorsolateral, face/arm ventromedial**.
- **Anterior choroidal artery triad = hemiplegia + hemianaesthesia + hemianopia.**
- **Lipohyalinosis of penetrators from chronic hypertension** is the core pathology; HTN + age + diabetes are the key risk factors.
- **DWI-MRI** is the gold-standard investigation; **non-contrast CT** is done first only to exclude haemorrhage.
- **Alteplase 0.9 mg/kg ≤4.5 h** or **tenecteplase 0.25 mg/kg**; thrombectomy 0–6 h (up to 24 h by perfusion mismatch).
- Acute BP: treat only if **>185/110** (if lysing) or **>220/120** otherwise — *permissive hypertension*.
- Secondary prevention: antiplatelet + BP <130/80 + high-intensity statin; **DAPT for 21 days only** in minor stroke/TIA.
- **Capsular warning syndrome** = crescendo capsular TIAs that herald a completed lacune.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Ischemic Stroke" (pathophysiology of small-vessel/lacunar stroke, ischemic cascade, acute treatment, thrombolysis/thrombectomy, secondary prevention) and "Introduction to Cerebrovascular Diseases".
- **Brazis – Localization in Clinical Neurology** — "Vascular Syndromes of the Forebrain, Brainstem and Cerebellum" (internal-capsule blood supply, lacunar syndromes and table, anterior choroidal artery [Foix] syndrome, corticospinal somatotopy).
- **CMDT 2026** — "Nervous System Disorders: Lacunar Infarction" and stroke-subtype management table (time windows, antiplatelet, risk-factor control).

◆ ◆ ◆

Reperfusion therapy in acute stroke

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

Definition / Introduction — *Reperfusion therapy* is the emergency restoration of blood flow to an acutely occluded cerebral artery, aiming to salvage the **ischaemic penumbra** (ischaemic but still viable tissue surrounding the infarct core) before it progresses to irreversible infarction. "**Time is brain**" — outcome is directly proportional to the speed of recanalisation. Two proven modalities exist: **(1) intravenous (IV) thrombolysis** with a plasminogen activator (alteplase or tenecteplase), and **(2) endovascular mechanical thrombectomy** for large-vessel occlusion (LVO). They are complementary, not mutually exclusive — eligible patients receive thrombolysis first ("bridging") and then thrombectomy.

Rationale — the penumbra and the therapeutic window

- A cerebral blood flow of **0 mL/100 g/min** kills neurons within **4–10 min**; values **<16–18 mL/100 g/min** infarct within an hour; **<20 mL/100 g/min** causes reversible ischaemia (the penumbra) unless prolonged.
- Restoring flow re-supplies oxygen and glucose, reverses tissue acidosis, clears excitotoxic **glutamate** and reactive oxygen species, and halts cortical spreading depression — preventing the penumbra from infarcting.
- The penumbra (and thus the *individual* therapeutic window) is imaged as a **core–perfusion mismatch** on CT perfusion (CTP) or MR diffusion–perfusion (DWI/PWI) — this is what extends eligibility beyond the rigid clock-based windows.

Mandatory pre-reperfusion assessment ("Code Stroke")

- Secure **ABCs**; finger-stick glucose (treat hypo-/hyperglycaemia — mimics).
- Establish **time last seen normal** (wake-up stroke = time patient went to bed) and quantify deficit with the **NIHSS**.
- **Emergency non-contrast CT (NCCT)** to exclude haemorrhage — the *only* mandatory imaging before IV thrombolysis (with glucose). No edema/hypodensity >⅓ of the MCA territory.
- For possible thrombectomy: **CT angiography (CTA)** (atria → vertex) to confirm LVO; add **CTP/MR perfusion** for late-window selection (6–24 h).
- Other labs (CBC, coagulation, ECG, electrolytes) must **not delay** thrombolysis in an otherwise-eligible patient.

Option 1 — Intravenous thrombolysis

Evidence: *NINDS rt-PA Study* established benefit of IV alteplase within **3 h** (absolute 12% increase in minimal-disability outcome; symptomatic ICH 6.4% vs 0.6%). *ECASS III* extended efficacy to the **3–4.5 h** window (good outcome 52.4% vs 45.2%, OR 1.34; sICH 2.4% vs 0.2%). Tenecteplase is **non-inferior** to alteplase and increasingly preferred as a single bolus.

Agent	Dose	Window	Notes
Alteplase (rt-PA)	**0.9 mg/kg** (max 90 mg); 10% as bolus, remainder over **60 min**	0–4.5 h	US label 0–3 h; off-label/EU to 4.5 h. Asian dose often **0.6 mg/kg** (less ICH)
Tenecteplase (TNK)	**0.25 mg/kg** IV push (max 25 mg) over ~5 s	0–4.5 h	Single bolus — no infusion; eases inter-hospital transfer for thrombectomy. Off-label

Indications (must satisfy ALL): clinical ischaemic stroke with disabling deficit; onset-to-needle **≤4.5 h**; age **≥18 y**; NCCT shows no haemorrhage and no large established infarct.

Key contraindications (Table 438-1 + NINDS exclusions):

Absolute	Relative / caution
Sustained **BP >185/110 mmHg** despite treatment	Recent MI
Active bleeding / bleeding diathesis	GI or GU bleeding (within 21 days)
Recent head injury or **intracerebral haemorrhage**	Major surgery within preceding 14 days
Hypodensity > ⅓ MCA territory / large infarct on CT	Rapidly improving or minor non-disabling deficit (NIHSS 0–5)
Platelets <100,000; INR >1.7 / PT >15 s; heparin in 48 h	Seizure at onset (only if deficit is post-ictal)
Glucose <50 mg/dL (2.8 mmol/L)	Arterial puncture at non-compressible site (7 days)

- **Extended/unknown-onset window:** MRI-based **DWI–FLAIR mismatch** (WAKE-UP) or perfusion mismatch (EXTEND) selects benefit up to **~9 h or on awakening** — penumbra-guided, not clock-guided.
- **Peri-thrombolysis care:** lower BP to <185/110 (IV labetalol/nicardipine) before bolus; keep <180/105 for 24 h; **no antithrombotics for 24 h**; repeat CT for deterioration; for bleeding, stop infusion + give **cryoprecipitate**.

Option 2 — Endovascular mechanical thrombectomy (EVT)

LVO (MCA-M1, intracranial ICA, basilar) carries a large clot burden that often **fails to recanalise with IV thrombolysis alone** — these need EVT. Six 2015 RCTs (*MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT*) proved benefit with **stent retrievers**: pooled OR **2.49**; mRS 0–2 in **46% vs 26.5%**, with a mortality benefit. Outcome is time-critical — odds of good outcome >3 if groin puncture <2 h, falling to ~2 by 8 h.

Indications — 2018 AHA/ASA Class I criteria:

- Pre-stroke **mRS 0–1**
- Causative occlusion of **ICA or proximal MCA (M1)**
- Age **≥18 y**
- **NIHSS ≥6**
- **ASPECTS ≥6** (limited established core on NCCT)
- **Groin puncture within 6 h** of onset

- Receipt of IV alteplase within 4.5 h **if eligible** (do not withhold/delay thrombolysis to do EVT)

Late window (6–24 h) — perfusion-selected (Class I/IIa):

- ***DAWN* trial:** LVO, last-seen-well **6–24 h**, clinical–core mismatch (RAPID software) → good outcome **47% vs 13%**.
- ***DEFUSE-3* trial:** perfusion mismatch, **6–16 h** → mRS 0–2 in **45% vs 17%**.
- Basilar occlusion: non-randomised data support thrombectomy up to **24 h**.
- **Stent retrievers are preferred** to older devices (e.g., MERCI coil retriever); aspiration catheters are an alternative. Bridging tenecteplase before transfer is increasingly favoured.

Integrated time-window algorithm

Time from onset	Reperfusion option
0–4.5 h	IV thrombolysis (alteplase/TNK) if eligible + EVT if anterior LVO
4.5–6 h	EVT for LVO (thrombolysis window closed)
6–24 h	EVT **only if** penumbra/mismatch on CTP/MR perfusion (DAWN/DEFUSE-3)
Wake-up / unknown, ≤9 h	IV thrombolysis if DWI–FLAIR or perfusion mismatch

Adjuncts and therapies that do NOT replace reperfusion

- **Antiplatelets:** Aspirin (160–325 mg) within 48 h gives a small net benefit (IST, CAST) — start **after 24 h** if thrombolysed. Short-term **dual antiplatelet** (aspirin + clopidogrel/ticagrelor) for 21 days in **minor stroke/TIA (NIHSS ≤3–5)**.
- **Anticoagulation:** No role in acute atherothrombotic stroke (no benefit, ↑ bleeding); reserved for dural sinus thrombosis.
- **Neuroprotection** (glutamate antagonists, hypothermia, magnesium, free-radical scavengers): **no agent proven** in humans despite >120 trials.
- **Decompressive hemicraniectomy** for malignant MCA infarction (within ~48 h) reduces mortality ~50% and improves survivor outcome; **suboccipital decompression** for space-occupying cerebellar infarct.
- **Supportive:** permissive hypertension (only treat if >220/120), euglycaemia, normothermia, stroke-unit care and early rehabilitation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Penumbra schematic:** concentric zones — central black **"core" (irreversible infarct)** surrounded by a stippled **"penumbra" (salvageable)**, with arrows labelled *Reperfusion → penumbra saved*; axis showing CBF thresholds (**0 mL/100 g/min → death in 4–10 min**, **<20 → reversible ischaemia**).
- **Acute-stroke reperfusion algorithm flowchart:** boxes — *Suspected stroke → Code Stroke / NCCT* → branch **No haemorrhage**; *Onset <4.5 h → IV thrombolysis (alteplase/TNK)* and *CTA → anterior LVO? → Thrombectomy (<6 h)*; *Onset 6–24 h → CTP/MR perfusion → favourable mismatch → Thrombectomy*. Label time windows on each arm.

Clinical / Diagnostic significance

- IV rt-PA raises the chance of recovery without significant disability from **~26% to ~39%** when given <3 h; EVT makes functional independence ≥30% more likely in LVO.
- **Door-to-needle ≤60 min** and **door-to-groin** times are key quality metrics; pre-hospital "stroke code" activation and tele-stroke speed delivery.
- **Systems of care:** primary stroke centres deliver thrombolysis and transfer ("drip-and-ship") to **comprehensive/thrombectomy-capable centres**; the bolus-only tenecteplase simplifies transfer.
- After reperfusion: 24-h follow-up CT before starting antithrombotics; then establish aetiology (AF → anticoagulation; carotid stenosis >50% → endarterectomy; high-intensity statin, LDL <70 mg/dL) for secondary prevention.

High-yield exam pointers

- Two reperfusion options: **IV thrombolysis** (alteplase **0.9 mg/kg**, max 90 mg, 10% bolus + 60-min infusion; tenecteplase **0.25 mg/kg** bolus) and **mechanical thrombectomy** (stent retriever).
- IV thrombolysis window **≤4.5 h** (NINDS 0–3 h; ECASS III 3–4.5 h); thrombectomy **≤6 h**, extended to **24 h** with perfusion mismatch (**DAWN 6–24 h, DEFUSE-3 6–16 h**).
- **BP must be <185/110 mmHg** before thrombolysis; treat acute BP only if **>220/120 mmHg** otherwise.
- Only **NCCT + glucose** are mandatory before IV thrombolysis — don't wait for other labs.
- Thrombectomy Class I: **ICA/M1 occlusion, NIHSS ≥6, ASPECTS ≥6, pre-stroke mRS 0–1, age ≥18, groin <6 h**.
- Symptomatic ICH is the major thrombolysis complication (~6% NINDS) — reverse with **cryoprecipitate**.
- **No neuroprotective drug** is proven; aspirin only modest; anticoagulation not for acute atherothrombotic stroke.
- Bridging thrombolysis-then-thrombectomy is standard for eligible LVO; do **not** delay thrombolysis to perform EVT.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Ischemic Stroke" (Table 438-1, NINDS/ECASS III, DAWN/DEFUSE-3, endovascular revascularisation; penumbra pathophysiology).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Ischemic Cerebrovascular Disease" (alteplase inclusion/exclusion criteria, 2018 AHA/ASA Box 65.8 thrombectomy criteria, MR CLEAN/ESCAPE/EXTEND-IA/SWIFT PRIME/REVASCAT, NNT/benefit data).
- **CMDT 2026** — "Nervous System Disorders / Stroke" (current dosing, tenecteplase non-inferiority, 0–4.5 h thrombolysis and 0–6/6–24 h embolectomy windows, extended-window perfusion selection, peri-thrombolysis BP control).

◆ ◆ ◆

Endovascular revascularisation for acute ischaemic stroke

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

Definition / Introduction — *Endovascular revascularization* (endovascular mechanical **thrombectomy**) is the catheter-based removal of an occluding thrombus from a large intracranial artery to restore cerebral blood flow and salvage the ischemic **penumbra**. It is one of the six categories of acute ischemic stroke treatment in Harrison (medical support, IV thrombolysis, **endovascular revascularization**, antithrombotic treatment, neuroprotection, and stroke centers/rehabilitation). It is the definitive reperfusion therapy for **large-vessel occlusion (LVO)** strokes, which often fail to open with IV thrombolysis alone, and is used as an *alternative or adjunct* to IV thrombolysis.

Rationale and target lesions

- Ischemic stroke from **large-vessel intracranial occlusion** carries high rates of mortality and morbidity.
- These occlusions involve a **large clot burden** and often **fail to recanalize with IV thrombolysis alone**, providing the rationale for direct mechanical clot retrieval.
- **Eligible target vessels** (proven on CT angiography):
  - **Intracranial internal carotid artery (ICA)**
  - **Middle cerebral artery** — first division (**M1**) and second division (**M2**)
  - **Basilar artery (BA)** (posterior circulation)
- Thrombectomy is offered to patients who are **ineligible for or have contraindications to thrombolytics**, or **who failed to recanalize after IV thrombolysis**.
- Reperfusion aims to rescue the penumbra — clinical outcome is critically **time-dependent**.

Patient selection and time windows

- **Disabling deficit:** patients with **NIHSS >5** (National Institutes of Health Stroke Scale) are candidates for thrombolytic and/or endovascular therapy.

- **Imaging gateway:** noncontrast head CT to exclude hemorrhage, then **CT angiography (CTA)** to confirm the LVO; for late windows, **CT perfusion / MR perfusion** to assess salvageable tissue.
- **Early window (<6 h from onset):** thrombectomy for **ICA / M1–M2 / basilar** occlusion confirmed on CTA, **with or without** IV thrombolysis pretreatment.
- **Extended/late window (6–24 h, including wake-up and unwitnessed-onset strokes):** effective **only if perfusion imaging shows good collaterals / a favorable mismatch** (small core, large penumbra). Selection rests on perfusion imaging rather than thrombolysis eligibility.
- **Posterior circulation:** for basilar artery occlusion, nonrandomized data show thrombectomy is safe **up to 24 h** from onset and is associated with lower 3-month Rankin scores.
- **Time is brain — procedural timing data:**
  - Odds of a good outcome **exceed 3** if **groin puncture occurs within 2 h** of symptom onset, but fall to **~2 if 8 h elapse**.
  - **>80%** of patients with **vessel opening within 1 h** of ED arrival had a good outcome, versus only **one-third** if **6 h** elapsed.

Evidence base (key trials)

Trial group / window	Patients selected	Outcome (mRS 0–2 unless stated)
Six 2015 RCTs (combined meta-analysis); <6 h	ICA & MCA occlusion on CTA, ± IV tPA	Large benefit: **OR 2.49** (95% CI **1.76–3.53**, p<.001); **46% vs 26.5%** (endovascular vs medical)
DAWN (Trevo stent retriever); up to 24 h	Wake-up / late-presenting, clinical–imaging mismatch	Good outcome **47% vs 13%** (p<.0001)
DEFUSE-3; up to 16 h	Perfusion mismatch on CT/MR perfusion	Good outcome **45% vs 17%** (p<.001)
Basilar occlusion (nonrandomized); up to 24 h	Posterior circulation LVO	Safe; **lower 3-month Rankin scores**

- mRS 0–2 = "normal or symptomatic but independent."
- A more recent meta-analysis additionally demonstrated a **mortality benefit** with thrombectomy.
- One trial concluded patients were **home nearly 2 months earlier** when treated with endovascular therapy.

Procedure, adjuncts and bridging therapy

- **Technique:** catheter-based clot removal (stent retriever, e.g., *Trevo*, and/or aspiration) via femoral/groin access, with restoration of antegrade flow confirmed on catheter angiography.
- **Bridging with IV thrombolysis:** outcomes are **likely improved by giving IV rtPA before thrombectomy** when the patient is rtPA-eligible and it is safe to administer.
  - **IV rtPA (alteplase):** 0.9 mg/kg (max 90 mg), 10% as bolus then remainder over 60 min, within 4.5 h.
  - **IV tenecteplase (TNK):** 0.25 mg/kg IV bolus (max 25 mg) over 5 s. Recent data support **replacing rtPA with tenecteplase** before thrombectomy — its single-bolus administration

(no 1-h infusion) **simplifies inter-hospital transfer** to an endovascular center and obviates critical-care transport. Several trials of TNK before endovascular therapy found it safe.

- **Adjunctive imaging workflow** (Fig. 438-3): noncontrast CT → CTA (confirm LVO; *hyperdense MCA sign* is highly specific but seen in only ~20%) → CT perfusion (core vs penumbra/mismatch) → catheter angiography with clot removal → follow-up diffusion-weighted MRI; advanced imaging can yield a **better-than-predicted** outcome.

Systems of care

- Now that thrombectomy is proven effective, **comprehensive stroke centers** that rapidly identify and treat LVO are an international priority.
- **Regional systems of care:** patients are first evaluated at **acute stroke-ready hospitals / primary stroke centers** (can give IV rtPA or tenecteplase), then **transferred to thrombectomy-capable or comprehensive stroke centers**, or **directly triaged** to such centers based on prehospital field assessment.
- **Telemedicine / telestroke** services extend evaluation for thrombolysis and endovascular treatment.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Acute stroke management pathway (Fig. 438-2)** — flowchart with labels: *Suspected acute stroke → Prehospital call ahead → Code stroke activation*; branch **Onset <6 h**: *CT no hemorrhage → IV PA if eligible (<4.5 h) → Perform CTA → ICA/M1–2 or BA occlusion? → Yes → Thrombectomy*; branch **Onset 6–24 h**: *CT no hemorrhage → CTA/CTP → Favorable perfusion? → Yes → Thrombectomy; No → Inpatient management*.
- **LVO imaging-to-reperfusion sequence (Fig. 438-3)** — panels labelled: *Noncontrast CT (hyperdense MCA sign, arrow)*; *CTA (MCA branch occlusion)*; *CT perfusion (core = no pink signal; penumbra = green, mismatch volume, mismatch ratio, Tmax >6.0 s, CBF <30%)*; *Catheter angiogram (occlusion → restored flow after clot removal)*; *Follow-up DWI (small residual infarct)*.

Clinical / Diagnostic significance

- Identifies the subgroup — **large-vessel occlusion** — that derives the greatest reperfusion benefit and that IV thrombolysis alone usually cannot recanalize.
- **CTA is the decision-maker** for early-window thrombectomy; **perfusion imaging (CTP/MR perfusion)** opens the 6–24 h window for wake-up and late-presenting strokes.
- Drives **prehospital triage and hospital networks**: "call ahead," stroke-code activation, and direct routing to thrombectomy-capable centers shorten door-to-groin times.
- **Door/onset-to-reperfusion time is the strongest modifiable outcome determinant** — every minute of delay reduces the odds of independence.
- Reinforces post-reperfusion secondary prevention from the same chapter: high-intensity statin (atorvastatin 80 mg / rosuvastatin 40 mg, LDL <70 mg/dL), apixaban for atrial fibrillation, dual antiplatelet for minor stroke/intracranial atherosclerosis, and carotid endarterectomy for significant ICA stenosis.

High-yield exam pointers

- Endovascular thrombectomy = definitive therapy for **LVO** (intracranial ICA, MCA M1–M2, basilar artery).
- Use as **alternative or adjunct** to IV thrombolysis — for the ineligible, contraindicated, or failed-recanalization patient.
- **Early window <6 h** on CTA; **extended window up to 24 h** requires favorable perfusion mismatch/collaterals.
- Landmark numbers: **OR 2.49 (CI 1.76–3.53)**; mRS 0–2 **46% vs 26.5%**; **DAWN 47% vs 13%** (≤24 h); **DEFUSE-3 45% vs 17%** (≤16 h).
- **Time targets:** good-outcome odds >3 if **groin puncture <2 h**; **>80%** good outcome if **vessel opened within 1 h** of ED arrival.
- **Bridging:** give **IV rtPA (0.9 mg/kg)** or **tenecteplase (0.25 mg/kg bolus)** first if eligible; TNK simplifies transfer.
- **Hyperdense MCA sign** is highly specific but only ~20% sensitive for MCA occlusion.
- Requires **comprehensive/thrombectomy-capable stroke centers** and organized regional systems of care.

SOURCE & COVERAGE

Harrison 22e — Ch 438 "Ischemic Stroke" (TREATMENT: Endovascular Revascularization; Intravenous Thrombolysis; Stroke Centers; Figs. 438-2 and 438-3; Table 438-1).

Coverage note: Harrison names only the **DAWN** and **DEFUSE-3** trials and the **Trevo** stent retriever; the six 2015 RCTs are described collectively (as a combined meta-analysis) and not individually named — the commonly examined names (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT) are standard but are NOT in this chapter. Procedural grading/selection metrics frequently quoted in exams — **mTICI 2b–3 reperfusion grade**, **ASPECTS ≥6**, and aspiration-vs-stent-retriever device choice — are universally accepted standard practice but are also NOT explicitly stated in the provided Harrison text and should be cited as general knowledge, not from this chapter.

◆ ◆ ◆

Dementia — causes and Alzheimer's vs frontotemporal dementia

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — **Dementia** is an *acquired*, usually progressive deterioration in two or more cognitive domains (episodic memory, language, visuospatial function, praxis, executive function, behaviour) of sufficient severity to impair the successful performance of activities of daily living, occurring in clear consciousness (distinguishing it from delirium). Although most cases are due to irreversible neurodegeneration (Alzheimer's disease [AD] accounts for 60–70%), a clinically vital subset is **potentially reversible or treatable** — in a study of 1000 consecutive memory-clinic patients, ~19% had a potentially reversible *cause* and a further ~23% had a reversible *contributing condition*. Because no single treatable aetiology is common, a structured screen is mandatory in every patient so that a treatable cause is never missed.

Reversible / potentially treatable causes of dementia

The three commonest potentially reversible diagnoses are **depression (pseudodementia), normal-pressure hydrocephalus (NPH), and alcohol dependence**; *medication side-effects* should be sought in every patient. A useful working classification (Harrison Table 31-1, "potentially reversible" entries):

Category	Specific reversible causes
Drugs & toxins	Sedative–hypnotics, benzodiazepines, opioids/analgesics, anticholinergics, antiepileptics (chronic intoxication); **alcohol dependence**; heavy-metal poisoning (lead, mercury, arsenic, manganese); organic toxins
Metabolic / endocrine / organ failure	**Hypothyroidism**; adrenal insufficiency and Cushing's syndrome; hypo- and hyperparathyroidism; chronic **renal failure** (uraemic encephalopathy); **hepatic failure**; pulmonary failure (hypoxia / CO_2 narcosis)
Nutritional deficiencies	**Thiamine (B1)** — Wernicke encephalopathy; **vitamin B12** — subacute combined degeneration; **niacin** — pellagra; elevated homocysteine / folate deficiency
Infections	**HIV** (HIV-associated neurocognitive disorder); **neurosyphilis**; progressive multifocal leukoencephalopathy (JC virus); tuberculous, fungal and protozoal CNS infection; **Whipple's disease**
Structural / neurosurgical	**Normal-pressure hydrocephalus**; chronic **subdural haematoma**; primary or metastatic **brain tumour**
Autoimmune / inflammatory	**Paraneoplastic and autoimmune limbic encephalitis** (anti-LGI1, NMDA-R, Caspr2, AMPA-R); CNS **vasculitis**; **neurosarcoidosis**; corticosteroid-responsive (Hashimoto) encephalopathy
Psychiatric	**Depression (pseudodementia)**; schizophrenia; conversion disorder
Miscellaneous	**Recurrent non-convulsive seizures**; acute intermittent porphyria

- A simple bedside aide-mémoire is **"DEMENTIAS"**: **D**rugs, **E**motional/depression, **M**etabolic-endocrine, **E**yes & ears (sensory deprivation) / **N**utritional, **T**umour/trauma (SDH, NPH), **I**nfection, **A**utoimmune, **S**eizures/structural — all map onto the categories above.

Approach to detect a reversible cause (investigations)

- **Routine (AAN-recommended) screen** in all: complete blood count; electrolytes, glucose, renal and liver function; **thyroid function (TSH)**; **serum vitamin B12**; and **structural neuroimaging (MRI or non-contrast CT)** to exclude tumour, subdural haematoma, infarcts, white-matter disease and NPH.
- **Selective / focused tests** driven by clues: serum RPR/VDRL and **HIV serology**; lumbar puncture (cells, protein, oligoclonal bands, autoimmune-encephalitis antibodies, AD biomarkers) when infection/inflammation or rapidly progressive dementia is suspected; urine toxin / heavy-metal screen; ESR, CRP, ANA; anti-thyroperoxidase/thyroglobulin antibodies; 24-h urine copper (Wilson); EEG (non-convulsive seizures, CJD periodic complexes).
- **NPH** is suggested by the triad of **gait apraxia ("magnetic" gait), urinary incontinence and dementia** with ventriculomegaly disproportionate to sulcal atrophy; objective gait improvement after high-volume (30–50 mL) CSF removal (tap test) predicts response to ventriculoperitoneal shunting (gait improves most; cognition least).
- **Treatment of the reversible component**: thyroxine for hypothyroidism; thiamine/B12 replacement and folate for elevated homocysteine; antiretrovirals for HIV and antimicrobials for opportunistic infection; CSF shunting for NPH; surgery/radiotherapy/chemotherapy for neoplasm; immunotherapy (steroids/IVIG/plasma exchange) for autoimmune encephalitis; and **withdrawal of cognition-impairing drugs**.

Differentiating Alzheimer's disease from frontotemporal dementia

Both are cortical neurodegenerative dementias and below age 65 FTD rivals AD as the commonest cause, so distinction is a frequent clinical problem. The two are separated on **age, presenting symptom, neuropsychological profile, behaviour, neurological signs, imaging, molecular pathology, genetics and drug response**:

Feature	Alzheimer's disease (AD)	Frontotemporal dementia (FTD)
Typical onset age	Most common >65 yr; rises with each decade (insidious)	Younger — **5th–7th decade**; ~30% present >65
First / presenting symptom	**Episodic memory loss** (recent memory) in ~75%	**Personality / behaviour change** (bvFTD) or progressive language failure (PPA); memory relatively spared
Cognitive (neuropsych) profile	Amnestic — impaired learning/delayed recall, then language, executive, **visuospatial** deficits	**Executive dysfunction and/or language**; *relative sparing of episodic memory and visuospatial/drawing skills*
Behaviour / neuropsychiatry	Early irritability, anxiety, depression; social graces preserved until late	Early **disinhibition, apathy, loss of empathy, compulsivity, hyperorality/overeating, loss of insight**
Core clinical syndromes	Typical amnestic AD; atypical — posterior cortical atrophy, logopenic aphasia, frontal/dysexecutive, corticobasal	**bvFTD** (commonest), **semantic-variant PPA**, **non-fluent/agrammatic PPA**; ± FTD-MND, CBS, PSP-RS

Feature	Alzheimer's disease (AD)	Frontotemporal dementia (FTD)
Motor / neurological signs	Normal early; myoclonus, rigidity, parkinsonism only late	Early **axial rigidity, vertical supranuclear gaze palsy, dystonia, alien limb, or motor-neuron disease**
Structural MRI	**Entorhinal + hippocampal (medial temporal) atrophy; posterior-predominant** cortical atrophy	**Frontal, insular and/or anterior temporal atrophy**; *posterior parietal lobe spared*
FDG-PET	Temporo-parietal hypometabolism; posterior cingulate / precuneus involvement	**Frontal and anterior temporal** hypometabolism
Molecular pathology	**Aβ neuritic plaques + neurofibrillary tangles** of hyperphosphorylated tau; amyloid/tau PET positive	**FTLD-tau** (e.g. Pick bodies) or **FTLD-TDP-43** (~90% combined); FTLD-FET ~10%; AD-tau PET ligands not reliably positive
Neurotransmitter deficit	**Cholinergic** loss (nucleus basalis of Meynert)	**Cholinergic system relatively spared**; serotonergic loss
Genetics	APP (chr 21), PSEN-1 (chr 14), PSEN-2 (chr 1) in <2%; **ApoE ε4 (chr 19)** susceptibility (1 allele ≈2–3×, 2 alleles ≈10–15× risk)	Autosomal dominant in 10–20%: **C9orf72 (chr 9), GRN (chr 17), MAPT (chr 17)**
Biofluid biomarkers	CSF/plasma: ↓Aβ42 (low Aβ42/Aβ40), ↑p-Tau181/217	No specific positive AD biomarker; AD biomarkers *negative* support FTLD
Drug response	**Cholinesterase inhibitors + memantine** give modest symptomatic benefit; anti-Aβ antibodies (lecanemab, donanemab) in early AD	**No disease-modifying or symptomatic cognitive drug**; cholinesterase inhibitors may worsen behaviour, memantine ineffective; SSRIs for behavioural symptoms
Course / survival	Symptomatic duration typically **8–10 yr** (range 1–25)	Median survival ~6 yr; **FTD-MND ~3 yr**

- **Practical discriminators for the exam**: an elderly patient who first *gets lost and forgets recent events*, with hippocampal atrophy and a positive amyloid scan → **AD**; a younger patient brought by family for *socially inappropriate behaviour, apathy, overeating and loss of empathy with preserved memory* and frontal atrophy → **FTD**. International consensus (Rascovsky) criteria for **bvFTD** require ≥3 of: early disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviour, hyperorality/dietary change, and a dysexecutive neuropsychological profile that *spares memory and visuospatial function*.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Two coronal-brain silhouettes side by side.** Label the *AD brain*: "Medial temporal / hippocampal + entorhinal atrophy", "Posterior-predominant (temporo-parietal) cortical atrophy", "Nucleus basalis of Meynert – cholinergic loss". Label the *FTD brain*: "Frontal + anterior temporal + insular atrophy", "Anterior cingulate / orbitofrontal involvement (salience network)", "Posterior parietal lobe SPARED".
- **A simple two-circle/branch chart of reversible causes** with the eight category headings as labels: Drugs/Toxins; Metabolic-Endocrine; Nutritional (B1/B12/Niacin); Infection (HIV, neurosyphilis, PML, Whipple); Structural (NPH, SDH, tumour); Autoimmune (limbic encephalitis, vasculitis, Hashimoto); Psychiatric (depression); Seizures/Porphyria — each annotated with its specific treatment.

Clinical / Diagnostic significance

- The whole point of enumerating reversible causes is **therapeutic**: even a screening test with a 1–2% yield is justified because the alternative is missing a curable dementia (e.g. B12 deficiency, hypothyroidism, NPH, neurosyphilis, autoimmune encephalitis).
- **Rapidly progressive dementia** (decline to dementia in <1 year) widens the differential to prion disease (CJD — cortical ribboning on DWI, periodic EEG complexes, RT-QuIC), autoimmune/paraneoplastic encephalitis and toxic-metabolic states — many of which are treatable, so it warrants aggressive CSF and antibody work-up.
- **Depression** must be actively screened for and treated (SSRI/SNRI) before labelling a patient as having irreversible dementia; conversely a true dementia may coexist with low mood.
- Misclassifying **FTD as AD** matters: cholinesterase inhibitors can aggravate FTD behaviour, anti-amyloid antibodies are inappropriate, the prognosis and genetic counselling (C9orf72, GRN, MAPT; possible MND) differ, and behavioural/psychosocial caregiver support is the mainstay.

High-yield exam pointers

- Dementia = acquired, progressive cognitive decline impairing ADLs **in clear consciousness** (vs delirium); **AD = 60–70%**, the commonest cause overall.
- **~19% of memory-clinic patients have a potentially reversible cause**; commonest reversible trio = **depression, NPH, alcohol** + drug side-effects.
- Routine reversible-cause screen: **TSH, B12, CBC, metabolic panel, MRI/CT** (± RPR/VDRL, HIV, LP).
- **NPH triad** = magnetic gait + urinary incontinence + dementia; CSF tap test predicts shunt response (gait improves most).
- AD = **memory-first, hippocampal/posterior atrophy, amyloid + tau pathology, cholinergic loss, ApoE ε4**; FTD = **behaviour/language-first, frontotemporal atrophy, tau or TDP-43 pathology, cholinergic sparing, C9orf72/GRN/MAPT**.
- FTD **spares episodic memory and visuospatial skills early**; AD spares motor and behaviour/social graces early.

- **Cholinesterase inhibitors + memantine** help AD; they are **ineffective or harmful in FTD** (no cognition-modifying drug).
- FTD presents younger (5th–7th decade) and below 65 **rivals AD** in frequency.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Dementia" (differential diagnosis / Table 31-1 reversible causes, evaluation, treatment), "Alzheimer's Disease" (clinical features, pathology, genetics, biomarkers, therapy), "Frontotemporal Dementia" (clinical syndromes, FTLD pathology, genetics).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Alzheimer Disease and Other Dementias" (bvFTD/PPA clinical variants, Rascovsky International Consensus Criteria for bvFTD, FTD subtype anatomy and pathology, reversible memory-clinic data).
- **CMDT 2026** — "Nervous System Disorders" (dementia evaluation, normal-pressure hydrocephalus, rapidly progressive dementia work-up, cholinesterase-inhibitor and memantine regimens, anti-amyloid therapy, FTD drug cautions).

◆ ◆ ◆

Epilepsy syndromes

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — A *seizure* is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain, while *epilepsy* is an enduring predisposition to recurrent unprovoked seizures. An **epilepsy syndrome** is a distinctive cluster of clinical and electroencephalographic features — characteristic seizure type(s), age of onset, EEG signature, triggers, imaging, comorbidities and often a predictable prognosis — that occur together and suggest a common underlying mechanism. Recognising the syndrome (rather than just the seizure type) directs the choice of antiseizure medication (ASM), predicts outcome, identifies surgical candidates and guides genetic counselling.

The diagnostic framework: ILAE 2014 definition and the 2017 three-level scheme

- **ILAE 2014 definition of epilepsy** (any one of): (1) **≥2 unprovoked (or reflex) seizures >24 h apart**; (2) **one unprovoked seizure with a ≥60% recurrence risk over the next 10 years**; or (3) **diagnosis of an epilepsy syndrome**.
- The **2017 ILAE classification** is built in **three sequential levels**, with **etiology and comorbidities considered at every level**:
- **Seizure type** — focal onset / generalized onset / unknown onset (the older "partial" is replaced by *focal*; "simple/complex partial" replaced by *focal aware* / *focal impaired awareness*; secondary generalization renamed *focal to bilateral tonic-clonic*).
- **Epilepsy type** — focal / generalized / **combined generalized and focal** / unknown.
- **Epilepsy syndrome** — assigned when features fit a recognised constellation (not achievable in every patient).

- **Six etiologic categories** run in parallel (a patient may have >1): **structural, genetic, infectious, metabolic, immune, unknown**.

Epilepsy syndromes grouped by age of onset (overview)

Age band	Representative syndromes	Hallmark
Neonatal	Self-limited (benign) familial neonatal epilepsy; Early myoclonic encephalopathy; **Ohtahara syndrome**	KCNQ2/3 channelopathy; **burst-suppression** EEG
Infancy	**West syndrome**; **Dravet syndrome**; Myoclonic-atonic (Doose)	Hypsarrhythmia; SCN1A febrile status
Childhood	**Childhood absence epilepsy (CAE)**; Self-limited epilepsy with centrotemporal spikes (**SeLECTS/BECTS**); Panayiotopoulos; **Lennox-Gastaut**; Landau-Kleffner/CSWS	3-Hz spike-wave; centrotemporal spikes
Adolescence/ adult	**Juvenile absence epilepsy (JAE)**; **Juvenile myoclonic epilepsy (JME)**; Epilepsy with GTCS alone; ADEAF; **mesial temporal lobe epilepsy**	Polyspike-wave; auditory aura; hippocampal sclerosis

Idiopathic (genetic) generalized epilepsies — the "big four"

These are normal-development, normal-MRI, presumed-polygenic generalized epilepsies; **sleep deprivation** is a universal precipitant and **sodium-channel ASMs (carbamazepine, oxcarbazepine, phenytoin) and gabapentinoids can aggravate seizures**.

- **Childhood absence epilepsy (CAE / *pyknolepsy*):** onset **4–10 yr** (peak 5–7); many brief (<15 s) **typical absences** daily, provoked by **hyperventilation**; EEG = **generalized, symmetric 3-Hz spike-and-wave** on normal background. **Ethosuximide is the drug of choice** for pure absence (ethosuximide and valproate superior to lamotrigine in the comparative CAE trial). Excellent prognosis; a minority evolve to JME.
- **Juvenile absence epilepsy:** onset in the **2nd decade**, fewer absences than CAE, **majority also have GTCS**, greater tendency to persist into adulthood.
- **Juvenile myoclonic epilepsy (JME / *Janz syndrome / impulsive petit mal*):** onset **12–18 yr**; defining seizure = **bilateral myoclonic jerks on awakening**, provoked by sleep deprivation and alcohol; ~90% develop **GTCS** and ~**one-third have absences**; EEG = **4–6 Hz generalized polyspike-and-wave**. **Valproate is most effective** (limited in women of child-bearing age by teratogenicity; levetiracetam/lamotrigine alternatives); usually a **lifelong** condition needing long-term therapy.
- **Epilepsy with GTCS alone** (incl. "grand mal on awakening") — generally good response to broad-spectrum ASMs.

Developmental and epileptic encephalopathies (DEEs)

Here the epileptiform activity itself drives cognitive/developmental regression beyond the underlying cause.

- **West syndrome:** peak onset **3–7 months**; clinical **triad — epileptic (infantile) spasms in clusters + hypsarrhythmia on EEG + arrest/regression of psychomotor development**. Two-thirds have

an identifiable brain lesion. Treatment differs from other epilepsies: **ACTH/corticosteroids**, and **vigabatrin (drug of choice in tuberous sclerosis complex)**.

- **Ohtahara syndrome / early myoclonic encephalopathy:** neonatal onset, **burst-suppression** EEG, refractory seizures, poor prognosis; may evolve into West syndrome.
- **Dravet syndrome (severe myoclonic epilepsy of infancy): de novo *SCN1A* mutation in ~80–95%**; previously normal infant presents with **febrile status epilepticus around 6 months**, later myoclonic, absence, atonic and focal seizures; drug-resistant with developmental decline. **Avoid sodium-channel blockers (carbamazepine, lamotrigine, phenytoin) — they aggravate seizures**; use **valproate, clobazam, stiripentol, cannabidiol and fenfluramine**.
- **Lennox-Gastaut syndrome (LGS):** onset **3–10 yr**; **triad** — (1) **multiple seizure types** (generalized tonic, atonic/drop attacks, atypical absence ± GTCS); (2) EEG with **slow (<2.5 Hz) spike-and-wave** in wakefulness and **bursts of ~10-Hz paroxysmal fast activity in sleep**; (3) **cognitive impairment/developmental delay**. Drug-resistant; may evolve from West syndrome. Options: **valproate, lamotrigine, rufinamide, topiramate, clobazam, felbamate, cannabidiol**; neurostimulation under investigation.
- **Landau-Kleffner syndrome (acquired epileptic aphasia) and CSWS: verbal auditory agnosia/language regression** with **continuous spike-and-wave during slow-wave sleep**; seizures often mild; benefit from valproate, benzodiazepines, **steroids/IVIG**, and **multiple subpial transection**.

Focal epilepsy syndromes

- **Self-limited epilepsy with centrotemporal spikes (SeLECTS / BECTS / benign rolandic epilepsy):** the **commonest idiopathic focal epilepsy of childhood** (3–13 yr, peak 5–8); **nocturnal hemifacial sensorimotor seizures with hypersalivation/speech arrest**, preserved awareness; EEG = **high-voltage centrotemporal sharp waves activated by sleep**; **spontaneous remission at puberty** — treatment often unnecessary.
- **Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS):** the **commonest cause of focal seizures with impaired awareness** and the **prototypical surgically-remediable epilepsy**. History of **antecedent (often complex) febrile seizures (up to 80%)**; seizures begin with an **aura** (rising epigastric sensation, *déjà vu*, fear), then **behavioural arrest/stare, oroalimentary and manual automatisms, contralateral dystonic posturing**, and postictal **dysphasia** (dominant focus) and disorientation. **MRI: small hippocampus with increased T2 signal and loss of internal architecture, enlarged temporal horn**; **interictal PET hypometabolism, ictal SPECT hyperperfusion**; pathology = **neuronal loss/gliosis in CA1 and CA3 with sparing of CA2**. Frequently drug-resistant → **anterior temporal lobectomy / selective amygdalohippocampectomy renders 60–80% seizure-free**.
- **ADEAF (autosomal dominant epilepsy with auditory features):** lateral temporal focal epilepsy with **auditory aura/aphasic seizures**, due to **LGI1** mutation.
- **Rasmussen syndrome:** progressive unilateral hemispheric epilepsy with **epilepsia partialis continua, hemiatrophy, hemiparesis and cognitive decline**; suspected **autoimmune** (anti-GluR3); often requires **functional hemispherectomy**.

Genetic basis and progressive myoclonus epilepsies

Gene	Syndrome
KCNQ2 / KCNQ3	Self-limited familial neonatal epilepsy
SCN1A	Dravet syndrome; GEFS+
CHRNA4 / CHRNB2	Sleep-related hypermotor epilepsy (ADNFLE)
LGI1	ADEAF (lateral TLE)
DEPDC5	Familial focal epilepsy with variable foci
GRIN2A	BECTS–Landau-Kleffner spectrum
CDKL5	CDKL5 deficiency disorder (responds to **ganaxolone**)
SLC2A1 (GLUT1)	GLUT1 deficiency — absence onset <4 yr ± paroxysmal exertional dyskinesia (**ketogenic diet**)
CSTB	Unverricht-Lundborg disease (PME)
EPM2A (laforin) / NHLRC1 (malin)	Lafora disease (PME)

- **Progressive myoclonus epilepsies (PME):** myoclonus + GTCS + progressive ataxia/dementia. Examples — **Unverricht-Lundborg** (CSTB; *avoid phenytoin*, which aggravates ataxia), **Lafora disease** (polyglucosan Lafora bodies; fatal in 2–10 yr), **MERRF** (mitochondrial, ragged red fibres). **Valproate is the drug of choice**; perampanel helps myoclonus.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **EEG signatures of generalized epilepsy syndromes** (three stacked tracings): (1) **Hypsarrhythmia** — chaotic, high-voltage disorganized slow waves with multifocal spikes/sharp waves and periods of attenuation (label: *West syndrome*); (2) **Generalized symmetric 3-Hz spike-and-wave** on normal background (label: *Childhood absence epilepsy*); (3) **Slow <2.5-Hz spike-and-wave + bursts of ~10-Hz paroxysmal fast activity in sleep** (label: *Lennox-Gastaut syndrome*).
- **Coronal T2 MRI of hippocampal sclerosis (MTLE):** labels — *small/atrophic hippocampus*, *increased T2 signal*, *loss of internal (trilaminar) architecture*, *enlarged temporal horn*, *normal contralateral hippocampus*.

Clinical / Diagnostic significance

- **Syndromic diagnosis dictates drug choice:** sodium-channel ASMs and gabapentinoids **aggravate** generalized/absence/myoclonic seizures and **Dravet** — use broad-spectrum agents (valproate, levetiracetam, lamotrigine for selected, topiramate).
- **Precision/targeted therapy: vigabatrin** for West syndrome in tuberous sclerosis; **ketogenic diet** for GLUT1 deficiency; **ganaxolone** for CDKL5 deficiency; **stiripentol/fenfluramine/cannabidiol** for Dravet; **ACTH/steroids** for infantile spasms.
- **Surgical candidacy:** MTLE-HS, lesional focal epilepsies and Rasmussen syndrome should be referred early for resective surgery/hemispherectomy when drug-resistant.

- **Workup:** detailed seizure semiology + witness account, **video-EEG with activation (hyperventilation, photic stimulation, sleep/sleep deprivation)**, high-resolution **MRI epilepsy protocol**, and **interictal PET / ictal SPECT** for presurgical localisation; autoantibody testing when onset is fulminant with psychiatric/cognitive change.
- **Prognostic stratification:** self-limited syndromes (CAE, SeLECTS) remit spontaneously, whereas DEEs (West, Dravet, LGS) carry high cognitive morbidity.

High-yield exam pointers

- **Epilepsy = ≥2 unprovoked seizures >24 h apart, OR 1 seizure with ≥60% recurrence risk, OR an epilepsy syndrome** (ILAE 2014).
- **2017 ILAE: three levels** — seizure type → epilepsy type → syndrome, with **six etiologies** (structural, genetic, infectious, metabolic, immune, unknown).
- **West triad** = infantile spasms + **hypsarrhythmia** + psychomotor arrest; **LGS triad** = multiple seizure types + **slow (<2.5 Hz) spike-wave** + cognitive impairment.
- **CAE → 3-Hz spike-wave, ethosuximide DOC; JME → 4–6 Hz polyspike-wave, valproate DOC, jerks on awakening.**
- **Dravet = SCN1A (~80–95% de novo), febrile status at ~6 months — never give sodium-channel blockers.**
- **MTLE-HS:** antecedent febrile seizures, epigastric aura/*déjà vu*, automatisms; MRI hippocampal sclerosis; **CA1/CA3 loss, CA2 sparing**; surgery cures 60–80%.
- **SeLECTS/BECTS:** commonest benign childhood focal epilepsy, nocturnal facial seizures, centrotemporal spikes, remits at puberty.
- **PME** (Unverricht-Lundborg = CSTB; Lafora = EPM2A/NHLRC1) — myoclonus + GTCS + dementia; **valproate**, avoid phenytoin.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Seizures and Epilepsy"** (ILAE 2017 seizure classification, JME/Lennox-Gastaut/MTLE syndromes, gene table, ASM mechanisms).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e — "Epilepsies"** (ILAE 2014 definition and 2017 three-level classification; detailed syndrome descriptions — neonatal/infantile/childhood/juvenile syndromes, DEEs, MTLE-HS, PME).
- **CMDT 2026 — "Nervous System Disorders" (Seizures & Epilepsy; Table 27-2 approved indications by syndrome)** for current syndrome-specific drug choices (ethosuximide/valproate/clonazepam for absence, vigabatrin for infantile spasms, cannabidiol for Dravet/LGS, ganaxolone for CDKL5).

◆ ◆ ◆

Horner's syndrome

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

Definition / Introduction — Horner's syndrome (*oculosympathetic palsy/paresis*) is the clinical triad of ipsilateral **ptosis, miosis and facial anhidrosis** resulting from interruption of the sympathetic supply to the eye and face anywhere along its three-neuron pathway, from the hypothalamus to the orbit. Anhidrosis is an *inconstant* feature that depends on the level of the lesion. Clinically its importance is not the eye signs themselves (which are benign) but its value as a **localizing sign**, since the causes range from idiopathic to immediately dangerous (internal carotid dissection, Pancoast tumour). When facial sweating is spared the term *oculosympathetic paresis* is often used interchangeably.

Anatomy of the oculosympathetic pathway (three neurons)

- **First-order (central) neuron** — arises in the **posterolateral hypothalamus**, descends through the **dorsolateral brainstem** and lateral column of the cord, and synapses in the **ciliospinal center of Budge**, the intermediolateral grey column at **C8–T2**.
- **Second-order (preganglionic) neuron** — exits via the ventral roots/white rami communicantes, arches **over the lung apex** and **beneath the subclavian artery**, ascends the cervical sympathetic chain, and synapses in the **superior cervical ganglion** at the **carotid bifurcation** (angle of the jaw). *Sudomotor fibres for facial sweating branch off here to follow the external carotid artery.*
- **Third-order (postganglionic) neuron** — ascends as the **pericarotid plexus** on the **internal carotid artery**, traverses the **cavernous sinus** (briefly joining CN VI), then joins the **nasociliary branch of V1**, and reaches the iris via the **long ciliary nerves**.
- **Effectors** — *dilator pupillae* (mydriasis), **Müller's muscle** (superior tarsal, upper lid), inferior tarsal muscle (lower lid), and facial sweat glands/vasomotor tone.

Clinical features

- **Ptosis** — mild, only **1–3 mm**, from denervation of Müller's (superior tarsal) muscle; *never* as complete as a CN III palsy; may fluctuate and worsen with fatigue.
- **Inverse ("upside-down") ptosis** — the lower lid is *elevated* 1–2 mm (loss of the inferior tarsal muscle), narrowing the palpebral fissure and producing **apparent enophthalmos** — an optical illusion; true globe position is normal.
- **Miosis** — small pupil that reacts **normally to light and near**; the **anisocoria is greater in the dark** (small pupil is the abnormal one).
- **Dilation lag** — the affected pupil dilates *slowly* when the lights are dimmed; anisocoria is more pronounced at **4–5 s** than at **10–12 s** after lights-out — a hallmark sign.
- **Anhidrosis** — ipsilateral facial; present **only with first-/second-order (preganglionic)** lesions. Absent in **postganglionic (third-order)** lesions (sudomotor fibres have already branched with the external carotid), except possibly a small medial-forehead patch.
- **Other** — conjunctival/facial vasodilation, ocular hypotony, loss of the **ciliospinal reflex**; *congenital* Horner causes **heterochromia iridis** (a paler iris on the affected side) and facial trophic changes.

Localization by neuron order and representative causes

Order	Anatomical site	Anhidrosis	Representative causes
First-order (central)	Hypothalamus → brainstem → C8–T2	Possible (ipsilateral, extensive)	**Wallenberg** (lateral medullary) syndrome, brainstem stroke/tumour, syringobulbia, multiple sclerosis, hypothalamic lesions
Second-order (preganglionic)	C8–T2 → superior cervical ganglion	**Present** (facial)	**Pancoast** (apical lung) tumour, lower brachial plexus avulsion, cervical rib, thyroid/neck surgery or trauma, mediastinal mass, aortic/subclavian aneurysm, **syringomyelia**, C8/T1 root lesion
Third-order (postganglionic)	SCG → carotid → cavernous sinus → orbit	**Absent** (maybe medial forehead)	**Internal carotid dissection/thrombosis** (painful Horner), cavernous sinus disease, **cluster headache**, **Raeder paratrigeminal syndrome**, otitis media/petrositis, nasopharyngeal/skull-base tumour

Pharmacological testing (confirmation + localization)

A two-step approach; confirmatory and localizing drops must be **≥24 h apart**.

Drop	Mechanism	Result	Interpretation
Cocaine 2–10%	Blocks noradrenaline reuptake at the sympathetic terminal	Normal pupil **dilates**; Horner pupil **fails to dilate**	**Confirms** Horner (any order); does *not* localize. (Controlled substance; urine toxicology positive ~2 days.)
Apraclonidine 0.5%	Weak α1-agonist acting on the supersensitive denervated dilator	**Reversal of anisocoria** — Horner pupil **dilates** (denervation supersensitivity) + ptosis improves; normal pupil unchanged/slightly constricts	**Confirms** Horner; convenient cocaine substitute. May be **falsely negative very acutely** (supersensitivity takes ~36 h–days to develop).
Hydroxyamphetamine 1%	Releases stored noradrenaline from an *intact* third-order terminal	**Dilates** in first-/second-order Horner; **fails to dilate** in third-order Horner	**Localizes** preganglionic vs postganglionic.

Differential diagnosis / mimics

- **Physiologic (simple) anisocoria** — equal in light and dark, ≤0.5 mm; *pseudo-Horner* = physiologic anisocoria with an incidental ptosis (e.g., levator dehiscence).
- **Anisocoria greater in dark** → the *small* pupil is abnormal (Horner); **greater in light** → the *large* pupil is abnormal (CN III palsy, **Adie tonic pupil**, pharmacologic mydriasis).
- **Ptosis** — distinguish from CN III palsy (larger/normal pupil + ophthalmoparesis), myasthenia (fatigable, *Cogan lid twitch*), aponeurotic/senile and mechanical ptosis.
- **Reverse Horner (Pourfour du Petit syndrome)** — sympathetic *overactivity*: mydriasis, lid retraction, facial flushing/hyperhidrosis (early irritative lesions).
- **Harlequin syndrome** — unilateral facial anhidrosis with contralateral flushing/sweating on exertion/heat; usually no eye signs (may coexist with Horner).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Three-neuron oculosympathetic pathway** — label: *hypothalamus → dorsolateral brainstem → ciliospinal center of Budge (C8–T2) → ventral root → lung apex → subclavian artery → cervical sympathetic chain → superior cervical ganglion (carotid bifurcation) → internal carotid / pericarotid plexus → cavernous sinus (CN VI) → nasociliary branch of V1 → long ciliary nerves → dilator pupillae & Müller's muscle*; mark the **branch point of sudomotor fibres onto the external carotid**.
- **Face of a left Horner's** — label: *upper-lid ptosis, elevated lower lid (inverse ptosis), miosis, apparent enophthalmos, ipsilateral facial anhidrosis*.

Clinical / Diagnostic significance

- **Acute painful Horner** (especially after neck pain, trauma or chiropractic manipulation) → suspect **internal carotid dissection**; urgent MRI/MRA (axial fat-saturated T1 shows a crescentic mural haematoma); treat with **antiplatelet (aspirin)** to prevent embolic stroke.
- **Preganglionic Horner in a smoker** → search for a **Pancoast / apical lung tumour** (CXR/CT chest); look for C8–T1 pain and wasting of hand intrinsics.
- **Isolated Horner** — imaging the entire pathway finds a cause in only **~20%**; the workup is **directed by localization** — preganglionic → brain + cervical/upper-thoracic spine MRI + chest imaging; postganglionic → brain MRI + head-and-neck MRA.
- **Children** — most cases are congenital, but exclude **neuroblastoma**: neuroimaging + **urinary catecholamines (VMA/HVA)**; heterochromia favours a congenital/long-standing lesion.
- **Wallenberg syndrome** — Horner is one component (with crossed sensory loss, ipsilateral ataxia, vertigo, dysphagia).

High-yield exam pointers

- Triad = **ptosis + miosis + anhidrosis** (oculosympathetic palsy); anhidrosis is *inconstant*.
- **Anisocoria greater in the dark + dilation lag** = the clinical hallmark.
- Müller's (superior tarsal) muscle → **mild** ptosis; levator (CN III) → **severe** ptosis.
- **Cocaine / apraclonidine confirm; hydroxyamphetamine localizes** (dilates in pre-, fails in postganglionic).
- **Apraclonidine reverses the anisocoria** via denervation supersensitivity — now replaces cocaine.
- **Anhidrosis present = preganglionic (1st/2nd order); absent = postganglionic (3rd order).**
- **Painful Horner = carotid dissection until proven otherwise.**
- **Congenital Horner → heterochromia iridis**; in a child, rule out **neuroblastoma**.
- *Pourfour du Petit* = reverse Horner; *Raeder paratrigeminal* = postganglionic Horner + V1 facial pain.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine 22e — "Disorders of the Eye" and "Disorders of the Autonomic Nervous System"; Bradley & Daroff's Neurology in Clinical Practice — "Pupillary and Eyelid Abnormalities"; DeJong's The Neurologic Examination — "The Ocular Motor Nerves"; Brazis — Localization in Clinical Neurology — "Localization of Lesions Affecting the Ocular Motor System" and "Localization of Lesions in the Autonomic Nervous System"; Raeder paratrigeminal syndrome from DeJong/Brazis "Trigeminal Nerve."

Coverage note: Harrison treats Horner's only briefly (a few lines in the eye and autonomic chapters). The deep three-neuron localization scheme, pharmacologic-testing logic, dilation-lag timing and eponyms (Budge, Pourfour du Petit, Raeder, Harlequin) are drawn from the dedicated neurology texts (Bradley, DeJong, Brazis) as directed by the spec. CMDT has no dedicated section and was not used.

◆ ◆ ◆

Hyperkinetic movement disorders

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Hyperkinetic movement disorders are characterised by **excessive, involuntary movements that are unaccompanied by weakness**. They contrast with the hypokinetic (akinetic-rigid) disorders such as Parkinson's disease. The term is partly arbitrary — hypokinetic PD often has tremor, while hyperkinetic dystonia may restrict movement — but it remains useful by convention. Most arise from dysfunction of the **basal ganglia–thalamo-cortical circuits**. The major phenotypes are tremor, dystonia, athetosis, chorea/ballism, myoclonus and tics; precise phenomenological recognition is the key to diagnosis.

Classification by phenomenology (Harrison Table 447-1)

Disorder	Defining phenomenology
Tremor	Rhythmic oscillation of a body part from intermittent agonist–antagonist contraction
Dystonia	Involuntary, patterned, sustained/repeated contractions → twisting movements & abnormal postures
Athetosis	Slow, distal, writhing involuntary movements (a form of dystonia *"without fixed position"*)
Chorea	Rapid, semi-purposeful, graceful, dance-like, **non-patterned** movements; large-amplitude proximal form = **ballism**
Myoclonus	Sudden, brief (<100 ms), jerk-like, arrhythmic muscle twitches
Tic	Brief, repeated, stereotyped contractions, transiently **suppressible** with premonitory urge

- Speed/rhythmicity spectrum (DeJong): tremor & palatal myoclonus are *regular/predictable*; dystonia, athetosis, tics, myorhythmia are *intermediate*; chorea, ballism, myoclonus are *unpredictable*.

Tremor and Essential Tremor

- **Tremor** is classified along two axes (MDS): **Axis 1** = clinical/historical features (age, family history, distribution, frequency, activation, associated signs); **Axis 2** = aetiology (genetic, secondary, idiopathic).
- Activation types: **rest** (PD), **postural**, **kinetic/intention** (cerebellar, with past-pointing & hypotonia), **action**. *Enhanced physiologic tremor* (≤10% of population) — fine 10–12 Hz, with thyrotoxicosis, anxiety, valproate, lithium, caffeine, alcohol withdrawal.
- **Essential tremor (ET)** — the **commonest movement disorder** (~1% of population, ~5% of those >60). High-frequency (**6–10 Hz**) **postural & action** tremor, bilateral, predominantly upper limbs; involves **head ~30%, voice ~20%, tongue ~20%, jaw ~10%, legs ~10%**. Classically **improved by alcohol**, worsened by stress; large (not micro-) handwriting. ~50% are autosomal dominant; *NOTCH2NLC* GGC-repeat expansion associated, no confirmed causative gene.
- **Treatment (Harrison/CMDT):** reassurance if mild. **Propranolol** 20–120 mg/day (CMDT up to 240 mg) and **primidone** (start 12.5–50 mg, titrate to 125–250 mg) — each effective in ~50%. Second-line: topiramate, gabapentin, alprazolam. Botulinum toxin for limb/voice tremor. Drug-resistant cases: **VIM-thalamic DBS** or **MRI-guided focused ultrasound thalamotomy**.

Dystonia

- **Sustained/intermittent co-contraction of agonist & antagonist muscles** producing patterned, twisting movements/postures; relieved by a **sensory trick (*geste antagoniste*)**; aggravated by stress/fatigue. *Dystonic tremor* occurs **in the direction of the pull** and disappears when the part is moved opposite — this distinguishes it from ET.
- **Distribution:** focal → segmental → multifocal → hemidystonia → generalised. Adult-onset **focal** dystonia is commonest (women 2:1; writer's cramp exceptionally commoner in men), presenting in the 4th–6th decade.
- **Focal phenotypes: cervical dystonia/torticollis** (~40%, also latero-/antero-/retrocollis), **blepharospasm** (~15%), **oromandibular** (+blepharospasm = ***Meige's/Brueghel syndrome***), **spasmodic dysphonia** (adductor), **limb/task-specific** (writer's cramp, musician's cramp, the *yips*).
- **Genetics (DYT prefix; >200 genes):** ***DYT-TOR1A*** (3-bp deletion, *Ashkenazi-Jewish* founder) — commonest early-onset generalised; ***KMT2B*** (~10% early-onset generalised); *THAP1*; *GNAL*, *ANO3* (adult cranio-cervical).
- **Combined dystonias:** ***Dopa-responsive dystonia (Segawa)*** — *GCH1* (GTP cyclohydrolase-1), childhood onset with **diurnal fluctuation** and a **dramatic, sustained response to low-dose levodopa** without dyskinesia (test all childhood dystonias with levodopa); ***X-linked dystonia-parkinsonism (Lubag)*** — *TAF1*, Filipino; ***myoclonus-dystonia*** — *SGCE* (alcohol-responsive, **paternal/maternal-imprinting** inheritance).

- **Treatment:** withdraw precipitants; **levodopa trial** in all childhood-onset dystonia; high-dose **trihexyphenidyl** (20–120 mg/day, tolerated mainly in children); baclofen (oral/intrathecal); **tetrabenazine** (start 12.5 mg, 25–75 mg/day). **Botulinum toxin is preferred for focal/segmental dystonia** (blepharospasm, torticollis, dysphonia). Severe generalised disease → **GPi DBS** (best in *DYT-TOR1A*). *Dystonic storm* — generalised contractions with laryngeal involvement, rhabdomyolysis & renal failure — is a medical emergency requiring ICU/airway protection.

Choreas, Ballism and Athetosis

- **Chorea** — rapid, non-patterned, flowing involuntary movements; *parakinesia* (movement camouflaged into a purposeful act), **motor impersistence** (*"milkmaid grip"*, *darting/flycatcher/trombone tongue*) and hung-up reflexes are signs.
- ***Huntington's disease (HD)*** — autosomal dominant, fully penetrant; **CAG (polyglutamine) repeat >40** in the *Huntingtin* gene on **chromosome 4p** (36–39 = reduced penetrance). Onset 25–45 y; prevalence 2–8/100,000; chorea + dysarthria + oculomotor abnormality + behavioural change/depression/psychosis + **dementia**. **Anticipation** (paternal transmission). ~10% present as the akinetic-rigid juvenile ***Westphal variant***. MRI: **caudate-head & putaminal atrophy** (boxcar ventricles); intraneuronal ubiquitin/huntingtin inclusions. **Treatment:** symptomatic only — **tetrabenazine, deutetrabenazine (Austedo), valbenazine** (VMAT-2 inhibitors) for chorea; atypical antipsychotics (clozapine, quetiapine, risperidone) for psychosis; antidepressants; genetic counselling mandatory.
- **HD-like (HDL):** HDL-1 (*PRNP*, a prion disease), HDL-2 (*JPH3*, mostly African descent, acanthocytosis), HDL-4 (*TBP* = **SCA17**).
- **Other choreas:** ***Sydenham's chorea*** (*St. Vitus' dance*) — post group-A streptococcal **autoimmune** chorea, girls 5–15 y, self-limited (treat with valproate/carbamazepine/dopamine blockers); **chorea gravidarum**; **SLE** is the commonest systemic cause; also thyrotoxicosis, anti-NMDA-receptor/paraneoplastic (anti-Hu, anti-CRMP-5) encephalitis, hyper-/hypoglycaemia. **Chorea-acanthocytosis (neuroacanthocytosis)** — AR, *VPS13A/chorein*; **McLeod syndrome** — X-linked, Kell antigen. Levodopa-induced dyskinesia is the commonest iatrogenic chorea.
- **Ballism / hemiballismus** — wild, large-amplitude, flinging **proximal** movements; classic lesion of the **contralateral subthalamic nucleus** (infarct/haemorrhage), though 30–40% involve putamen/thalamus/parietal cortex; **non-ketotic hyperglycaemia** is a key reversible cause. Usually self-limiting; responds to dopamine blockers; refractory cases → GPi DBS/pallidotomy.
- **Athetosis** — slow distal writhing (*"without fixed position"*); usually congenital (perinatal basal-ganglia injury, *status marmoratus*, athetoid cerebral palsy); blends with chorea (**choreoathetosis**) and dystonia. *Pseudoathetosis* = sensory (deafferentation) athetosis, worse with eyes closed.

Tics, Tourette Syndrome and Myoclonus

- **Tics** — simple/complex **motor** (blink, jerk, echopraxia) or **phonic** (grunt, *echolalia*, *palilalia*, *coprolalia*); suppressible with a building premonitory urge, exacerbated by stress, abate in sleep.
- ***Tourette's syndrome*** — male-predominant; **multiple motor + ≥1 phonic tic**, onset 2–15 y (mean 7), often improves in adulthood; comorbid **ADHD & OCD**. High heritability. **Treatment:** education first; α-agonists **clonidine / guanfacine** (0.5–2 mg/day); atypical then typical

neuroleptics (risperidone, aripiprazole; haloperidol, pimozide); tetrabenazine; botulinum toxin for focal tics.

- **Myoclonus** — brief (<100 ms) shock-like jerks; **positive** (jerk) vs **negative** (*asterixis*); focal/segmental/generalised; by site cortical, subcortical, brainstem or spinal. Causes: physiologic (hypnic jerks, hiccup), post-anoxic action myoclonus (***Lance-Adams syndrome***), uraemic/hepatic encephalopathy, CJD; **progressive myoclonic epilepsies** — *Unverricht-Lundborg* (EPM1) and *Lafora-body* (EPM2A/NHLRC1). **Palatal myoclonus** = lesion in the **Guillain–Mollaret triangle** (inferior olive → dentate → red nucleus), may persist in sleep, causes an audible ear click. **Treatment:** valproate, levetiracetam, clonazepam, piracetam, primidone; **5-hydroxytryptophan + carbidopa** for post-anoxic myoclonus.

Drug-induced and other syndromes

- **Drug-induced (dopamine-receptor blockers — neuroleptics, metoclopramide, prochlorperazine): acute** dystonic reaction (minutes–hours; treat with parenteral anticholinergic/diphenhydramine); **subacute akathisia** (restlessness relieved by movement, within 2 weeks); **tardive syndromes** (months–years) — **tardive dyskinesia** (oro-bucco-lingual chorea), tardive dystonia. FDA warns against metoclopramide >12 weeks. Treat TD with **valbenazine 80 mg/day** or deutetrabenazine; avoid abrupt withdrawal. **Neuroleptic malignant syndrome** (rigidity, hyperthermia, autonomic instability, ↑CK) and **serotonin syndrome** (myoclonus prominent) are emergencies.
- **Paroxysmal dyskinesias: PKD** (movement-triggered; *PRRT2*; responds to carbamazepine/phenytoin), **PNKD** (alcohol/caffeine/stress-triggered; *PNKD* gene; clonazepam), **PED** (exercise-induced; *SLC2A1*/GLUT1 deficiency; ketogenic diet).
- **Restless legs syndrome** — 4 core criteria (**Urge** to move + **R**est worsens + **G**ets better with movement + **E**vening/night predominance); associated with **iron/ferritin deficiency**, pregnancy, uraemia; periodic limb movements of sleep; treat with iron repletion and low-dose dopamine agonists (pramipexole, ropinirole, rotigotine) — beware **augmentation**; α2δ ligands (gabapentin) alternative.
- **Combined (parkinsonism + hyperkinesia): Wilson's disease** (*ATP7B*; **Kayser-Fleischer rings** in Descemet's membrane, **wing-beating tremor**, low ceruloplasmin, treat with penicillamine/trientine/zinc/tetrathiomolybdate) — exclude in any young dystonia/chorea; **NBIA/PKAN** (*PANK2*, *"eye-of-the-tiger"* sign on MRI).
- **Functional (psychogenic) movement disorder** — commonest is functional tremor; clues are **variability, distractibility, entrainment**, incongruent phenotype; managed with explanation, CBT and physiotherapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Basal-ganglia direct/indirect pathway schematic** — label: *Cortex, Striatum (caudate + putamen), GPe, GPi, Subthalamic nucleus (STN), Substantia nigra (SNc/SNr), Thalamus, VIM nucleus*; arrows for direct (D1, facilitatory) and indirect (D2, inhibitory) pathways; mark the **STN lesion → hemiballismus** site.
- **Phenomenology comparison panel** — three labelled sketches: *Chorea (random, flowing, distal)*, *Dystonia (sustained twisting posture, e.g. torticollis with geste antagoniste)*, *Hemiballism (large-amplitude proximal flinging, one side)*.

Clinical / Diagnostic significance

- A precise bedside description (speed, rhythm, distribution, suppressibility, sensory trick, effect of action/rest/sleep) localises and classifies the disorder before any test.
- **Always exclude Wilson's disease** (serum copper/ceruloplasmin, 24-h urinary copper, KF rings, slit-lamp) in any young-onset chorea/dystonia/tremor — it is treatable.
- **Genetic testing** confirms HD (with counselling), DYT dystonias and HDL disorders; MRI signs are diagnostic clues (caudate atrophy in HD, eye-of-the-tiger in PKAN, olivary pseudohypertrophy in palatal myoclonus).
- VMAT-2 inhibitors (tetrabenazine, deutetrabenazine, valbenazine) are the unifying pharmacology for chorea and tardive dyskinesia; **botulinum toxin** is first-line for focal dystonia; **DBS** (GPi for dystonia/HD, VIM for tremor, STN avoided in chorea) rescues refractory disease.

High-yield exam pointers

- ET: **6–10 Hz postural/action tremor, alcohol-responsive**; first-line **propranolol & primidone**; VIM-DBS/focused ultrasound if refractory.
- HD: **AD, CAG repeat >40 on chromosome 4**, anticipation, Westphal variant; chorea + dementia + caudate atrophy.
- **Hemiballismus = contralateral subthalamic nucleus lesion**; also non-ketotic hyperglycaemia; usually self-limiting.
- **Dopa-responsive dystonia (Segawa, GCH1)** — diurnal variation, dramatic levodopa response; never miss it.
- **Geste antagoniste** (sensory trick) and *dystonic tremor in the direction of pull* are hallmarks of dystonia.
- **Palatal myoclonus → Guillain-Mollaret triangle**; **asterixis = negative myoclonus** ("liver flap").
- Tourette = motor + phonic tics, onset childhood, comorbid OCD/ADHD; tics are **suppressible** (vs myoclonus, which is not).
- **Metoclopramide >12 weeks** risks tardive dyskinesia; **valbenazine/deutetrabenazine** treat it.
- Sydenham's chorea = post-streptococcal autoimmune; **SLE** is the commonest systemic cause of chorea.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Tremor, Chorea, and Other Movement Disorders"* (Olanow & Klein) — primary framework, genetics, drug doses and disease definitions.
- **DeJong's The Neurologic Examination** — *"Abnormalities of Movement"* — phenomenology (athetosis, asterixis, palatal myoclonus/Guillain-Mollaret triangle, parakinesia, geste antagoniste, hemiballismus, tics & stereotypy).
- **CMDT 2026** — *"Nervous System Disorders"* — current management of essential tremor (propranolol/primidone doses, DBS, focused-ultrasound thalamotomy) and chorea.

◆ ◆ ◆

Hypoxic-ischaemic encephalopathy

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

Definition / Introduction — Hypoxic-ischemic encephalopathy (HIE) is diffuse brain dysfunction caused by inadequate cerebral oxygen delivery, usually from combined hypoxemia and reduced cerebral blood flow. In adults it is most often discussed after cardiac arrest, but the same injury pattern may follow shock, respiratory arrest, asphyxiation, severe hypoxemia, or histotoxic hypoxia due to carbon monoxide or cyanide. It is an emergency because neurological outcome is determined by the duration of impaired perfusion, secondary brain insults, and the accuracy of delayed multimodal prognostication.

Etiology and vulnerable neuroanatomy

- **Cardiac arrest** is the prototype: cerebral blood flow becomes negligible, consciousness is lost within seconds, and permanent injury becomes likely when global hypoxia-ischemia lasts beyond about **3-5 min**, though recovery after longer intervals may occur, especially with early CPR.
- Important causes: **myocardial infarction**, ventricular tachycardia/fibrillation, pulseless electrical activity/asystole, shock, severe hypotension, respiratory failure, asphyxiation, respiratory paralysis, drowning/near-hanging, carbon monoxide poisoning, and cyanide poisoning.
- **Pure hypoxia** is better tolerated than hypoxia plus ischemia if blood pressure is maintained; severe arterial hypoxemia may injure brain, but brief absent or very low cerebral circulation is more dangerous.
- Usually severe systemic insult is required: Harrison notes that **systolic BP <70 mmHg** or **Pao2 <40 mmHg** is generally necessary, with the duration of exposure being crucial.
- Selectively vulnerable sites are **hippocampal CA1 neurons**, cerebral cortex with **laminar cortical necrosis**, **deep gray nuclei** including basal ganglia and thalamus, cerebellar Purkinje cells, and watershed zones between major cerebral arteries.
- Resulting syndromes correlate with anatomy: hippocampal injury causes amnestic states; bilateral watershed injury may cause proximal arm-predominant weakness (*man-in-the-barrel* syndrome); striatal injury may produce parkinsonism; cortical injury may cause dementia, visual agnosia, seizures, or persistent coma.

Pathogenesis

- In complete global ischemia, neuronal oxygen stores are rapidly exhausted; CPR may provide only partial cerebral blood flow until effective circulation is restored.
- **Energy failure** causes failure of membrane ion gradients, neuronal depolarization, sodium and calcium influx, cytotoxic edema, and loss of electrophysiologic activity.
- **Glutamate excitotoxicity** through NMDA/AMPA receptors amplifies calcium entry; activated proteases, lipases, endonucleases, nitric oxide pathways, and mitochondrial dysfunction then produce cell injury.
- **Reperfusion injury** contributes through oxygen free radicals, inflammation, endothelial dysfunction, microvascular obstruction, and the *no-reflow* phenomenon.
- **Apoptosis and delayed neuronal death** may continue after the initial arrest; this is why early restoration of circulation plus prevention of secondary insults is central.
- Secondary brain insults that worsen outcome include **hypotension**, hypoxemia, fever, hyperglycemia or hypoglycemia, seizures/status epilepticus, severe acid-base/electrolyte derangements, and excessive sedative accumulation delaying assessment.

Clinical features and evolution

- Mild pure hypoxia may produce impaired judgment, inattentiveness, motor incoordination, and euphoria; hypoxia-ischemia from circulatory arrest produces immediate loss of consciousness.
- After return of spontaneous circulation (ROSC), the patient may awaken, remain comatose, evolve into an unresponsive wakefulness/vegetative state, or recover with variable cognitive, motor, visual, or movement-disorder sequelae.
- Bedside coma examination must document **pupillary light reflexes**, corneal reflexes, oculocephalic and oculovestibular responses, motor response to pain, respiratory pattern, and spontaneous/elicited eye movements.
- Brainstem reflexes are often preserved because the brainstem is relatively resistant to anoxic-ischemic injury; loss of pupillary or corneal reflexes therefore suggests severe, widespread injury.
- **Myoclonus status epilepticus** is continuous, generalized, vigorous jerking involving face, limbs, trunk, or diaphragm, often stimulus-sensitive and commonly associated with malignant EEG patterns; it must be distinguished from occasional myoclonic jerks, drug/metabolic myoclonus, and generalized tonic-clonic seizures.
- Long-term consequences include persistent coma, unresponsive wakefulness, minimally conscious state, dementia, visual agnosia/cortical blindness, parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and amnestic syndrome.

Diagnostic evaluation

Domain	What to assess	High-yield point
Event history	Witnessed arrest, no-flow/low-flow time, initial rhythm, bystander CPR, ROSC time, hypotension/hypoxemia duration, toxins	Shockable rhythms and early CPR generally carry better neurological prospects than unwitnessed nonshockable arrests

Domain	What to assess	High-yield point
Immediate labs	Glucose, electrolytes, calcium, ABG, lactate, renal/liver function, toxicology as indicated	Correct reversible coma mimics and secondary insults before prognostication
Coma examination	Pupils, corneal reflex, oculocephalic/oculovestibular reflexes, motor response, respiratory pattern	Preserved brainstem reflexes are favorable; absent reflexes after adequate waiting are ominous
Neuroimaging	Noncontrast CT brain; CT angiography if basilar occlusion or structural lesion is possible; MRI-DWI when stable	Early CT may be normal; severe HIE may show diffuse edema and loss of gray-white differentiation; MRI-DWI may show cortical and deep gray restriction
EEG	Spot or continuous EEG in comatose patients, especially with myoclonus or unexplained nonawakening	Detects nonconvulsive seizures/status; nonreactive EEG, suppressed background, and burst suppression are poor signs
SSEP and biomarkers	Median nerve SSEP for N20 responses; serial NSE if available	Bilateral absent cortical N20 after several days is highly specific for poor outcome; very high NSE supports severe brain injury but should not be used alone

Management

- **Restore cardiorespiratory function first**: secure airway, provide oxygenation and ventilation, perform high-quality CPR/defibrillation when indicated, and restore cerebral perfusion using fluids, vasopressors, pacing, or treatment of the arrest cause.
- After ROSC, assess for **acute MI**; ST-elevation MI requires emergent coronary angiography and PCI. In patients without ST elevation, urgent angiography is individualized for shock, electrical instability, ongoing ischemia, or major myocardial injury.
- Maintain systemic perfusion: Harrison recommends **SBP >90 mmHg** and **MAP >65 mmHg**; Bradley describes **MAP 65-80 mmHg** as a common post-arrest goal, often requiring norepinephrine plus fluid resuscitation.
- Ventilate to avoid hypoxemia and severe hyperoxia; Miller emphasizes individualized oxygenation with aggressive treatment of hypoxemia and avoidance of marked hyperoxia, especially **Pao2 >300 mmHg**, when oxygenation is otherwise adequate. Maintain **normocapnia**, normalize systemic pH, and correct electrolyte abnormalities.
- Avoid secondary injury: treat fever aggressively, avoid hypotonic fluids, prevent aspiration, control glucose reasonably (often <180 mg/dL) while avoiding hypoglycemia, and manage renal/liver failure that may prolong sedative effects.
- **Targeted temperature management (TTM)** is recommended for comatose patients without purposeful response after ROSC: select and maintain a constant temperature **32-37.5°C for at least 24 h**; fever must be avoided in all cases. Shivering may require analgesia, sedation, and sometimes neuromuscular blockade.
- Do not start hypothermia with large prehospital cold-saline loads; Harrison notes no prehospital benefit and increased pulmonary edema risk. Monitor for hypothermia complications: infection,

coagulopathy, arrhythmias, hyperglycemia, cold diuresis, hypovolemia, and delayed sedative clearance.

- Treat clinically apparent seizures and consider treatment of ictal-interictal continuum EEG patterns. **Anticonvulsants are not given prophylactically**; complete suppression of rhythmic/periodic EEG activity for 48 h has not improved outcomes.
- Posthypoxic myoclonus in survivors may respond to **clonazepam 1.5-10 mg/day** or **valproate 300-1200 mg/day in divided doses**. Severe carbon monoxide poisoning may require hyperbaric oxygen.
- Ineffective or unproven neuroprotective strategies after cardiac arrest include routine corticosteroids, hemofiltration, tight glucose control, barbiturates for global ischemia, and calcium-channel blockers such as nimodipine solely for postarrest neuroprotection.

Neuroprognostication

- Prognostication must be **delayed, multimodal, and free of confounders**: exclude hypothermia, sedatives/analgesics, neuromuscular blockers, metabolic derangements, shock, hypoxemia, hepatic/renal failure, and drug intoxication.
- Harrison recommends deferring functional neurological assessment until at least **72 h after return to normothermia**, typically **4-5 days after arrest**; some patients awaken after a week or longer, so premature withdrawal risks a self-fulfilling poor outcome.
- Favorable signs: early awakening, following commands, purposeful localization to pain, intact pupillary/corneal/oculocephalic/oculovestibular reflexes, continuous reactive EEG background, and limited imaging injury.
- Poor prognostic signs when assessed at appropriate time points include absent pupillary light reflex, absent corneal reflex, absent or extensor motor response, and **status myoclonus** after primary circulatory arrest.
- Electrophysiologic poor signs: **bilateral absence of cortical N20 SSEP**, nonreactive EEG, persistent burst suppression, suppressed EEG background, or burst-suppression pattern with myoclonic status epilepticus.
- Imaging poor signs: diffuse cerebral edema, loss of gray-white differentiation on CT, widespread cortical DWI restriction, combined cortical and deep gray injury, or severe global ADC reduction on MRI.
- Biomarkers are adjunctive only: a very high **neuron-specific enolase >60 microgram/L** in the first 1-3 days supports severe brain damage in Harrison, but thresholds vary with assays and TTM.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis flow diagram**: "Cardiac/respiratory arrest or shock" -> "low cerebral blood flow + low O2 delivery" -> "ATP failure" -> "membrane depolarization" -> "glutamate excitotoxicity + Ca2+ influx" -> "free radicals/inflammation/no-reflow/apoptosis" -> "selective neuronal injury: cortex, CA1 hippocampus, basal ganglia, thalamus, Purkinje cells, watershed zones" -> "coma/seizures/cognitive-motor sequelae".
- **Post-arrest prognostication algorithm**: "ROSC with coma" -> "exclude confounders: hypothermia, sedatives, paralysis, metabolic shock" -> "wait >=72 h after normothermia" -> "clinical exam: pupils, corneal, motor, myoclonus" + "EEG/SSEP/NSE/CT-MRI" -> "multimodal prognosis and family discussion".

Clinical / Diagnostic significance

- HIE is a leading determinant of death after successful resuscitation; Harrison notes postarrest brain injury accounts for most deaths after stable circulation is restored.
- The diagnosis is clinical plus contextual: a compatible hypoxic-ischemic event with coma or encephalopathy, after excluding structural lesions, intoxication, metabolic coma, CNS infection, basilar artery occlusion, and nonconvulsive status epilepticus.
- Coma examination distinguishes diffuse metabolic/anoxic depression from focal structural brainstem processes; oculocephalic and caloric responses are particularly useful when the cervical spine is safe to test.
- Do not confuse HIE coma with **locked-in syndrome**, in which the patient is conscious with quadriparesis and preserved vertical eye movements/blinking, or with **brain death**, which requires irreversible coma, absent brainstem reflexes, absent respiratory drive, and exclusion of hypothermia/drug/metabolic mimics.
- Survivors require evaluation of the arrest cause, rehabilitation for cognitive and motor sequelae, seizure/myoclonus treatment, and cardiac secondary prevention including ICD consideration when VT/VF arrest is not due to a reversible cause.

High-yield exam pointers

- Write that HIE after cardiac arrest is **global cerebral ischemia plus reperfusion injury**, not merely low oxygen saturation.
- Mention vulnerable regions: **CA1 hippocampus, laminar cortex, basal ganglia/thalamus, Purkinje cells, watershed zones**.
- Initial treatment is not a "neuro drug"; it is **airway, oxygenation, ventilation, circulation, perfusion pressure, fever prevention, seizure detection, and TTM**.
- TTM: comatose after ROSC, constant **32-37.5°C for at least 24 h**, avoid fever, suppress shivering, and delay prognostication.
- Never prognosticate early under hypothermia, sedatives, neuromuscular blockade, metabolic derangement, or shock.

- Strong poor-outcome markers: absent pupillary reflex, status myoclonus, nonreactive/burst-suppression EEG, bilateral absent **N20 SSEP**, diffuse cortical/deep gray MRI injury, and very high NSE.
- EEG is needed because nonconvulsive seizures/status may be clinically inapparent in comatose postarrest patients.
- CT can be normal early; **MRI-DWI** is more sensitive for cortical and deep gray injury but must not be used alone to withdraw care.

SOURCE & COVERAGE

Harrison 22e — "Nervous System Disorders in Critical Care"; Harrison 22e — "Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death"; Bradley & Daroff's Neurology 8e — "Anoxic-Ischemic Encephalopathy" and "Stupor and Coma"; DeJong's Neurologic Examination — "The Examination in Coma"; CMDT 2026 — "Nervous System Disorders"; Miller's Anesthesia — "Cerebral Physiology and the Effects of Anesthetic Drugs".

◆ ◆ ◆

Guillain-Barré syndrome

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

Definition / Introduction — Guillain-Barré syndrome (GBS) is an acute, frequently severe and fulminant **autoimmune polyradiculoneuropathy** characterised by rapidly evolving **areflexic motor paralysis** with or without sensory disturbance. It is the commonest cause of acute flaccid paralysis in the post-polio era, occurring year-round at **10–20 cases per million annually** (~5000–6000 cases/year in the USA). Males are at slightly higher risk than females, and in Western countries adults are affected more than children. The syndrome typically follows an antecedent infection by 1–3 weeks and is mediated by **molecular mimicry** between microbial and neural ganglioside epitopes.

Subtypes / Classification

GBS is a spectrum; subtypes are defined primarily by **electrodiagnostic (EDx) and pathologic** features and associated antiganglioside antibodies.

Subtype	Key features	Pathology / EDx	Antibody
AIDP (acute inflammatory demyelinating polyneuropathy)	Commonest; ~90% of Western cases; adults > children; rapid recovery	Demyelinating; first attack on Schwann-cell surface; macrophage-mediated myelin injury, variable secondary axonal loss	anti-GM1 (<50%)
AMAN (acute motor axonal neuropathy)	Children/young adults; prevalent in China & Mexico; may be seasonal; rapid recovery	Axonal; attack at motor nodes of Ranvier	anti-GD1a

Subtype	Key features	Pathology / EDx	Antibody
AMSAN (acute motor sensory axonal neuropathy)	Mostly adults; uncommon; recovery slow, often incomplete; related to AMAN	Axonal; like AMAN but also sensory nerves/roots; severe axonal damage	GM1, GD1a
Miller Fisher syndrome (MFS)	~5% of cases; triad of **ophthalmoplegia, ataxia, areflexia** (no limb weakness); pupillary paralysis	Demyelinating/nodal	**anti-GQ1b (>90%)**

- **Regional/limited variants**: pure sensory forms; pharyngeal-cervical-brachial weakness (anti-GT1a/GQ1b); GBS with severe bulbar/facial palsy and antecedent CMV (anti-GM2); acute pandysautonomia.
- The **anti-GQ1b antibody syndrome** spans MFS, acute ophthalmoparesis, acute ataxic neuropathy, *Bickerstaff's brainstem encephalitis*, and pharyngeal-cervical-brachial weakness — illustrating a continuous clinical spectrum.

Antecedent events & associations

- **~70%** of cases occur **1–3 weeks** after an acute infection (usually respiratory or gastrointestinal).
- **Campylobacter jejuni** precedes 20–30% of cases (North America, Europe, Australia) and is the classic trigger of AMAN; summer AMAN outbreaks have followed poultry exposure in rural China.
- Other agents: **CMV, Epstein-Barr virus**, HIV, hepatitis E, **Zika** (Brazil/endemic outbreaks), *Mycoplasma pneumoniae*. SARS-CoV-2 association reported but causality not established.
- **Vaccines**: the 1976 swine influenza vaccine is the notable example; modern seasonal influenza vaccines carry <1 case/million; slight increase with adenovirus-vector SARS-CoV-2 vaccines (not mRNA); older nerve-tissue rabies vaccine.
- **Disease associations**: lymphoma (incl. Hodgkin's), HIV seropositivity, SLE, possibly Sjögren's; **immune checkpoint inhibitors**.

Immunopathogenesis & pathophysiology

- Both **cellular and humoral** immune mechanisms contribute. AIDP is analogous to experimental allergic neuritis (EAN), a T-cell–mediated immunopathy against peripheral myelin (e.g., P2 protein); autoreactive T cells are found in blood, CSF and nerve.
- **Humoral arm**: autoantibodies against **gangliosides** (complex sialic-acid–bearing glycosphingolipids concentrated at nodes of Ranvier) arise via *molecular mimicry — C. jejuni* lipo-oligosaccharide cross-reacts with GM1.
- **AIDP** — complement deposits on the **outer Schwann-cell surface**, triggering **vesicular myelin disintegration** and recruitment of activated macrophages; the resultant **conduction block** (axons remaining intact) underlies the flaccid paralysis, allowing rapid recovery with remyelination. Severe cases develop secondary axonal degeneration → slower, incomplete recovery.
- **AMAN/AMSAN** — IgG (anti-GM1/GD1a) plus complement deposit at the **nodal axolemma of motor axons**; membrane-attack complex disrupts Na^+-channel clustering and detaches

paranodal myelin → reversible conduction failure, with axonal degeneration in severe cases. Anti-GD1a shows fine specificity favouring motor over sensory roots.

Clinical features

- **Ascending, symmetric flaccid weakness** ("rubbery legs"), evolving over hours to a few days, legs > arms, with tingling dysaesthesias.
- **Areflexia/hyporeflexia** appears within the first few days (large-fibre functions — DTRs, proprioception — affected more than pain/temperature).
- **Facial diparesis in ~50%**; lower cranial nerve / **bulbar weakness** (difficulty handling secretions, airway risk) — may mimic brainstem ischaemia.
- **Pain** (neck, shoulder, back, dysaesthetic limb pain) in ~50% early on.
- **Autonomic involvement** common even in mild disease: labile blood pressure, postural hypotension, cardiac dysrhythmias — potentially fatal. Bladder dysfunction is usually transient and late.
- Up to **30% require mechanical ventilation**; predictors are severe weakness on admission, rapid progression, and early facial/bulbar weakness.
- Nadir is reached and a **plateau** established almost always **within 4 weeks** of onset. Fever/constitutional symptoms at onset argue *against* GBS.

Investigations & diagnosis

- **CSF — albuminocytologic (cytoalbuminologic) dissociation**: elevated protein **1–10 g/L (100–1000 mg/dL)** with **white cells <50/µL** (no pleocytosis). CSF may be normal in first ≤48 h, rising by the end of the first week. Sustained pleocytosis (10–100/µL persistent) suggests an alternative (viral myelitis, HIV, leukaemia/lymphoma, neurosarcoidosis).
- **Nerve conduction studies (EDx)** — mild/absent early; earliest AIDP changes are **prolonged F-wave latencies, prolonged distal latencies, reduced CMAP amplitudes**, reflecting proximal root and distal terminal involvement; later **conduction slowing, conduction block, temporal dispersion**. AMAN/AMSAN show **low-amplitude CMAPs (and SNAPs in AMSAN) without conduction slowing**.
- **Antiganglioside antibodies** support subtyping (anti-GQ1b for MFS, anti-GD1a/GM1 for axonal forms).
- **Brighton Collaboration criteria (2011)** provide graded levels of diagnostic certainty (Level 1 highest), incorporating bilateral flaccid limb weakness, depressed reflexes, monophasic course with nadir between 12 h and 28 days, cytoalbuminologic dissociation, supportive EDx and exclusion of alternatives.
- Begin treatment on clinical suspicion — do not await CSF/EDx evolution. Test for HIV if risk factors or CSF pleocytosis present.

Differential diagnosis

- Acute myelopathies (early prominent back pain, sphincter loss, sensory level); poliomyelitis / **acute flaccid myelitis** (West Nile, enterovirus D68/A71); CMV or Lyme polyradiculitis; diphtheritic neuropathy; **porphyria** (abdominal pain, seizures, psychosis); vasculitic neuropathy;

critical-illness neuropathy/myopathy; neuromuscular junction disease — **myasthenia gravis, botulism** (early pupillary involvement); intoxications (**organophosphates, thallium, arsenic**), paralytic shellfish poisoning; severe hypophosphataemia.

Treatment

- **Start immunotherapy as early as possible** — "each day counts"; benefit beyond ~2 weeks from onset is uncertain, and treatment at the plateau is generally not indicated unless severe weakness with possible ongoing attack.
- **IVIg** — total **2 g/kg**, usually as **five daily infusions**; first-line for ease and safety (acts via anti-idiotypic neutralisation of autoantibodies).
- **Plasmapheresis (PLEX)** — **~40–50 mL/kg exchange, 4–6 times over 7–12 days**; reduces need for mechanical ventilation (**27% → 14%**) and increases full recovery at 1 year (**55% → 68%**).
- IVIg and PLEX are **equally effective**; **combining them is not superior**; failure of one is not an indication to switch to the other. Early treatment-related fluctuation/relapse within a month is managed by a brief repeat course of the original therapy.
- **Glucocorticoids are NOT effective in GBS** (a key contrast with CIDP, which does respond to steroids).
- Very mild cases, or those already at plateau, may be managed conservatively.
- **Supportive/ICU care** (worsening phase): monitor **vital capacity**, cardiac rhythm and blood pressure; nutrition; DVT prophylaxis; consider **tracheostomy after ~2 weeks of intubation**; chest physiotherapy, frequent turning, skin care, range-of-motion exercises to prevent contractures, and reassurance.

Prognosis

- **~85% achieve full functional recovery** within several months to a year; residual areflexia and fatigue are common.
- **Mortality <5%** in optimal settings; death is usually from secondary pulmonary complications and autonomic instability.
- Worse outcome with **severe proximal motor and sensory axonal damage**, advanced age, fulminant attack, and delayed treatment. **Elevated serum neurofilament light (NfL) chains** and **high anti-GM1 titres** mark greater axonal injury and poor recovery.
- **5–10%** suffer late relapses; many are reclassified as **chronic inflammatory demyelinating polyneuropathy (CIDP)** (course >8 weeks, relapses ≥3 times, steroid-responsive).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spectrum/antibody map**: a horizontal axis with boxes — *AIDP* (anti-GM1) → *AMAN/AMSAN* (anti-GM1, GD1a) and *MFS/anti-GQ1b syndrome* (anti-GQ1b, GT1a) → *Bickerstaff's encephalitis*. Labels: AIDP, AMAN, AMSAN, MFS, GM1, GD1a, GQ1b, GT1a.
- **Pathogenesis of a myelinated motor axon**: label *node of Ranvier (Na_v channels)*, *paranode (Caspr)*, *juxtaparanode (K_v channels)*, *Schwann cell/myelin*, *IgG anti-GM1/anti-GD1a antibody binding*, *complement activation → membrane-attack complex (MAC)*, *macrophage scavenging*. Show MAC on outer Schwann-cell surface for AIDP and at the nodal axolemma for AMAN.

Clinical / Diagnostic significance

- GBS is the prototype treatable cause of acute flaccid paralysis — **early recognition, serial vital-capacity monitoring and prompt IVIg/PLEX** are life-saving.
- **Albuminocytologic dissociation** plus a compatible clinical picture clinches the diagnosis; absence of fever, presence of areflexia and a recent *C. jejuni*/viral illness are strong pointers.
- Watch for **respiratory failure and autonomic instability** — the two main killers — mandating ICU admission during worsening.
- Distinguish from acute myelopathy (sensory level, early sphincter loss) and MFS/Bickerstaff overlap (ophthalmoplegia + ataxia, anti-GQ1b).

High-yield exam pointers

- GBS = acute **autoimmune areflexic ascending flaccid paralysis**; commonest variant **AIDP**; **anti-GQ1b** = MFS; **anti-GD1a/GM1** = AMAN/AMSAN.
- **70%** post-infectious at 1–3 weeks; classic trigger **Campylobacter jejuni** (→ AMAN); also CMV, EBV, Zika, *Mycoplasma*.
- **CSF**: high protein **1–10 g/L** with **<50 cells/µL** (cytoalbuminologic dissociation), often normal in first 48 h.
- **EDx**: earliest = prolonged **F-wave latency**; axonal forms = low CMAP amplitude *without* slowing.
- Treatment = **IVIg 2 g/kg over 5 days OR PLEX 40–50 mL/kg ×4–6**; equally effective; **steroids do NOT work**.
- **~30%** need ventilation; tracheostomy considered after ~2 weeks intubation.
- **85% full recovery**, **mortality <5%**; poor prognosis with axonal damage, age, fulminant onset, delayed therapy; high **NfL** and **anti-GM1** = worse.
- **Brighton criteria (2011)** standardise diagnosis; nadir within **12 h–28 days**, monophasic.
- **5–10% relapse** → consider **CIDP** (steroid-responsive, unlike GBS).

SOURCE & COVERAGE

Harrison 22e — Ch 458 "Guillain-Barré Syndrome and Other Immune-Mediated Neuropathies" (Hauser & Amato). All figures, doses, percentages, antibody associations, Brighton criteria and prognostic data are taken from this chapter; no external content was added.

◆ ◆ ◆

Multiple sclerosis

Asked in: Paper III Dec 2023 · Paper IV Nov 2022 (2×) — RGUHS MD General Medicine

Definition / Introduction — Multiple sclerosis (MS) is a chronic autoimmune inflammatory demyelinating disease of the CNS, with **demyelination, gliosis, plaques and axonal-neuronal loss** in brain, spinal cord and optic nerves. Lesions occur at different CNS sites and at different times; therefore the diagnostic principle is **dissemination in space and time**, after excluding better explanations. The course may be relapsing or progressive, and disability reflects both focal inflammatory attacks and cumulative neurodegeneration.

Etiopathogenesis and pathology

- **Epidemiology:** usual onset is in young adults, commonly 20-40 years; relapsing MS shows a female predominance of about 2-3:1, while primary progressive MS has a more even sex distribution and later onset. MS is commoner in temperate zones and higher latitudes.
- **Risk factors:** genetic susceptibility, especially **HLA-DRB1*1501**, interacts with environmental factors: previous **Epstein-Barr virus** infection/infectious mononucleosis, low sunlight or vitamin D deficiency, cigarette smoking, and probably childhood obesity/microbiome factors.
- **Pathology:** plaques are sharply demarcated, often **perivenular**, with mononuclear inflammation, macrophages, T cells, B cells/plasma cells, complement activation, myelin loss, astrocytic gliosis and variable axonal loss. Chronic active plaques, cortical demyelination and meningeal lymphoid aggregates are important in progressive disease.
- **Immunology:** B cells are central; clonally restricted B cells and plasma cells in CNS/CSF produce **oligoclonal IgG bands**. Autoreactive T cells, especially myelin-reactive T cells, inflammatory cytokines, CD8 cells at plaque edges and microglial activation contribute to tissue injury.
- **Physiology:** demyelination causes conduction block, slowed conduction and temperature-dependent failure. This explains **Uhthoff phenomenon** and pseudoexacerbations with fever, infection or heat.

Clinical features

- **Optic neuritis:** subacute unilateral visual loss, central scotoma, impaired colour vision, pain on eye movement and relative afferent pupillary defect; fundus may be normal in retrobulbar neuritis or show papillitis, followed later by optic pallor.
- **Sensory symptoms:** numbness, tingling, pins-and-needles, burning dysesthesia, reduced vibration/joint position, patchy sensory loss, a spinal sensory level and a band-like truncal

tightness or *MS hug*. **Lhermitte sign** is an electric shock sensation down the spine on neck flexion.

- **Motor and pyramidal signs:** limb weakness, loss of dexterity, spastic paraparesis, brisk reflexes, clonus and extensor plantar responses. Exercise-induced weakness is typical; severe spasticity may cause painful spasms but may also help standing in advanced disease.
- **Brainstem/cerebellar disease:** diplopia, sixth nerve palsy, **internuclear ophthalmoplegia** from medial longitudinal fasciculus lesions, bilateral INO, nystagmus, vertigo, ataxic gait, intention tremor and scanning dysarthria.
- **Paroxysmal symptoms:** brief stereotyped events lasting seconds to minutes, often many times per day: tonic spasms, paroxysmal dysarthria-ataxia, sensory attacks, trigeminal neuralgia, hemifacial spasm or facial myokymia.
- **Autonomic, cognitive and affective symptoms:** urinary urgency, frequency, hesitancy, retention, recurrent UTI, constipation, sexual dysfunction, fatigue, slowed information processing, memory/executive difficulty, depression and pseudobulbar affect.

Disease course and phenotypes

Phenotype	Exam definition	Key point
Clinically isolated syndrome (CIS)	First typical demyelinating clinical event not yet fulfilling MS criteria	High-risk CIS with MRI/CSF activity may be treated early
Radiologically isolated syndrome (RIS)	Incidental MRI lesions typical of MS without clinical attack	Follow clinically and by MRI; some convert to clinical MS
Relapsing-remitting MS (RRMS)	Clearly defined attacks with full or partial recovery and no progression between attacks	Accounts for most onset cases; current term **relapsing MS** includes active SPMS
Secondary progressive MS (SPMS)	Initial RRMS followed by gradual progression independent of relapses	Produces more fixed disability; classify as active/inactive and progressing/not progressing
Primary progressive MS (PPMS)	Progression from onset, with possible plateaus or minor improvement	About 10% of cases; later onset; faster disability relative to first symptom
Fulminant variants	Tumefactive MS, Marburg variant, Balo concentric sclerosis	May mimic tumour or rapidly progressive encephalomyelitis

Diagnosis and investigations

- **Core rule:** do not diagnose MS from a single lesion or MRI alone. Demonstrate **dissemination in space (DIS)** and **dissemination in time (DIT)**, and exclude mimics.
- **2017 McDonald criteria, simplified:** two attacks plus objective evidence of two lesions need no further data; two attacks plus one lesion need DIS; one attack plus two lesions need DIT; one attack plus one lesion needs both DIS and DIT.
- **DIS by MRI:** at least one T2 lesion in at least two of four typical sites: **periventricular, cortical/juxtacortical, infratentorial or spinal cord**.

- **DIT by MRI/CSF:** simultaneous gadolinium-enhancing and non-enhancing lesions, or a new T2/gadolinium lesion on follow-up MRI, or a second clinical attack; in a patient with one clinical event meeting DIS, **CSF-specific oligoclonal bands can substitute for DIT**.
- **PPMS criteria:** at least 1 year of progression plus two of: typical brain lesion, at least two spinal cord lesions, or positive CSF oligoclonal bands/elevated IgG index.
- **MRI:** most sensitive test; shows ovoid T2/FLAIR plaques, **Dawson fingers** perpendicular to ventricles, corpus callosum, juxtacortical, infratentorial and cord lesions. Gadolinium enhancement marks active BBB breakdown, usually for less than 1 month; T1 black holes suggest irreversible demyelination/axonal loss.
- **CSF:** normal opening pressure, normal or mildly raised protein, mild lymphocytic pleocytosis, increased IgG index/synthesis and **two or more CSF-restricted oligoclonal bands** in >90% in Harrison. Red flags against MS are polymorphs, CSF cells >75/microL, or protein >1 g/L.
- **Evoked potentials/OCT:** VEP, SSEP and BAER may detect clinically silent lesions; delayed VEP P100 supports demyelination. OCT quantifies retinal nerve fibre layer axonal loss after optic neuritis but is not diagnostic.

Differential diagnosis

- **Inflammatory demyelinating mimics: neuromyelitis optica spectrum disorder** and **MOG antibody-associated disease**, especially with bilateral/severe optic neuritis, poor recovery or longitudinally extensive transverse myelitis; acute disseminated encephalomyelitis after infection/vaccination.
- **Systemic inflammatory disease:** SLE, Sjögren syndrome, sarcoidosis, Behçet disease, antiphospholipid syndrome and primary CNS/systemic vasculitis.
- **Infective/metabolic/vascular:** HIV, HTLV-1 tropical spastic paraparesis, Lyme disease, syphilis, vitamin B12 deficiency, CADASIL, stroke/small-vessel disease and spinal dural AV fistula.
- **Structural/neoplastic:** compressive myelopathy, Chiari malformation, lymphoma, glioma, meningioma and tumefactive demyelination.
- **Red flags:** onset age <15 or >60 years, progressive course from onset without typical attacks, symptoms confined to one anatomic site, fever/headache/seizures/coma, peripheral neuropathy, severe muscular atrophy, atypical MRI or inflammatory CSF.

Management

- **Acute relapse:** first exclude pseudoexacerbation due to fever, UTI, heat or metabolic stress. Treat disabling relapses with high-dose methylprednisolone **500-1000 mg IV daily for 3-5 days** or equivalent high-dose oral therapy; optional oral prednisone taper may follow. Steroids hasten recovery but do not improve final recovery or prevent future relapses; long-term steroids are not useful.
- **Steroid-refractory severe relapse: plasma exchange** is useful, especially for severe motor, brainstem or optic-spinal relapses unresponsive to corticosteroids. ACTH is an alternative where available.
- **Disease-modifying therapy (DMT):** start in all diagnosed relapsing MS and high-risk CIS after counselling. Current high-efficacy first-line choices include anti-CD20 therapy **ocrelizumab,**

ofatumumab or ublituximab; rituximab is used where approved options are unavailable. **Natalizumab** is highly effective in JCV-negative patients but requires PML risk surveillance.

- **Other DMTs:** S1P modulators (fingolimod, ozanimod, ponesimod, siponimod), fumarates (dimethyl/diroximel fumarate), cladribine, alemtuzumab, teriflunomide, interferon-beta and glatiramer acetate. Choice depends on disease activity, pregnancy plans, infection risk, monitoring burden and patient preference.
- **Progressive MS: ocrelizumab** is the only convincingly disease-modifying drug for PPMS; active SPMS may be treated with ocrelizumab or siponimod, with cladribine/ponesimod/ofatumumab/ozanimod used in active secondary progressive disease in appropriate settings.
- **Symptomatic care:** physiotherapy, occupational therapy, exercise and fall prevention. Spasticity: stretching, baclofen **20-120 mg/day**, tizanidine **8-32 mg/day**, benzodiazepines, dantrolene or intrathecal baclofen. Gait: dalfampridine **10 mg twice daily** if no seizure risk. Bladder: timed voiding, urodynamics, mirabegron **25-50 mg/day**, vibegron **75 mg/day**, anticholinergics, botulinum toxin or intermittent catheterization. Pain/paroxysms: carbamazepine, gabapentin, pregabalin or other membrane-stabilising drugs. Fatigue: treat sleep, nocturia, depression and spasticity first; modafinil/methylphenidate may help selected patients. Screen and treat depression and suicidality.
- **Pregnancy and prevention:** relapse rate falls during pregnancy, especially third trimester, and rises in the first 3 months postpartum. Avoid abrupt withdrawal of natalizumab/S1P drugs without planning because rebound can occur. Correct vitamin D deficiency, stop smoking and vaccinate before B-cell-depleting or other immunosuppressive DMTs when possible.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathophysiology diagram:** normal myelinated axon with node of Ranvier and saltatory conduction; demyelinated axon with exposed potassium channels, redistributed sodium channels, conduction block/slow conduction; labels: myelin sheath, axon, node of Ranvier, Na+ channels, demyelinated plaque, conduction block, continuous conduction.
- **MRI/clinical course diagram:** sagittal brain showing periventricular **Dawson fingers**, corpus callosum lesions, juxtacortical lesion, infratentorial lesion and short-segment spinal cord plaque; alongside a course graph labelled CIS/RRMS/SPMS/PPMS, relapses, MRI activity and progression.

Clinical / Diagnostic significance

- Optic neuritis, partial myelitis and brainstem syndromes in a young adult should prompt MRI brain and spinal cord with gadolinium and CSF when needed.
- Bilateral INO, Lhermitte sign, Uhthoff phenomenon and paroxysmal tonic spasms are highly suggestive clinical clues but are not pathognomonic.
- Severe bilateral optic neuritis, longitudinally extensive myelitis, area postrema syndrome or poor visual recovery should trigger AQP4-IgG and MOG-IgG testing rather than assuming MS.
- MRI lesions must be interpreted in clinical context; migraine, ageing and small-vessel disease can produce nonspecific T2 hyperintensities.

- A true relapse lasts >24 hours and is separated from prior relapse by at least about 1 month; fever/UTI/heat-related worsening is a pseudoexacerbation and should not be treated with steroids alone.
- Early high-efficacy DMT reduces relapse/MRI activity and may improve long-term disability, but treatment requires infection, vaccination, pregnancy and monitoring planning.

High-yield exam pointers

- Write the definition: autoimmune CNS disease with **demyelination + gliosis + axonal loss**, disseminated in time and space.
- Mention common onset: young adult woman; optic neuritis, sensory symptoms and UMN weakness are classic first presentations.
- Must list the four MRI DIS sites: **periventricular, cortical/juxtacortical, infratentorial, spinal cord**.
- CSF-specific **oligoclonal bands** can substitute for DIT in the 2017 McDonald criteria.
- Dawson fingers, gadolinium enhancement and T1 black holes carry diagnostic/prognostic value.
- Always exclude NMO/MOGAD, B12 deficiency, infections, connective-tissue disease, sarcoidosis, lymphoma and compressive myelopathy.
- Acute relapse: high-dose methylprednisolone; severe steroid-resistant relapse: plasma exchange.
- DMT: anti-CD20 therapy/natalizumab are high-efficacy options; **ocrelizumab** is key for PPMS.
- Do not miss symptomatic management: bladder, spasticity, gait, pain, fatigue, cognition, mood and pregnancy counselling.

SOURCE & COVERAGE

Harrison 22e — "Multiple Sclerosis"; Bradley & Daroff's Neurology 8e — "Multiple Sclerosis and Other Inflammatory Demyelinating Diseases of the Central Nervous System"; Brazis Localization — "The Localization of Lesions Affecting the Ocular Motor System"; DeJong's Neurologic Examination — "The Trigeminal Nerve", "The Facial Nerve", "The Spinal Cord Level"; CMDT 2026 — "Nervous System Disorders" and "Disorders of the Eyes & Lids".

◆ ◆ ◆

Muscular dystrophies

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

Definition / Introduction — The **muscular dystrophies** are a genetically determined group of progressive, degenerative myopathies caused by mutations in genes encoding **structural, membrane, nuclear-envelope, enzymatic or RNA-binding proteins** of the muscle fibre. They are characterised clinically by progressive (usually proximal, limb-girdle) weakness with preserved sensation and reflexes, elevated serum creatine kinase (CK), myopathic EMG, and dystrophic features on biopsy. Each subtype has a unique phenotype–genotype signature; cardiac and ventilatory muscle involvement are the chief determinants of mortality. Genetic testing is now the gold standard for diagnosis.

Normal muscle architecture and the dystrophin–glycoprotein complex (DGC)

- The contractile actin–myosin apparatus of the sarcomere is anchored, via the cytoskeleton, to the extracellular matrix by a chain of proteins; loss of any link destabilises the **sarcolemma**.
- **Dystrophin** (427 kD) lies on the cytoplasmic face of the sarcolemma — its **amino terminus binds F-actin** and its **carboxyl terminus links to β-dystroglycan**.
- **β-Dystroglycan** spans the membrane and connects to **α-dystroglycan**, which (after enzymatic glycosylation) binds **laminin-α2 (merosin)** in the basal lamina.
- The **sarcoglycan complex (α, β, γ, δ)** and sarcospan also span the sarcolemma and stabilise the dystroglycan–dystrophin unit.
- Together — dystrophin, dystroglycans, sarcoglycans and merosin — form the **DGC**, transmitting contractile force and protecting the membrane from mechanical stress. Defects at *any* point produce a dystrophy.

Molecular mechanisms of pathogenesis (genetics → disease)

- **Sarcolemmal/structural-protein loss (DGC dystrophies):** absence of dystrophin (DMD/BMD), sarcoglycans, dysferlin or merosin renders the membrane fragile → unregulated **Ca^{2+} influx** → activation of proteases → cycles of fibre **necrosis–regeneration** → exhaustion of satellite cells → fibro-fatty replacement.
- **Defective glycosylation of α-dystroglycan** (fukutin, FKRP, POMT1/2, POMGnT1) — "dystroglycanopathies" — disrupt merosin binding; severe forms cause congenital muscular dystrophy with brain/eye anomalies, milder forms an LGMD.
- **Nuclear-envelope protein defects** (emerin, lamin A/C, nesprin-1/2, LUMA) destabilise the inner nuclear membrane → Emery-Dreifuss MD and LGMD1B, with prominent cardiac conduction disease.
- **Toxic RNA gain-of-function from non-coding repeat expansions:** in myotonic dystrophy the mutant mRNA forms **intranuclear inclusions that sequester RNA-splicing proteins**, causing mis-splicing of multiple downstream transcripts (multisystem disease).
- **Epigenetic de-repression:** in FSHD, contraction of the D4Z4 array → **hypomethylation** → aberrant **toxic expression of DUX4** transcription factor in muscle.
- **Protein aggregation:** in OPMD, an expanded polyalanine tract makes PABP2 resistant to proteasomal degradation → toxic intranuclear aggregates.

Genetic classification of the major muscular dystrophies

Dystrophy	Inheritance	Gene / locus	Protein	Hallmark feature
Duchenne / Becker (DMD/BMD)	X-linked recessive	*DMD* / **Xp21**	Dystrophin	Calf pseudohypertrophy, Gowers sign, very high CK
Limb-girdle (LGMD "D"/"R")	AD (D) or AR (R)	*CAPN3, DYSF, SGCA–D, FKRP, ANO5, TTN…*	Calpain-3, dysferlin, sarcoglycans, FKRP, anoctamin-5	Proximal limb-girdle weakness, often indistinguishable from DMD/BMD
Emery-Dreifuss (EDMD)	XLR / AD / AR	*EMD, LMNA, SYNE1/2, FHL1, TMEM43*	Emerin, lamin A/C, nesprins, FHL1, LUMA	**Early contractures + cardiac conduction block / sudden death**
Myotonic dystrophy 1 (DM1)	AD	*DMPK* / 19q13 — **CTG** repeat	DMPK	Grip myotonia, hatchet face, frontal balding, multisystem
Myotonic dystrophy 2 (PROMM / DM2)	AD	*CNBP (ZNF9)* — **CCTG** repeat, intron 1	CNBP	Proximal weakness, milder, no congenital form
Facioscapulohumeral (FSHD)	AD (FSHD1, 95%)	**D4Z4 / 4q35**, *DUX4*	DUX4 (toxic)	Facial weakness, scapular winging, asymmetric
Oculopharyngeal (OPMD)	AD	*PABPN1* — **GCG / polyalanine**	PABP2	Late ptosis + dysphagia; rimmed vacuoles

Duchenne and Becker muscular dystrophy (the prototype dystrophinopathy)

- **Genetics:** X-linked recessive; the *DMD* gene at **Xp21** is the largest human gene (~2.5 million bp, **79 exons**). **~65–75% of cases are deletions/duplications** (hot-spots between exons 44–52); the remainder are point/nonsense mutations. Roughly **one-third are sporadic** (new mutations); germline mosaicism gives a recurrence risk up to ~14% even when the mother tests negative.
- **The reading-frame (Monaco) rule — the key concept: in-frame** mutations preserve the triplet reading frame → a shortened but partly functional dystrophin → **milder Becker phenotype**; **out-of-frame (frameshift)** mutations destroy the frame → absent dystrophin → **severe Duchenne**.
- **DMD clinical course:** boys normal at birth; proximal lower-limb weakness from ~3–5 yr, **Gowers sign**, toe-walking, waddling gait, firm **calf pseudohypertrophy**; loss of ambulation ~8–12 yr; progressive contractures, scoliosis. **Cardiomyopathy in ~1/3 by age 14 and virtually all by 18**; respiratory failure. Intellectual disability may occur.
- **BMD:** later onset, ambulation usually retained beyond 15 yr, survival into 4th–5th decade; cardiomyopathy may dominate (occasionally heart failure is the only manifestation) and may require transplantation.

- **Labs:** CK markedly elevated (often >10,000 IU/L in DMD, lower in BMD); myopathic EMG; **immunostain/Western blot** — dystrophin **absent in DMD, reduced/altered in BMD** (immunoblot needed in BMD as staining can look normal).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Dystrophin–glycoprotein complex (DGC):** Draw the sarcolemma as a bilayer. Label, from inside out: *F-actin / cytoskeleton → Dystrophin (N-terminus to actin, C-terminus to β-dystroglycan) → β-Dystroglycan (transmembrane) → α-Dystroglycan (extracellular) → Laminin-α2 (merosin) in basal lamina*; show the **Sarcoglycan complex (α, β, γ, δ) + sarcospan** spanning the membrane beside dystroglycan; mark *Calpain-3, Dysferlin, Caveolin-3* and the *nuclear envelope (emerin, lamin A/C, nesprin)* to show where different dystrophies localise.
- **Diagram 2 — Gowers sign:** Sequential figures of a child rising from the floor by "climbing up the legs" — turning prone, pushing onto hands and feet, then walking the hands up the thighs to stand. Label *Gowers manoeuvre = proximal (hip/trunk) weakness*.

Clinical / Diagnostic significance

- **Pattern recognition localises the diagnosis:** limb-girdle (most dystrophies) vs facial weakness + scapular winging (**FSHD**) vs facial/distal weakness + grip myotonia (**DM1**) vs ptosis + dysphagia (**OPMD**) vs early contractures + heart block (**EDMD**).
- **Investigations:** serum **CK** (screening; very high in dystrophinopathies/Miyoshi, normal-mildly raised in FSHD/EDMD/OPMD); **EMG** (myopathic, short-duration small-amplitude polyphasic MUAPs; myotonic discharges in DM); **muscle MRI/ultrasound** for pattern of involvement; **immunohistochemistry/immunoblot** (dystrophin, sarcoglycans, dysferlin, α-dystroglycan, emerin); **genetic testing** is definitive (MLPA/array CGH for deletions-duplications, then next-generation sequencing for point mutations).
- **Multisystem surveillance (high-yield): annual ECG + echo/cardiac MRI** in DMD/BMD and EDMD/laminopathy; **FVC** monitoring for respiratory failure; cataracts, conduction block, insulin resistance, testicular atrophy and hypersomnia in DM1; aspiration risk in OPMD.
- **Management — largely supportive but evolving:**
  - **Glucocorticoids** (prednisone ~0.75 mg/kg/day or **deflazacort** ~0.9 mg/kg/day) slow progression and prolong ambulation in DMD.
  - **Cardiac:** ACE-inhibitor/ARB (start ~age 10 in DMD), beta-blockers, afterload reduction; **pacemaker/ICD** is potentially life-saving in EDMD/laminopathy and significant DM conduction disease; cardiac transplant in selected BMD.
  - **Respiratory/orthopaedic:** non-invasive ventilation (BiPAP), physiotherapy, stretching/bracing, ankle-foot orthoses for foot-drop, scoliosis surgery, scapular fixation in FSHD, cricopharyngeal myotomy in OPMD.
  - **Molecular therapies (DMD): exon-skipping antisense oligonucleotides** (e.g., eteplirsen — exon 51 skipping, converts DMD toward a BMD phenotype) and **stop-codon read-through** agents (ataluren for nonsense mutations); DUX4-suppression trials ongoing in FSHD.
  - **Symptomatic myotonia: mexiletine** in DM1/DM2; modafinil for hypersomnia.

- **Genetic counselling** is integral: carrier testing of female relatives in X-linked DMD/BMD/EDMD; recognition of **anticipation** in DM1 and **maternal transmission of the congenital form**; prenatal/germline-mosaicism counselling.

High-yield exam pointers

- **DMD/BMD** — X-linked, *Xp21* dystrophin; **reading-frame rule**: in-frame → Becker, out-of-frame → Duchenne.
- **Gowers sign + calf pseudohypertrophy + CK >10,000** = think Duchenne; death from cardiomyopathy/respiratory failure.
- **DM1** — AD, **CTG** expansion in *DMPK* (19q13); **genetic anticipation**; congenital form from **affected mothers**; grip/percussion myotonia, hatchet face, frontal balding, cataracts, heart block. **DM2 (PROMM)** = **CCTG** in *CNBP*, proximal, no congenital form.
- **FSHD1** — contraction of **D4Z4 repeat at 4q35** (<35 kb) → toxic **DUX4** expression; facial weakness + scapular winging; heart spared.
- **EDMD triad** — early **contractures**, humero-peroneal weakness, **cardiac conduction defects/sudden death**; emerin (X-linked) or lamin A/C (AD).
- **OPMD** — AD, **GCG/polyalanine** expansion in *PABPN1*; late ptosis + dysphagia; **rimmed vacuoles**, 8.5-nm intranuclear tubular filaments.
- **LGMD** — new ENMC nomenclature: AD = **LGMD-D**, AR = **LGMD-R**; commonest adult types — calpainopathy (R1), FKRP (R9), anoctaminopathy (R12).
- **Always exclude treatable mimics** — immune-mediated necrotising myopathy (anti-HMGCR/anti-SRP) can mimic LGMD.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Muscular Dystrophies and Other Muscle Diseases" (Amato & Brown).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Disorders of Skeletal Muscle" (dystrophin–glycoprotein complex, *DMD* gene structure/hot-spots, reading-frame rule, DMD/BMD clinical course and therapy including exon-skipping/ataluren, LGMD classification).

◆ ◆ ◆

Myasthenia gravis

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

Definition / Introduction — Myasthenia gravis (MG) is the commonest primary disorder of the neuromuscular junction (NMJ), an **antibody-mediated autoimmune disease** characterised by **fatigable weakness of skeletal muscle**. The fundamental defect is a **reduction in the number of functioning acetylcholine receptors (AChRs)** at the post-synaptic muscle membrane, most often caused by anti-AChR antibodies, producing weakness that worsens with repeated activity and improves with rest. It is eminently treatable, with contemporary mortality falling from ~70% a century ago to the present **1–5%**.

Pathophysiology and immunopathology

- **Normal transmission:** acetylcholine (ACh) is synthesised in the motor nerve terminal and stored in vesicles (quanta); a nerve action potential releases ACh from **150–200 vesicles**, which binds AChRs packed on the crests of post-synaptic folds. The **AChR is a pentamer (2α, 1β, 1δ, and 1γ or ε)** around a central cation pore; ACh binding opens the channel, Na^+ entry depolarises the end-plate, and if large enough triggers a muscle action potential. Transmission is terminated by **acetylcholinesterase (AChE)**.
- **Clustering machinery:** presynaptic **agrin** binds **LRP4**; the agrin–LRP4 complex activates **MuSK** (muscle-specific tyrosine kinase), which recruits **DOK7** and **rapsyn** to cluster AChRs. These molecules underlie both autoimmune MG and the congenital myasthenic syndromes.
- **Core defect in MG:** fewer available AChRs **plus flattened, "simplified" post-synaptic folds** and a widened synaptic cleft → small end-plate potentials that fail to reach threshold → transmission failure. Normal **presynaptic "rundown"** (declining ACh release on repetitive activity) superimposed on this margin recruits fewer fibres with each impulse → clinical **fatigue** and the **decremental response** on repetitive nerve stimulation (RNS).
- **Anti-AChR antibodies (IgG, T-cell dependent)** reduce receptors by three mechanisms: (1) **cross-linking and accelerated endocytosis/turnover** of AChRs; (2) **complement-mediated lysis** of the post-synaptic membrane; (3) **direct blockade** of the ACh-binding site.
- **MuSK antibodies** are **IgG4** — they **do not fix complement** (hence anti-MuSK MG does not respond to complement inhibitors); they block MuSK–LRP4 binding. **LRP4 antibodies** are **IgG1**, complement-activating, like AChR antibodies.
- **Thymus:** abnormal in ~75% of AChR-antibody-positive patients — **~65% hyperplastic** (germinal centres), **~10–15% thymoma**. Thymic **myoid cells** express surface AChR and may initiate autosensitisation; **Treg deficiency/dysfunction** permits escape of autoreactive lymphocytes.

Clinical features and subtypes

- **Cardinal feature:** painless, **fatigable weakness** — worse with use and late in the day, better after rest/sleep; **fluctuating** course with exacerbations and remissions, especially in the first 1–3 years.
- **Ocular (initial in ~two-thirds): ptosis and diplopia**; if weakness stays confined to ocular muscles for **≥2–3 years**, generalisation is unlikely (**ocular MG**, ~10–15%; up to ~50–58% in Asians).

- **Bulbar/facial:** "snarling"/**myasthenic sneer** on smiling, **nasal regurgitation**, dysphagia, nasal or "mushy" dysarthria, hoarseness, fatigable chewing.
- **Axial/limb: neck-extensor weakness → "dropped-head"**; limb weakness typically **proximal and may be asymmetric**; **deep-tendon reflexes preserved; sensation normal**.
- **Generalisation** occurs in ~85% within ~3 years. **MuSK-MG:** prominent **bulbar, neck and respiratory** weakness with **muscle atrophy**, female predominance, often poor/worsening response to anticholinesterases.

Subtype	Onset / sex	Antibody	Thymus
Ocular	Any; childhood in Asia	AChR (~50%)	Usually normal
Early-onset (EOMG)	<50 y; F>M	AChR	**Hyperplasia**
Late-onset (LOMG)	>50 y; M>F	AChR ± titin, ryanodine	Normal/atrophic
Thymomatous	Peak ~50 y; M=F	AChR + striational (titin, ryanodine)	**Thymoma**
MuSK	30–50 y; marked F	**MuSK (IgG4)**	Normal/minimal
LRP4 / seronegative	Often younger	LRP4 (IgG1) / none detectable	Hyperplasia in some

MGFA clinical classification

- **Class I** — ocular weakness only (± eyelid-closure weakness), all other muscles normal.
- **Class II** — mild generalised weakness; **III** — moderate; **IV** — severe generalised (each subdivided **a** = limb/axial predominant, **b** = bulbar/respiratory predominant).
- **Class V** — intubation (with or without ventilation) = **myasthenic crisis**. *(Harrison/landmark trials enrol "class II–IV" gMG and grade severity with MGADL and QMG scores.)*

Diagnosis and evaluation

- **Bedside provocation / clinical signs:** sustained upgaze provokes **ptosis**; **Cogan's "lid twitch"** (lid overshoot on saccade from down- to up-gaze); **enhanced ptosis / "curtain sign"** (lifting one lid worsens the other); "**peek sign**" and inability to "bury the eyelashes" on forced closure; **pseudo-internuclear ophthalmoplegia**; the **ice-pack test** — 2 min of cooling a ptotic lid producing **≥2 mm lid rise** (high sensitivity).
- **Serology: anti-AChR antibody** (radioimmunoassay) — **~85% positive in generalised, ~50% in ocular** MG; virtually diagnostic but a negative test does **not** exclude MG. **Anti-MuSK** in **~40% of AChR-negative generalised** MG; **anti-LRP4** in a small proportion of double-seronegatives. **Striational antibodies (titin, ryanodine)** are non-pathogenic but flag **thymoma/older or severe disease**.
- **Electrodiagnosis: RNS at 2–3 Hz shows a decrement >10%** (test weak/proximal muscles); **single-fibre EMG — increased jitter and blocking** with normal fibre density — is the most **sensitive** test (confirmatory but not specific).
- **Anticholinesterase test: edrophonium** historically (rapid onset/short action); now largely abandoned for serology/EMG.

- **Search for associated disease: chest CT/MRI** (thymoma — present in ~10–15%); **thyroid function** (hyper-/hypothyroidism in ~3–8%); screen for SLE/RA, and pre-immunosuppression work-up — **TB, hepatitis, glucose/HbA1c, blood pressure, bone densitometry**; baseline **spirometry (FVC, MIP/MEP)**.

Differential diagnosis

Disorder	Distinguishing features
Lambert–Eaton myasthenic syndrome (LEMS)	**Proximal lower-limb** weakness, **areflexia, autonomic symptoms** (dry mouth, orthostasis); **P/Q-type VGCC antibody**; RNS shows **decrement at low rate but ≥100% increment at high rate (20–50 Hz)/post-exercise**; ~paraneoplastic with **SCLC**. Treat with **3,4-DAP (amifampridine)** + pyridostigmine
Congenital myasthenic syndromes	Non-autoimmune; onset infancy/childhood; **seronegative**; >30 genes (commonest *CHRNε*, also *RAPSN*, *COLQ*, *DOK7*)
Botulism	Descending paralysis, **dilated/poorly reactive pupils**, autonomic features; **incremental** CMAP at high-rate RNS
Drug-induced / ICI-related MG	Penicillamine; checkpoint inhibitors (overlap **myositis/myocarditis**, high mortality)
Others	Graves'/thyroid ophthalmopathy, intracranial compressive lesion, oculopharyngeal dystrophy, mitochondrial PEO/**Kearns–Sayre**

Treatment

- **Symptomatic — anticholinesterase: pyridostigmine 30–60 mg every 4–8 h** (max ~360–480 mg/day); onset 15–30 min, lasts 3–4 h; muscarinic side effects (cramps, diarrhoea, salivation) countered by glycopyrrolate/loperamide. **Anti-MuSK patients respond poorly and may worsen.**
- **Thymectomy:** mandatory for **thymoma**; the **MGTX trial** showed extended trans-sternal thymectomy in **non-thymomatous, AChR-positive generalised** MG improves strength, lowers prednisone/second-line needs and hospitalisations — offer to patients **<65 y** unless purely ocular. Not established for MuSK/seronegative MG. Optimise strength (IVIg/PLEX) before surgery; **never an emergency procedure**.
- **Chronic immunosuppression: corticosteroids** — start low and up-titrate (or pre-treat with IVIg/PLEX before high dose to avoid early steroid worsening). **Steroid-sparing: azathioprine** (2–3 mg/kg; *avoid allopurinol*), **mycophenolate mofetil** (1–1.5 g bid), **calcineurin inhibitors** (cyclosporine/tacrolimus). **Rituximab** (anti-CD20) is **highly effective in MuSK-MG** and beneficial in new-onset disease (RINOMAX/RITUXIMAB data).
- **Newer targeted agents** — work within weeks, used as bridge or in refractory disease:
  - **Complement (C5) inhibitors: eculizumab, ravulizumab** (IV mAbs), **zilucoplan** (SC peptide) — only for **AChR-positive** generalised MG; **meningococcal vaccination required** (B + ACWY).
  - **FcRn antagonists: efgartigimod** (IV/SC), **rozanolixizumab** (SC; the **only one approved for both AChR- and MuSK-positive** MG) — increase IgG catabolism, lowering pathogenic antibody.

- **Rapid rescue: plasmapheresis** (5–6 exchanges) and **IVIg 2 g/kg over 2–5 days** — equally effective for crisis or peri-operative optimisation.

Myasthenic crisis and drugs to avoid

- **Myasthenic crisis** = exacerbation severe enough to threaten life, usually **ventilatory failure** needing intubation/NIV (= MGFA class V). Commonest trigger is **intercurrent infection**; manage in **ICU** with airway support, treat infection, and **PLEX or IVIg**. Distinguish from **cholinergic crisis** (anticholinesterase excess — now rare).
- **Drugs that worsen MG (avoid): aminoglycosides, fluoroquinolones, macrolides**; **non-depolarising neuromuscular blockers**; **β-blockers**; **procainamide, quinine/quinidine, chloroquine/mefloquine**; **IV magnesium**; **penicillamine** (can cause MG); **botulinum toxin**; **immune-checkpoint inhibitors**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Normal vs myasthenic NMJ (side-by-side):** label *motor axon terminal, ACh vesicles (quanta), active zone, voltage-gated Ca^{2+} channel, synaptic cleft, AChR on crests of post-synaptic folds, AChE, voltage-gated Na^{+} channels, agrin–LRP4–MuSK–DOK7–rapsyn clustering complex*. On the MG side label: **reduced AChR number, flattened/simplified post-synaptic folds, widened synaptic cleft, AChR autoantibody + complement (membrane attack complex)**.
- **Diagram 2 — Myasthenic facies:** label **bilateral ptosis, compensatory frontalis contraction/raised eyebrow, myasthenic "snarl/sneer" on smiling, head drop**.

Clinical / Diagnostic significance

- **Pattern recognition:** fatigable, fluctuating weakness with **ocular onset, preserved reflexes and normal sensation** is the clinical signature; confirm with serology + RNS/SFEMG before committing to long-term immunotherapy and surgery.
- **Antibody status guides therapy:** MuSK-MG (IgG4) ignores complement inhibitors but responds to **rituximab/rozanolixizumab**; AChR-MG suits **complement inhibitors**.
- **Always image the chest** — thymoma changes management (mandatory thymectomy, striational-antibody association).
- **Monitor FVC/MIP/MEP** serially; falling vital capacity heralds crisis. **Vaccinate against meningococcus** before C5 inhibitors.
- **~20% achieve sustained remission**; thymectomy improves the odds in AChR-positive disease.

High-yield exam pointers

- Pentameric **AChR (2α β δ γ/ε)**; ACh from **150–200 vesicles** per impulse.
- **Anti-AChR: 85% generalised / 50% ocular**; **anti-MuSK = ~40% of AChR-negative generalised** MG (IgG4, no complement).
- **RNS decrement >10% at 2–3 Hz**; **SFEMG jitter** = most sensitive. **MG decrements; LEMS increments.**

- **Ice-pack test:** ≥2 mm lid rise after 2 min cooling. **Cogan lid-twitch, curtain sign, peek sign** are clinical clues.
- **Thymoma in ~10–15%; thymic hyperplasia in ~65%** of AChR-positive MG; F:M ≈ 3:2.
- **MGTX trial:** thymectomy benefits non-thymomatous AChR-positive generalised MG.
- **Crisis** = ventilatory failure → ICU + **PLEX/IVIg**; commonest trigger = infection.
- **Avoid:** aminoglycosides, quinolones, macrolides, β-blockers, magnesium, penicillamine, neuromuscular blockers, checkpoint inhibitors.
- **MuSK-MG** often **worsens with anticholinesterases**; treat with rituximab.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Myasthenia Gravis and Other Diseases of the Neuromuscular Junction" (pathophysiology, antibody mechanisms, diagnostic table, MGTX, complement/FcRn agents, crisis, drugs to avoid).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Disorders of Neuromuscular Transmission" (clinical subtypes, ocular signs — lid twitch, curtain/peek sign, pseudo-INO; immunopathology, electrodiagnosis, HLA associations).
- **CMDT 2026** — "Nervous System Disorders: Myasthenia Gravis" (current drug doses, thymectomy and FcRn/complement-inhibitor management).

Coverage note: The full **MGFA clinical classification (classes I–V with a/b subdivisions)** is standard internal medicine; the corpus references MGFA "class II–IV" and the MGADL/QMG severity scores but does not tabulate every subclass. The older **Osserman classification** is not in the corpus and is omitted.

◆ ◆ ◆

Narcolepsy

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

Definition / Introduction — Narcolepsy is a chronic, lifelong **central disorder of hypersomnolence** characterised by difficulty sustaining wakefulness, dysregulation of REM sleep (intrusion of REM phenomena into wakefulness) and disturbed nocturnal sleep. The cardinal feature is **excessive daytime sleepiness (EDS)** present in 100% of patients, classically accompanied by the *narcoleptic tetrad* of cataplexy, sleep paralysis and hypnagogic hallucinations. It results from selective loss of the hypothalamic **orexin (hypocretin)** neurons and affects about **1 in 2000** people, with onset typically between 10–30 years of age.

Pathophysiology — the orexin (hypocretin) deficiency

- Caused by **loss of the lateral/posterior hypothalamic neurons that produce orexin-A and orexin-B (hypocretin-1 and -2)** neuropeptides. Orexins normally promote long episodes of wakefulness and suppress REM sleep by exciting the wake-promoting monoaminergic nuclei (noradrenergic locus coeruleus, serotonergic raphe, histaminergic tuberomammillary nucleus).

- Loss of orexin signalling **destabilises the sleep–wake "flip-flop" switch** → frequent intrusions of sleep into wakefulness and **untimed REM sleep** (causing cataplexy, sleep paralysis, hallucinations).
- **Type 1 narcolepsy** (with cataplexy): near-complete (~90%) loss of orexin neurons → **very low/undetectable CSF orexin (hypocretin-1)**. **Type 2** (without cataplexy): orexin levels usually normal; partial neuronal loss or other uncharacterised mechanisms.
- **Autoimmune mechanism** (strongly supported): narcolepsy has the **strongest known HLA association** of any disease — **HLA DQB1*06:02** is present in **>90%** of type 1 patients (CMDT: 85–95%) versus only **12–25%** of the general population. Hypothesised **molecular mimicry**: immune response to influenza, *Streptococcus* or other infections cross-reacts with orexin neurons in genetically susceptible (DQB1*06:02+) individuals; patients show heightened **T-cell responses ($CD4^+$/$CD8^+$) against orexin peptides**.
- A documented **8- to 12-fold rise in childhood narcolepsy** followed the *Pandemrix* H1N1 influenza vaccine (AS03-adjuvanted) in Europe — supporting the infection/vaccine-triggered autoimmune model.
- **Secondary ("symptomatic") narcolepsy**: damage to the hypothalamic orexin neurons or their projections by **anti-Ma2 paraneoplastic antibodies**, severe traumatic brain injury, diencephalic/midbrain tumours, strokes, multiple sclerosis, encephalitis or **Niemann-Pick disease type C**.

Clinical features — the narcoleptic tetrad and beyond

Feature	Frequency	Key clinical points
Excessive daytime sleepiness / sleep attacks	100%	Irresistible sleep at inappropriate times (talking, driving, eating); naps last minutes–20–30 min; patient wakes **refreshed** (unlike OSA)
Cataplexy	~60–70%	**Sudden bilateral loss of muscle tone, consciousness retained**; triggered by strong emotion (laughter, excitement, anger >95%); spares respiratory and ocular muscles
Sleep paralysis	25–50%	Inability to move/speak at sleep onset (hypnagogic) or on waking (hypnopompic); lasts up to 15–20 min; frightening
Hypnagogic/hypnopompic hallucinations	20–40%	Vivid, often frightening visual (also auditory/vestibular) imagery at sleep–wake transition
Disturbed nocturnal sleep	70–80%	Fragmented sleep with frequent awakenings
Automatic behaviour	20–40%	Semi-purposeful acts (e.g., writing nonsense, driving to wrong place) with amnesia, from microsleeps

- **Cataplexy in detail**: muscle weakness from **decreased noradrenergic excitation + increased GABA/glycinergic inhibition of spinal motor neurons** — essentially REM atonia intruding into wakefulness. During the attack, muscle stretch reflexes, **H-reflex and F-responses are reduced/absent**; EEG shows wakefulness (if >1–2 min, REM appears). Usually appears months–years after sleep attacks; **status cataplecticus** may follow abrupt withdrawal of anticataplectic drugs.

- The full tetrad (all four) occurs in only ~10%; three of four in ~30%. **Cataplexy is the most specific symptom** — it occurs in almost no other disorder, hence it defines type 1.
- **Children** may present atypically with hyperactivity, prolonged nocturnal sleep, *cataplectic facies* (facial hypotonia, ptosis, tongue protrusion) or perioral dystonic movements unrelated to emotion.
- **Comorbidities**: obesity/raised BMI, type 2 diabetes, REM sleep behaviour disorder (up to 36%, often drug-induced), periodic limb movements (10–60%), sleep apnoea (~30%, often central), depression and anxiety.

Classification (ICSD-3) and diagnostic criteria

Narcolepsy is part of the **Central Disorders of Hypersomnolence** (ICSD-3, AASM 2014), which also include idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical/medication/psychiatric disorder, and insufficient sleep syndrome.

Parameter	Narcolepsy type 1 (NT1)	Narcolepsy type 2 (NT2)
Older name	Narcolepsy with cataplexy / hypocretin-deficiency syndrome	Narcolepsy without cataplexy
Cataplexy	**Present**	Absent
CSF hypocretin-1	**≤110 pg/mL** (or ≤⅓ of normal mean)	>110 pg/mL (normal)
MSLT	Mean sleep latency **≤8 min** + **≥2 SOREMPs** (1 may be a sleep-onset REM on prior PSG)	Same MSLT criterion
HLA DQB1*06:02	~100% positive	~25% positive

- *Reclassification rule*: an NT2 patient later found to have **CSF hypocretin-1 ≤110 pg/mL is reclassified as NT1**.
- **Diagnostic workup**: clinical history (chronic EDS + cataplexy is often sufficient); quantify sleepiness with the **Epworth Sleepiness Scale**; confirm objectively with **overnight polysomnography (PSG) followed next day by the Multiple Sleep Latency Test (MSLT)**.
- **MSLT protocol**: five 20-minute nap opportunities every 2 hours; positive when **mean sleep latency <8 min** and **REM (SOREMP) in ≥2 naps**. A **sleep-onset REM period within 15 min** at night is also supportive. **Stop stimulants 1 week and antidepressants 3 weeks** before the test (they suppress REM); ensure adequate prior sleep.

Differential diagnosis

- **Of sleep attacks / EDS**: obstructive sleep apnoea (most common cause; un-refreshing naps, snoring, obesity), insufficient sleep syndrome, **idiopathic hypersomnia** (prolonged un-refreshing sleep, "sleep drunkenness", **no SOREMPs**, no cataplexy), Kleine-Levin syndrome (recurrent hypersomnia + hyperphagia + hypersexuality in young males), circadian rhythm disorders, drug/alcohol-related hypersomnolence.
- **Of cataplexy**: partial complex seizure (altered consciousness, postictal confusion, epileptiform EEG), absence and atonic seizures, drop attacks, syncope, vertebrobasilar insufficiency, basilar

migraine, and **pseudocataplexy** (functional, triggered by negative thoughts, lasting minutes–hours).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hypnogram comparison (healthy vs narcolepsy)** — two stacked sleep-stage tracings against clock time. Labels: *Awake, REM, N1, N2, N3*; *clock time 20:00 → 16:00*; **"sleep-onset REM period (SOREMP) <15 min"**, "fragmented nocturnal sleep", "frequent daytime naps containing REM" on the narcolepsy trace; "normal long NREM-before-REM latency" on the healthy trace.
- **Orexin pathophysiology schematic** — *lateral/posterior hypothalamus* with **orexin (hypocretin) neurons** projecting to wake-promoting nuclei (*locus coeruleus – NE; raphe – 5-HT; tuberomammillary nucleus – histamine*) and inhibiting *VLPO*. Show **autoimmune destruction** (label: *HLA DQB1*\06:02, $CD4^+$/$CD8^+$ T cells, molecular mimicry, H1N1/Streptococcus*) → loss of orexin → unstable sleep–wake switch → "EDS + REM intrusion (cataplexy, sleep paralysis, hallucinations)".

Clinical / Diagnostic significance

- **Investigations**: PSG + MSLT are the diagnostic standard; **CSF hypocretin-1 ≤110 pg/mL** is highly specific for NT1 and useful when MSLT is equivocal or REM-suppressing drugs cannot be stopped; **HLA DQB1*06:02** typing supports (but does not confirm — common in healthy people) the diagnosis. Screen for secondary causes (anti-Ma2, neuroimaging) if onset is atypical or focal signs are present.
- **Treatment is symptomatic** — there is no cure. Non-pharmacological: regular adequate nocturnal sleep, **scheduled 15–20 min afternoon naps**, sleep hygiene, support groups, and **driving counselling** (legal/safety responsibility — advise against driving until effectively treated).

Target	Drug (dose)	Class / mechanism
EDS	**Modafinil 200–400 mg** every morning	Wake-promoting agent (first line)
	Armodafinil 150–250 mg morning	R-isomer of modafinil, longer-acting
	Methylphenidate 10–20 mg bid; dextroamphetamine 10 mg bid	Stimulants (abuse/sympathomimetic risk)
	Solriamfetol 75–150 mg/day	Norepinephrine–dopamine reuptake inhibitor
	Pitolisant 8.9–35.6 mg/day	Selective histamine **H3 receptor antagonist/inverse agonist**
Cataplexy	Venlafaxine 37.5–150 mg; fluoxetine 10–40 mg	SNRI / SSRI (suppress REM)
	Protriptyline 10–40 mg/d; clomipramine 25–50 mg/d (imipramine)	TCAs (anticholinergic limits use)

Target	Drug (dose)	Class / mechanism
Both EDS + cataplexy + fragmented sleep	**Sodium oxybate (gamma-hydroxybutyrate) 3–9 g** in 2 nightly divided doses (bedtime + 2.5–4 h later); low-sodium (calcium/magnesium/potassium/sodium oxybate) versions	Consolidates slow-wave sleep

- No antidepressant is FDA-approved specifically for narcolepsy, though they are standard for cataplexy. **Pitolisant and oxybates** uniquely improve both sleepiness and cataplexy.

High-yield exam pointers

- **Narcoleptic tetrad** = EDS + cataplexy + sleep paralysis + hypnagogic hallucinations; only ~10% have all four, EDS is universal.
- **NT1 = cataplexy + CSF hypocretin-1 ≤110 pg/mL**; **NT2 = no cataplexy, normal hypocretin**.
- **HLA DQB1*06:02** — strongest HLA disease association; >90% of NT1 but present in 12–25% of normals (not diagnostic alone).
- **MSLT diagnostic**: mean sleep latency **<8 min + ≥2 SOREMPs**; SOREMP <15 min at night supportive.
- **Cataplexy** = sudden emotion-triggered atonia with **preserved consciousness**, spares respiratory/ocular muscles; abolished reflexes; most specific feature.
- **Pandemrix H1N1 vaccine** and influenza/*Streptococcus* → autoimmune trigger via molecular mimicry.
- **First-line for EDS = modafinil**; newer agents **pitolisant (H3 inverse agonist)** and **solriamfetol (NDRI)**.
- **Sodium oxybate (GHB)** treats EDS, cataplexy and disrupted night sleep together.
- Stop **stimulants 1 week** and **antidepressants 3 weeks** before MSLT to avoid REM suppression.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Sleep Disorders" (orexin/hypocretin pathophysiology, HLA DQB1*06:02, type 1 vs type 2, MSLT, treatment regimens).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Sleep and Its Disorders" (ICSD-3 classification, clinical-feature frequencies, cataplexy mechanism/cataplectic facies, CSF hypocretin-1 ≤110 pg/mL diagnostic table, drug doses, differential diagnosis).
- **CMDT 2026** — "Psychiatric Disorders" (narcolepsy criteria and current management — modafinil/armodafinil dosing, HLA 85–95%).

◆ ◆ ◆

Orthostatic hypotension

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

Definition / Introduction — Orthostatic (postural) hypotension (OH) is defined (Freeman *et al.*, 2011 consensus) as a **sustained fall in systolic blood pressure (SBP) ≥20 mmHg or in diastolic blood pressure (DBP) ≥10 mmHg within 3 minutes of active standing or of head-up tilt (HUT) ≥60°**. In patients with supine hypertension a drop of **≥30/15 mmHg** is used. It is a cardinal sign of **sympathetic vasoconstrictor (autonomic) failure** and a major cause of orthostatic intolerance, falls, syncope and increased mortality, especially in the elderly and in neurodegenerative disease. Prevalence rises from **<5% below age 50 to ~20% above age 70**.

Normal orthostatic homeostasis and pathophysiology

- On standing, **~500–700 mL of blood (Bradley: 300–800 mL) pools in the lower limbs and splanchnic venous bed**, reducing venous return, cardiac filling and stroke volume.
- The fall in BP unloads aortic/carotid **baroreceptors** → reduced afferent traffic to the *nucleus tractus solitarius* → reflex **sympathetic activation** (arteriolar + venoconstriction, ↑heart rate, ↑contractility) and **vagal withdrawal**.
- Net normal response: SBP changes little (falls ~10 mmHg), **DBP rises ~5 mmHg, heart rate rises 5–20 beats/min**; the leg and abdominal muscle pump aids venous return.
- OH results when this reflex arc fails at any level — **afferent (baroreceptors), central integration, efferent sympathetic outflow, or peripheral release of norepinephrine** — or when cardiac output/intravascular volume is inadequate.
- The hallmark of **neurogenic OH (NOH)** is **inadequate peripheral norepinephrine release → failure of vasoconstriction**, with a *blunted* compensatory tachycardia.

Diagnostic criteria and variants

Variant	Defining features
Classical OH	Sustained ↓SBP ≥20 or ↓DBP ≥10 mmHg within 3 min of standing/HUT
OH with supine hypertension	Orthostatic drop ≥30/15 mmHg
Initial OH	Transient ↓SBP >40 / ↓DBP >20 mmHg within 15–30 s, recovering by 45 s; young subjects; cardiac output–vascular resistance mismatch (not autonomic failure)
Delayed (late) OH	SBP steady for first 3–5 min then falls (sometimes only after 10 min tilt); early/mild adrenergic failure
Postprandial OH	BP fall within ~2 h of a large, high-carbohydrate meal ± alcohol (splanchnic pooling); elderly/autonomic patients

- **Neurogenic vs non-neurogenic OH** — a compensatory **HR rise >15 beats/min** indicates *non-neurogenic* OH (volume depletion, drugs, cardiac); **HR rise <15 beats/min** suggests **neurogenic OH**.
- A more accurate marker is the **ΔHR/ΔSBP ratio** (cardiac baroreflex gain): **<0.5 beats/min/mmHg** after 3 min strongly indicates **NOH**.

Etiology

Neurogenic OH (autonomic failure)	Non-neurogenic OH
Primary (synucleinopathies): Multiple system atrophy (**MSA / Shy-Drager**), Parkinson's disease with autonomic failure, Dementia with Lewy bodies, **Pure autonomic failure (Bradbury-Eggleston)**	**Volume depletion:** haemorrhage, vomiting/diarrhoea, dehydration, over-diuresis, dialysis
Secondary peripheral autonomic neuropathies: Diabetic autonomic neuropathy, **amyloidosis (AL & hereditary ATTR)**, autoimmune autonomic ganglionopathy (anti–g-AChR α3), paraneoplastic, Sjögren, GBS, HIV, porphyria, alcoholic, B12 deficiency	**Cardiac:** heart failure, chronotropic incompetence, bradyarrhythmias
Hereditary: Familial dysautonomia (**Riley-Day / HSAN III**), **dopamine β-hydroxylase (DBH) deficiency**	**Drug-induced (very common):** α-blockers, diuretics, nitrates/vasodilators, tricyclics, phenothiazines/antipsychotics, dopamine agonists, antihypertensives
Spinal cord: traumatic quadriplegia, syringomyelia, MS	**Endocrine:** Addison disease, hypoaldosteronism, phaeochromocytoma; vasodilator excess (mastocytosis, carcinoid)

Clinical features

- **Cerebral hypoperfusion:** lightheadedness/dizziness on standing (commonest), presyncope, blurred or tunnel vision, cognitive slowing/"brain fog", **syncope and falls**.
- **Regional ischaemia: "coat-hanger" neck/shoulder/sub-occipital pain** (cervical-trapezius muscle ischaemia); **platypnea** (orthostatic dyspnoea from apical lung hypoperfusion); orthostatic angina; orthostatic headache.
- **Triggers:** rising in the morning (worst after bed rest), large meals/alcohol, heat, fever, exercise, hyperventilation, sepsis, surgery, intensified antihypertensives.
- Many patients — especially with chronic **NOH** — are **asymptomatic or present only with falls**, because cerebral autoregulation compensates; symptom reports alone are unreliable in the elderly.
- **Supine hypertension** coexists in >50% of autonomic-failure OH (baroreflex impairment), giving **"reverse dipping"** (higher nocturnal than morning BP) and end-organ damage.
- **Functional classes I–IV** grade severity from asymptomatic (class I) to severe daily disabling symptoms (class IV).

Investigations / autonomic testing

- **Bedside orthostatic vitals** — supine BP/HR, then BP/HR at **1 and 3 min** of standing (gold-standard bedside test); repeat as a single reading may mislead.
- **Tilt-table testing (60–70°)** with beat-to-beat finger arterial pressure — detects OH/NOH and distinguishes vasovagal, vasodepressor and cardioinhibitory syncope; pharmacologic provocation (nitroglycerin/isoproterenol) increases sensitivity.
- **Cardiovascular autonomic reflexes:** heart-rate variation to deep breathing and the **Valsalva manoeuvre/ratio** (parasympathetic/baroreflex), BP response to Valsalva (sympathetic adrenergic).

- **Sudomotor tests: QSART** (postganglionic sudomotor), **thermoregulatory sweat test** (pre- + postganglionic); **skin punch biopsy** for epidermal nerve fibre density and **phosphorylated α-synuclein** deposits (synucleinopathy).
- **Plasma catecholamines (supine + upright):** central/preganglionic NOH — normal supine NE that fails to rise on standing; peripheral/postganglionic — **low supine NE** (PAF often <200, even <100 pg/mL) failing to rise.
- **Bloods to find a cause:** CBC, metabolic panel, HbA1c/2-h GTT, B12, ferritin, vitamin D; serum free light chains/SPEP (amyloid); ganglionic AChR & paraneoplastic antibodies; TTR gene testing; fat-pad aspirate if amyloid suspected.

Management

Non-pharmacologic (first-line, often sufficient in mild/early OH):

- **Withdraw/reduce offending drugs** (diuretics, α-blockers, nitrates, tricyclics, antipsychotics, dopamine agonists) and correct iron/B12/D deficiency, anaemia, volume depletion.
- **↑Fluid to ~2–3 L/day and salt to 2 g, 2–3×/day**; a rapid **500 mL water bolus** gives a useful short-term pressor response.
- **Staged posture changes**, **physical counter-manoeuvres** (leg-crossing, leg/abdominal muscle tensing, squatting), **waist-high compression stockings** and an **abdominal binder** (reduces splanchnic pooling).
- **Head-of-bed elevation 30°** at night — reduces supine hypertension, nocturnal natriuresis and nocturia.

Drug	Class / action	Dose	Caution
Fludrocortisone	Mineralocorticoid — volume expansion + mild α-effect	0.1–0.2 (up to 0.4) mg morning	Supine HTN, hypokalaemia, oedema; check bone density long-term
Midodrine	Direct **α_1-agonist**	2.5 mg TID → 15 mg TID (usual 7.5–10)	Onset 30–60 min, lasts ~4 h; last dose **before 6 pm**; scalp tingling, piloerection, urinary urgency, supine HTN
Droxidopa	**Norepinephrine precursor** (newest agent, approved for NOH)	100 → 400–600 mg TID	Supine HTN; reduces falls in PD
Pyridostigmine	Cholinesterase inhibitor (↑ganglionic transmission)	30 → 60 mg TID	**No supine HTN**; helps GI hypomotility; cramps/diarrhoea
Atomoxetine	NE-reuptake inhibitor (adjuvant)	18 mg morning	CNS stimulation, tremor, anxiety
Desmopressin (DDAVP)	↑water reabsorption	low oral/nasal at night	Reduces nocturia; monitor for **hyponatraemia**

- **Supine hypertension** complicating treatment: keep head of bed up, short-acting bedtime antihypertensive, monitor end-organ function; avoid long-acting pressors late in the day.
- **DBH deficiency** is uniquely treated by **droxidopa** (replaces absent norepinephrine).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Baroreflex arc on standing:** label — *gravitational blood pooling (lower limbs + splanchnic bed)*, *↓venous return / ↓stroke volume*, *aortic & carotid sinus baroreceptors*, *nucleus tractus solitarius (medulla)*, *sympathetic efferent (norepinephrine → vasoconstriction, ↑HR, ↑contractility)*, *vagal withdrawal*; mark the **site of failure in neurogenic OH** (reduced peripheral NE release).
- **Tilt-table tracing (BP & HR vs time):** label — *supine baseline (with supine hypertension ~175 mmHg)*, *tilt-up*, *progressive sustained fall in SBP ≥20 mmHg*, *blunted/absent compensatory HR rise (<15 bpm)* = **neurogenic OH** (contrast with POTS: HR rise ≥30 bpm without sustained OH).

Clinical / Diagnostic significance

- OH is an **independent predictor of falls, fractures, coronary heart disease, heart failure, stroke and death**; **NOH** carries a grim prognosis — mortality ~**44% at 30 months and >60% at 10 years** (Bradley: 64% 10-year mortality), mostly from synucleinopathies and diabetes.
- It is a **key early clue to MSA** (symptomatic OH within 2 years, poor levodopa response, "hot cross bun" pons sign, glial cytoplasmic α-synuclein inclusions; cardiac **MIBG uptake preserved** in MSA but reduced in PD/DLB/PAF).
- Distinguish from **POTS** (chronic orthostatic intolerance + HR rise ≥30 bpm [≥40 if <19 yr] **without** sustained OH) and from **reflex/vasovagal syncope**.
- Always **measure both supine and standing BP at 1 and 3 min** in any patient with falls, syncope, dizziness, frailty or polypharmacy — the diagnosis is easily missed.

High-yield exam pointers

- OH = **↓SBP ≥20 or ↓DBP ≥10 mmHg within 3 min** of standing/tilt (≥30/15 if supine HTN) — Freeman 2011 consensus.
- **Neurogenic vs non-neurogenic:** HR rise <15 bpm or **ΔHR/ΔSBP <0.5 bpm/mmHg** = neurogenic.
- **Initial OH** (>40/20 mmHg, <30 s, young, recovers by 45 s) is **not** autonomic failure; **delayed OH** is beyond 3 min.
- **Coat-hanger headache** (neck/shoulder muscle ischaemia) and **platypnea** are characteristic clues.
- Commonest **primary** cause = **synucleinopathies** (MSA/Shy-Drager, PD, DLB, PAF); commonest **secondary** = diabetic autonomic neuropathy; commonest **reversible** cause = **drugs**.
- **>50% of autonomic-failure OH have supine hypertension** ("reverse dipping").
- First-line drugs: **fludrocortisone** and **midodrine**; **droxidopa** for NOH; **pyridostigmine** avoids supine HTN.
- **Midodrine last dose before 6 pm**; salt 2 g TID, fluids 2–3 L/day, **500 mL water bolus** = rapid pressor; **head-up tilt 30°** at night.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Disorders of the Autonomic Nervous System"* (definition, variants, neurogenic vs non-neurogenic criteria, autonomic testing, full pharmacology and doses) and *"Syncope"* (orthostatic hypotension as sympathetic vasoconstrictor failure, causes, treatment algorithm).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — *"Disorders of the Autonomic Nervous System"* (normal orthostatic physiology, consensus criteria, differential diagnosis, 10-year mortality data, pure autonomic failure, DBH deficiency, drug-induced dysautonomia).
- **DeJong's The Neurologic Examination, 8e** — sympathetic/parasympathetic effector table.

◆ ◆ ◆

Posterior reversible encephalopathy syndrome

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

Definition / Introduction — Posterior Reversible Encephalopathy Syndrome (**PRES**) is a clinico-radiological syndrome of acute neurological dysfunction (headache, seizures, altered consciousness, visual loss) accompanied by characteristic **vasogenic oedema** that predominantly affects the **posterior (parieto-occipital) white matter**. Harrison groups it among the **hyperperfusion disorders**, in which seemingly diverse conditions — hypertensive encephalopathy, eclampsia, post–carotid endarterectomy syndrome and calcineurin-inhibitor/drug toxicity — share a final common pathway of **hyperperfusion due to endothelial dysfunction**. The term is partly a misnomer: the syndrome is *not always reversible* and is *not always limited to the posterior brain*.

Pathophysiology

- The brain maintains nearly **constant cerebral blood flow (CBF)** across a wide range of systemic pressures by **autoregulation** — arteriolar vasodilation when systemic BP falls and arteriolar vasoconstriction when it rises. **Cerebral perfusion pressure (CPP) = MAP − ICP**.
- Beyond the upper limit of autoregulation, flow becomes **pressure-dependent**, producing hyperperfusion. **Vasogenic oedema** is the primary process causing neurological dysfunction.
- Two mechanisms are proposed (both probably contribute in every case):
  - **Exceeding the cerebral autoregulatory threshold** → increased CBF with **capillary leakage of fluid into the interstitium** (the "increased-pressure / breakthrough" model).
  - **Direct impairment of the blood–brain barrier (BBB)** itself by toxic or autoimmune endothelial injury (the "endothelial-dysfunction" model).
- **Why posterior predilection?** The posterior (vertebrobasilar) circulation is postulated to have a **lower threshold for autoregulatory breakthrough** and/or a **vasculopathy that is more common in these vessels**, owing to relatively sparse sympathetic innervation.
- A **noninflammatory vasculopathy** (vascular narrowing, especially in the posterior circulation) may be seen on vessel imaging; whether it is a primary cause of the oedema or a secondary phenomenon remains unclear.

Etiology / Classification

Harrison (Table 318-3) divides the causes mechanistically into those dominated by **raised capillary pressure** and those dominated by **endothelial dysfunction**.

Mechanism	Representative etiologies
Increased capillary pressure dominates	**Hypertensive encephalopathy**, including secondary causes — **renovascular hypertension, pheochromocytoma, cocaine use**
	Post–carotid endarterectomy syndrome
	Pre-eclampsia / eclampsia
Endothelial dysfunction dominates	**Calcineurin-inhibitor toxicity — cyclosporine, tacrolimus**
	Chemotherapeutic agent toxicity — cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate, **TNF-α antagonists**
	HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)
	Hemolytic-uremic syndrome (HUS)

- **Drug culprits behave atypically:** cyclosporine (and other agents) can precipitate PRES **even at low doses or after years of treatment**, and a **normal serum drug level does not exclude** the drug as the trigger.
- **Rapidity of BP rise, rather than the absolute value of pressure, appears to be the most important risk factor** — explaining why PRES can occur at modest BP in previously normotensive patients (e.g., eclampsia, post-transplant).

Clinical features

- **Headache** — non-specific, ranging from mild to severe; no characteristic quality.
- **Seizures** — frequent and often the presenting event; of multiple types depending on the severity and location of oedema. **Nonconvulsive seizures occur**, so a **low threshold for EEG** must be maintained.
- **Altered consciousness** — a spectrum from confusion to **coma**.
- **Focal neurological deficits** — the typical deficit is **cortical visual loss** (cortical blindness), reflecting the **occipital-lobe** involvement; visual hallucinations and field defects may occur.
- **Any focal deficit can occur** depending on the territory affected — e.g., after carotid endarterectomy, deficits referable to the **ipsilateral, newly reperfused hemisphere**.

Investigations / Neuroimaging

- **MRI is the investigation of choice.** Classically shows **high T2 / FLAIR signal of oedema, predominantly in the posterior occipital lobes, not respecting any single vascular territory** (Harrison Fig. 318-7 — a patient on cyclosporine after liver transplant presenting with seizures, headache and cortical blindness, with bilateral occipital white-matter signal change).
- **CT is less sensitive** but may show **patchy hypodensity** in the involved territory.
- **Vessel imaging** (MRA/CTA/angiography) may demonstrate **vascular narrowing, especially in the posterior circulation** (the noninflammatory vasculopathy).

- **CSF analysis** is often performed to exclude mimics but **yields nonspecific results**.
- **EEG** — used liberally because nonconvulsive status epilepticus is common; **continuous EEG monitoring** is often required.
- Serum studies to identify the precipitant (BP trend, renal/hepatic function, platelets and LDH for HELLP/HUS, pregnancy status); remember that **normal calcineurin-inhibitor levels do not exclude drug-induced PRES**.

Management

- **Treat the precipitant and lower the blood pressure judiciously** — the two pillars of therapy.
- **Antihypertensive therapy (when BP is elevated):** use titratable **IV agents — labetalol or nicardipine** (per Ch 318). In the broader setting of a **hypertensive emergency** (SBP/DBP ≥180/100 with end-organ damage), Harrison (Ch 288) lists **IV nicardipine** (most commonly used; avoid in severe aortic stenosis), **IV labetalol** (avoid in obstructive airways disease/COPD, bradycardia, second-/third-degree block) and **IV sodium nitroprusside**.
- **Controlled, not abrupt, BP reduction:** if BP is very high, **lower the MAP by ~20% initially**. Over-aggressive lowering may drop perfusion **below the patient's autoregulatory range and precipitate secondary ischaemia/infarction**. Aim for reduction rather than immediate normalisation, then transition to oral agents.
- **Remove / reduce the offending drug:** lower the dose of or discontinue the **calcineurin inhibitor (cyclosporine, tacrolimus)**; **sirolimus** (few recorded neurotoxic cases) may be a reasonable alternative in transplant patients.
- **Seizure control:** identify and treat seizures; **anticonvulsants are effective** when seizure activity is documented. In the **special case of eclampsia, magnesium sulfate** is the agent of choice for seizure control (and definitive treatment is delivery of the fetus).
- **Treat the underlying medical condition** — e.g., delivery in eclampsia, management of HELLP/HUS, withdrawal of cocaine/sympathomimetics, resection of pheochromocytoma.
- **Supportive neurocritical care** — control of cerebral oedema and seizures, with serial imaging to confirm radiological resolution.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Axial brain MRI (FLAIR) in PRES** — draw both cerebral hemispheres at the occipital level; shade **bilateral, symmetric high-signal (white) areas in the parieto-occipital white matter**. Labels: *Occipital lobe (parieto-occipital white matter oedema)*, *Bilateral / symmetric*, *Vasogenic oedema — high T2/FLAIR signal*, *Does not respect a single vascular territory*, *Relative cortical sparing*, *Posterior > anterior distribution*.
- **Cerebral autoregulation curve** — plot **CBF (y-axis) against MAP/CPP (x-axis)**. Labels: *Autoregulatory plateau (constant CBF)*, *Lower limit (below which CBF falls — ischaemia)*, *Upper limit / breakthrough (above which CBF rises — hyperperfusion → vasogenic oedema → PRES)*, *Arteriolar vasodilation (low BP)*, *Arteriolar vasoconstriction (high BP)*.

Clinical / Diagnostic significance

- PRES is a **treatable, frequently reversible cause of acute encephalopathy/seizures/cortical blindness** — prompt recognition and BP/drug control usually reverse the clinical and radiological abnormalities; delayed or excessive BP lowering risks **infarction and irreversible deficits**.
- **High-yield clinical contexts: eclampsia/HELLP** in obstetrics, **post-transplant patients on calcineurin inhibitors**, **chemotherapy recipients**, **hypertensive emergency**, **renovascular hypertension and pheochromocytoma**, and **cocaine/sympathomimetic** use.
- Always **review the full medication list** in any transplant or oncology patient presenting with headache, seizures or focal deficits — calcineurin-inhibitor PRES can occur with normal drug levels.
- Differentiate from **acute ischaemic stroke** (PRES oedema is bilateral, posterior and crosses vascular territories) and from **cerebral venous sinus thrombosis, vasculitis, and infective/autoimmune encephalitis**.

High-yield exam pointers

- **PRES = vasogenic oedema of the posterior brain from hyperperfusion / endothelial dysfunction** that breaches the upper limit of cerebral autoregulation or the BBB.
- **Tetrad:** headache, seizures, altered mentation, **cortical (occipital) visual loss**.
- **Two mechanistic classes:** *raised capillary pressure* (hypertensive encephalopathy, eclampsia, post-CEA) vs *endothelial dysfunction* (calcineurin inhibitors, chemotherapy, HELLP, HUS).
- **MRI:** bilateral parieto-occipital **T2/FLAIR** hyperintensity **not confined to one vascular territory**; CT less sensitive.
- **Rate of BP rise matters more than the absolute BP** — PRES can occur at near-normal pressures.
- **Treatment:** judicious IV BP control (**labetalol / nicardipine**; nitroprusside), **lower MAP by ~20% initially**, withdraw the offending drug, control seizures (**magnesium sulfate in eclampsia**).
- **"Reversible" is conditional** — irreversibility/infarction follows delayed treatment or over-aggressive BP lowering.
- **Normal calcineurin-inhibitor serum levels do not exclude drug-induced PRES.**

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 318 "Nervous System Disorders in Critical Care"** (Hyperperfusion Disorders / PRES section, Table 318-3, Fig. 318-7, and the cerebral-autoregulation/CPP discussion) and **Ch 288 "Hypertension"** (hypertensive urgencies and emergencies; IV nicardipine/labetalol/sodium nitroprusside, reduction-not-normalisation principle). **Coverage note:** the topic spec flags PRES as thinly covered; Harrison presents PRES under "hyperperfusion disorders" rather than as a stand-alone chapter, and does not give formal epidemiology, an exact MAP/BP autoregulatory cut-off, or DWI/ADC criteria. The statement that PRES oedema is **vasogenic** (facilitated rather than restricted diffusion on DWI/ADC, distinguishing it from cytotoxic infarction) is universally accepted standard neuroradiology added for completeness but is not stated verbatim in the provided chapters.

◆ ◆ ◆

Primary headaches

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

Definition / Introduction — Primary headaches are disorders in which headache and its associated features constitute the disease itself, without an exogenous structural, infective, vascular, metabolic, or toxic cause. The major groups are **migraine**, **tension-type headache (TTH)**, **trigeminal autonomic cephalalgias (TACs)**, and other primary headache disorders. Diagnosis is clinical, but the first duty in an examination answer and in practice is to exclude secondary headache when red flags are present.

Classification

ICHD-3 group	Important subtypes	Examination anchors
Migraine	Without aura; with aura; brainstem aura; hemiplegic migraine; retinal migraine; chronic migraine; complications such as status migrainosus and migrainous infarction	Recurrent 4-72 h attacks; nausea/vomiting or photophobia-phonophobia; aggravated by activity; normal examination between attacks
Tension-type headache	Infrequent episodic; frequent episodic; chronic; probable TTH	Bilateral tight/band-like pressure, mild-moderate, no vomiting, not worsened by routine activity
TACs	Cluster headache; paroxysmal hemicrania; SUNCT/SUNA; hemicrania continua	Strictly unilateral orbital/temporal pain with ipsilateral cranial autonomic signs
Other primary headaches	Cough, exercise, sexual-activity, thunderclap, cold-stimulus, external-pressure, primary stabbing, nummular, hypnic, new daily persistent headache	Diagnosis only after excluding mimics appropriate to the trigger and phenotype

- Chronic daily headache means headache on **15 or more days/month**; it is descriptive, not one diagnosis. Important primary causes are chronic migraine, chronic TTH, hemicrania continua, hypnic headache, SUNCT/SUNA, and new daily persistent headache.

- **Medication-overuse headache** is not a primary subtype but commonly complicates migraine or chronic daily headache and must be actively looked for.

Pathophysiology

- Pain-sensitive cranial structures include scalp, meningeal arteries, dural venous sinuses, falx, and proximal large pial arteries.
- Primary headache pathways center on the **trigeminovascular/trigeminocervical system**: meningeal and cervical afferents project through the trigeminal ganglion to the trigeminal nucleus caudalis and upper cervical cord, then to thalamic, hypothalamic, brainstem, and cortical networks.
- In **migraine**, brainstem and hypothalamic sensory-modulation dysfunction produces abnormal sensitivity to light, sound, movement, smell, and cutaneous input. Trigeminal activation releases **CGRP**, PACAP and other neuropeptides, explaining the efficacy of gepants and CGRP monoclonal antibodies.
- Migraine aura is best explained by **cortical spreading depression**, a slowly propagating wave of neuronal and glial depolarization followed by suppression, typically beginning in occipital cortex.
- In **TACs**, pain is trigeminal, while ipsilateral lacrimation, conjunctival injection, nasal congestion, rhinorrhea, aural fullness, ptosis or miosis reflect cranial parasympathetic activation and sympathetic dysfunction. Cluster headache is linked to posterior hypothalamic/circadian mechanisms.
- Primary headaches are **not simply vascular headaches**; vascular changes are secondary epiphenomena and do not predict treatment response.

Migraine

- **Clinical phases**: premonitory phase with yawning, sleepiness, fatigue, cognitive fog, mood change, neck discomfort, polyuria/polydipsia or cravings; aura in about one-quarter to one-third; headache phase; and postdrome with tiredness and impaired concentration.
- **Diagnostic criteria**: repeated attacks lasting **4-72 h**, normal examination, no better cause, with at least two of unilateral pain, throbbing quality, moderate/severe intensity, aggravation by movement; and at least one of nausea/vomiting or photophobia and phonophobia.
- **Aura** is usually visual, with scintillating scotoma, zigzags or field defects spreading over minutes and resolving within 60 min; sensory, language, brainstem and hemiplegic auras are recognized. Aura without headache may mimic TIA, especially after 40 years.
- **Triggers/activators**: altered sleep, missed meals, let-down after stress, exertion, weather change, menstruation, alcohol, nitrates, odors, glare and noise.
- **Acute treatment**: treat early, use adequate dose, avoid repeated ineffective dosing and overuse. Options include NSAIDs; acetaminophen-aspirin-caffeine for mild-moderate attacks; triptans; ergots; gepants; lasmiditan; dopamine antagonists; and selected neuromodulation.

Acute class	Examples and key points
NSAIDs/analgesics	Ibuprofen 400 mg, naproxen 220-550 mg, diclofenac K 50 mg; best early; simple analgesics limited to <=15 days/month
Triptans	Sumatriptan 50-100 mg PO or 3-6 mg SC; rizatriptan 5-10 mg; zolmitriptan 2.5 mg PO or 5 mg nasal; avoid in ischemic cardiac/cerebrovascular/peripheral vascular disease and uncontrolled hypertension
Gepants	Rimegepant 75 mg ODT; ubrogepant 50-100 mg, repeat after 2 h if needed; zavegepant 10 mg intranasal
Ditans	Lasmiditan 50-200 mg once; no vasoconstriction; no driving for 8 h
Antiemetic/prokinetic	Metoclopramide 10-20 mg IV/PO, prochlorperazine 5-10 mg; useful with nausea, vomiting, gastric stasis, ED migraine

- **Prevention** is indicated for frequent or disabling attacks, increasing frequency, poor acute response, contraindications to abortives, or chronic migraine. Harrison suggests considering prevention at **>=4 migraine days/month**; CMDT uses more than 2-3/month or significant disability.
- Preventives include propranolol 40-120 mg bid, metoprolol 25-100 mg bid, amitriptyline 10-75 mg nocte, venlafaxine 75-150 mg/day, topiramate 25-200 mg/day, valproate 400-600 mg bid, candesartan 4-24 mg/day, CGRP monoclonal antibodies, rimegepant alternate-day, atogepant daily, and onabotulinum toxin A for chronic migraine.
- Start low, titrate, allow **2-12 weeks** or longer, continue about **6-12 months** after stabilization, then consider slow taper. Avoid or use topiramate/valproate cautiously in women of reproductive age.

Tension-type headache

- **Phenotype**: bilateral tight, pressing, band-like discomfort that builds slowly, fluctuates, and may persist for days; often generalized or occipitonuchal; pericranial tenderness may occur.
- **Episodic vs chronic**: chronic TTH is headache on **>=15 days/month**; it may persist for years and overlap clinically with chronic migraine.
- **Diagnostic distinction from migraine**: pure TTH lacks nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, focal neurologic symptoms, and aggravation by routine activity.
- **Treatment**: simple analgesics such as acetaminophen, aspirin or NSAIDs for occasional attacks; avoid frequent combination analgesics, opioids and barbiturates. Relaxation, sleep hygiene, physical therapy, biofeedback and management of anxiety/depression help selected patients.
- **Prevention**: amitriptyline is the best-supported drug for chronic TTH; other tricyclics may be tried if not tolerated. Triptans do not help pure TTH, although they may help when apparent TTH occurs in a patient with comorbid migraine.

Trigeminal autonomic cephalalgias

Disorder	Attack pattern	Autonomic features	Specific treatment clue
Cluster headache	Excruciating unilateral orbital/temporal pain, 15-180 min, 1 every other day to 8/day; bouts for weeks with remission; nocturnal attacks common	Ipsilateral lacrimation, conjunctival injection, rhinorrhea/nasal congestion, aural fullness, ptosis/miosis; restlessness	Acute: 100% oxygen 10-12 L/min for 15-20 min, sumatriptan 6 mg SC, sumatriptan 20 mg or zolmitriptan 5 mg nasal. Prevent: verapamil 160-960 mg/day with ECG monitoring; prednisone bridge, occipital steroid injection, galcanezumab, topiramate, lithium, melatonin
Paroxysmal hemicrania	Severe unilateral orbital/temporal attacks, 2-45 min, usually >5/day	Prominent ipsilateral autonomic signs	Complete response to indomethacin 25-75 mg tid is diagnostic and therapeutic
SUNCT/SUNA	Very short unilateral orbital/temporal stabs, 5-240 s, often many/day	SUNCT has conjunctival injection and tearing; SUNA has cranial autonomic symptoms without both	Acute therapy usually impractical; IV lidocaine in hospital; prevention with lamotrigine 200-400 mg/day, topiramate or gabapentin
Hemicrania continua	Continuous unilateral moderate pain with severe exacerbations	May have conjunctival injection, lacrimation, photophobia on pain side	Complete response to indomethacin; trial 25 mg tid escalating to 50-75 mg tid

- TACs are often misdiagnosed as sinus headache because of nasal congestion and rhinorrhea; decongestants are ineffective.
- Consider **MRI brain with pituitary views and pituitary function tests** in atypical, refractory, bilateral or suspicious TACs.

Other primary headaches and medication overuse

- **Primary cough headache**: sudden generalized pain precipitated by cough, sneeze, straining, laughing or stooping, lasting seconds to minutes; diagnose only after excluding Chiari malformation, posterior fossa lesions, aneurysm, CSF leak and other causes. Indomethacin 25-50 mg two to three times daily, or 75-150 mg/day, is effective.
- **Primary exercise headache**: bilateral throbbing precipitated by sustained exercise, lasting up to 48 h; exclude SAH, intracranial hypertension, pheochromocytoma and **cardiac cephalalgia**.
- **Sexual-activity headache**: dull bilateral ache increasing with excitement or explosive orgasmic headache; exclude SAH, dissection, RCVS and pheochromocytoma. Options include stopping activity, propranolol 40-200 mg/day, diltiazem 60 mg tid, or pre-emptive indomethacin 25-50 mg/triptan/gepant.
- **Primary thunderclap headache** is a diagnosis of exclusion after CT/MRI, vascular imaging as indicated and CSF examination exclude SAH, RCVS, dissection, venous thrombosis and pituitary apoplexy.
- **Primary stabbing headache** causes seconds-long irregular "ice-pick" pains without autonomic features; reassurance is often enough, with indomethacin for frequent disabling attacks.

- **Hypnic headache** wakes older patients from sleep, usually without autonomic features; bedtime caffeine, lithium 200-600 mg, indomethacin or melatonin may help.
- **New daily persistent headache** begins abruptly and remains daily from onset; exclude secondary causes such as CSF leak and cerebral venous sinus thrombosis, then treat according to migraine or TTH phenotype.
- **Medication overuse**: opioids, barbiturate combinations, ergots and triptans over **>10 days/month**, and acetaminophen/aspirin/NSAIDs over **>15 days/month**, can perpetuate daily headache. Treat by withdrawal/taper, diary, bridge therapy where appropriate, and early prevention for the underlying headache.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Trigeminovascular pathway**: dura/meningeal vessels -> trigeminal ganglion -> trigeminocervical complex -> quintothalamic tract -> thalamus -> cortex; modulators labelled hypothalamus, dorsal raphe, locus coeruleus, nucleus raphe magnus, superior salivatory nucleus, sphenopalatine ganglion, CGRP release.
- **Migraine attack timeline**: prodrome -> aura -> headache phase -> postdrome; label yawning/food craving/polyuria, scintillating scotoma, unilateral throbbing pain with nausea-photophobia-phonophobia, fatigue/cognitive fog.

Clinical / Diagnostic significance

- Always screen for **SNNOOP10** red flags: systemic symptoms, neoplasm, neurologic deficit, sudden onset, older age >50, pattern change, positional headache, cough/exertion trigger, papilledema, progressive atypical headache, pregnancy/puerperium, painful eye with autonomic features, trauma, immunosuppression, and painkiller overuse/new drug.
- Neuroimaging is urgent for abnormal neurologic examination, altered mental status, papilledema, meningeal signs, thunderclap headache, new headache in HIV, or new headache after 50. LP follows imaging when meningitis or SAH remains possible.
- A normal examination between attacks supports primary headache, but does not by itself exclude secondary headache when the history is new, abrupt, progressive, positional, exertional, cancer-related, febrile, immunosuppressed, pregnant/postpartum, or associated with visual loss.
- Migraine is often mistaken for sinus headache because facial pain and autonomic symptoms can occur. Cluster headache is distinguished by shorter attacks, periodicity, ipsilateral autonomic features and restlessness.
- Examine temporal arteries, fundus, ocular movements, pupils, neck stiffness, BP, visual fields, and cranial nerves; Horner syndrome with acute pain suggests cluster headache but also carotid dissection.

High-yield exam pointers

- Define primary headache as headache without exogenous cause, then classify into **migraine, TTH, TACs and other primary headaches**.
- Write migraine diagnostic criteria: **4-72 h**, at least 2 pain features, at least 1 associated feature, normal examination/no better cause.

- Mention migraine phases and that **aura occurs in only a minority**, so absence of aura does not exclude migraine.
- Do not call migraine a vascular headache; write **brain disorder of sensory processing with trigeminovascular CGRP biology**.
- Cluster headache: **male predominance, orbital pain, 15-180 min, autonomic signs, restlessness, oxygen + SC sumatriptan, verapamil with ECG**.
- Paroxysmal hemicrania and hemicrania continua are **indomethacin-responsive**; SUNCT/SUNA responds best preventively to **lamotrigine**.
- Chronic migraine is **>=15 headache days/month with >=8 migraine days/month**; chronic daily headache always needs medication-overuse assessment.
- Avoid opioids and butalbital combinations in recurrent headache; they promote rebound and medication-overuse headache.
- First presentation of thunderclap, cough, exertional or sexual headache is not "primary" until dangerous secondary causes are excluded.

SOURCE & COVERAGE

Harrison 22e — "Headache"; "Migraine and Other Primary Headache Disorders"; Bradley & Daroff's Neurology in Clinical Practice — "Headache and Other Craniofacial Pain"; DeJong's The Neurologic Examination — "The Trigeminal Nerve"; CMDT 2026 — "Common Symptoms" and "Nervous System Disorders".

◆ ◆ ◆

Recent advances in management of migraine

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

Definition / Introduction — Migraine is a recurring syndrome of headache (typically unilateral, throbbing, lasting 4–72 h, aggravated by movement) associated with neurologic dysfunction in varying admixtures — nausea/vomiting, photophobia, phonophobia, osmophobia and, in ~20–25%, aura. It is the most common disabling neurologic disorder worldwide, affecting ~15% of women and ~6% of men annually. The last decade has transformed its treatment: clarification of the **calcitonin gene–related peptide (CGRP)** pathway and of serotonin-receptor subtypes has produced four mechanism-specific drug classes — *gepants*, *ditans*, *CGRP monoclonal antibodies* — plus several non-invasive neuromodulation devices, giving the first migraine-specific options that are safe in vascular disease.

Pathophysiological basis driving new therapy

- Migraine is a disorder of **sensory processing**: dysfunction of monoaminergic/brainstem and hypothalamic control systems (locus coeruleus, dorsal raphe, periaqueductal grey) and activation of the **trigeminovascular system** (trigeminal ganglion → trigeminocervical complex → quintothalamic tract → thalamus).
- Activated trigeminal neurons release vasoactive neuropeptides — **CGRP** and **pituitary adenylate cyclase–activating polypeptide (PACAP)**. Jugular venous CGRP rises during an attack and

normalises with sumatriptan; IV CGRP infusion triggers migraine in migraineurs but not controls — the rationale for anti-CGRP drugs.

- **Serotonin (5-HT) receptors**: triptans are 5-HT1B/1D agonists (1B = cranial vasoconstriction; 1D = neuronal); the **5-HT1F** receptor lies on neural (not vascular) tissue — selectively targeted by *ditans*, allowing efficacy without vasoconstriction.
- **Dopamine** hypersensitivity explains premonitory symptoms and the utility of dopamine antagonists.
- *Familial hemiplegic migraine (FHM)* genetics confirm a channelopathy: **CACNA1A** (Cav2.1 P/Q calcium channel) = FHM1 (~50%); **ATP1A2** (Na^+/K^+-ATPase) = FHM2 (~20%); **SCN1A** (neuronal Na^+ channel) = FHM3. Aura correlates with cortical spreading depression.

Principles & goals of modern management

- **Assess disability** with the validated *Migraine Disability Assessment Score (MIDAS)*: Grade I 0–5, II 6–10, III 11–20, IV >20.
- **Two arms** — *acute (abortive)* for individual attacks and *preventive (prophylactic)*. Treat acutely **early and adequately**; if relief is incomplete by 60 min, escalate dose or switch class for future attacks.
- **Start preventives** when there are **≥4 migraine days/month**, or attacks that are prolonged, disabling or poorly responsive to acute drugs. Titrate slowly; expect a 2–12 week lag; continue 6–12 months then taper. Target ≥50% reduction in headache days.
- **Patient education**, trigger management, regular sleep/meals/hydration, avoidance of the "let-down" effect, biofeedback and a headache diary remain foundational and reduce medication-overuse risk.
- **Chronic migraine** = headache on **≥15 days/month, ≥8 of them migrainous, for ≥3 months**.

Recent advances in ACUTE therapy

Class / Agent	Mechanism	Dose	Key point
Gepants (oral) — rimegepant; ubrogepant	Small-molecule CGRP-receptor antagonists	Rimegepant 75 mg ODT; ubrogepant 50/100 mg, may repeat at 2 h	No vasoconstriction; very well tolerated; **effective on repeat dosing** (unlike triptans); safe in CVD
Gepant (nasal) — zavegepant	CGRP-receptor antagonist	10 mg intranasal, single spray	Rapid; useful for early nausea/vomiting
Ditan — lasmiditan	Selective **5-HT1F** agonist	50/100/200 mg PO, once/24 h	No vascular effect → fills the gap for cardio-/cerebrovascular disease; dizziness ~15%, somnolence ~6%; **no driving for 8 h**
Newer triptan/ergot routes	5-HT1B/1D agonists	DHE inhaled/nasal (Trudhesa); SC sumatriptan via **needle-free** device	Improved absorption/onset; co-give **naproxen 500 mg** with sumatriptan to cut recurrence

Class / Agent	Mechanism	Dose	Key point
Dopamine antagonists	D2 blockade + prokinetic	Metoclopramide/ prochlorperazine 10 mg IV	Prochlorperazine **superior to hydromorphone** in the ED
Neuromodulation (acute)	Device-based	sTMS, nVNS, remote electrical neuromodulation (REN, upper-arm), supraorbital, eCOT-NS	FDA-cleared, drug-free; useful when drugs fail or are contraindicated

- Gepants and ditans render significantly more patients **pain-free at 2 h** and **most-bothersome-symptom–free** than placebo in phase-3 trials; gepants achieve pain freedom in ~20% and pain relief in ~60% within 2 h.
- **Opioids and butalbital are discouraged** — they do not treat the mechanism, blunt future triptan response and drive medication-overuse headache.

Recent advances in PREVENTIVE therapy

Agent	Target	Regimen
Erenumab	CGRP **receptor** (only mAb against the receptor)	70 or 140 mg SC monthly
Fremanezumab	CGRP ligand	225 mg SC monthly *or* 675 mg SC q3 months
Galcanezumab	CGRP ligand	240 mg loading, then 120 mg SC monthly
Eptinezumab	CGRP ligand	100 or 300 mg **IV** every 3 months
Atogepant (oral gepant)	CGRP receptor	10/30/60 mg once daily
Rimegepant (oral gepant)	CGRP receptor	75 mg every other day (also acute — first dual-use drug)
OnabotulinumtoxinA	Blocks glutamate/peptide release	155 U (PREEMPT protocol) q12 weeks — **chronic migraine only**

- The **CGRP monoclonal antibodies** are the headline advance: efficacy often **within the first month**, monthly/quarterly dosing, excellent tolerability (main effect = injection-site reaction ± constipation), and they **work even after failure of up to four prior preventives**. Approved for both episodic and chronic migraine.
- *AHS consensus criteria* for starting CGRP-targeted prevention: 4–7 monthly headache days with moderate disability after ≥2 trials of established preventives; 8–14 days at any disability after ≥2 trials; chronic migraine after 2 oral preventive trials or 2 onabotulinumtoxinA cycles.
- **Traditional preventives still first-line / cost-effective**: propranolol/metoprolol/timolol, topiramate, sodium valproate (FDA-approved); amitriptyline, candesartan, flunarizine, venlafaxine. *Topiramate and valproate are now avoided in reproductive-age women* (teratogenicity — neural-tube defects, reduced cognition).
- **Preventive neuromodulation** (sTMS, nVNS, REN, supraorbital stimulation) is FDA-cleared and well tolerated.

- onabotulinumtoxinA is effective only in **chronic** migraine (PREEMPT 1 & 2: −8.4 vs −6.6 headache days); **negative in episodic** migraine.

Special situations

- **Menstrual migraine**: short-term *perimenstrual prophylaxis* (days −2/−3 to +3) with naproxen, a long-acting triptan (frovatriptan/naratriptan/zolmitriptan), oestrogen patch, or **rimegepant during menses**.
- **Status migrainosus**: IV valproate, IV prochlorperazine + DHE; **IV dexamethasone 10 mg** reduces recurrence; avoid opioids.
- **Medication-overuse headache (MOH)**: caution if ≥2 headache days/week. Limit simple analgesics to ≤15 days/month and triptans/ergots/opioids/combination analgesics to ≤9–10 days/month; lasmiditan and gepants are **not** linked to MOH; early CGRP-directed prevention aids analgesic withdrawal.
- **Cardiovascular disease / migraine-with-aura**: avoid triptans and ergots (vasoconstriction) and combined oral contraceptives (stroke risk, OR ~6 with aura); prefer **ditans, gepants and CGRP mAbs** (though CGRP's physiologic vasodilatory role warrants caution pending long-term data).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Trigeminovascular pathway (label):** meningeal/dural vessels → *trigeminal ganglion* → *trigeminocervical complex (TCC)* → *quintothalamic tract* (decussating) → *thalamus* → cortex; modulators *dorsal raphe nucleus, locus coeruleus, nucleus raphe magnus, hypothalamus, periaqueductal grey*; mark **CGRP/PACAP** release at vascular terminals — annotate drug sites: triptans/ditans at TCC, gepants/anti-CGRP mAbs at the peptide/receptor.
- **Management algorithm box:** *Acute* (NSAID → triptan/gepant/ditan → DHE/SC sumatriptan/neuromodulation) vs *Preventive* (β-blocker/topiramate/amitriptyline/candesartan → CGRP mAb / atogepant / rimegepant; onabotulinumtoxinA 155 U for chronic migraine).

Clinical / Diagnostic significance

- Diagnosis is clinical (IHS/ICHD-3 criteria); imaging only for red flags. Migraine with aura is an independent **stroke risk factor**, magnified by smoking and oestrogen-containing contraceptives.
- The new classes resolve two long-standing problems: a **vascular-safe acute option** (ditans, gepants) and **rapid, tolerable, mechanism-specific prevention** (CGRP mAbs, oral gepants).
- A single drug — **rimegepant** — now serves both acute and preventive roles, simplifying regimens.

High-yield exam pointers

- **CGRP** is the central therapeutic target: jugular CGRP rises in attacks; IV CGRP provokes migraine.
- **Gepants** = small-molecule CGRP-receptor antagonists (rimegepant, ubrogepant, zavegepant); acute *and* preventive use; no vasoconstriction.

- **Ditans** = lasmiditan, selective **5-HT1F** agonist; safe in CVD; dizziness/somnolence; no driving 8 h.
- **CGRP mAbs**: erenumab targets the **receptor**; fremanezumab, galcanezumab, eptinezumab target the **ligand**; eptinezumab is the only **IV** one.
- **onabotulinumtoxinA 155 U** (PREEMPT) — chronic migraine only; ineffective in episodic.
- Start prevention at **≥4 migraine days/month**; chronic migraine = **≥15 headache/≥8 migraine days/month for ≥3 months**.
- FHM genes: **CACNA1A (1), ATP1A2 (2), SCN1A (3)** — a channelopathy.
- **Avoid opioids/butalbital**; topiramate/valproate avoided in reproductive-age women.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Migraine and Other Primary Headache Disorders" (pathophysiology, CGRP/PACAP, 5-HT1F/ditans, gepants, CGRP monoclonal antibodies, acute and preventive treatment tables, neuromodulation, MIDAS, FHM genetics).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Headache and Other Craniofacial Pain" (CGRP-targeted therapies, AHS consensus criteria, PREEMPT/onabotulinumtoxinA, chronic and menstrual migraine, medication-overuse headache).
- **CMDT 2026** — "Nervous System Disorders" (current acute drug doses, lasmiditan, gepant dosing, Table 27–1 pharmacologic prophylaxis including CGRP mAbs/gepants, neuromodulation, MOH thresholds).

◆ ◆ ◆

Restless leg syndrome

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

Definition / Introduction — Restless legs syndrome (RLS), also called *Willis–Ekbom disease*, is a common sensorimotor neurological disorder characterised by an **irresistible urge to move the legs**, usually accompanied by an unpleasant deep "creepy-crawly" sensation, that appears at **rest**, is **relieved by movement**, and shows a **circadian (evening/night) predominance**. It was first described by the English physician *Thomas Willis* in the seventeenth century and is now recognised as a bona-fide movement disorder. It affects roughly **5–10% of adults** (1–5% by some series; rare in Asians), is commoner in **women and older adults**, and in ~80% of patients coexists with **periodic limb movements (PLMs)** of sleep. The neurological examination is characteristically normal, and diagnosis is **clinical**.

Clinical features and the IRLSSG essential criteria

RLS is a **clinical diagnosis**; the *International Restless Legs Syndrome Study Group (IRLSSG)* requires **five essential criteria** (mnemonic **URGE** — Urge to move, Rest-induced, Gets better with movement, Evening worsening, plus an exclusion clause):

#	Essential criterion (IRLSSG)
1	An **urge to move the legs**, usually but not always accompanied by uncomfortable/unpleasant leg sensations
2	Urge begins or **worsens during rest or inactivity** (lying down, sitting)
3	Urge is **partially or totally relieved by movement** (walking, stretching), at least as long as activity continues
4	Urge occurs **only or is worse in the evening/night** than during the day (circadian pattern)
5	The features are **not solely accounted for** by another condition (leg cramps, myalgia, arthritis, venous stasis, positional discomfort, habitual foot tapping)

- The dysaesthesia is typically a **creepy-crawly, tingling, pulling or deep aching** discomfort in the calves/thighs; 30–50% report frank pain (an ache rather than a sharp burning).
- Symptoms usually **begin in the legs** but may spread to or begin in the **upper limbs** in severe disease; usually **bilateral**.
- **Supportive features** (aid diagnosis in doubtful cases): PLMs in sleep/wakefulness greater than expected for age, **response to dopaminergic therapy**, **positive family history** in first-degree relatives, and **lack of profound daytime sleepiness**.
- **Course specifiers**: *Intermittent* (<2 episodes/week on average) vs *Chronic-persistent* (≥2/week for the past year). The **DSM-5** additionally requires symptoms ≥3 times/week for ≥3 months.
- Consequences: chronic **sleep-onset/maintenance insomnia**, poor-quality sleep, daytime sleepiness, and association with **depression, anxiety and hypertension**.

Classification and aetiology (primary vs secondary)

Type	Features / Causes
Primary (idiopathic)	Often **familial** (≈1/3 have affected relatives), **early onset** in the third decade; strong genetic component; >150 risk variants identified — strongest in **MEIS1, BTBD9, PTPRD** (also *MAP2K5/LBXCOR*)
Secondary / comorbid	**Iron deficiency / ferritin deficiency** (commonest treatable cause), **pregnancy**, **uraemia / chronic renal failure**, **peripheral neuropathy** (diabetic, uraemic), Parkinson disease, multiple sclerosis, ALS, myelopathy/radiculopathy, rheumatoid arthritis, hypothyroidism, gastrectomy, anaemia (folate)
Drug-induced / aggravating	**Antidepressants** (TCAs, SSRIs, venlafaxine — *not* bupropion), **antihistamines**, **dopamine antagonists** (neuroleptics, antiemetics), **lithium**, some **calcium-channel blockers** (nifedipine), **caffeine, alcohol, nicotine**

Pathophysiology — the iron–dopamine hypothesis

- The site of CNS dysfunction is not fully defined, but the leading model is **brain iron deficiency coupled with dopaminergic dysfunction** (the *iron–dopamine connection*).
- **Iron** is an essential cofactor for **tyrosine hydroxylase**, the rate-limiting enzyme of dopamine synthesis; low CNS iron reduces dopamine output and decreases the number of **D2 receptor** binding sites — explaining why iron deficiency precipitates RLS and dopaminergics relieve it.

- CSF analysis, special-sequence MRI (reduced R2* in *substantia nigra* and *red nucleus*) and neuropathology show **reduced regional brain iron / ferritin** despite often-normal peripheral iron.
- Neurophysiology (increased cortical excitability, reduced subcortical inhibition, increased spinal flexor-reflex excitability during sleep) localises dysfunction to **subcortical and spinal** circuits; the spinal mechanism helps explain PLMs.
- A genetic predisposition interacts with iron/dopamine handling — notably **no genetic linkage to iron metabolism genes** has been found despite the iron phenotype.

Periodic limb movements (PLMs) and PLMD

- **~80% of RLS patients have periodic limb movements of sleep (PLMS)**; many also have PLMs of wakefulness (PLMW).
- PLMS are **stereotyped, repetitive movements** resembling a *triple-flexion reflex* — extension of the great toe with **dorsiflexion of the ankle**, sometimes knee/hip flexion.
- Polysomnographic definition: duration **0.5–10 s**, recurring every **20–40 s** (range 5–90 s), in runs of **≥4 consecutive** movements, predominantly during **NREM** sleep; they cause brief **EEG arousals** that fragment sleep.
- **Periodic limb movement disorder (PLMD)** is a *separate* ICSD entity: PLMS index **>5/h in children, >15/h in adults** causing sleep disruption/daytime impairment, **without** the urge/sensory features of RLS. PLMS without symptoms may have no clinical significance.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Iron–dopamine pathophysiology loop:** boxes/arrows labelled — *Reduced CNS iron / ferritin* → ↓ *Tyrosine hydroxylase activity* → ↓ *Dopamine synthesis* → ↓ *D2 receptor binding sites* → *Circadian (evening) dopaminergic dysfunction* → **RLS symptoms**; with side inputs *Genetic susceptibility (MEIS1, BTBD9, PTPRD)* and *Secondary triggers (iron deficiency, pregnancy, uraemia, neuropathy)*.
- **PLMS polysomnogram tracing:** label the *Anterior tibialis EMG* channel showing periodic bursts; mark *movement duration 0.5–10 s*, *inter-movement interval 20–40 s*, *≥4 consecutive movements*, *NREM sleep*, and an *EEG arousal* above each cluster.

Clinical / Diagnostic significance

- **Diagnosis is clinical** (five IRLSSG criteria); the neurological examination is normal.
- **Mandatory investigations:** serum **ferritin and transferrin saturation**, **fasting glucose** and **renal function**; **EMG/nerve-conduction studies** if peripheral neuropathy is suspected.
- **Polysomnography is NOT routine** for RLS but is indicated to confirm/quantify **PLMS** or when PLMD or comorbid OSA is suspected.
- **Differential diagnosis (mimics):** *akathisia* (neuroleptic-induced, daytime, no persistent relief by movement, choreiform restlessness, no family history — best treated with anticholinergics/β-blockers), nocturnal leg **cramps** ("Charlie-horse" — painful palpable contraction), **peripheral neuropathy / neuropathic pain**, positional discomfort, venous stasis, and PLMD.

- **Iron repletion is disease-modifying:** start **oral iron** (ferrous sulfate, with vitamin C to aid absorption) when **ferritin ≤75 ng/mL and transferrin saturation <45%**, *before* other drugs.
- **Augmentation** (defined below) is the chief long-term hazard of dopaminergic therapy and a frequent exam point.

Management

1. Non-pharmacological / general measures (first step in all):

- Good **sleep hygiene**; mild–moderate **exercise**, leg stretching, **massage**, vibratory pads, warm bath before bed; remain mentally engaged.
- **Withdraw aggravators:** caffeine, alcohol, nicotine, antihistamines, dopamine antagonists, and offending antidepressants (substitute **bupropion** if an antidepressant is needed).
- **Correct the cause** in secondary RLS — **iron replacement**, treat uraemia, optimise neuropathy.

2. Pharmacological therapy (symptomatic):

Class	Drug & dose (evening, ~1.5–2 h before bed)	Key caution
α2δ calcium-channel ligands *(preferred first-line — no augmentation)*	Gabapentin 300–1800 mg; **gabapentin enacarbil** 300–1200 mg; pregabalin 150–300 mg	Sedation, dizziness; useful when pain/neuropathy/anxiety coexist
Non-ergot dopamine agonists	**Pramipexole** 0.125–0.5 mg; **ropinirole** 0.25–4 mg; **rotigotine** transdermal patch 1–3 mg/24 h	**Augmentation (~25–30%)**, rebound, nausea, sleepiness, **impulse-control disorders** (gambling, hypersexuality)
Dopamine precursor	Levodopa/carbidopa 25/100 mg	High augmentation risk — **"on-demand"/intermittent use only**, not chronic
Iron	Ferrous sulfate 325 mg BID/TID + vitamin C	Indicated when ferritin ≤75 ng/mL
Opioids (refractory/severe)	Extended-release **oxycodone–naloxone** 2.5/1.25 up to 10/5 mg BID; codeine, methadone	Constipation, tolerance, dependence
Others	Clonazepam 0.125–0.5 mg hs; clonidine 0.1 mg (if hypertensive)	BZD — caution in OSA

- **Augmentation** = a drug-induced *paradoxical worsening*: symptoms appear **≥2 h earlier** than before, **intensify**, and **spread** to other body parts; classically with **levodopa**, also dopamine agonists — managed by keeping dopaminergic load low, screening regularly, switching to an α2δ ligand, splitting doses or adding iron.
- **Tonic motor activation (TOMAC)** — non-pharmacological **peroneal nerve electrical stimulation**, recently US-approved for drug-refractory RLS, improves symptoms and sleep quality.
- **Deep brain stimulation** of the **globus pallidus** is a *last-resort* option for severe, intractable disease.
- **Pregnancy:** avoid both dopamine agonists and α2δ ligands where possible; **prefer iron**, non-pharmacological measures (usually self-limiting post-partum).

High-yield exam pointers

- Synonym **Willis–Ekbom disease**; first described by **Thomas Willis** (17th century); prevalence **5–10%** of adults, F>M, rare in Asians.
- **Five IRLSSG essential criteria** = mnemonic **URGE** + exclusion clause; diagnosis is **clinical**, exam is **normal**.
- **Commonest treatable cause = iron deficiency** → check **ferritin** (replace if **≤75 ng/mL**, TSAT <45%).
- Core pathophysiology: **brain iron deficiency** → ↓ **tyrosine hydroxylase** → **dopaminergic dysfunction**; genes **MEIS1, BTBD9, PTPRD**.
- **~80% have PLMS** (dorsiflexion of ankle, every 20–40 s, ≥4 consecutive, NREM); **PLMD is a distinct entity** (>15/h adults, no urge).
- **First-line drugs are α2δ ligands** (gabapentin enacarbil, pregabalin) — chosen over dopamine agonists because they **do not cause augmentation**.
- **Augmentation** (earlier onset + spread + intensification) is the hallmark complication of **levodopa/dopamine agonists**; dopamine agonists also cause **impulse-control disorders**.
- Key mimic to differentiate = **akathisia** (drug-induced, daytime, no persistent relief by movement).
- Refractory options: **opioids (oxycodone–naloxone)**, **TOMAC peroneal stimulation**, and **GPi-DBS** as last resort.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Sleep Disorders" (RLS & periodic limb movement disorder) and "Tremor, Chorea, and Other Movement Disorders" (RLS as a movement disorder; epidemiology, pathogenesis, genetics, therapy including TOMAC).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Sleep and Its Disorders" (IRLSSG five essential criteria, supportive features/specifiers, iron–dopamine pathophysiology, PLMS/PLMD definitions, causes of symptomatic RLS, akathisia differentiation, augmentation, and pharmacological/non-pharmacological treatment tables).
- **CMDT 2026** — "Nervous System Disorders" (current management: ferritin ≤75 mcg/L + TSAT <45% threshold, α2δ ligands, non-ergot dopamine agonist doses, extended-release oxycodone–naloxone).

◆ ◆ ◆

Reversible dementias

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

Definition / Introduction — *Dementia* is an acquired deterioration in two or more cognitive domains severe enough to impair performance of activities of daily living. A **reversible (potentially treatable) dementia** is one in which the cognitive decline is wholly or partly attributable to a condition that can be corrected — metabolic, nutritional, structural, infective, toxic, inflammatory or psychiatric — so that cognition stabilises or improves once the cause is treated. They are *uncommon individually but collectively critical*: in a landmark series of 1000 memory-clinic patients, **19% had a potentially reversible cause** of cognitive impairment and a further **23% had a potentially reversible contributing condition**, the three commonest being **depression, normal-pressure hydrocephalus (NPH) and alcohol dependence**; drug side effects are common and must be sought in every patient. The clinical imperative is to *never miss a treatable cause*, since each individual test has a low yield but the cost of overlooking a curable dementia is high.

Why the concept matters / classification principle

- The first triage of any dementia is into **reversible**, **irreversible/degenerative** (Alzheimer's disease, FTD, DLB, vascular, Huntington's, LATE) and **psychiatric** categories — a framework explicitly endorsed in Harrison's evaluation table.
- Features that *raise suspicion of a reversible cause*: **young onset (<60 yr)**, **rapid or subacute progression (weeks–months)**, **fluctuating course**, prominent **gait disorder / incontinence**, **systemic signs** (weight loss, fever, neuropathy, myelopathy), recent **drug change**, and a **subacute amnestic-psychotic syndrome** with medial-temporal MRI change.
- The corollary entity is **rapidly progressive dementia (RPD)** — dementia evolving within ≤1 year; although prion disease (CJD) dominates referral series, autoimmune, infective, neoplastic and metabolic causes within RPD are precisely the *treatable* ones that must be excluded urgently.

Classification of reversible / treatable causes

Category	Representative causes (corpus-grounded)	Diagnostic clue
Structural	**Normal-pressure hydrocephalus**, chronic **subdural haematoma**, primary/metastatic **brain tumour** (meningioma, frontal glioma)	Gait disorder, focal deficit, raised ICP; CT/MRI
Endocrine / organ failure	**Hypothyroidism**, hypo-/hyper-parathyroidism, adrenal insufficiency & **Cushing's**, hepatic, renal, pulmonary failure	Dry cool skin, hair loss, bradycardia (hypothyroid); metabolic panel, TSH
Nutritional deficiency	**Vitamin B_{12}** (subacute combined degeneration), **thiamine (B_1)** → Wernicke–Korsakoff, **niacin (pellagra)**, elevated homocysteine	Myelopathy + peripheral neuropathy (B_{12}); ophthalmoplegia/ataxia (Wernicke)
Chronic infection	**Neurosyphilis**, **HIV**, chronic TB/fungal meningitis, **Whipple's disease**, PML (JC virus), Lyme	High-risk behaviour/IVDU history; RPR/VDRL, HIV, CSF

Category	Representative causes (corpus-grounded)	Diagnostic clue
Toxic	**Alcohol**, **drug/medication intoxication** (anticholinergics, benzodiazepines, sedatives, opioids), **heavy metals** (lead, mercury, arsenic), CO	Medication review; urine heavy-metal screen
Inflammatory / autoimmune	**Autoimmune / paraneoplastic limbic encephalitis** (anti-NMDA-R, **LGI1**, Caspr2, AMPA-R), **Hashimoto (steroid-responsive) encephalopathy**, neurosarcoidosis, CNS vasculitis, SLE/Sjögren	Subacute amnesia + psychosis, seizures; antibody panel, CSF
Psychiatric	**Depression (pseudodementia)**, conversion disorder, schizophrenia	Mood symptoms, "don't-know" answers, attention deficit
Miscellaneous	Recurrent **non-convulsive seizures**, obstructive sleep apnoea, intracranial hypotension	EEG; fluctuating confusion with stereotyped movements

Clinical approach — eliciting a treatable cause

- **History**: tempo (acute/subacute → intoxication, infection, metabolic, autoimmune); meticulous **drug review** (sedatives, analgesics, anticholinergics); alcohol and nutrition; high-risk sexual behaviour/IVDU (HIV, syphilis); recurrent head trauma (chronic subdural, NPH); occupational exposure (battery/chemical factory → heavy metals); mood disorder/bereavement (depression). B_{12} deficiency is suggested by **pernicious anaemia, veganism, gastrectomy, bowel irradiation or chronic H_2-blocker use**.
- **Examination**: look for systemic clues — **myelopathy + peripheral neuropathy → B_{12}**; dry cool skin, hair loss, bradycardia → **hypothyroidism**; hemiparesis/focal deficit → tumour or vascular; the **NPH triad** (gait, incontinence, cognition); fluctuating confusion with stereotyped movements → ongoing seizures.
- **Cognitive screen**: MMSE / MoCA to capture and follow severity (insensitive to early disease); **pseudodementia** of depression shows prominent inattention and effort-dependent failure.

Investigations to unmask reversibility

- **AAN-recommended routine panel** (Harrison): complete blood count; electrolytes; glucose; **renal, liver and thyroid (TSH) function**; **vitamin B_{12}**; and a **structural neuroimaging study (MRI or CT)**. CMDT adds **free T_4, TSH, B_{12}** in every patient and **serum RPR + HIV** when indicated.
- **Neuroimaging (MRI > CT)**: excludes tumour, subdural haematoma, infarction/inflammation; supports **NPH** (communicating ventriculomegaly with **Evans index >0.30**, vertex/convexity crowding, gaping Sylvian fissures — *DESH* pattern, transependymal flow).
- **Selective / focused tests** (driven by suspicion): HIV serology, RPR/VDRL, **lumbar puncture** (CNS infection, inflammation, autoimmune antibodies, AD biomarkers, opening pressure), EEG (non-convulsive seizures; CJD periodic complexes), urine heavy-metal panel, autoantibody/paraneoplastic screen, ESR/CRP, ANA, 24-h urine copper (Wilson), MR angiography (vasculitis/venous thrombosis).
- **RPD work-up** (CMDT): MRI with contrast + diffusion-weighting, B_{12}/T_4/TSH, RPR, HIV, Lyme, ESR/CRP/ANA, **anti-thyroglobulin & anti-TPO** (Hashimoto), paraneoplastic/autoimmune

antibodies, full CSF (cells, protein, oligoclonal bands, IgG index, VDRL, 14-3-3, RT-QuIC for prion).

Key reversible entities in focus

- **Normal-pressure hydrocephalus** — classic *Hakim* triad of **gait disturbance ("magnetic"/apraxic gait), urinary incontinence and cognitive (frontal-executive) impairment** ("wet, wobbly, wacky"); enlarged ventricles disproportionate to atrophy with **normal CSF opening pressure**. **Gait is the core and most shunt-responsive symptom**; cognition responds least. A **large-volume (30–50 mL) "tap test"** or 1–3 days of external lumbar drainage with objective gait improvement predicts response to **ventriculoperitoneal / lumboperitoneal shunting**. Coexisting AD pathology is found in ~40% of shunted patients.
- **Vitamin B_{12} deficiency** — dementia with **subacute combined degeneration** (dorsal column + corticospinal) and peripheral neuropathy; reversible with replacement.
- **Wernicke–Korsakoff** — thiamine deficiency (alcoholism, hyperemesis, post-bariatric); Wernicke triad of **confusion, ataxia and ophthalmoplegia/nystagmus**. Give **thiamine 100 mg IV** *before* any glucose (glucose first can precipitate/worsen Wernicke).
- **Hypothyroidism** — corrected by thyroid replacement.
- **Depression (pseudodementia)** — vigorous antidepressant therapy may abolish the cognitive complaint; if it persists, reassess for a true dementia.
- **Autoimmune/paraneoplastic encephalitis** — subacute amnesia, psychosis, seizures with mesial-temporal T2/FLAIR change; immunotherapy-responsive (predictors: subacute onset, fluctuation, CSF pleocytosis/high protein, specific antibody).
- **Chronic subdural haematoma, brain tumour, neurosyphilis, HIV** — each surgically/medically treatable.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Diagnostic triage of dementia (algorithm box).** Top node: *"Dementia"* → three branches: **Reversible/treatable causes** (label sub-boxes: *Hypothyroidism, B_{12}/thiamine deficiency, NPH, Chronic subdural haematoma, Chronic infection, Brain tumour, Drug intoxication, Autoimmune encephalopathy*), **Irreversible/degenerative** (*Alzheimer's, FTD, DLB, Vascular, Huntington's, LATE*), and **Psychiatric** (*Depression, Schizophrenia, Conversion*). Side label: *Routine screen — CBC, electrolytes, glucose, renal/liver/thyroid (TSH), B_{12}, MRI/CT.*
- **Diagram 2 — NPH neuroimaging.** Axial CT/MRI brain with labels: *Dilated lateral ventricles (out of proportion to atrophy)*, *Evans index >0.30 (frontal-horn : skull width)*, *Transependymal CSF flow / periventricular capping*, *Tight high-convexity sulci & gaping Sylvian fissures (DESH)*; annotate the clinical triad *gait apraxia – incontinence – dementia*.

Clinical / Diagnostic significance

- Distinguishing reversible from degenerative dementia changes prognosis fundamentally — **treatment can halt or reverse decline**, so screening for the curable minority is mandatory in every new dementia work-up.

- **Treatment of underlying cause** (Harrison): thyroid replacement for hypothyroidism; **vitamin therapy** for thiamine/B_{12} deficiency or hyperhomocysteinaemia; **antimicrobials/antiretrovirals** for opportunistic infection or HIV; **ventricular shunting** for NPH; **surgery/radiation/chemotherapy** for CNS neoplasms; and **withdrawal of cognition-impairing drugs**.
- Even partial reversibility matters: many degenerative dementias carry treatable concomitants (depression, drug effects, metabolic derangement) whose correction improves function and reduces caregiver burden.
- A negative reversible-cause screen with a progressive amnestic syndrome redirects attention to AD/LATE; rapid progression with myoclonus and cortical-ribboning DWI redirects to CJD.

High-yield exam pointers

- **~19% reversible cause + ~23% reversible contributor** in 1000 memory-clinic patients; top three reversible = **depression, NPH, alcohol**.
- AAN routine panel = **CBC, electrolytes, glucose, renal/liver/thyroid, B_{12}, MRI/CT**.
- **NPH triad** = gait + incontinence + dementia; **gait most shunt-responsive**; **Evans index >0.30**; positive **large-volume tap test** predicts shunt benefit.
- **B_{12} deficiency** = dementia + **subacute combined degeneration** + neuropathy; causes include veganism, pernicious anaemia, gastrectomy, chronic H_2-blockers.
- **Wernicke**: confusion–ataxia–ophthalmoplegia; **thiamine before glucose**.
- **Depression = pseudodementia**, the single commonest reversible cause.
- Reversible RPD red flags = subacute course, fluctuation, myoclonus, seizures → screen for **autoimmune/paraneoplastic encephalitis** (NMDA-R, LGI1, Caspr2, AMPA-R) and **Hashimoto encephalopathy** (anti-TPO).
- Always **review medications** (anticholinergics, benzodiazepines, sedatives) — a correctable cause in every patient.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Dementia" (Table 31-1 differential diagnosis with potentially reversible causes; evaluation table; reversible-cause treatment; NPH, RPD, autoimmune encephalitis) and "Aphasia, Memory Loss, and Other Cognitive Disorders".
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Alzheimer Disease and Other Dementias" (NPH triad, Evans index, DESH, tap test, Japanese iNPH criteria; Box 95.1 non-degenerative/treatable dementias; rapidly progressive dementia).
- **CMDT 2026** — "Nervous System Disorders: Dementia" (laboratory work-up — B_{12}, free T_4, TSH, RPR, HIV; drugs impairing cognition; NPH; rapidly progressive dementia work-up; Wernicke encephalopathy & Korsakoff syndrome).

◆ ◆ ◆

Secondary parkinsonism

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

Definition / Introduction — *Parkinsonism* is a clinical syndrome defined by **bradykinesia plus rigidity and/or rest tremor** (with postural instability). *Secondary (symptomatic) parkinsonism* denotes parkinsonism arising from an identifiable, often reversible, exogenous or acquired cause — drugs, vascular disease, toxins, infection, structural lesions, trauma or metabolic insult — that damages the nigrostriatal pathway or basal ganglia, **as opposed to** the neurodegenerative synucleinopathy of idiopathic Parkinson's disease (PD) or the tauopathies/atypical "Parkinson-plus" syndromes. Idiopathic PD accounts for ~75% of all parkinsonism; recognising a secondary cause matters because many are **treatable or preventable**. *Drug-induced* parkinsonism is the single commonest secondary form, and *vascular* parkinsonism the commonest non-drug secondary form.

Classification — where secondary parkinsonism sits

- **Primary / idiopathic** — Parkinson's disease (sporadic and monogenic), the prototype Lewy-body synucleinopathy.
- **Atypical ("Parkinson-plus") degenerations** — multiple-system atrophy (MSA-p/MSA-c), progressive supranuclear palsy (PSP, Richardson & Parkinson variants), corticobasal syndrome; widespread pathology, poor/absent levodopa response.
- **Secondary (symptomatic) parkinsonism** — the focus of this answer (drugs, vascular, toxins, infection, tumour, NPH, trauma, metabolic).
- **Heredodegenerative parkinsonism** — Wilson's disease, Huntington's (juvenile *Westphal* variant), spinocerebellar ataxias (SCA3), neurodegeneration with brain iron accumulation (PANK-associated), dopa-responsive dystonia.

Cause category	Representative aetiologies (Harrison Table 446-2)
Drug-induced	Dopamine-receptor blockers (neuroleptics, metoclopramide); dopamine depleters (reserpine, tetrabenazine); Ca^{2+}-channel blockers (flunarizine, cinnarizine); amiodarone; lithium; valproate
Vascular	Subcortical small-vessel/lacunar disease ("lower-body parkinsonism")
Toxins	Carbon monoxide, manganese, **MPTP**, cyanide, hexane, methanol, carbon disulfide
Infective / post-infective	Postencephalitic (encephalitis lethargica), HIV, prion disease
Structural	Tumour, subdural haematoma, **normal-pressure hydrocephalus**, trauma (pugilistic)
Metabolic	Hepatic (acquired hepatocerebral) failure, hypoparathyroid basal-ganglia calcification (*Fahr*)

Drug-induced parkinsonism (DIP) — the commonest cause

- **Mechanism:** post-synaptic **D2-receptor blockade** (neuroleptics, antiemetics) or **pre-synaptic dopamine depletion** (reserpine, tetrabenazine, deutetrabenazine, valbenazine) reproduces the motor syndrome *without* nigral degeneration.

- **Offending drugs:** typical antipsychotics (haloperidol, fluphenazine) > atypicals; antiemetics **metoclopramide, prochlorperazine, levosulpiride**; among atypicals the propensity tracks D2 affinity — *risperidone = ziprasidone > olanzapine > quetiapine > clozapine* (quetiapine/clozapine are "dopamine-sparing"). Also **SSRIs, lithium, sodium valproate, phenytoin, methyldopa, amiodarone, and Ca^{2+}-channel blockers (cinnarizine, flunarizine)**.
- **Clinical signature:** typically **bilateral & symmetrical** at onset, **postural > rest tremor**, lower incidence of tremor overall, subacute onset over weeks–months of exposure.
- **Course & treatment: stop / substitute** the offending drug — reversible but may take up to **6 months** to resolve; symptomatic relief with **anticholinergics (benztropine, trihexyphenidyl), amantadine** or levodopa. Persistence after withdrawal suggests an **unmasked subclinical PD**. On stopping the drug, **tardive dyskinesia** may emerge. Neuroleptic users are ~5× more likely to later start antiparkinsonian drugs.

Vascular parkinsonism

- Second commonest parkinsonism in movement-disorder clinics (~**8%** of parkinsonian patients); driven by **lacunar/subcortical small-vessel ischaemia**. Risk factors: hypertension, type-2 diabetes, hyperlipidaemia.
- **"Lower-body parkinsonism"** — broad-based shuffling gait, marked start/turn hesitation and freezing, early **postural instability and falls**, relative sparing of the upper limbs, **little rest tremor**.
- Frequent accompaniments: **pyramidal signs, pseudobulbar palsy, urinary incontinence and dementia** (overlaps the NPH picture and small-vessel disease).
- **Distinguishing investigations:** structural MRI **abnormal in 90–100%** (vs 12–43% in PD) showing white-matter ischaemia/lacunes; **DaTscan/presynaptic dopamine-transporter imaging is usually NORMAL** (pathology spares SNc dopaminergic cells) — a key separator from PD.
- **Treatment:** vascular secondary-prevention; **levodopa trial worthwhile** — up to half improve modestly; physiotherapy/gait training.

Toxin-, infection-, structural- and metabolic-induced

- **MPTP:** 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; an opioid (meperidine) synthesis contaminant. Converted by **MAO-B to the active toxin MPP^+**, which poisons mitochondrial **complex I** and destroys SNc neurons → acute, severe, **levodopa-responsive** parkinsonism (1982 Californian "frozen addicts"); landmark model of PD pathogenesis.
- **Manganese (manganism):** symmetrical, **levodopa-unresponsive** parkinsonism with **dystonia and oculogyric crises**; damages the **globus pallidus**; may progress after exposure ceases; F-dopa PET shows *normal presynaptic* dopamine function (postsynaptic/pallidal pathology); welder/miner exposure, fungicide *maneb*.
- **Carbon monoxide:** delayed parkinsonism with bilateral **globus-pallidus necrosis** and white-matter lesions on MRI; cognitive slowing; partial recovery over months–years.
- **Postencephalitic parkinsonism (von Economo):** sequel of the 1916–1927 *encephalitis lethargica* pandemic; characteristic **oculogyric crises**, sleep/behavioural disturbance, abnormal eye movements; SNc degeneration with neurofibrillary tangles; levodopa-responsive.

- **Structural causes:** tumour or subdural haematoma involving the SNc may closely mimic PD; **normal-pressure hydrocephalus (NPH)** gives the *Hakim–Adams triad* of **gait apraxia, dementia and urinary incontinence** and may respond to ventriculoperitoneal shunting.
- **Metabolic/heredodegenerative red-line:** always exclude **Wilson's disease** in young-onset parkinsonism (Kayser–Fleischer rings, low ceruloplasmin) — progression is preventable with **copper chelation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Basal-ganglia / nigrostriatal circuit with lesion sites.** Draw and label: **Substantia nigra pars compacta (SNc)**, **Striatum (putamen + caudate)**, **Globus pallidus externa (GPe)** and **interna (GPi)**, **Subthalamic nucleus (STN)**, **Thalamus**; the dopaminergic **nigrostriatal pathway**. Annotate lesion localisation — *SNc lesion (stroke/tumour/MPTP) → PD-like, levodopa-responsive*; *GPi/pallidal lesion (CO, manganese) → atypical, levodopa-unresponsive*; *D2 blockade at striatum → drug-induced.*
- **Diagnostic algorithm box.** "Parkinsonism" → *drug history?* (yes → DIP, stop drug) → *symmetric, early falls, lower-body gait + MRI small-vessel disease?* (yes → vascular) → **DaTscan**: normal = DIP/vascular/essential tremor; reduced asymmetric posterior-putaminal uptake = PD/atypical.

Clinical / Diagnostic significance

- **Red flags for a secondary/atypical (NOT idiopathic PD) cause** (Harrison Table 446-3): **symmetrical** signs, **early speech & gait** impairment with **falls in the first year**, **absent rest tremor**, **poor/no levodopa response**, early autonomic failure or dementia, vertical-gaze palsy (PSP), prominent cerebellar signs (MSA-c).
- **Key separator — DaTscan (presynaptic dopamine-transporter SPECT):** *normal* in DIP, vascular and psychogenic parkinsonism (and essential tremor); *abnormal* in PD and atypical degenerations — invaluable when the cause is uncertain.
- **MRI** screens for vascular disease, NPH, tumour, basal-ganglia signal change (manganese T2 pallidal hyperintensity, CO pallidal necrosis).
- **Reversibility is the management theme:** withdraw culprit drugs/toxins; control vascular risk; shunt NPH; chelate Wilson's. Where dopaminergic agents are tried (vascular, MPTP, postencephalitic, structural SNc), response guides prognosis.
- If an antipsychotic remains essential, switch to a **dopamine-sparing agent (quetiapine/clozapine)** or, for PD-psychosis, the 5-HT2A inverse agonist **pimavanserin**.

High-yield exam pointers

- Parkinsonism = **bradykinesia + rigidity ± rest tremor**; PD ≈ 75% of cases; ~24% clinical misdiagnosis rate without strict (UK Brain Bank / MDS) criteria.
- **Commonest secondary cause = drug-induced** (neuroleptics, **metoclopramide**, cinnarizine/flunarizine, reserpine/tetrabenazine, lithium, valproate).
- DIP is **symmetrical, postural-tremor predominant, reversible** (may take up to 6 months); treat by stopping the drug ± anticholinergics/amantadine.

- **Vascular parkinsonism = "lower-body parkinsonism"**, falls, pyramidal/pseudobulbar signs, MRI small-vessel disease, **normal DaTscan**, poor but worth-trying levodopa response.
- **MPTP → MPP^+ via MAO-B → complex-I inhibition**; manganese & CO damage the **globus pallidus** → levodopa-unresponsive parkinsonism.
- **Oculogyric crises** = postencephalitic and acute drug-induced dystonic reactions; **Hakim triad** (gait + dementia + incontinence) = NPH.
- Always exclude **Wilson's disease** in patients < 40 years — treatable with copper chelators.
- **DaTscan normal** in drug-induced/vascular/psychogenic/essential tremor; **abnormal** in PD and atypical parkinsonism.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Parkinson's Disease" (Differential Diagnosis of Parkinsonism, Table 446-2; Atypical, Secondary and Other Forms of Parkinsonism; Features Suggesting an Atypical/Secondary Cause, Table 446-3) and "Tremor, Chorea, and Other Movement Disorders".
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — "Parkinson Disease and Other Movement Disorders" (Vascular, Postencephalitic, Drug-Induced and Toxin-Induced Parkinsonism; DaTscan; "red-flag" Box 96.2).
- **CMDT 2026** — "Nervous System Disorders" (Drug-Induced Abnormal Movements / drug-induced parkinsonism; management).

◆ ◆ ◆

Temporal lobe epilepsy

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

Definition / Introduction — Temporal lobe epilepsy (TLE) is a **focal (localization-related) epilepsy** in which seizures arise from neuronal networks within one temporal lobe, classically producing **focal seizures with impaired awareness** preceded by a stereotyped aura. Its commonest form, the **mesial temporal lobe epilepsy (MTLE) syndrome**, is *the most common syndrome associated with focal seizures with impairment of consciousness* and is defined by distinctive clinical, EEG, and pathologic features, the hallmark substrate being **hippocampal sclerosis** demonstrable on high-resolution MRI. It is clinically important because MTLE *tends to be refractory to anticonvulsants but responds well to surgical intervention*.

Classification and seizure semiology

- **Terminology (ILAE 2017):** the term *partial* is obsolete — seizures are **focal** or **generalized**. The old categories "simple/complex partial" are eliminated; focal seizures are now described by **awareness (intact vs impaired)**, **onset (motor vs nonmotor)**, and whether they **evolve to bilateral tonic-clonic** seizures (formerly "secondary generalization").
- **Two anatomical subtypes:**
  - **Mesial TLE** — arises from hippocampus/amygdala/parahippocampal gyrus; usually due to **hippocampal sclerosis**; the prototypic surgically remediable syndrome.

- **Lateral (neocortical) TLE** — arises from the lateral temporal neocortex; includes the genetic form **ADEAF** (autosomal dominant epilepsy with auditory features) due to **LGI1 (10q24)** mutations, presenting with **ictal auditory symptoms or aphasia**, onset usually **10–25 years**.

- **Aura (focal seizure with intact awareness)** — a focal seizure without cognitive disturbance, stereotypic for the patient; temporal-lobe auras include:
  - **Olfactory** hallucinations of acrid odors (e.g., burning rubber, bleach) and **gustatory** sensations (bitter, metallic).
  - **Epigastric "rising" sensation** ascending to the head; auditory phenomena (simple or complex sounds).
  - **Experiential/psychic** symptoms — intense **fear**, a dreamlike state, **depersonalization**, *déjà vu*, and **micropsia/macropsia** (objects appearing smaller or larger).
- **Focal seizure with impaired awareness** — aura → **motionless stare / behavioral arrest** (onset of impaired awareness) → **automatisms** (chewing, lip-smacking, swallowing, "picking" hand movements, or elaborate behaviors). **Unilateral dystonic posturing** of a limb may occur.
- **Postictal state** — **disorientation**, **anterograde amnesia**, and transient deficits from postictal inhibition (e.g., **dysphasia** when the focus is in the dominant hemisphere). Recovery takes seconds to hours. A focal seizure may **evolve to a bilateral tonic-clonic** seizure.

Characteristics of the mesial temporal lobe epilepsy syndrome (Table 436-3)

Domain	Features
History	**History of febrile seizures**; family history of epilepsy; early onset; rare generalized seizures; seizures may **remit and reappear**; seizures often **intractable**
Clinical	**Aura common**; **behavioral arrest/stare**; **complex automatisms**; **unilateral posturing**; postictal disorientation; **memory loss**; **dysphasia** (dominant-hemisphere focus)
EEG	**Unilateral or bilateral anterior temporal spikes**
Functional imaging	**Hypometabolism on interictal PET**; **hyperperfusion on ictal SPECT**; material-specific memory deficits on **intracarotid amobarbital (Wada) test**
MRI	**Small hippocampus** with **increased T2 signal** and **loss of trilaminar (internal laminar) architecture**; small temporal lobe; **enlarged temporal horn**
Pathology	Highly selective loss of specific hippocampal cell populations in most cases; **granule cell layer dispersion**; **gliosis**

Pathophysiology — hippocampal sclerosis and epileptogenesis

- Seizures reflect a **shift in the normal balance of excitation and inhibition** in the CNS; in MTLE this is anchored in **hippocampal sclerosis**, which appears *essential to the pathophysiology for many patients*.
- **Selective neuronal loss:** many patients show highly selective loss of neurons that normally **inhibit the main excitatory neurons of the dentate gyrus**, with **reorganization (sprouting) of surviving neurons** that increases network excitability.

- **Epileptogenesis** — the transformation of a normal network into a chronically hyperexcitable one. A precipitating injury (e.g., prolonged/complex febrile seizure, head trauma, infection) creates a focal region of structural change → **local hyperexcitability** → further structural change → spontaneous seizures, typically after a **latent interval of months to years**.
- Additional mechanisms: chronic alterations in **glutamate and GABA receptor function** and induction of **inflammatory cascades**.
- **Risk factors / associations:** an antecedent history of **febrile seizures** (complex febrile seizures carry a 2–5% epilepsy risk) and a **family history of epilepsy**; TLE usually presents in **childhood**, related either to mesial temporal sclerosis (MTLE) or to other focal abnormalities such as **cortical dysgenesis**.

Investigations

- **Routine interictal EEG** — may be normal or show **anterior temporal spikes/sharp waves**; because the medial temporal focus is deep, the scalp EEG can be **nonlocalizing**.
- **Inpatient video-EEG monitoring** — captures habitual seizures to **localize and lateralize** the focus and correlate semiology with EEG/imaging; the cornerstone of presurgical evaluation.
- **High-resolution MRI (3 T)** — demonstrates the **hippocampal sclerosis triad**: high T2 signal, blurred internal laminar architecture, and reduced hippocampal volume (Fig. 436-1).
- **Functional/adjunctive imaging** — interictal **PET** (hypometabolism), ictal **SPECT** (hyperperfusion), and **MEG** to verify the epileptogenic zone.
- **Neuropsychological testing, intracarotid amobarbital (Wada) test, and functional MRI** — lateralize **language and memory** before resection.
- **Invasive monitoring** when noninvasive data are insufficient: **robot-assisted stereo-EEG (depth electrodes)** or subdural electrodes; intraoperative **electrocorticography and functional mapping** delineate **eloquent cortex**.
- **Differentiate from** psychogenic nonepileptic seizures and syncope; bizarre stereotyped paroxysmal behaviour should not be dismissed as non-epileptic without EEG.

Management — medical and surgical

- **Medical (first line for focal seizures):** drugs of choice are **carbamazepine** (or **oxcarbazepine / eslicarbazepine**), **lamotrigine**, **phenytoin**, and **levetiracetam** — broadly similar efficacy; choice is driven by pharmacokinetics, toxicity, and comorbidity. Aim for **monotherapy** at the maximally tolerated dose.

Drug	Typical adult dose	Key caution
Carbamazepine	600–1800 mg/d	Leukopenia, aplastic anemia, hepatotoxicity; *HLA-B linked* SJS in Asian/European ancestry
Oxcarbazepine	900–2400 mg/d	Avoids "toxic epoxide"; hyponatremia
Lamotrigine	150–500 mg/d	**Rash / Stevens-Johnson** — slow titration (lower with valproate)

Drug	Typical adult dose	Key caution
Levetiracetam	1000–3000 mg/d	No major interactions; irritability/psychiatric effects
Phenytoin	300–400 mg/d (3–6 mg/kg)	Nonlinear kinetics; gum hypertrophy, hirsutism, osteoporosis
Valproic acid	—	Useful when seizures generalize; teratogenic, hepatotoxic
Topiramate / Zonisamide	200–400 mg/d	Renal stones; cognitive slowing
Lacosamide / Brivaracetam / Perampanel / Gabapentin	adjunctive	Add-on options for focal seizures
Cenobamate	100–400 mg/d	For focal epilepsy uncontrolled by up to 3 drugs

- **Refractory MTLE → surgery:** because MTLE often fails subsequent drug trials, give an **efficient but relatively brief medical trial, then refer for surgical evaluation** rather than years of uncontrolled seizures.
  - **Anteromedial temporal lobectomy** or the more limited **amygdalohippocampectomy** is the commonest procedure.
  - Outcome: **~70% of well-selected patients become seizure-free** and a further **15–25% achieve ≥90% seizure reduction**; clinically significant surgical complications are **<5%**. Patients generally continue antiseizure drugs postoperatively.
  - **Stereotactic laser thermal (interstitial) ablation** — a less invasive means of destroying the focus.
- **Palliative neurostimulation** (for non-resectable / multifocal / eloquent-cortex foci): **vagus nerve stimulation (VNS)** (open-loop, left vagus; limited efficacy), **responsive neurostimulation (RNS)** (closed-loop intracranial; ~15% seizure-free), and **anterior thalamic deep brain stimulation (DBS)**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Coronal MRI of hippocampal sclerosis (Fig. 436-1):** outline both temporal lobes at the level of the hippocampal bodies. Labels — *Left hippocampus (small, high T2 signal, loss of internal architecture)*, *Normal right hippocampus*, *Enlarged left temporal horn*, *T2-weighted MRI, 3 Tesla*.
- **Hippocampal circuit schematic:** Labels — *Dentate gyrus (granule cell loss + dispersion)*, *CA1*, *CA3*, *Loss of inhibitory interneurons*, *Mossy-fibre sprouting / aberrant excitatory reorganization*, *Amygdala*, *Entorhinal cortex*.

Clinical / Diagnostic significance

- A **stereotyped aura (déjà vu, rising epigastric sensation, olfactory hallucination) followed by stare and automatisms** is the bedside signature of TLE and should prompt MRI of the temporal lobes.

- **Dysphasia/anterograde amnesia** postictally helps **lateralize** the focus to the dominant hemisphere — relevant to surgical risk to memory and language.
- The **concordance** of video-EEG, MRI hippocampal sclerosis, interictal PET hypometabolism and ictal SPECT defines a **surgically remediable** syndrome — one of the few epilepsies where surgery can be curative.
- Recognizing drug-resistance early avoids prolonged morbidity (injury, psychosocial harm, increased mortality including SUDEP) and the chance of seizure freedom with timely surgery.
- Identifying **lateral TLE / ADEAF (LGI1)** matters for genetic counselling and prognosis distinct from MTLE.

High-yield exam pointers

- **MTLE = commonest cause of focal seizures with impaired awareness**; substrate = **hippocampal sclerosis**.
- **Hippocampal sclerosis triad on MRI:** small hippocampus + increased T2 signal + loss of internal (trilaminar) architecture.
- **EEG:** unilateral/bilateral **anterior temporal spikes**; scalp EEG may be nonlocalizing (deep focus).
- Classic history: **antecedent febrile seizures + family history of epilepsy + early onset + drug-refractory** course.
- Semiology: **aura → behavioral arrest/stare → oroalimentary & manual automatisms → postictal confusion ± dysphasia**.
- Pathology: selective hippocampal neuronal loss, **granule cell dispersion, gliosis**; epileptogenesis after a **latent period**.
- Drugs of choice (focal): **carbamazepine, oxcarbazepine, lamotrigine, phenytoin, levetiracetam**.
- **Surgery (anteromedial temporal lobectomy/amygdalohippocampectomy): ~70% seizure-free**, complications **<5%**.
- Non-resectable foci → **VNS / RNS / thalamic DBS**; **Wada test** assesses language & memory before resection.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — **Ch 436 "Seizures and Epilepsy"** (MTLE syndrome, Table 436-3, Fig. 436-1 hippocampal sclerosis, focal seizure semiology, epileptogenesis, Table 436-9 antiseizure drugs, surgical/neurostimulation treatment). Coverage note: Harrison addresses TLE within the broader seizures/epilepsy chapter and does not give a separate "Engel" surgical outcome classification or detailed dual-pathology discussion; carbamazepine/phenytoin dose ranges and the SJS/HLA association quoted are from Table 436-9 and the drug-selection text. No fabricated specifics added.

◆ ◆ ◆

Tic douloureux

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

Definition / Introduction — *Tic douloureux* (trigeminal neuralgia, TN) is a chronic, episodic facial pain syndrome characterised by **paroxysms of excruciating, electric shock-like or lancinating pain** confined to one or more divisions of the **fifth cranial (trigeminal) nerve**, classically the maxillary (V2) and mandibular (V3) divisions on one side. The pain is brief (seconds to ≤2 minutes), stereotyped, triggered by innocuous cutaneous or intraoral stimuli, and — in the *classical* form — occurs **without any demonstrable objective sensory or motor deficit**. The term "tic" reflects the involuntary wince the patient gives at the height of each spasm. It is the prototype of a hyperexcitable cranial neuralgia and one of the most painful conditions in clinical medicine.

Epidemiology & Aetiopathogenesis

- **Incidence** ~4–8 per 100,000 per year; ~60% occur in **women**; onset is after age 40 in ~90% of cases, with incidence rising progressively with age (middle-aged and elderly predominate).
- **Pathophysiology** — Symptoms arise from **ectopic generation of action potentials** in pain-sensitive afferents of the trigeminal root, just before it enters the lateral surface of the pons (the *root entry zone*).
  - A compressing vessel or lesion causes **focal demyelination of large myelinated (non-nociceptive) fibres**, rendering them hyperexcitable; these become **electrically (ephaptically) coupled** to adjacent small unmyelinated/poorly myelinated pain fibres.
  - This *cross-talk* explains why innocuous tactile stimuli carried by large fibres can ignite paroxysms of pain — the basis of **trigger zones**.
- **Neurovascular compression** is the commonest cause: an aberrant or ectatic vessel — most often the **superior cerebellar artery**, occasionally AICA/PICA or the **superior petrosal vein** — loops onto the nerve root. Age-related **brain sagging and vascular tortuosity/thickening** explain the prevalence in later life.
- The trigeminal root is uniquely **ensheathed by oligodendrocyte (CNS-type) myelin for up to ~7 mm** after leaving the pons; this is why a **demyelinating MS plaque** at the root entry zone produces TN, and why TN in a young or bilateral patient should prompt a search for multiple sclerosis.

Clinical Features

- **Character**: superficial, stabbing, "electric-shock", shooting or lancinating; each jab lasts seconds, recurring as single jabs or clusters, day and night, for weeks–months before remitting.
- **Distribution**: unilateral, in V2 and/or V3 (lips, gums, cheek, chin); **isolated V1 (ophthalmic) involvement is extremely rare**.
- **Trigger zones**: typically near the **nasolabial fold**, lips, or tongue; the trigger may be remote from the felt pain. Provoking acts include **washing the face, shaving, brushing teeth, chewing, talking, smiling, or a cold draught of air**.
- Patients hold the face still while talking and may avoid eating, leading to **weight loss, dehydration, and depression**.

- **Course**: exacerbating–remitting over years; remissions may last months but the disorder usually recurs, with attacks becoming more frequent and remissions shorter over time. A residual dull ache may linger between jabs in advanced disease.
- *Pretrigeminal neuralgia*: some patients have prodromal toothache/sinusitis-like pain for hours before classical TN develops in the same distribution.
- **Cardinal negative sign**: in *classical* TN, **examination is normal** — no sensory loss, no masticatory weakness. Objective sensory loss or jaw weakness redefines the problem as **trigeminal neuropathy** (a secondary/structural cause).

ICHD-3 Classification (etiological subtypes)

Subtype	Defining feature	Examination	Implication
Classical TN	Neurovascular compression with **nerve-root atrophy or displacement** (on MRI/at surgery)	Normal	Microvascular decompression candidate
Secondary TN	Underlying disease — **MS plaque, cerebellopontine-angle tumour, brainstem/pontine infarct, mass**	Often abnormal; may show **concomitant continuous pain**	Treat the cause; surgery inappropriate in MS
Idiopathic TN	No cause and **no morphological nerve change** despite vessel contact	Normal	Medical therapy

- *Secondary causes (Brazis): MS plaque, cerebellopontine-angle tumour (meningioma, schwannoma), aberrant superior cerebellar artery, cavernous malformation, lipoma, brainstem/pontine infarction, Chiari malformation, basilar invagination.*

Differential Diagnosis

Condition	Discriminating points
Dental/sinus/jaw disease	Local pathology; pain not lancinating/triggered
Migraine / cluster headache	Deep-seated, **steady** pain, longer duration; *cluster-tic* = rare coexistence
Paroxysmal hemicrania, SUNCT/SUNA	Prominent **cranial autonomic features** (lacrimation, conjunctival injection); distinct frequency/duration
Giant-cell (temporal) arteritis	Superficial facial pain but **not shock-like**; myalgia, systemic symptoms, **elevated ESR/CRP**
Glossopharyngeal neuralgia	Identical-quality pain but in **throat/tonsillar fossa**, radiating to ear; triggered by swallowing; may cause bradycardia/syncope
Trigeminal neuropathy	**Objective sensory loss / jaw weakness** → mass, zoster, connective-tissue disease, *numb-chin (mental neuropathy)* may signal malignancy
Atypical/persistent idiopathic facial pain	Constant **burning**, ill-defined, often in middle-aged women with depression

Investigations

- **High-resolution, contrast-enhanced brain MRI (± MR angiography)** in essentially all patients — to exclude secondary causes (demyelinating plaque, pontine lacunar infarct, CPA tumour, skull-base infiltration) and to demonstrate the offending vessel/neurovascular conflict before planning decompression.
- **Secondary cause is more likely if** age <40 years, bilateral symptoms, or any objective neurological sign.
- **ESR / CRP** if temporal arteritis is suspected.
- **Blink-reflex / trigeminal-evoked studies and EMG are normal** in idiopathic TN (abnormal results suggest a structural lesion).

Management

A. Medical therapy (first line for classical/idiopathic TN) — sodium-channel-blocking anticonvulsants are the drugs of choice.

Drug	Dose	Notes / toxicity
Carbamazepine *(drug of choice)*	Start **100 mg** with food; ↑100 mg/day q1 –2 days; maintenance ~**200 mg QID**; **>1200 mg/day gives no extra benefit**	Effective in **50–75%**; dizziness, imbalance, sedation, **agranulocytosis** (monitor CBC), hyponatraemia, deranged LFTs
Oxcarbazepine	300–1200 mg BID	Probably equi-efficacious, **less marrow toxicity** but watch **hyponatraemia**
Phenytoin	300–400 mg/day	Useful if above fail/not tolerated; **IV fosphenytoin 15–20 mg PE/kg** aborts a severe acute attack
Lamotrigine	up to 400 mg/day	Add-on / alternative
Baclofen	10–20 mg TID	Alone or in combination
Topiramate	50 mg BID	Alternative
Gabapentin / pregabalin	gabapentin up to 3600 mg/day	Benign profile; *especially useful in MS-related TN*

- Monitor **CBC, LFTs and serum sodium** for the first months and yearly. If effective, continue ~1 month then taper to test for remission.
- *Proparacaine* anaesthetisation of the ipsilateral conjunctival sac can give temporary relief in an acute crisis.

B. Surgical / interventional therapy (drug failure or intolerance) — initial relief in ≥80% of patients.

Procedure	Mechanism	Efficacy / drawbacks
Microvascular decompression (MVD) — *Jannetta*, via suboccipital craniotomy	Separates offending vessel from nerve root (**non-destructive**)	**>70% relief**, low recurrence; best for **classic lancinating** pain; major-surgery risks; preop **MRA** essential

Procedure	Mechanism	Efficacy / drawbacks
Gamma-knife stereotactic radiosurgery	Focused radiation to nerve root	Complete relief in ~½ (often **delayed onset**); low risk of numbness; **recurrence in ~⅓ over 2–3 yr**; less effective than MVD but few serious complications; no GA needed
Radiofrequency thermal rhizotomy	Heat lesion of ganglion/nerve (**destructive**)	**>95% short-term** relief; recurrence up to ⅓; facial numbness, **masseter weakness**, corneal denervation/**neurokeratitis** with V1 lesions
Percutaneous balloon compression	Mechanical injury to ganglion (under GA)	Similar short/long-term relief; commonly causes ipsilateral facial numbness
Peripheral alcohol/glycerol block	Absolute alcohol 0.5–0.75 mL to mental/infraorbital/supraorbital nerve	Low morbidity, temporary numbness, **corneal sensation preserved**; relapse in 6–18 months

- In **MS-related TN**, open surgical exploration/MVD is inappropriate; ablative (less invasive) techniques may help.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Trigeminal nerve and its three sensory divisions on the face** — label: *Ophthalmic (V1), Maxillary (V2), Mandibular (V3)* dermatomes; *Gasserian (semilunar/trigeminal) ganglion in Meckel's cave*; *superior orbital fissure (V1), foramen rotundum (V2), foramen ovale (V3)*; mark the typical **trigger zone at the nasolabial fold**.
- **Neurovascular conflict at the root entry zone** — label: *pons*, *trigeminal root entry zone*, *superior cerebellar artery looping onto nerve*, *zone of focal demyelination*, and adjacent *site of microvascular decompression (Teflon pledget)*.

Clinical / Diagnostic significance

- TN is a **clinical diagnosis**; the triad of *paroxysmal, triggerable, unilateral V2/V3 shock-like pain with a normal examination* is highly specific.
- A **normal neurological examination is reassuring**, but any objective deficit (sensory loss, jaw deviation, corneal hypoaesthesia) mandates MRI to exclude a structural lesion — *re-labelled trigeminal neuropathy*.
- **Young or bilateral** TN → think **multiple sclerosis** (demyelinating plaque at the root entry zone).
- An **isolated numb chin (mental neuropathy)** can be the sole herald of systemic malignancy — never dismiss it.
- Carbamazepine response is so characteristic that a good response supports the diagnosis; failure should prompt re-evaluation for a secondary cause.

High-yield exam pointers

- **Tic douloureux = trigeminal neuralgia**; paroxysmal lancinating pain, **V2/V3 > V1**, unilateral, seconds-long, with **trigger zones** (nasolabial fold).
- Incidence **4–8/100,000/yr**; **~60% women**; onset >40 yr in 90%.

- Cause = **neurovascular compression, most often the superior cerebellar artery**, at the **root entry zone**, causing focal demyelination and ephaptic cross-talk.
- **No objective sensory/motor loss in classical TN** — its presence ⇒ *trigeminal neuropathy / secondary cause*.
- **ICHD-3**: classical (vascular compression + atrophy), secondary (MS, tumour — may have *continuous* background pain), idiopathic.
- **Carbamazepine is the drug of choice** (effective 50–75%); alternatives — oxcarbazepine, phenytoin, lamotrigine, baclofen, gabapentin, topiramate.
- Severe acute attack — **IV fosphenytoin 15–20 mg PE/kg**.
- Surgery of choice in drug failure = **microvascular decompression (Jannetta, >70% durable relief)**; ablative options — RF rhizotomy, balloon compression, gamma-knife.
- **Young/bilateral TN ⇒ exclude MS**; obtain **high-resolution contrast MRI + MRA**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Trigeminal Neuralgia, Bell's Palsy, and Other Cranial Nerve Disorders"* (clinical features, incidence, pathophysiology, drug doses, surgical options).
- **Bradley & Daroff's Neurology in Clinical Practice, 8e** — *"Headache and Other Craniofacial Pain"* (ICHD-3 classical/secondary/idiopathic classification, root-entry-zone pathology, medical and surgical management) and *"Cranial and Facial Pain"*.
- **Brazis – Localization in Clinical Neurology** — *"Cranial Nerve V: The Trigeminal Nerve"* (secondary causes, trigger physiology, trigeminal neuropathy vs neuralgia).
- **CMDT 2026** — *"Nervous System Disorders – Trigeminal Neuralgia"* (current drug regimens, surgical success rates, MRI to exclude secondary causes).

◆ ◆ ◆

Cluster headache — treatment and prevention

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

Definition / Introduction — Cluster headache is a relatively rare (population frequency ~0.1%) but highly stereotyped *trigeminal autonomic cephalalgia (TAC)* characterised by attacks of deep, retro-orbital, excruciating, explosive, strictly **unilateral** pain lasting 15–180 minutes, accompanied by **ipsilateral cranial autonomic features** and a striking **circadian/circannual periodicity**. Attacks occur from once every other day to eight times a day, are often nocturnal (~50%), and men are affected about three times more often than women. Because attacks peak rapidly and are agonising, management has two arms that must run together: **fast-acting abortive (acute) therapy** for individual attacks and **transitional + maintenance preventive therapy** to suppress attacks until the bout naturally remits.

Goals and general principles of management

- Two parallel objectives: (1) **abort the acute attack** rapidly, and (2) **prevent attacks** until the bout is over — *the most satisfactory strategy is preventive suppression of attacks for the duration of the cluster bout, while every patient also needs an acute treatment at some time.*

- Tailor preventive choice to **bout length and pattern**: short-bout episodic patients suit a brief "transitional" course; patients with long bouts or **chronic cluster headache** (remission <3 months without treatment) need agents that are **safe for prolonged use**.
- Avoid known **triggers during a bout**, notably **alcohol**.
- Oral sumatriptan and simple analgesics/decongestants are **ineffective** — patients mislabelled with "sinus headache" are commonly mistreated.

Acute (abortive) attack treatment

Attacks peak within minutes, so only **rapid-onset, parenteral/inhaled/intranasal** routes work; oral drugs are too slow.

Modality	Regimen (Harrison 22e)	Notes
High-flow oxygen	100% O_2 at **10–12 L/min for 15–20 min** via non-rebreather	High flow + high O_2 content essential; *ultra-high flow with a demand valve* may help some patients; first-line, very safe
Sumatriptan SC	**6 mg SC** (3–4 mg SC also effective where available)	Aborts attack in **10–15 min**; **no tachyphylaxis** with repeated use
Sumatriptan nasal	**20 mg** intranasal	Useful when patient prefers not to self-inject
Zolmitriptan nasal	**5 mg** intranasal	Effective alternative nasal triptan
Non-invasive vagus nerve stimulation (nVNS)	**Three 2-min cycles** consecutively at onset on the side of pain; may repeat after 9 min	**FDA-cleared for acute treatment of episodic** cluster headache

- **Oral sumatriptan is NOT effective** for acute attacks or for prevention.
- Triptan cautions: avoid in established/uncontrolled coronary or cerebrovascular disease and uncontrolled hypertension; respect total daily triptan limits.

Preventive treatment (Table 441-8)

Preventives are split into **short-term (transitional)** therapy — to gain rapid control while a slow maintenance drug is titrated — and **long-term (maintenance)** therapy. Choice depends on bout length.

Setting	Agent and dose (Harrison 22e)
Short-term / transitional (episodic CH)	**Prednisone** 1 mg/kg up to **60 mg/day, tapering over ~21 days** (e.g. 60 mg/day ×7 days then rapid taper)
	Verapamil 160–960 mg/day (started during bout)
	Galcanezumab 300 mg SC
	Greater occipital nerve (GON) injection — local anaesthetic + corticosteroid
Long-term / maintenance (episodic CH and prolonged/chronic CH)	**Verapamil** 160–960 mg/day
	nVNS 6–24 stimulations/day

Setting	Agent and dose (Harrison 22e)
	Melatonin 9–12 mg/day
	Topiramate 100–400 mg/day
	Lithium 400–800 mg/day

- **Glucocorticoids** are the most reliable *transitional* drug for short bouts: a 10-day course of prednisone (60 mg/day for 7 days, then rapid taper) often interrupts the bout while verapamil takes effect.
- **Greater occipital nerve injection** (lidocaine + corticosteroid, ipsilateral) is proven in **randomised controlled trials**, giving benefit lasting **up to 6–8 weeks** — an excellent transitional option.
- **Galcanezumab** is a **calcitonin gene-related peptide (CGRP) monoclonal antibody**, FDA-approved for **episodic** cluster headache; **300 mg SC** reduces attack frequency, is well tolerated, and is often an effective option.

Verapamil — the first-line maintenance preventive

- **Most experts favour verapamil** as first-line prevention for **chronic cluster headache and prolonged bouts**; it compares favourably with lithium in practice.
- **Dosing:** start **40–80 mg twice daily**; titrate in **80-mg increments**; effective doses may be as high as **960 mg/day** — often far exceeding cardiac doses.
- **Common side effects:** constipation, leg/ankle swelling, gingival hyperplasia.
- **Key safety concern — cardiac conduction:** verapamil slows **AV-nodal conduction** and can cause **heart block**; monitor the **PR interval on ECG**.
  - ~**20%** develop ECG abnormalities, possible at doses as low as **240 mg/day**, and these can worsen over time even on a stable dose.
- **ECG monitoring schedule:** baseline ECG in **all** patients; repeat ECG **10 days after each dose increase above 240 mg/day**; on long-term verapamil, ECG **every 6 months**.

Neuromodulation and refractory / chronic disease

When medical therapy fails in **chronic** cluster headache, neuromodulation is considered:

- **Sphenopalatine ganglion (SPG) stimulation** with an implanted battery-free stimulator — effective in **RCTs** for both aborting attacks and reducing attack frequency over time.
- **nVNS** — compares favourably with standard of care in open-label experience (and is FDA-cleared for acute episodic attacks).
- **Occipital nerve stimulation (ONS)** — beneficial in open-label use.
- **Deep-brain stimulation (DBS) of the posterior hypothalamic grey matter** — successful in about **50%** of treated patients, but its risk–benefit ratio makes it **inappropriate until all less invasive options are exhausted**.
- Destructive trigeminal procedures are *not* part of cluster-headache management (they are seldom useful even in the related TACs and cause long-term complications).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Stepwise management algorithm of cluster headache** — three columns/boxes:
- *Acute attack* → labels: **100% O_2 10–12 L/min × 15–20 min**, **Sumatriptan 6 mg SC**, **Sumatriptan 20 mg / Zolmitriptan 5 mg nasal**, **nVNS (3 × 2-min cycles)**.
- *Transitional prevention* → labels: **Prednisone 60 mg taper over 21 days**, **GON injection (LA + steroid)**, **Galcanezumab 300 mg SC**.
- *Maintenance prevention* → labels: **Verapamil 160–960 mg/day (first-line)**, **Lithium 400–800 mg/day**, **Topiramate 100–400 mg/day**, **Melatonin 9–12 mg/day**, **nVNS** → arrow to **Refractory chronic CH → SPG stimulation / ONS / DBS posterior hypothalamus**.
- **Side-of-pain autonomic features sketch** — a face with right-sided labels: **conjunctival injection / lacrimation**, **rhinorrhoea / nasal congestion**, **ptosis + miosis (partial Horner)**, **aural fullness**, with the central label **posterior hypothalamic "pacemaker" activation**.

Clinical / Diagnostic significance

- **Restless behaviour** (pacing, rocking, head-rubbing) during an attack is a useful bedside clue distinguishing cluster headache from migraine (where patients lie still) and supports starting abortive therapy promptly.
- **Baseline ECG before verapamil** and serial monitoring are mandatory because of dose-dependent AV block — a frequently tested safety pearl.
- Because TACs over-represent **pituitary tumour–related headache**, pituitary imaging (MRI) and pituitary function tests (prolactin, growth hormone) should be obtained when clinically indicated before committing to lifelong therapy.
- High-flow oxygen is the safest abortive and is preferred in patients with vascular contraindications to triptans.
- Distinguish from indomethacin-responsive TACs: **paroxysmal hemicrania and hemicrania continua respond completely to indomethacin** — verapamil/oxygen do not abort them — so an indomethacin trial is diagnostically and therapeutically decisive in the differential.

High-yield exam pointers

- **Two arms:** rapid abortive therapy **plus** preventive suppression for the whole bout.
- **Acute first-line: 100% O_2 10–12 L/min for 15–20 min** and **sumatriptan 6 mg SC** (no tachyphylaxis).
- **Oral sumatriptan is useless** in cluster headache (too slow).
- **Verapamil = first-line maintenance preventive**, 160–960 mg/day; titrate in 80-mg steps with **ECG monitoring** (PR interval, AV block).
- **Transitional bridge:** prednisone 60 mg taper over ~21 days and/or **greater occipital nerve injection** (benefit 6–8 weeks).
- **Galcanezumab (anti-CGRP mAb) 300 mg SC** — FDA-approved for **episodic** cluster headache.
- Other maintenance options: **lithium, topiramate, melatonin, nVNS**.

- **Refractory chronic CH:** SPG stimulation, occipital nerve stimulation, DBS of posterior hypothalamus (~50% success).
- Counsel **alcohol avoidance** during the cluster bout.

> **SOURCE & COVERAGE**
> Harrison's Principles of Internal Medicine, 22e — Ch 441 "Migraine and Other Primary Headache Disorders" (Trigeminal Autonomic Cephalalgias / Cluster Headache section; Tables 441-7 and 441-8). All drugs, doses, monitoring rules and neuromodulation data are taken from this chapter. Coverage note: triptan cardiovascular cautions are standard, universally-accepted internal medicine added for completeness and are not elaborated in this specific chapter section.

◆ ◆ ◆

Wernicke encephalopathy

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

Definition / Introduction — Wernicke encephalopathy is an acute, potentially fatal neuropsychiatric emergency due to **thiamine (vitamin B1) deficiency**. It classically presents with **confusion, ophthalmoplegia/nystagmus, and gait ataxia**, but the complete triad is absent in many patients. It is the acute stage of the Wernicke-Korsakoff spectrum; delayed or inadequate treatment may leave irreversible amnesia and confabulation.

Etiology and risk settings

- **Thiamine physiology:** thiamine is a water-soluble vitamin with small body stores; continuous dietary supply is needed. It acts as thiamine pyrophosphate in carbohydrate, amino-acid, and lipid metabolism, including alpha-ketoacid decarboxylation and transketolase reactions.
- **Alcohol use disorder** is the commonest setting in adult medicine: alcohol reduces intake, impairs intestinal absorption and metabolism/storage of thiamine, and increases urinary losses.
- **Non-alcoholic high-risk states:** hyperemesis gravidarum, anorexia/eating disorders, systemic malignancy, AIDS, chronic protein-calorie undernutrition, prolonged fasting or starvation, dieting, prolonged IV feeding, refeeding after starvation, hemodialysis/peritoneal dialysis, and gastrointestinal or **bariatric/metabolic surgery**.
- **Precipitating event:** IV glucose, carbohydrate loading, enteral/parenteral nutrition, or refeeding in a thiamine-depleted patient may acutely precipitate Wernicke encephalopathy and lactic acidosis.
- **Associated deficiency syndromes:** wet beriberi causes high-output heart failure with tachycardia, cardiomegaly, edema and warm extremities; dry beriberi causes symmetric sensorimotor polyneuropathy with pain, paresthesia and loss of reflexes, legs more than arms.

Pathogenesis and vulnerable neuroanatomy

- Thiamine deficiency impairs cerebral energy metabolism, especially in metabolically active periventricular and diencephalic structures; pyruvate may accumulate and transketolase activity falls.

- Characteristic sites are **periaqueductal gray**, tectal plates, **medial thalami**, **mammillary bodies**, walls of the third and fourth ventricles, cerebellar vermis, pons, medulla, dentate nuclei, cranial nerve nuclei and vestibular nuclei.
- Eye signs reflect involvement of **cranial nerve III, VI and VIII nuclei**, medial longitudinal fasciculus and periaqueductal/brainstem ocular motor pathways.
- Gait ataxia reflects combined involvement of the **cerebellar vermis**, vestibular pathways and often peripheral neuropathy; truncal/gait ataxia is more prominent than limb ataxia.
- Autonomic features such as **hypothermia** and **postural hypotension** reflect hypothalamic and brainstem autonomic pathway involvement.
- Korsakoff amnesia reflects damage in the **mammillary bodies, mammillothalamic tract, medial dorsal/anterior thalamic nuclei, hippocampal-parahippocampal circuits and related limbic memory pathways**.
- Pathology evolves from congestion and **petechial hemorrhages** to glial proliferation, myelin pallor, shrinkage and discoloration in the same regions seen on MRI.

Clinical features

Component	Exam-ready points
Mental status	Confusion is the commonest feature, developing over days to weeks: inattention, apathy, disorientation, impaired short-term memory and reduced mental control. Stupor or coma is uncommon but possible.
Ocular signs	Horizontal gaze-evoked nystagmus, vertical nystagmus on upgaze, bilateral lateral rectus weakness/sixth nerve palsy, conjugate gaze palsy, ophthalmoplegia; sluggish pupils and light-near dissociation may occur.
Ataxia	Broad-based gait, truncal instability, inability to stand/walk unaided; limb ataxia is less prominent. Vertigo may be absent despite vestibular nuclear involvement.
Peripheral/ autonomic	Peripheral neuropathy, pain/paresthesia, reduced reflexes, hypothermia, postural hypotension; look for malnutrition, liver disease and alcohol withdrawal.
Korsakoff syndrome	Usually follows repeated or inadequately treated Wernicke episodes: severe anterograde and retrograde amnesia, impaired learning, disorientation to time/place and early confabulation, with relative preservation of alertness, attention and social behavior.

- The classic triad is useful but insensitive: Bradley notes all three elements in fewer than half of patients; a Spanish series found the triad in 39% of alcoholic and 29% of non-alcoholic patients.
- In alcohol use disorder, Wernicke encephalopathy may coexist with withdrawal delirium, hepatic encephalopathy, head injury, subdural hematoma, hypoglycemia, sepsis and electrolyte disturbances.

Diagnosis and investigations

- **Diagnosis is clinical and urgent.** Do not wait for laboratory confirmation before giving parenteral thiamine.
- **Caine criteria:** suspect Wernicke encephalopathy when any **two of four** are present: (1) dietary deficiency/malnutrition, (2) oculomotor abnormality, (3) cerebellar dysfunction or impaired gait,

(4) altered mental status or memory impairment. These criteria are more sensitive than requiring the full triad.

- **Therapeutic response** supports the diagnosis: improvement in ocular signs or confusion within 1-2 days is strongly suggestive, but absence of immediate full recovery does not exclude the diagnosis.
- **Laboratory tests:** draw blood before treatment if feasible, but never delay therapy. Tests include whole-blood/serum thiamine, urinary thiamine excretion, erythrocyte transketolase activity before and after thiamine pyrophosphate, and serum pyruvate. Harrison uses >25% stimulation of transketolase activity after thiamine pyrophosphate as abnormal.
- **MRI brain** is the best imaging test when available: symmetric T2/FLAIR and diffusion abnormalities in periaqueductal regions, tectal plates, medial thalami and mammillary bodies; cerebellar vermis, pons, medulla, dentate nuclei, basal ganglia and cranial nerve nuclei may be involved. SWI may show petechial hemorrhage in mammillary bodies.
- **CT brain** is much less sensitive but may be needed to exclude trauma, hemorrhage, hydrocephalus or stroke. CSF is usually normal or shows only mild protein elevation.
- **Differential diagnosis:** alcohol intoxication or withdrawal delirium, hepatic encephalopathy, uremic encephalopathy, sepsis-associated encephalopathy, hypoglycemia, stroke/posterior circulation disease, encephalitis, sedative/opioid intoxication, electrolyte disorders and Marchiafava-Bignami disease.

Management

Situation	Treatment
Suspected/established Wernicke encephalopathy	Give **thiamine immediately before glucose**. CMDT recommends empiric **thiamine 500 mg IV three times daily for 3-5 days** when Caine criteria are met; Bradley gives 500 mg IV acutely followed by 100 mg three times daily during the first week. Harrison recommends **200 mg IV three times daily** in acute thiamine deficiency with neurologic signs until no further acute improvement, then oral thiamine.
At-risk coma/intoxication or emergency dextrose	Give IV thiamine first; CMDT coma protocol gives **thiamine 100 mg IV**, followed by 50% dextrose 25 g and naloxone when indicated.
Alcohol withdrawal prophylaxis	Hydration, electrolyte correction and vitamins; CMDT uses **thiamine 100 mg IV daily for 3 days**, then oral thiamine for prevention. Harrison advises oral multivitamins with **50-100 mg oral thiamine daily** for a week or more in withdrawal.
After acute phase	Continue oral thiamine until nutrition is secure; correct diet, protein-calorie malnutrition and coexisting B-vitamin deficiencies.

- **Magnesium repletion is essential** because magnesium is required for thiamine activation; thiamine response may be poor if magnesium is low.
- Treat associated alcohol withdrawal with benzodiazepines when indicated, correct hypokalemia/hypomagnesemia/hypophosphatemia, screen for trauma, infection, hypoglycemia and liver disease, and arrange alcohol-use-disorder treatment and nutritional rehabilitation.

- Oral thiamine alone is inadequate initially in suspected Wernicke encephalopathy because absorption is unreliable in debilitated and alcoholic patients.

Prognosis, complications and prevention

- Untreated Wernicke encephalopathy is progressive and may cause death, coma or permanent Korsakoff syndrome.
- Even with treatment, early studies reported mortality of **10-20%**; delayed recognition is common because the full triad is often absent and non-alcoholic cases are overlooked.
- Ocular signs usually improve rapidly, often within hours to 24 h, although fine horizontal nystagmus may persist in about **60%**. Gait improves slowly and may remain abnormal for months in more than one-third of patients.
- Korsakoff syndrome is often persistent; treatment is mainly supportive supervision and rehabilitation, as controlled evidence for cholinesterase inhibitors or memantine is not consistent.
- Prevention is mandatory in all high-risk patients: give thiamine before carbohydrate, during alcohol withdrawal, before/with refeeding, after bariatric surgery, during prolonged vomiting or hyperemesis, and in dialysis patients with unexplained encephalopathy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Triad and lesion-map diagram:** central label "Thiamine deficiency"; arrows to "Confusion", "Ophthalmoplegia/nystagmus", "Gait/truncal ataxia"; side labels "mammillary bodies", "medial thalami", "periaqueductal gray", "tectal plate", "CN III/VI/VIII nuclei", "cerebellar vermis", "hypothalamic autonomic pathways".
- **Emergency treatment flowchart:** "At-risk delirium/coma/malnutrition/alcohol use" -> "Draw thiamine labs if feasible" -> "Thiamine IV before glucose" -> "High-dose IV thiamine + Mg/B-complex/electrolytes" -> "MRI if needed; exclude trauma/sepsis/hepatic/uremic causes" -> "Oral thiamine + nutrition + abstinence plan".

Clinical / Diagnostic significance

- Wernicke encephalopathy is a **medical emergency**, not a retrospective diagnosis; treatment is safe, inexpensive and should precede imaging and laboratory confirmation.
- The most important diagnostic trap is waiting for the full triad; use **Caine criteria** in any malnourished, alcoholic, hyperemesis, post-bariatric, refeeding or dialysis patient with delirium, ataxia or ocular signs.
- Always give **thiamine before dextrose** in at-risk patients; glucose administration increases thiamine requirement and may precipitate or worsen Wernicke-Korsakoff syndrome.
- MRI helps confirmation but a negative CT or absent MRI lesion does not exclude the diagnosis.
- Distinguish from delirium tremens: DT has autonomic hyperactivity, tremor, hallucinations and withdrawal timing; Wernicke has nutritional risk plus ocular motor signs and gait ataxia, and both can coexist.
- Persistent amnesia after the acute delirium clears suggests **Korsakoff syndrome**.

High-yield exam pointers

- Write the triad: **confusion + ophthalmoplegia/nystagmus + gait ataxia**.
- Mention that the full triad is absent in many cases; use **two of four Caine criteria**.
- Never give glucose first in an at-risk patient; **thiamine before dextrose** is a must-write line.
- High-dose parenteral thiamine is required for suspected disease: **500 mg IV three times daily for 3-5 days** is the current empiric emergency regimen.
- Add **magnesium correction**, B-complex vitamins, nutrition and alcohol-withdrawal management.
- MRI lesions: **mammillary bodies, medial thalami, periaqueductal gray/tectal plate**.
- Korsakoff syndrome: **anterograde and retrograde amnesia with confabulation** after repeated or undertreated episodes.
- Prevention is needed in alcohol use disorder, hyperemesis, bariatric surgery, starvation/refeeding, prolonged IV feeding and dialysis.

SOURCE & COVERAGE

Harrison 22e — "Vitamin and Trace Mineral Deficiency and Excess"; "Alcohol and Alcohol Use Disorders"; Bradley & Daroff's Neurology 8e — "Deficiency Diseases of the Nervous System"; "Toxic and Metabolic Encephalopathies"; Brazis Localization — "Cranial Nerve VIII: The Vestibulocochlear Nerve"; "The Localization of Lesions Affecting the Hypothalamus and Pituitary"; DeJong's Neurologic Examination — "An Overview of Brainstem and Cranial Nerve Anatomy"; "The Mental Status Examination"; CMDT 2026 — "Nervous System Disorders"; "Nutrition, Nutritional Disorders, & Obesity"; "Substance Use Disorders"; "Liver, Biliary Tract, & Pancreas Disorders".

Respiratory system

Acute interstitial pneumonia

Asked in: Paper III May 2022 · Paper III Jul 2020 (2×) — RGUHS MD General Medicine

Definition / Introduction — *Acute interstitial pneumonia* (**AIP**), historically termed *Hamman-Rich syndrome*, is a rare and often fatal idiopathic interstitial pneumonia (IIP) characterised by the **acute onset of respiratory distress and hypoxemia** in a previously healthy individual, with **diffuse alveolar damage (DAD)** as its histopathologic hallmark. It is essentially the **idiopathic (cryptogenic) counterpart of ARDS**: the clinical, radiologic, and pathologic picture is indistinguishable from ARDS but **no precipitating cause is identified**. AIP is grouped among the *acute/subacute* idiopathic interstitial pneumonias and carries a mortality of **>50% within 6 months** of presentation.

Where AIP sits — classification of interstitial lung disease

The interstitial lung diseases (ILDs / diffuse parenchymal lung diseases) are first divided into those of **known** and **unknown** cause; AIP belongs to the largest "unknown cause" group, the **idiopathic interstitial pneumonias (IIPs)**.

ILD of known cause	ILD of unknown cause
Exposure — asbestosis, silicosis, radiation, drugs (methotrexate, amiodarone, nitrofurantoin, bleomycin, chemotherapeutics)	**Idiopathic interstitial pneumonias (IIPs)** — IPF, NSIP, RB-ILD, DIP, COP, **AIP**, lymphocytic interstitial pneumonia
Systemic / CTD — RA, scleroderma, polymyositis-dermatomyositis, SLE, Sjögren	**Granulomatous** — sarcoidosis
Granulomatous with vasculitis — GPA (Wegener's), Churg-Strauss; **HP**	**Other** — LAM, pulmonary alveolar proteinosis, Langerhans cell histiocytosis, pleuroparenchymal fibroelastosis

- Among IIPs, AIP is one of only a few that **present acutely (days–weeks)**; most IIPs (e.g., IPF) are chronic and indolent.
- Other ILDs that can present *acutely* and enter the differential of AIP: **eosinophilic pneumonia, hypersensitivity pneumonitis (HP), granulomatosis with polyangiitis (GPA),** and an **acute exacerbation of IPF**.
- Because of overlapping clinical, imaging, and histopathologic features, a **multidisciplinary diagnosis** (pulmonologist + radiologist + pathologist ± rheumatologist) is the accepted standard for all IIPs, AIP included.

Clinical features & natural history

- **Demographics / onset:** AIP affects previously healthy adults with **no antecedent lung disease**; onset is abrupt.
- A **prodrome resembling an acute upper respiratory tract infection** (viral-like illness — fever, myalgia, cough) is common and precedes rapidly worsening dyspnea.
- **Acute respiratory distress and refractory hypoxemia** develop over days to a few weeks, frequently progressing to respiratory failure requiring mechanical ventilation.
- **Course / prognosis:** fulminant — **mortality >50% within 6 months**; **recurrences are common** in survivors. Importantly, those who do recover can show **substantial recovery of lung function**.

- **Physical signs (general to ILD):** end-inspiratory fine **bibasal crackles (rales)**; tachypnea, cyanosis and signs of advanced disease (digital clubbing, cor pulmonale) reflect severity.
- A central diagnostic difficulty is that AIP is **hard to distinguish from ARDS and from an acute exacerbation of an unsuspected underlying pulmonary fibrosis** — making AIP largely a **diagnosis of exclusion**.

Investigations

- **HRCT thorax (standard of care):** the most common findings are **patchy, bilateral ground-glass opacities**, with **dependent regions of air-space consolidation** — a picture that mirrors ARDS.
- **Pulmonary function tests:** like other ILDs, AIP produces a **restrictive defect** — reduced **TLC**, symmetrically reduced **FEV1 and FVC** (preserved/normal FEV1:FVC ratio), and a reduced **DLCO**; in the acute setting testing is often limited by the patient's critical status.
- **Arterial blood gases:** type I respiratory failure with widened A–a gradient.
- **Exclusion work-up (essential, as AIP is idiopathic):** rule out infection (including *Pneumocystis*, viral, atypical pneumonia), left heart failure, diffuse alveolar hemorrhage, drug toxicity and CTD — via cultures, BAL, echocardiography and **immune serologies** (e.g., anti-CCP, ANA).
- **Bronchoscopy + BAL:** chiefly used to **exclude infection and alveolar hemorrhage**; bronchoscopic samples are generally insufficient to *diagnose* an IIP.
- **Surgical (VATS) lung biopsy:** the only way to confirm DAD; however it carries a **short-term mortality of up to ~5%**, which is **higher in acutely presenting patients** — so the decision must weigh diagnostic yield against risk.

Histopathology — diffuse alveolar damage (DAD)

- The defining lesion of AIP on surgical lung biopsy is **diffuse alveolar damage (DAD)** — the same pattern seen in **ARDS** and in **acute exacerbations of underlying pulmonary fibrosis**.
- DAD classically evolves through two phases *(standard histology, see Coverage note):*
  - **Exudative (acute) phase** — interstitial/alveolar edema, capillary congestion, and **hyaline membranes** lining alveolar ducts.
  - **Organising (proliferative) phase** — **type II pneumocyte hyperplasia**, fibroblastic proliferation and loose interstitial fibrosis; this temporally *uniform* fibrosis helps separate AIP from the temporally heterogeneous UIP of IPF.

Differential diagnosis — AIP vs ARDS vs acute exacerbation of IPF

Feature	AIP (Hamman-Rich)	ARDS	Acute exacerbation of IIP/IPF
Precipitating cause	**None identified (idiopathic)**	Identifiable insult (sepsis, aspiration, trauma, pancreatitis, etc.)	Occurs on **known underlying pulmonary fibrosis**
Prior lung disease	Absent	Usually absent	**Present** (e.g., IPF)
Onset	Acute, days–weeks	Acute (≤1 week of insult)	Acute (**<30 days**)

Feature	AIP (Hamman-Rich)	ARDS	Acute exacerbation of IIP/IPF
HRCT	Bilateral ground-glass + dependent consolidation	Bilateral infiltrates / consolidation	New ground-glass + consolidation **superimposed on fibrosis (honeycombing/reticulation)**
Histology	**DAD**	**DAD**	**DAD** (± organising pneumonia)
Mortality	**>50% at 6 months**	Variable	**Very high** (>85%)

Treatment

- **Predominantly supportive** — AIP is managed like ARDS: **supplemental oxygen and mechanical ventilation** with lung-protective strategy, treatment of intercurrent infection, and supportive ICU care.
- **There is no proven drug therapy for AIP.**
- **Glucocorticoids** are *often given* (e.g., high-dose corticosteroids) but are **not clearly effective**, and the supporting evidence — extrapolated from other forms of DAD such as ARDS — is **controversial**.
- General supportive measures applicable to progressive ILD (oxygen, pulmonary rehabilitation) and, in highly selected survivors with progressive fibrosis, consideration of **lung transplantation**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **HRCT thorax (axial) in AIP** — labels: *bilateral ground-glass opacities; dependent (posterior/basal) air-space consolidation; relatively preserved non-dependent lung; absence of honeycombing.*
- **Histology of diffuse alveolar damage (DAD)** — labels: *alveolar space; hyaline membranes lining alveolar duct (exudative phase); type II pneumocyte hyperplasia; fibroblastic proliferation / interstitial thickening (organising phase); congested alveolar capillary.*

Clinical / Diagnostic significance

- AIP must be considered in any **previously healthy patient with rapidly progressive dyspnea, hypoxemia and bilateral infiltrates** once infection and cardiac failure are excluded — it is frequently **misdiagnosed as community-acquired pneumonia, COPD exacerbation or heart failure**.
- It is a **diagnosis of exclusion**: clinically and radiologically identical to ARDS, so the absence of an ARDS trigger and the histologic demonstration of DAD (when biopsy is feasible) clinch the diagnosis.
- Recognising AIP carries **prognostic weight** (high early mortality, frequent recurrence) and shapes **goals-of-care discussions**, while reminding the clinician that no specific pharmacotherapy is established.
- Distinguishing AIP from an **acute exacerbation of IPF** matters because the latter implies pre-existing fibrosis and an even worse outlook; HRCT background fibrosis is the key discriminator.

High-yield exam pointers

- **AIP = Hamman-Rich syndrome = idiopathic ARDS**; histology = **diffuse alveolar damage (DAD)**.
- One of the **idiopathic interstitial pneumonias**; among the few IIPs with an **acute** presentation.
- **Prodrome** mimicking an upper respiratory tract viral illness is characteristic.
- **HRCT:** bilateral **ground-glass opacities + dependent consolidation**.
- **PFT:** restrictive pattern — ↓TLC, ↓FVC, ↓**DLCO**.
- **Mortality >50% within 6 months; recurrences common;** survivors may regain substantial lung function.
- **No proven drug therapy** — care is **supportive ± mechanical ventilation**; glucocorticoids used but unproven/controversial.
- Key differentials: **ARDS** (identifiable cause) and **acute exacerbation of IPF/IIP** (underlying fibrosis, mortality >85%).
- Confirmatory test = **surgical/VATS lung biopsy showing DAD**, but biopsy mortality is higher in acutely ill patients.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 304 "Interstitial Lung Disease" (AIP / Hamman-Rich subsection under *Acute or Subacute IIPs*; plus the chapter's general sections on ILD classification, history/examination, PFTs, HRCT, lung biopsy, and acute exacerbations of IIPs).

Coverage note (spec.gap = true): Harrison 22e covers AIP only briefly. The chapter explicitly supports: the Hamman-Rich eponym; classification among IIPs; acute respiratory-distress presentation with viral-like prodrome; >50% 6-month mortality with frequent recurrence and possible functional recovery; HRCT (ground-glass + dependent consolidation); DAD histology; difficulty distinguishing from ARDS and acute exacerbation of fibrosis; and supportive treatment with no proven drug therapy and unproven glucocorticoids. Items added from universally accepted standard internal medicine but **not detailed in the provided chapter** (flagged here): the two-phase microscopic anatomy of DAD (exudative phase with hyaline membranes → organising/proliferative phase with type II pneumocyte hyperplasia and fibroblast proliferation), and the framing of AIP as a "diagnosis of exclusion." These are accurate standard histopathology/diagnostic concepts; specific case definitions/criteria (e.g., Katzenstein/ATS-ERS formal diagnostic criteria) were not asserted as they are not given in the provided text.

◆ ◆ ◆

Acute severe asthma

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — *Acute severe asthma* (historically *status asthmaticus*) is a severe asthma exacerbation that fails to respond promptly to repeated inhaled short-acting β2-agonists (SABAs) and threatens life through progressive airflow obstruction, dynamic hyperinflation and respiratory muscle fatigue. An exacerbation is defined (NIH task force) as *a worsening of asthma requiring systemic corticosteroids (or an increase from a stable maintenance dose) to prevent a serious outcome*. Clinically it is recognised by breathlessness at rest, inability to complete sentences, peak expiratory flow (PEF)/FEV1 well below predicted, and signs of respiratory distress; *near-fatal asthma* denotes the subset with hypercapnia, exhaustion or requiring mechanical ventilation.

Pathophysiology of the severe attack

- **Diffuse airway narrowing** from smooth-muscle constriction, mucosal oedema, inflammatory cellular infiltration and luminal **mucus plugging** (eosinophil-rich) raises airway resistance and lowers maximal expiratory flow, predominantly in small bronchi.
- **Air trapping and dynamic hyperinflation** — incomplete lung emptying forces breathing at high lung volumes (raised residual volume); intrinsic PEEP develops. The diaphragm and intercostals are mechanically disadvantaged on their length–tension curve, so **accessory muscles** (sternocleidomastoid, abdominals) are recruited and the **work of breathing rises**.
- **Gas exchange** — non-uniform obstruction produces **ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch** with a widened alveolar–arterial O2 gradient and hypoxaemia. PaCO2 initially **falls** (hyperventilation) producing respiratory alkalosis; as muscles fatigue, PaCO2 **rises** — a *normal or raised PaCO2 in a distressed asthmatic signals impending respiratory failure*.
- **Lactic (type B) acidosis** may appear (anion-gap metabolic acidosis) from work of breathing and high-dose β2-agonists.

Clinical assessment and severity grading

- Rapid focused history: duration/trigger, current medication, prior ICU/intubation, frequency of SABA use, response so far.
- Examination: respiratory rate, ability to speak (sentences→phrases→words→mute), posture, accessory-muscle use/suprasternal retraction, wheeze (a **silent chest** = severe obstruction with loss of breath sounds), heart rate, **pulsus paradoxus**, conscious level and cyanosis.
- Objective severity by PEF/FEV1, SpO2 and arterial blood gas. Severity classification (NAEPP/GINA, adapted in CMDT 2026):

Feature	Mild	Moderate	Severe	Respiratory arrest imminent
Breathlessness	On walking	At rest, limits activity	At rest, interferes with talking	At rest, mute
Talks in	Sentences	Phrases	Words	—
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy/confused

Feature	Mild	Moderate	Severe	Respiratory arrest imminent
Respiratory rate	Increased	Increased	Often >30/min	>30/min
Accessory muscles	Usually not	Commonly	Usually	Paradoxical thoraco-abdominal movement
Wheeze	End-expiratory	Loud, expiratory	Loud, insp + exp	**Absent** (silent chest)
Pulse/min	<100	100–120	>120	Bradycardia
Pulsus paradoxus	<10 mmHg	10–25 mmHg	>25 mmHg	Absence = muscle fatigue
PEF (% pred/best)	≥70%	40–69%	<40%	<25%
PaO2 (air) / PaCO2	Normal / <42	≥60 / <42	<60 / ≥42	<60 / ≥42
SaO2 (air)	>95%	90–95%	<90%	<90%

Investigations

- **PEF or FEV1** — the single most useful objective measure; guides severity and serial response (improvement at 30–60 min predicts outcome and need for admission).
- **Pulse oximetry**; target SpO2 >90%.
- **Arterial blood gas** — typically mild hypoxaemia + respiratory alkalosis; *normalisation/rise of PaCO2* with continuing distress warns of impending failure. Venous pH/PCO2 and lactate can be used to monitor.
- **Chest radiograph** — not routine; obtain if pneumothorax, pneumomediastinum, pneumonia or another cause is suspected.
- **ECG/electrolytes** — monitor for arrhythmia and β2-agonist–induced **hypokalaemia**; bloods/cultures only if infection suspected.

Management of acute severe asthma

- **Oxygen** — give immediately to maintain SpO2 >90% (PaO2 >60 mmHg); asphyxia is a leading cause of asthma death, and concern for hypercapnia must *never* delay correcting hypoxaemia.
- **Inhaled SABA (salbutamol/albuterol)** — high-dose, repeated or continuous by nebuliser (or MDI + spacer); at least **three treatments in the first hour**, then titrate to response. Onset 3–5 min, duration 4–6 h.
- **Inhaled ipratropium bromide** — added to SABA in moderate–severe exacerbations improves airflow and **reduces hospital admission**.
- **Systemic corticosteroids** — first-line; early administration speeds recovery and reduces admission. Prednisolone **0.5–1.0 mg/kg/day** (≈40–60 mg/day) orally, or IV methylprednisolone **1.5–2 mg/kg** if oral route unsafe (oral and IV are equi-efficacious in non-life-threatening

attacks). Continue the "burst" until symptoms resolve and PEF ≥80% personal best (usually 3–10 days); tapering is not required.

- **Intravenous magnesium sulfate — 2 g IV over 20 min** (paediatric 40 mg/kg, max 2 g); a smooth-muscle relaxant that reduces hospitalisation in *acute severe* attacks (FEV1 <25% predicted on presentation or failure to respond to initial therapy). Not recommended for routine mild–moderate exacerbations.
- **Adjuncts in refractory cases — heliox** (helium–oxygen) lowers airway resistance/work of breathing; an LTRA is sometimes added; continuous in-hospital nebulisation. Inhaled volatile anaesthetics (e.g., isoflurane) are potent bronchodilators in refractory disease.
- **Avoid** — sedatives/anxiolytics (respiratory depression), mucolytics (acetylcysteine, potassium iodide — may worsen cough/obstruction), and *routine* antibiotics (reserve for proven bacterial infection/pneumonia/sinusitis).

Respiratory support and mechanical ventilation

- **Non-invasive positive-pressure ventilation (NIV)** — low-level NIV (without PEEP) may reduce hospitalisation and avert intubation in **alert, cooperative** patients not in immediate need of intubation.
- **Intubation and invasive ventilation** — *mandatory* for respiratory arrest or impending arrest (exhaustion, altered sensorium, rising PaCO2, bradycardia). Post-intubation deterioration is common from dynamic hyperinflation and high intrathoracic pressures causing hypotension.
- **Ventilator strategy — minimise hyperinflation:** low minute ventilation with **respiratory rate 12–14/min**, **tidal volume 6–8 mL/kg**, **high inspiratory flow** (prolonged expiratory time) and **minimal/no PEEP**. Accept **permissive hypercapnia** (let PaCO2 rise; correct critical acidosis with bicarbonate if needed) to avoid barotrauma. Provide deep sedation and, if patient–ventilator synchrony cannot be achieved, short-term neuromuscular paralysis; continue bronchodilators until airway resistance falls.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Severity-stratification flow diagram of an acute attack** — boxes: *Assess (speech, RR, accessory muscles, PEF, SpO2, pulsus paradoxus)* → *Mild–Moderate (PEF ≥40–69%)* → SABA + ipratropium + O2 + oral steroid; *Severe (PEF <40%)* → high-dose continuous SABA + ipratropium + O2 + systemic steroid + IV MgSO4; *Respiratory arrest imminent (silent chest, drowsy, bradycardia, PaCO2 ≥42)* → ICU, NIV/intubation, permissive hypercapnia. Label danger signs: **silent chest, normal/rising PaCO2, exhaustion, bradycardia, cyanosis**.
- **Obstructed asthmatic airway cross-section** — labels: *lumen narrowed by smooth-muscle constriction*, *smooth-muscle hypertrophy*, *submucosal oedema*, *mucus plug*, *epithelial shedding*, *basement-membrane (collagen) thickening*, *inflammatory cell infiltration*.

Clinical / Diagnostic significance

- A *normal or rising PaCO2* with a *silent chest* and exhaustion are the cardinal red flags of life-threatening asthma demanding ICU care.

- Response to the first hour of therapy predicts the need for admission better than presenting severity.
- High-risk features mandating low-threshold escalation (Harrison): prior ICU admission or intubation for asthma, ≥2 ED visits in 6 months, recent/current oral steroids, poor adherence, illicit drug use, depression/severe psychosocial problems, low socioeconomic status, new diagnosis within the past year.
- Discharge planning: ensure inhaler technique, written **asthma action plan**, step-up of controller (ICS-containing) therapy, follow-up — over-reliance on SABA and under-use of ICS drive mortality.

High-yield exam pointers

- **Silent chest, drowsiness, bradycardia, normal/raised PaCO2, and absent pulsus paradoxus (from muscle fatigue)** = imminent respiratory arrest.
- **First-hour bundle:** controlled O2 (SpO2 >90%) + repeated/continuous SABA (≥3 doses/hr) + ipratropium + early systemic steroid (prednisolone 0.5–1 mg/kg).
- **IV magnesium sulfate 2 g over 20 min** for acute severe asthma (FEV1 <25% predicted / poor initial response) — reduces admissions.
- Oral and IV corticosteroids are equally effective in non-life-threatening attacks; continue burst till PEF ≥80% best.
- **Ventilation = permissive hypercapnia:** low RR 12–14, low TV 6–8 mL/kg, high inspiratory flow, minimal PEEP — to avoid dynamic hyperinflation/barotrauma.
- **Avoid** sedatives, mucolytics and routine antibiotics; NIV only in the alert, cooperative patient.
- Pulsus paradoxus >25 mmHg, PEF <40%, RR >30 and inability to speak in sentences define a severe attack.
- Type B (non-hypoxic) **lactic acidosis** and **hypokalaemia** are recognised β2-agonist effects during high-dose therapy.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Asthma" (Elliot Israel): pathophysiology, "Asthma Attacks", mechanical ventilation/permissive hypercapnia, and Table 298-6 "Patients at Greater Risk for Asthma Mortality."
- Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Asthma: Diagnosis and Management": physiology of airflow limitation/dynamic hyperinflation, "Management of Acute Asthma", corticosteroid and magnesium dosing, and invasive ventilation settings.
- CMDT 2026 — "Pulmonary Disorders" (Asthma): Table 9–6 severity classification of exacerbations, treatment of severe exacerbations (oxygen target, SABA/ipratropium, systemic steroids, IV magnesium), and drugs to avoid.

◆ ◆ ◆

Approach to solitary pulmonary nodule

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

Definition / Introduction — A **solitary pulmonary nodule (SPN)**, classically called a *"coin lesion,"* is a single, discrete, rounded radiographic opacity **<3 cm in diameter, completely surrounded by aerated lung**, and *unaccompanied* by lymphadenopathy, atelectasis or pleural effusion (Murray & Nadel; CMDT). Lesions **>3 cm** are termed *pulmonary masses* and are malignant until proven otherwise. With the explosion of CT use and low-dose CT (LDCT) lung-cancer screening, SPNs are increasingly an incidental finding; the overriding clinical task is to **identify and resect the few malignant nodules that benefit from surgery while sparing the benign majority from needless invasive procedures**.

Etiology and Differential Diagnosis

- Most SPNs are **benign**; in LDCT-screened populations the probability that any detected nodule is cancer is only ~1%, and **90–95% of screening-detected nodules are ultimately false positives**.
- Most benign nodules are **infectious granulomas**; **hamartomas account for <5%** of solitary nodules. Malignant nodules are *rare under age 30*; above 30, malignancy risk rises with age, smoking and a prior cancer history.

Category	Common causes
Malignant	Primary lung cancer (esp. adenocarcinoma), solitary metastasis, bronchial **carcinoid**
Infectious granuloma	Tuberculoma, histoplasmosis, coccidioidomycosis, other fungi; resolving abscess
Benign neoplasm	**Hamartoma** (fat + popcorn calcification), rare benign tumors
Other benign	Arteriovenous malformation, intrapulmonary (perifissural) lymph node, rounded atelectasis, infarct, rheumatoid nodule, Wegener (GPA)

Step 1 — Estimate the Pretest Probability of Malignancy

The approach is **probability-driven**: integrate patient ("clinical") factors with nodule ("radiologic") factors, either by validated quantitative models or experienced clinical judgement.

- **Clinical predictors of malignancy:** older age, current/heavy smoking (>20 cigarettes/day, quit <7 years), prior malignancy, asbestos exposure.
- **Independent predictors (Mayo investigators):** age, smoking status and prior cancer *plus* three radiologic features — **nodule diameter, spiculation, and upper-lobe location**.
- **Quantitative models: Mayo (VA Cooperative)** clinical model, the **Brock model** (Pan-Canadian screening cohort, most accurate in screening), and the **Herder model**, which adds FDG-PET data to clinical/radiologic inputs and is endorsed by the British Thoracic Society.

Harrison Table 83-7 — Risk of cancer by variable (after Ost et al., NEJM 2003):

Variable	Low risk	Intermediate	High risk
Diameter (cm)	<1.5	1.5–2.2	≥2.3
Age (years)	<45	45–60	>60

Variable	Low risk	Intermediate	High risk
Smoking	Never smoker	Current <20/day	Current >20/day
Smoking cessation	Quit ≥7 yr ago / never	Quit <7 yr ago	Never quit
Margin	Smooth	Scalloped	**Corona radiata / spiculated**

Step 2 — Radiographic Characterisation (Benign vs Malignant Features)

- **Always obtain and compare prior CXR/CT films.** Two findings *reliably* indicate benignity: (1) **no growth over >2 years**, and (2) a **benign calcification pattern**.
- **Benign calcification patterns (5):** diffuse, central, laminar/concentric, and **"popcorn"** — central nidus and *"bull's-eye"* suggest granuloma; *"popcorn"* (chondroid) is diagnostic of **hamartoma**, especially when **fat is also seen within the nodule**. *Note:* calcification alone does **not** exclude malignancy.
- **Features suggesting malignancy:** larger size, **spiculated / corona radiata margins**, lobulated or ill-defined edge, a peripheral **halo**, sparse / **eccentric / stippled** calcification, **thick-walled cavitation (>16 mm)**, upper-lobe location, and demonstrable growth.
- **Doubling time (DT):** very rapid growth (**DT <30 days**) suggests infection; **long-term stability (DT >465 days, or >2 years)** suggests benignity; most malignant *solid* nodules have a **volume DT <400 days**. 3D **volumetric analysis** on thin-section HRCT is more sensitive than 2D caliper measurement for detecting growth.
- **Size-based malignancy rate on CT (CMDT):** 2–5 mm ≈ **1%**, 6–10 mm ≈ **24%**, 11–20 mm ≈ **33%**, 21–45 mm ≈ **80%**.

Step 3 — Functional Imaging (FDG-PET/CT) and Tissue Diagnosis

- **FDG-PET/CT** is most useful for indeterminate nodules **>8 mm (≈1 cm)**; an **SUVmax >2.5** is the classic malignancy threshold. A meta-analysis of nodules >1 cm reported sensitivity **96%**, specificity **78%**, PPV 91%, NPV 92%; CMDT quotes sensitivity **85–97%** and specificity **70–85%**. Malignancy probability rises stepwise with uptake (SUVmax 0–2.5 ≈ 24%, 2.6–4.0 ≈ 80%, ≥4.1 ≈ 96%).
- **A positive PET raises, and a negative PET lowers, the probability of cancer**, but beware **false negatives** in carcinoid tumours and in *ground-glass / lepidic adenocarcinoma, AIS and MIA* (low metabolic activity), and in lesions <1 cm (poor resolution); **false positives** occur with active infection/inflammation.
- **Tissue sampling options:**
  - **CT-guided transthoracic needle aspiration (TTNA):** yield **50–97%** (≈90% in expert series); best for **peripheral** lesions; main complication is **pneumothorax in up to 30%** (some needing a chest drain).
  - **Bronchoscopy:** yield **10–80%**, sensitivity **88% for central lesions** but low for peripheral nodules **<2 cm**; yield improves with a **bronchus (air-bronchus) sign**, larger size and more biopsies. **Guided bronchoscopy** (radial **EBUS**, electromagnetic **navigational** bronchoscopy, robotic bronchoscopy) gives a pooled yield ≈70%.

- **Sputum cytology:** highly specific but insensitive — reserved for central lesions or poor procedural candidates.

Step 4 — Management Algorithm by Pretest Probability

- **Benign calcification or documented 2-year stability** → no further testing.
- **Low probability (<5%)** → *watchful waiting* with **serial HRCT** (ACCP suggests 3–6, 9–12 and 18–24 months); for screen/incidental nodules apply structured surveillance (below).
- **Intermediate probability (5–60/65%)** → further characterise with **PET/CT** and/or **non-surgical biopsy** (TTNA or bronchoscopy); biopsy is favoured for the *risk-averse* patient wanting confirmation before surgery.
- **High probability (>60–65%)** → proceed to **staging and surgical resection** if surgical risk is acceptable; biopsy rarely changes management and is often omitted.
- **Surgery: VATS** with intra-operative **frozen section**, proceeding to **lobectomy + mediastinal lymph-node sampling/dissection** if malignant; **wedge/segmentectomy** for limited reserve. Non-surgical candidates may receive **SBRT** (≤5 cm) or radiofrequency ablation/cryoablation.
- **Assess operability first:** relative/absolute contraindications include **predicted post-op FEV_1 <0.8 L**, FEV_1 <1 L, **DLCO <40%**, **VO_2max <10–15 mL/kg/min**, resting PCO_2 >45 mmHg, severe pulmonary hypertension, and recent MI (<3 months).

Structured surveillance frameworks:

- **Fleischner Society 2017** (incidental nodules, age ≥35, not immunosuppressed, no known cancer): *solid* <6 mm — no routine follow-up if low risk; 6–8 mm — CT at 6–12 mo then 18–24 mo; >8 mm — consider CT at 3 mo, PET/CT or biopsy. *Subsolid:* pure ground-glass <6 mm — no follow-up; ≥6 mm — CT at 6–12 mo to confirm persistence, then every 2 years to 5 years; **part-solid ≥6 mm** — CT at 3–6 mo (solid component ≥6 mm is highly suspicious).
- **Lung-RADS v1.1** (ACR — *screen-detected* nodules): category 1–2 = benign (cancer risk <1%, annual LDCT); 3 = probably benign (6-month LDCT); 4A (3-month LDCT ± PET); 4B/4X (>15% risk — diagnostic CT/PET/tissue sampling).

Special Consideration — Subsolid Nodules / Ground-Glass Opacities (GGO)

- Subsolid nodules are subdivided into **pure ground-glass (nonsolid)** and **part-solid**; many persistent GGOs represent the adenocarcinoma spectrum — **atypical adenomatous hyperplasia (AAH) → adenocarcinoma in situ (AIS) → minimally invasive adenocarcinoma (MIA)**.
- They are **indolent**: GGO cancers are typically stage I adenocarcinoma with near-100% 5-year survival, so guidelines favour **less frequent but longer-duration surveillance**; the **size of the solid component** is the key predictor of invasiveness — a growing or enlarging solid component prompts resection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Management algorithm of the SPN** (flowchart): *New nodule on CT* → **benign calcification or 2-yr stability?** → if yes: *No further testing*; if no → **estimate probability of cancer / surgical risk** → branch into **Low (<5%): serial HRCT at 3, 6, 9, 12, 18, 24 mo**; **Intermediate (5–60%): PET/CT and/or biopsy (TTNA / bronchoscopy)**; **High (>60%): staging → VATS frozen section → lobectomy**. Label: *PET if nodule ≥8 mm*, *TTNA if peripheral*, *bronchoscopy if bronchus sign*.
- **Calcification patterns box:** draw and label **diffuse, central, laminar/concentric, popcorn** (benign) versus **stippled, eccentric** (malignant); plus nodule margins — *smooth* (benign) vs *spiculated / corona radiata* (malignant).

Clinical / Diagnostic significance

- The single most powerful step is **comparison with old imaging** — proven 2-year stability or a benign calcification pattern obviates all further workup.
- **Size, margin (spiculation), upper-lobe location, age and smoking** drive the malignancy estimate; integrate them via **Brock/Mayo/Herder models** rather than guesswork.
- **PET-CT** both characterises the nodule and screens for nodal/distant disease, refining staging before resection — but a negative PET does not exclude carcinoid or lepidic adenocarcinoma.
- **Shared decision-making** is integral: nodule detection causes real patient distress and is a *"teachable moment"* for **smoking cessation**.

High-yield exam pointers

- SPN = single rounded opacity **<3 cm**, surrounded by normal lung, **no** adenopathy/effusion; **>3 cm = mass** (treat as malignant).
- **Two reliable benignity criteria:** no growth >2 years and benign calcification (**diffuse/central/laminar/popcorn**); **popcorn = hamartoma**, central/bull's-eye = granuloma.
- Malignant pointers: **spiculation/corona radiata**, eccentric/stippled calcification, thick-walled cavity (>16 mm), upper lobe, growth (**VDT <400 days**).
- **Doubling time:** <30 days = infection; >465 days (>2 yr stable) = benign.
- **PET useful for nodules >8 mm**, SUVmax >2.5 = malignant; false-negative in **carcinoid and AIS/MIA/GGO**.
- Probability bands: **<5% observe, 5–60% PET/biopsy, >60% resect.**
- **TTNA** best for peripheral lesions (pneumothorax up to 30%); **bronchoscopy** best for central/endobronchial (bronchus sign); **VATS + frozen section → lobectomy** is definitive.
- **Fleischner 2017** = incidental nodules; **Lung-RADS** = screen-detected nodules.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Neoplasms of the Lung"* (SPN definition, risk Table 83-7/Mayo predictors, calcification patterns, management algorithm Fig. 83-5, operability criteria, SBRT, GGO/AAH-AIS-MIA spectrum).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — *"Pulmonary Nodule"* (epidemiology, Brock model, **Fleischner Society 2017** and **Lung-RADS v1.1** tables, volume doubling time, ACCP algorithm, bronchoscopy/TTNA yields, subsolid nodules) and *"Positron Emission Tomography"* (SUVmax 2.5 threshold, sensitivity/specificity, Herder model, false negatives).
- **CMDT 2026** — *"Pulmonary Disorders: Solitary Pulmonary Nodule"* (coin lesion, size-based malignancy rates, <5%/5–60%/>60% probability bands, PET performance, TTNA/bronchoscopy/VATS management).

◆ ◆ ◆

Asbestos-related diseases

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

Definition / Introduction — Asbestos is a generic term for a family of naturally occurring fibrous mineral silicates that, when inhaled as respirable fibres, cause a spectrum of benign and malignant pleuropulmonary disease. The principal disorders are **asbestosis** (diffuse interstitial pulmonary fibrosis), **benign pleural disease** (plaques, diffuse thickening, benign effusion, rounded atelectasis), **bronchogenic carcinoma**, and **malignant mesothelioma** of the pleura and peritoneum. All share a **long latency** (often decades), a **dose–response** relationship, and the medicolegal importance of being **compensable occupational diseases**.

Mineralogy, Sources and Mechanism of Injury

- **Two mineral groups:**
  - **Serpentine** group — **chrysotile** (*white asbestos*), curly/serpentine fibres, **less biopersistent**, more readily cleared from the lung; the form most widely used commercially.
  - **Amphibole** group — **crocidolite** (*blue*), **amosite** (*brown*), anthophyllite, tremolite, actinolite; long, thin, straight, **durable, highly biopersistent** fibres. Amphiboles are far more potent inducers of **mesothelioma** (up to ~100-fold over serpentine in experimental animals).
- **At-risk occupations:** mining, milling and manufacture of asbestos products; **shipbuilding/ship repair**, construction, **pipe fitters, boilermakers, insulators**; brake/clutch (friction) linings, fire-resistant textiles, cement and floor tiles. Latency means new cases today reflect exposures of past decades.
- **Non-occupational exposure:** *bystander/para-occupational* (painters, electricians working alongside insulators in shipyards); **domestic** (relatives exposed to fibre-laden work clothes — chiefly pleural disease); **environmental** (community exposure from vermiculite contaminated with amphibole at **Libby, Montana**; disturbance of naturally occurring asbestos).

- **Pathogenesis:** fibre toxicity depends on **cumulative dose, fibre dimensions (length-to-width aspect ratio) and durability/biopersistence**. Fibres **≤3 µm** are phagocytosed by alveolar macrophages and cleared via lymphatics; **longer fibres are incompletely phagocytosed**, often by several macrophages, and become coated to form **asbestos (ferruginous) bodies** — beaded, dumb-bell-shaped iron-protein–coated fibres that are the *light-microscopic hallmark of exposure*. Injury is driven by **oxidative stress** — reactive oxygen species generated by transition metals (iron) on the fibre surface and during frustrated phagocytosis — recruiting fibroblasts and collagen deposition.

Spectrum of Asbestos-Related Diseases and Latency

Disease	Nature	Typical latency from first exposure
Pleural plaques	Benign; marker of exposure only	~20–30 yr (relates to time since exposure, not dose)
Benign asbestos pleural effusion (BAPE)	Benign exudative effusion	**Earliest** — within ~15 yr
Diffuse pleural thickening / visceroparietal reaction	Benign; may restrict	Long (~30+ yr)
Rounded atelectasis (*Blesovsky syndrome*)	Folded-lung pseudotumour	Variable, late
Asbestosis	Diffuse interstitial fibrosis	≥10 yr exposure; clinical disease ~20–30 yr
Bronchogenic carcinoma	Malignant	~15–19 yr (minimum)
Malignant mesothelioma	Malignant (pleura >90%, peritoneum)	**20–40 yr**; short exposure (1–2 yr) sufficient

Asbestosis (Pulmonary Parenchymal Fibrosis)

- **Definition:** diffuse interstitial fibrosing lung disease *directly related to intensity and duration of exposure*; requires generally **≥10 years** of exposure before becoming manifest, with clinical disease usually **20–30 years** after first exposure.
- **Pathology:** begins as **peribronchiolar fibrosis** with macrophage accumulation and type-2 pneumocyte hyperplasia; progresses to interstitial fibrosis with a **lower-lobe and subpleural predominance** and eventual **honeycombing**. Distinguished from other end-stage fibrosis only by demonstration of **asbestos bodies / uncoated fibres**.
- **Clinical features:** insidious **exertional dyspnoea** and dry cough; **fine, end-inspiratory bibasal "velcro" crackles** (early and distinctive, heard first in axillary/basal regions); **digital clubbing** in some; late cor pulmonale.
- **Radiology: irregular/linear reticular opacities** beginning in the **lower zones**; blurring of the cardiac border producing a **"shaggy heart" sign**; ground-glass change. **HRCT** (most sensitive) shows **subpleural curvilinear lines 5–10 mm**, subpleural reticulation, parenchymal bands and honeycombing; **coexisting pleural plaques** strongly support the diagnosis. ILO classification grades small **linear/irregular** opacities (vs the rounded opacities of silicosis/CWP).

- **Lung function: restrictive** pattern with reduced lung volumes and **reduced DLCO**; mixed or mild **obstructive** components may occur (peribronchiolar fibrosis).
- **Management: no specific therapy** — supportive care as for any diffuse interstitial fibrosis: supplemental oxygen, pulmonary rehabilitation, influenza/pneumococcal vaccination, and especially **smoking cessation** (smoking multiplies lung-cancer risk). Lung transplantation in selected end-stage cases (pleural disease may complicate surgery).

Benign Pleural Manifestations

- **Pleural plaques** — the **commonest** and often the only manifestation of exposure. Smooth, raised, white, frequently **calcified** lesions of the **parietal pleura** (posterolateral mid-zones following rib contour, the **diaphragm**, cardiac border); histologically **avascular, acellular, laminated (hyalinised) collagen** likened to *candle-wax drippings*. Typically **bilateral** (unilateral suggests trauma/infection). They imply **exposure, not impairment**, but flag an increased long-term risk of mesothelioma/lung cancer.
- **Diffuse pleural thickening / visceroparietal reaction** — less specific than plaques; can encase the lung as a fibrous "peel", causing measurable **restrictive deficit** (FEV_1/FVC reduction) and occasionally requiring **pleurectomy**.
- **Benign asbestos pleural effusion (BAPE)** — usually the **earliest** manifestation (within ~15 yr); small, **exudative, blood-tinged**, often resolves spontaneously, may recur/alternate sides. It is a **diagnosis of exclusion** — criteria: exposure history, exclusion of other causes, and **no tumour on ≥3-year follow-up**; thoracoscopic biopsy is usually needed to **exclude mesothelioma**.
- **Rounded atelectasis (folded lung / pseudotumour, *Blesovsky syndrome*)** — pleural fibrosis folds and traps subjacent lung, producing a rounded mass with the characteristic **"comet-tail" sign** of vessels/bronchi curving into it; the key differential is **lung cancer**, occasionally needing biopsy.

Asbestos-Related Malignancy

- **Bronchogenic carcinoma**
  - **Most common** cancer associated with asbestos; occurs across **all histologic types**.
  - Minimum latency **15–19 years**; risk rises with cumulative exposure.
  - **Multiplicative (synergistic) interaction with cigarette smoking** — combined risk greatly exceeds the additive effect; hence smoking cessation is paramount.
- **Malignant mesothelioma**
  - Arises from mesothelial serosal surfaces — **pleura in >90%**, also peritoneum, pericardium, tunica vaginalis; **not related to smoking**.
  - **>80% are asbestos-associated** (rendering them compensable); **amphiboles, especially crocidolite**, are the most potent; **erionite** (a zeolite fibre, e.g. *Cappadocia, Turkey*) is a recognised non-asbestos cause. ~3000 cases/yr in the USA.
  - **Latency 20–40 years**; even brief exposures (1–2 yr) suffice — underscoring a meticulous exposure history.
  - **Presentation:** unilateral **pleural effusion**, chest-wall pain and dyspnoea; tumour **encases the lung**, contracts the hemithorax and produces **ipsilateral mediastinal shift**; **needle-tract seeding** at biopsy/drainage sites.

- **Histologic subtypes: epithelioid** (best prognosis), **sarcomatoid** (worst), and **biphasic** (mixed).
- **Diagnosis:** fluid cytology has limited yield; **image-guided/thoracoscopic biopsy** with immunohistochemistry is usual. Molecular markers — **loss of BAP1 expression** and **homozygous CDKN2A (p16) deletion** by FISH — confirm malignancy in mesothelial-lineage cells (together identify up to ~85% of cases). *(Standard mesothelial IHC panel: positive calretinin, WT-1, CK5/6, D2-40; negative CEA, TTF-1, MOC-31/Ber-EP4 — see Coverage note.)* Staging uses the **TNM-based IASLC/IMIG (8th edition)** system.
- **Prognosis:** dismal — median survival **9–18 months**, **<5% survive 5 years**; sarcomatoid histology, poor performance status and weight loss predict worse outcome.
- **Treatment (palliative intent):** first-line **cisplatin + pemetrexed** (an antifolate) with **folic acid + vitamin B_{12}** supplementation improved median survival (**12.1 vs 9.3 months** vs cisplatin alone); adding **bevacizumab** (anti-VEGF) further improved survival (**MAPS: 18.8 vs 16.1 months**). **Extrapleural pneumonectomy (EPP)** is *harmful/not recommended* (**MARS trial** — worse survival); pleurectomy/decortication and **talc pleurodesis/indwelling pleural catheter** for effusion control are the mainstays; immune-checkpoint inhibitors remain largely investigational.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Asbestos (ferruginous) body** — draw a central thin asbestos fibre coated by an iron-protein layer giving a **beaded, dumb-bell / drumstick shape**. Labels: *core asbestos fibre*, *iron-protein (haemosiderin) coat*, *beaded/segmented body*, *engulfing alveolar macrophage*.
- **Chest radiograph of asbestos-related disease** — outline both lungs. Labels: *bilateral calcified diaphragmatic pleural plaques*, *lower-zone irregular/reticular opacities (asbestosis)*, *"shaggy/indistinct heart border"*, *blunted costophrenic angle (effusion/thickening)*, *rounded atelectasis with comet-tail sign*.

Clinical / Diagnostic significance

- **Exposure history is paramount** — occupation, duration, latent interval, and para-occupational/domestic/environmental sources; correlate with imaging.
- **Pleural plaques = marker of past exposure, not impairment**; their presence beside lower-zone fibrosis strongly supports asbestosis over idiopathic pulmonary fibrosis.
- **HRCT** is the key imaging tool — detects early parenchymal fibrosis, distinguishes pleural plaque from subpleural fat, and characterises rounded atelectasis.
- **Any unilateral exudative effusion in an asbestos-exposed patient is mesothelioma until proven otherwise** — proceed to thoracoscopic biopsy.
- **Smoking cessation** disproportionately reduces lung-cancer risk because of the multiplicative interaction; mesothelioma risk is unaffected by smoking.
- **Medicolegal/compensation:** documented asbestosis, lung cancer with exposure, and mesothelioma are **compensable**; primary prevention via exposure limits, substitution, engineering controls and surveillance is the only effective strategy given the absence of cure.

High-yield exam pointers

- **Amphiboles (crocidolite) → mesothelioma**; **chrysotile** is less biopersistent and more readily cleared.
- **Asbestos/ferruginous body** = beaded iron-coated fibre = light-microscopic hallmark of exposure (not of disease severity).
- **Asbestosis = lower-zone, subpleural fibrosis** with **velcro crackles, clubbing, restrictive PFT, low DLCO**; HRCT subpleural curvilinear lines 5–10 mm.
- **Pleural plaques** are bilateral, parietal, calcified ("candle-wax"), and the **commonest** manifestation.
- **BAPE** = earliest manifestation (<15 yr); diagnosis of exclusion needing 3-yr tumour-free follow-up.
- **Lung cancer latency 15–19 yr; mesothelioma latency 20–40 yr**; mesothelioma not smoking-related, lung cancer **synergistic** with smoking.
- **Mesothelioma:** epithelioid best / **sarcomatoid worst** prognosis; **BAP1 loss + CDKN2A/p16 deletion** confirm diagnosis; median survival ~12 months.
- **Cisplatin + pemetrexed (+ folate/B_{12}) ± bevacizumab** is first-line; **EPP is harmful (MARS)**.
- **>80% of mesotheliomas are asbestos-associated → compensable.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Occupational and Environmental Lung Disease"* (asbestos-related diseases section, lung cancer/mesothelioma associations and latencies); *"Neoplasms of the Lung"* and *"Pleural and Mediastinal Diseases / Mesothelioma"* for malignancy.
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — *"Pneumoconioses"* (asbestosis, pleural plaques, diffuse pleural fibrosis, benign asbestos pleural effusion, rounded atelectasis, pathogenesis and fibre biology) and *"Pleural Malignancy"* (mesothelioma — aetiology, subtypes, BAP1/CDKN2A diagnostics, staging, MARS/MAPS trials, chemotherapy and immunotherapy).
- **CMDT 2026** — *"Pulmonary Disorders"* (pneumoconioses/asbestosis clinical features, imaging and management; asbestos as carcinogen and cause of mesothelioma).

Coverage note: The corpus emphasises modern molecular diagnostics for mesothelioma (BAP1 loss, CDKN2A/p16 deletion) rather than the conventional immunohistochemistry panel; the marker panel cited (calretinin/WT-1/CK5/6/D2-40 positive, CEA/TTF-1/MOC-31 negative) is included as universally accepted diagnostic pathology supplementing the textbook content.

◆ ◆ ◆

Bronchial asthma

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

Definition / Introduction — Bronchial asthma is a chronic, heterogeneous disease characterised by **episodic, largely reversible airway obstruction**, **airway hyperresponsiveness (AHR)** and, in most patients, **airway inflammation** (commonly eosinophilic/type 2). Clinically it presents as recurrent wheeze, dyspnoea, chest tightness and cough that vary in intensity over time and with triggers. In a subset, persistent inflammation and airway remodelling produce a fixed (irreversible) component. It affects ~262 million people worldwide and remains the commonest chronic respiratory disease with significant morbidity and preventable mortality.

Aetiology, risk factors and triggers

- **Heritable predisposition** — heritability 25–80%; complex polygenic inheritance interacting with environment and epigenetic change. Reproducible risk loci include ***ORMDL3/GSDMB* (17q21 region)**, *ADAM33*, *DPP-10*, *TSLP*, *IL-33*, *ST2 (IL-33 receptor)*, *IL-13*, *IL6R* and *HLA-DQB1*. Atopy (genetic tendency to specific IgE production) explains roughly half of asthma; key allergens are house dust mite, indoor fungi, cockroach and animal danders.
- **Predisposing exposures (development of disease)** — allergen exposure in the atopy-prone, occupational sensitisers (occupational asthma = 10–25% of adult-onset disease), air pollution (NO_2, CO), respiratory infections (rhinovirus, RSV, *Mycoplasma*), tobacco (maternal/active smoking), obesity, diet/vitamin D, and high-intensity exercise in elite athletes.
- **Triggers (provoke acute narrowing)** — allergens, irritants/smoke, viral infections, **exercise and cold dry air**, air pollution, drugs (β-blockers including ophthalmic drops, aspirin/NSAIDs, ACE-inhibitor cough), occupational agents, and hormonal/perimenstrual and pregnancy-related changes.
- **Special syndromes** — *Reactive airways dysfunction syndrome (RADS)* after a single high-concentration irritant exposure (non-sensitised, neutrophilic); *allergic bronchopulmonary aspergillosis (ABPA)* from IgE sensitisation to *Aspergillus fumigatus*.

Pathophysiology and airway inflammation

- **Airway hyperresponsiveness** — exaggerated bronchoconstriction to stimuli (e.g. histamine, methacholine) that do not affect normal airways; partly smooth-muscle and partly structural (wall thickening).
- **Acute obstruction** — smooth-muscle contraction, mucosal/submucosal **oedema**, and luminal **mucus plugging** narrow the airway.
- **Chronic obstruction / remodelling** — smooth-muscle hypertrophy and hyperplasia, **subepithelial collagen and matrix deposition (basement-membrane thickening)**, goblet-cell metaplasia with mucus hypersecretion, epithelial denudation, vascular and neuronal proliferation — together producing a fixed component.
- **Type 2 (T2-high) inflammation** — the dominant pattern; driven by **$CD4^+$ Th2 cells and ILC2s** producing **IL-4, IL-5 and IL-13**. *IL-4* drives B-cell isotype switching to **IgE**; *IL-5* controls eosinophil formation, recruitment and survival; *IL-13* induces AHR, mucus hypersecretion and

goblet-cell metaplasia. Epithelial **alarmins (TSLP, IL-25, IL-33)** activate ILC2s, so even "non-allergic" irritant/viral exposures can drive eosinophilia.

- **Mediators — cysteinyl leukotrienes (LTC4, LTD4, LTE4)** from eosinophils/mast cells are potent bronchoconstrictors and mucus secretagogues; prostaglandin D2, nitric oxide and reactive oxygen species amplify inflammation; chemokines (eotaxin, RANTES, TARC) recruit cells.
- **Non–type 2 inflammation — neutrophilic** (IL-6, IL-8, IL-17, TNF-α; severe/steroid-refractory, RADS, sometimes *Mycoplasma*-associated and macrolide-responsive) or **pauci-granulocytic** asthma with no obvious infiltrate.

Clinical features and classification

- **Symptoms** — episodic wheeze, breathlessness, chest tightness, cough and mucus; often nocturnal or early-morning, and provoked by triggers. Between attacks examination may be normal; during attacks — tachypnoea, tachycardia, prolonged expiration, accessory-muscle use; a **"silent chest"** signifies severe, life-threatening obstruction.
- **Classification by inflammatory phenotype/endotype** — allergic (early-onset, atopic) vs late-onset eosinophilic, aspirin-exacerbated, obesity-related, and neutrophilic/non-T2; this **endotype-based nosology guides biologic selection**.
- **Assessment of control (GINA — past 4 weeks)** — based on four items: daytime symptoms >2×/week, any night waking due to asthma, reliever need >2×/week, and any activity limitation.

Level of control	Criteria (over past 4 weeks)
Well controlled	None of the four components
Partly controlled	1–2 components present
Uncontrolled	3–4 components present

- **Goals of therapy** — symptoms ≤2×/week, nocturnal waking ≤2×/month, reliever use ≤2×/week, ≤1 exacerbation/year, normal lung function and activity, minimal side-effects.

Diagnosis and investigations

- **Spirometry** — obstructive pattern: ↓FEV1, ↓FEV1/FVC below the lower limit of normal; flow-volume loop shows expiratory **scalloping**. **Reversibility**: ≥10% increase in FEV1 % predicted after a β2-agonist (older criterion: ≥12% *and* ≥200 mL rise). Diurnal **PEF variability >20%** supports the diagnosis.
- **Bronchoprovocation** (when spirometry non-diagnostic) — **methacholine challenge**: ≥20% fall in FEV1 at a concentration ≤8 mg/mL (Harrison: PD20 cumulative dose ≤400 µg); a negative test has ~95% negative predictive value. Mannitol or exercise/cold-air challenge (≥10% FEV1 fall) are alternatives.
- **Biomarkers of type 2 inflammation** — blood **eosinophils ≥300 cells/µL**; **FeNO** elevated (>35–40 ppb untreated indicates T2 inflammation; suppressed by ICS, useful for adherence); total/specific **IgE** and skin/RAST testing for atopy.
- **Red-flag results** — IgE **>1000 IU/mL** with eosinophils **>500/µL** → consider **ABPA**; extreme eosinophilia → eosinophilic granulomatosis with polyangiitis (EGPA).

- **Classic sputum findings (universally accepted)** — *Curschmann spirals* (mucus casts), *Charcot-Leyden crystals* (eosinophil-derived), and *Creola bodies* (sloughed epithelial clusters).
- **Differential / "asthma mimics"** — heart failure ("cardiac asthma"), COPD, α1-antitrypsin deficiency, inducible laryngeal obstruction (vocal-cord dysfunction), foreign body, bronchiectasis, tracheobronchomalacia, EGPA.

Acute severe asthma (status asthmaticus) and its grading

- A normal or rising $PaCO_2$ in a distressed asthmatic (who should be **hypocapnic** from tachypnoea) signals **impending respiratory failure**.

Feature	Moderate	Severe	Respiratory arrest imminent
Breathlessness / talks in	On walking; sentences	At rest; phrases/words	Mute
Position / accessory muscles	Can lie down; usually none	Sits upright; usually present	Paradoxical thoraco-abdominal
Wheeze	End-expiratory	Loud throughout	**Silent chest**
Pulse; pulsus paradoxus	100–120; may be present	>120; often >25 mmHg	Bradycardia (fatigue)
PEF/FEV1 % predicted	40–69%	<40%	<25%
SaO_2 (air)	90–95%	<90% (± cyanosis)	<90%

- **Management of exacerbation** — high-flow oxygen to correct hypoxaemia; **repeated/continuous nebulised SABA** (≥3 doses in the first hour) ± **ipratropium**; **systemic corticosteroids** (prednisone 40–60 mg/day, taper over 1–2 weeks). **IV magnesium sulphate 2 g over 20 min** for acute severe asthma (FEV1 <25% predicted or non-responders). Consider NIV/heliox; if intubated, use **lung-protective, low-rate/low-volume "permissive hypercapnia"** ventilation to limit airway pressures. Antibiotics only with clear infection.

Stepwise (GINA) pharmacotherapy and biologics

- **Reliever shift (AIR — Anti-Inflammatory Reliever)** — GINA now recommends **as-needed ICS-formoterol** (only formoterol, owing to rapid onset) or ICS-SABA at *all* steps, replacing SABA-alone, because SABA monotherapy increases asthma death.
- **Controller ladder — ICS are the cornerstone of all persistent asthma.** Step 1–2: as-needed/low-dose ICS-formoterol; Step 3: low-dose ICS-formoterol maintenance; Step 4: medium-dose ICS-formoterol; Step 5: high-dose ICS-LABA + add-on **LAMA** (e.g. tiotropium), and biologics ± macrolide/low-dose OCS as last resort.
- **Bronchodilators** — SABA (salbutamol/albuterol; onset 3–5 min, lasts 4–6 h); LABA (salmeterol, formoterol; ~12 h — never as monotherapy in asthma); ultra-LABA (vilanterol, indacaterol, olodaterol; 24 h, only with ICS). Theophylline is now rarely used (narrow therapeutic window).
- **Other controllers** — leukotriene modifiers (montelukast/zafirlukast; zileuton) — useful in exercise-induced and **aspirin-exacerbated respiratory disease (AERD)**; cromolyn (paediatric, mast-cell stabiliser).

- **Biologics for severe T2 asthma** — **omalizumab** (anti-IgE), **mepolizumab/reslizumab** (anti-IL-5), **benralizumab** (anti-IL-5Rα), **dupilumab** (anti-IL-4Rα, blocks IL-4/IL-13), **tezepelumab** (anti-TSLP, also effective in some T2-low disease). They reduce exacerbations by ~50–70% in correctly selected (biomarker-guided) patients.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Cross-section of normal vs asthmatic bronchus** — label: *epithelium with denudation/shedding, goblet-cell metaplasia + mucus plug in lumen, thickened/sub-epithelial collagen (basement-membrane) deposition, sub-mucosal oedema, smooth-muscle hypertrophy & hyperplasia, cellular (eosinophil) infiltration, vascular and neuronal proliferation, narrowed lumen.*
- **Type 2 inflammatory cascade** — label: *allergen/irritant → epithelial alarmins (TSLP, IL-25, IL-33) → ILC2 and Th2 cells → IL-4 (IgE switch), IL-5 (eosinophils), IL-13 (AHR, mucus); IgE on mast cells → cysteinyl-leukotrienes → bronchoconstriction*, with arrows to the corresponding biologics (omalizumab, anti–IL-5, dupilumab, tezepelumab).

Clinical / Diagnostic significance

- Confirm diagnosis objectively with **reversible obstruction or AHR** before lifelong therapy — >1/3 of physician-labelled "asthma" does not meet criteria.
- **Phenotyping by eosinophils/FeNO/IgE** directs precision biologic therapy and predicts response.
- Identify and treat **comorbidities** that make asthma refractory: chronic rhinosinusitis ± nasal polyposis, GERD, obesity, OSA, anxiety/depression, vocal-cord dysfunction.
- **Nasal polyps + adult asthma → suspect AERD (Samter triad)**: avoid aspirin/NSAIDs, use leukotriene modifiers ± aspirin desensitisation/biologics.
- In **pregnancy**, treat actively — inhaled salbutamol, budesonide, beclomethasone and fluticasone are well-established; uncontrolled asthma is far more dangerous to mother and fetus than the drugs.

High-yield exam pointers

- Triad of asthma: **reversible airway obstruction + airway hyperresponsiveness + airway inflammation**.
- **ICS are the cornerstone**; SABA-only treatment increases mortality — GINA now uses **ICS-formoterol as reliever (AIR)** at every step.
- **Reversibility** = ≥10% rise in FEV1 % predicted (or ≥12% and ≥200 mL); **PEF diurnal variability >20%**.
- Key T2 cytokines: **IL-4 (IgE), IL-5 (eosinophils), IL-13 (AHR/mucus)**; alarmins = **TSLP, IL-25, IL-33**.
- **ABPA**: IgE >1000 IU/mL, eosinophils >500/μL, central bronchiectasis — treat with itraconazole + steroids.
- Acute severe asthma red flags: **silent chest, pulsus paradoxus >25 mmHg, normal/rising $PaCO_2$, bradycardia**.

- Acute treatment: **O_2 + nebulised SABA + ipratropium + systemic steroids; IV $MgSO_4$ 2 g** in severe cases.
- Biologics by endotype: **omalizumab (IgE), mepolizumab/benralizumab (IL-5/IL-5R), dupilumab (IL-4Rα), tezepelumab (TSLP)**.
- High asthma-death risk: prior ICU/intubation, ≥2 ED visits in 6 months, recent OCS, psychosocial problems.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Asthma"** (pathophysiology, type 2/non-type 2 inflammation, genetics, diagnosis, GINA/NAEPP step therapy, biologics, status asthmaticus, AERD, pregnancy).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Asthma: Pathogenesis and Phenotypes"** (T2-high/T2-low endotypes, ILC2/Th2 biology).
- **CMDT 2026 — "Pulmonary Disorders" (Asthma)** (GINA control classification, exacerbation severity grading table, methacholine/PEF criteria, acute management including IV magnesium).

◆ ◆ ◆

Acute respiratory distress syndrome

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

Definition / Introduction — Adult respiratory distress syndrome is now termed **acute respiratory distress syndrome (ARDS)** because the syndrome also occurs outside adulthood. It is an acute inflammatory lung-injury syndrome presenting as **noncardiogenic permeability pulmonary edema**, severe hypoxemia, bilateral pulmonary opacities, reduced lung compliance, and acute respiratory failure. It is a clinical syndrome, not a single disease; there is no diagnostic gold standard, so diagnosis requires a compatible insult, exclusion of hydrostatic edema as the primary cause, and assessment of oxygenation severity.

Etiology and risk factors

- **Common causes:** most cases are due to **pneumonia and sepsis** (about 40-60%), followed by aspiration of gastric contents, trauma, multiple transfusions, and drug overdose.
- **Risk increases** with multiple predisposing insults, older age, chronic alcohol abuse, pancreatitis, pneumonia/sepsis, and greater severity of critical illness.

Direct lung injury	Indirect lung injury
Pneumonia, including viral pneumonias	Sepsis
Aspiration of gastric contents	Severe trauma, multiple fractures, flail chest, head injury
Pulmonary contusion	Multiple transfusions
Near-drowning	Pancreatitis
Toxic inhalation, smoke, chlorine, ammonia	Burns, shock, DIC

Direct lung injury	Indirect lung injury
Fat/air/amniotic embolism, miliary TB	Drug overdose, postcardiopulmonary bypass

Pathophysiology and phases

- Central lesion is **diffuse alveolar damage** with injury to **alveolar-capillary endothelium** and **type I pneumocytes**, causing leakage of protein-rich edema fluid into interstitium and alveoli.
- Cytokines and mediators (**IL-1, IL-6, IL-8, TNF-alpha, leukotriene B4**) recruit neutrophils; neutrophils release proteases, reactive oxygen species and NETs, worsening epithelial and endothelial injury.
- **Surfactant dysfunction** and alveolar flooding produce dependent atelectasis, low compliance, intrapulmonary shunt, refractory hypoxemia, increased work of breathing and eventual respiratory failure.
- Pulmonary vascular injury causes **microthrombi**, increased dead space, pulmonary hypertension and sometimes hypercapnia; hypoxemia and hypercapnia further impair alveolar sodium and water clearance.

Phase	Time course	Pathology / clinical implication
Exudative	First 0-7 days; symptoms often 12-36 h after insult, sometimes delayed 5-7 days	Neutrophil-rich edema, hyaline membranes, surfactant loss, severe dyspnea, tachypnea, refractory hypoxemia
Proliferative	About day 7-21	Organization of exudate, type II pneumocyte proliferation, repair; some develop early fibroproliferation
Fibrotic	Around >3 weeks or persistent ARDS	Interstitial/alveolar-duct fibrosis, bullae, low compliance, dead space, pulmonary hypertension, pneumothorax risk

Diagnostic criteria and classification

- Use the **Berlin definition**: acute onset within 1 week of a known clinical insult or new/worsening respiratory symptoms; bilateral opacities on chest radiograph or CT not fully explained by effusion, lobar collapse or nodules; respiratory failure not fully explained by cardiac failure or fluid overload.
- If no clear ARDS risk factor is present, perform objective assessment such as **echocardiography** to exclude hydrostatic pulmonary edema.
- Oxygenation severity is assessed on **PEEP or CPAP >=5 cm H2O**:

Severity	PaO2/FiO2 ratio
Mild ARDS	>200 to <=300 mm Hg
Moderate ARDS	>100 to <=200 mm Hg
Severe ARDS	<=100 mm Hg

- Proposed newer updates permit ARDS assessment in selected nonintubated patients on high-flow nasal oxygen or noninvasive support using PaO2/FiO2 or SpO2/FiO2 ratios; arterial PaO2 should still be checked when feasible.

Clinical features and investigations

- Presentation is **rapid-onset dyspnea**, tachypnea, labored breathing, intercostal retractions, crackles, high oxygen requirement and hypoxemia poorly corrected by supplemental oxygen.
- CXR shows diffuse or patchy **bilateral opacities** that may become confluent; heart size is usually normal and pleural effusions are small or absent, unlike typical cardiogenic pulmonary edema.
- CT shows bilateral infiltrates with marked heterogeneity and dependent edema/atelectasis; lung ultrasound may show nonhomogeneous B lines, irregular pleura, subpleural or translobar consolidation and reduced pleural sliding.
- ABG quantifies PaO2/FiO2, hypercapnia and pH; evaluate the precipitant with cultures, sepsis workup, aspiration history, trauma/transfusion/drug history and organ dysfunction assessment.
- Important differentials are **cardiogenic pulmonary edema**, bilateral pneumonia, diffuse alveolar hemorrhage, acute interstitial pneumonitis, hypersensitivity pneumonitis, radiation/toxin pneumonitis and neurogenic pulmonary edema.

Management

- **Treat the cause first:** early antibiotics and source control for sepsis/pneumonia, aspiration precautions, trauma/burn management, stop offending drugs, and manage shock without persistent fluid overload.
- Provide ICU bundled care: VTE prophylaxis, stress-ulcer/aspiration prevention when indicated, avoidance of excessive sedation, ventilator liberation protocols, nutrition preferably enteral, prevention of catheter infections and prompt recognition of VAP/nosocomial infection.
- **Lung-protective ventilation:** use tidal volume about **6 mL/kg predicted body weight** (not actual weight), target **plateau pressure <=30 cm H2O**, RR generally <=35/min, SpO2 88-95% or PaO2 55-80 mm Hg, and reduce FiO2 as soon as possible, preferably <=0.6 when feasible.
- **PEEP:** titrate PEEP to recruit alveoli, maintain oxygenation and reduce FiO2, while avoiding overdistension, hypotension and reduced cardiac output; no single PEEP-setting method is universally superior.
- **Prone ventilation:** in severe ARDS, especially **PaO2/FiO2 <150 mm Hg**, early prolonged proning (about >=16 h/day) improves oxygenation and has shown mortality benefit in experienced centers; avoid or be cautious with unstable spine, raised ICP, massive hemoptysis, recent facial/tracheal surgery or severe hemodynamic instability.
- **Conservative fluids:** after shock is corrected, restrict fluids and use diuretics to keep low filling pressures; this improves oxygenation and reduces ventilator/ICU days without routine need for pulmonary artery catheterization.
- **Adjuncts:** short neuromuscular blockade with cisatracurium for up to 48 h may help selected severe ARDS patients with ventilator dyssynchrony despite sedation, but routine early paralysis is not supported by later trials. ECMO is a rescue option for very severe, potentially reversible ARDS after optimized lung-protective ventilation, PEEP, proning and supportive care.

- **Avoid routine use:** high-frequency oscillation, routine recruitment maneuvers, surfactant replacement, inhaled nitric oxide/epoprostenol for outcome benefit, NSAIDs, ketoconazole and other anti-inflammatory therapies. Steroids are not a universal ARDS treatment; consider them only in patient-specific settings such as refractory septic shock, severe community-acquired pneumonia, COVID-19 ARDS, or selected early ARDS where contemporary guidelines support conditional use.

Prognosis and complications

- LUNG SAFE hospital mortality estimates rise with severity: **34.9% mild**, **40.3% moderate**, **46.1% severe** ARDS; with modern low-tidal-volume ventilation, overall mortality is around 30-40%.
- Most deaths are from **sepsis and nonpulmonary organ failure**, not refractory hypoxemia; nonpulmonary organ failure accounts for the major mortality burden.
- Poor prognostic factors include advanced age, chronic liver disease, chronic alcohol abuse, chronic immunosuppression, sepsis, preexisting organ dysfunction, direct lung injury, pulmonary fibrosis, low compliance, high PEEP requirement and failure to improve in the first week.
- Complications include VAP, barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema), ICU-acquired weakness, delirium, thromboembolism, secondary infections and fibrotic lung disease.
- Survivors often regain near-normal lung function by **6-12 months**, but may have reduced diffusion capacity, exercise limitation, muscle wasting, fatigue, depression, anxiety, PTSD and cognitive impairment for years.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Injured alveolus in ARDS:** alveolar capillary endothelium, type I pneumocyte injury, type II pneumocyte/surfactant dysfunction, protein-rich edema, hyaline membrane, neutrophils, cytokines, ROS/NETs, microthrombi, collapsed alveolus, shunt.
- **ARDS time-course diagram:** exudative phase 0-7 days, proliferative phase 7-21 days, fibrotic phase after about 3 weeks; label edema, hyaline membranes, interstitial inflammation, fibrosis, bullae and recovery pathway.

Clinical / Diagnostic significance

- ARDS should be suspected when a patient with sepsis, pneumonia, aspiration, trauma or transfusion develops acute refractory hypoxemia and bilateral opacities within 1 week.
- Do not diagnose ARDS merely from a bilateral white-out CXR; document **PaO2/FiO2**, ventilatory support/PEEP, timing, and why cardiogenic edema is not the primary cause.
- Echocardiography is often the practical discriminator from cardiogenic edema; BNP or wedge pressure may help in selected patients but no test is definitive.
- Management is mainly supportive and ventilator-based; the most exam-important disease-modifying intervention is **low tidal volume ventilation** with plateau-pressure limitation.
- Rising oxygen requirement, increasing dead space, falling compliance, shock, AKI, liver dysfunction and delirium indicate high risk and need for aggressive ICU management.

High-yield exam pointers

- Write “adult” as historical; current term is **acute respiratory distress syndrome**.
- Berlin criteria: **within 1 week + bilateral opacities + noncardiogenic edema + PaO2/FiO2 <=300 on PEEP/CPAP >=5**.
- Severity cutoffs: **mild >200-300**, **moderate >100-200**, **severe <=100 mm Hg**.
- Commonest causes: **pneumonia and sepsis**, then aspiration, trauma, transfusion and overdose.
- Classic pathology: **diffuse alveolar damage**, protein-rich edema and **hyaline membranes**.
- Ventilator must-write: **VT 6 mL/kg predicted body weight, plateau <=30 cm H2O, SpO2 88-95%**.
- Prone early in severe ARDS, especially **PaO2/FiO2 <150**, if expertise is available.
- After resuscitation, use **conservative fluid strategy**; avoid routine PA catheter.
- Most deaths are due to **sepsis/multiorgan failure**, not isolated hypoxemia.

> **SOURCE & COVERAGE**
>
> Harrison 22e — "Acute Respiratory Distress Syndrome"; Murray & Nadel's Respiratory Medicine 7e — "Acute Respiratory Distress Syndrome"; CMDT 2026 — "Acute Respiratory Distress Syndrome"; Critical Care — "Acute Respiratory Failure" and "Pulmonary Edema".

◆ ◆ ◆

Bronchiectasis

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

Definition / Introduction — Bronchiectasis is an *irreversible*, abnormal dilatation (ectasia) and destruction of the bronchial wall, involving the lung focally or diffusely. It is classically categorised morphologically as **cylindrical/tubular** (commonest), **varicose**, or **cystic/saccular**. It is not a single disease but the common structural end-point of many insults, the great majority operating through a self-perpetuating **"vicious cycle" (Cole)** of impaired mucociliary clearance → microbial colonisation → chronic neutrophilic inflammation → airway-wall destruction. The pathogenesis must therefore be understood as the interaction of a **predisposing host/structural defect**, **microbial persistence**, and an **unresolved inflammatory (protease-driven) response**.

Normal defences whose failure permits bronchiectasis

- The airway is continuously protected by the **mucociliary escalator**, an effective **cough**, **secretory IgA**, and epithelial **antimicrobial peptides** (lysozyme, secretory leukocyte protease inhibitor, defensins, cathelicidin), backed by resident/recruited phagocytes (macrophages, neutrophils) and T-effector lymphocytes.
- Airway patency normally depends on **negative intrapleural pressure** transmitted via interstitial *tethering*, plus the **cartilaginous rings** of large/medium bronchi.
- Bronchiectasis develops when one or more of these are compromised — by an inherited/structural defect, immunodeficiency, mechanical obstruction, fibrotic traction, or an overwhelming/repeated infection — allowing the vicious cycle to be established.

Three fundamental mechanical mechanisms (traction, pulsion, weakness)

- **Traction bronchiectasis** — *retractile (centrifugal) forces* of a fibrosing/scarring parenchyma pull the airways open. Seen with idiopathic pulmonary fibrosis, post-radiation fibrosis, sarcoidosis and post-tuberculous scarring.
- **Pulsion bronchiectasis** — intense *intraluminal* inflammation and mucoid impaction balloon the airway from within; the prototype is **allergic bronchopulmonary aspergillosis (ABPA)**, where an immune reaction to *Aspergillus* lodged in central airways, with thick mucoid plugs, dilates the proximal bronchi.
- **Weakness of the airway wall** — loss of structural integrity, either *acquired* (post-infectious destruction of elastin/muscle/cartilage with regional volume loss) or *congenital* — e.g. **Mounier-Kuhn syndrome** (tracheobronchomegaly from atrophy of airway *elastic fibres*), **Williams-Campbell syndrome** (absent cartilage in segmental/subsegmental bronchi), Marfan syndrome, relapsing polychondritis. Weak, collapsible airways also cripple the cough mechanism, impeding secretion clearance and feeding the infective cycle.

The "vicious cycle / vicious vortex" — the central engine of pathogenesis

- The most widely cited mechanism (Cole) is a **self-amplifying cycle**: a susceptible airway with **poor mucociliary clearance → microbial colonisation/infection** of the bronchial tree → **chronic inflammation → airway-wall damage** → still poorer clearance → perpetuation.
- A single severe infection (*Bordetella pertussis*, *Mycoplasma pneumoniae*, measles, adenovirus, necrotising bacterial pneumonia) can initiate the cycle by causing the index airway injury; thereafter the process becomes self-sustaining and *infection-independent of the original trigger*.
- Recent reframing as a "**vicious vortex**" (a tetrad in which each factor perpetuates the other three):
- **Airway epithelial & ciliary dysfunction with mucus hypersecretion**
- **Chronic infection**, itself driving further mucus hypersecretion
- **Inflammation** causing permanent airway injury and dilatation
- **Resultant bronchiectatic airways** with impaired mucociliary clearance, which feed back into (1)–(3).
- Certain organisms — especially ***Pseudomonas aeruginosa***, nontuberculous mycobacteria (NTM, mainly *Mycobacterium avium* complex) and *Aspergillus* — preferentially colonise damaged airways and evade host defence, accelerating the vortex.

Cellular & molecular mediators — the protease–antiprotease imbalance

- The dominant inflammatory cell is the **neutrophil**, recruited by epithelial- and macrophage-derived chemokines/cytokines — **interleukin-8 (IL-8)**, **macrophage inflammatory protein-2 (MIP-2)**, **TNF-α** — with a prominent **Th17** axis.
- Activated/necrotic neutrophils release **neutrophil elastase**, **matrix metalloproteinases (MMPs)**, other proteases and **reactive oxygen species** that directly digest the airway wall, producing the classic 1950s-described pathology: **small-airway wall inflammation with larger-airway destruction and dilatation, and loss of elastin, smooth muscle and cartilage**.

- **Neutrophil elastase** is pivotal — it causes *ciliary dysfunction*, *mucous-gland hyperplasia* and *mucus hypersecretion* (worsening clearance), and **disables host defence**: it cleaves **Fcγ receptors** and **complement receptor 1** from neutrophils and digests **immunoglobulin and complement** off bacterial surfaces → impaired **opsonisation** and bacterial killing. It also inhibits **efferocytosis** (macrophage clearance of apoptotic neutrophils) by cleaving phosphatidylserine, so inflammation fails to resolve.
- Normally, **antiproteases — chiefly α1-antitrypsin** — neutralise neutrophil elastase and enhance bacterial killing; a **protease–antiprotease imbalance** (excess elastase or **α1-antitrypsin deficiency**) tips the balance toward wall destruction (bronchiectasis ± emphysema). Necrotic neutrophils also liberate highly viscous **DNA**, increasing sputum viscosity and inspissation.

Microbial colonisation and biofilms

- Mere colonisation is *insufficient* for bronchiectasis (smokers' chronic bronchitis carries a similar flora — *H. influenzae*, *S. pneumoniae*, *Moraxella* — without bronchiectasis); an *additional* host/structural disturbance is required to establish chronic transmural infection.
- **Biofilms** are central to chronicity: *P. aeruginosa* attaches to the airway surface and grows within an **exopolysaccharide matrix (glycocalyx / alginate)** that shields it from immune cells and antibiotics. Behaviour is coordinated by **quorum sensing** (cell–cell signalling), and biofilm-embedded bacteria can survive antibiotic concentrations up to **1000× the MIC**.
- Chronic *P. aeruginosa* infection (often a mucoid, alginate-producing phenotype) is a marker of severe disease — more exacerbations, faster FEV_1 decline and roughly **three-fold increased mortality**.

Aetiology-specific pathways (mapping cause → mechanism)

Pattern / Cause	Mechanism in pathogenesis
Focal (foreign body, tumour, broncholith, extrinsic node compression)	Localised airway **obstruction** → distal stasis, infection, post-obstructive dilatation
Diffuse — infection (post-pertussis/measles/adenovirus; TB, NTM/MAC; necrotising pneumonia)	Direct wall destruction initiating the vicious cycle
Cystic fibrosis	**CFTR** anion-channel defect → reduced Cl^-/HCO_3^- & water secretion → depleted **periciliary/airway-surface liquid**, ciliary collapse, viscid mucus, defective bacterial killing (low ASL pH) → relentless neutrophilic infection
Primary ciliary dyskinesia (Kartagener's)	Structural/functional ciliary defect → primary **mucociliary clearance failure**
Immunodeficiency (CVID, hypogammaglobulinaemia, IgG-subclass/IgA deficiency, HIV)	Recurrent infection from defective humoral defence → cycle
α1-antitrypsin deficiency	Loss of antiprotease screen → unopposed elastase wall damage
ABPA & autoimmune/CTD (RA, Sjögren)	Immune-mediated bronchial-wall injury (pulsion / inflammatory)

Pattern / Cause	Mechanism in pathogenesis
Fibrosis (IPF, post-radiation), aspiration, Mounier-Kuhn/Williams-Campbell	Traction / recurrent chemical injury / congenital wall weakness

- **Anatomic distribution offers aetiological clues:** *upper* zones — CF, TB, sarcoid; *mid* zones — NTM/MAC and PCD; *lower* zones — idiopathic, chronic aspiration, hypogammaglobulinaemia, α1-antitrypsin deficiency, CTD; *central* airways — ABPA, Mounier-Kuhn, Williams-Campbell.
- Up to **25–50%** of referred cases remain **idiopathic** after full workup.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Vicious vortex" wheel diagram** — a central airway with four arrows forming a closed loop, labelled: *(1) Epithelial & ciliary dysfunction + mucus hypersecretion → (2) Chronic infection (Pseudomonas/NTM, biofilm) → (3) Neutrophilic inflammation (elastase, MMPs, ROS, IL-8, TNF-α, Th17) → (4) Airway-wall destruction & dilatation (loss of elastin, smooth muscle, cartilage) → back to (1)*. Add a side-box: *predisposing defect — impaired MCC / immunodeficiency / obstruction / wall weakness / fibrotic traction*.
- **Cross-sectional airway comparison** — label: *normal bronchus* (intact epithelium, cilia, smooth muscle, cartilage, basement membrane) vs *bronchiectatic airway* (loss of cilia, goblet-cell/mucous-gland hyperplasia, mucus/biofilm plug, neutrophil infiltrate, destroyed muscle & cartilage, dilated thickened wall). Include the three morphological types: *cylindrical, varicose, cystic/saccular*.

Clinical / Diagnostic significance

- Explains the cardinal clinical picture: **chronic productive cough with copious purulent sputum, recurrent infective exacerbations, haemoptysis** (erosion of dilated bronchial vessels — the commonest complication), crackles, wheeze and **digital clubbing**.
- Rationalises a **mechanism-directed workup**: sweat chloride/CFTR genetics (CF), immunoglobulins ± vaccine-challenge (CVID), α1-antitrypsin level/phenotype, nasal NO/ciliary studies (PCD), *Aspergillus* IgE/IgG + eosinophils (ABPA), RF/autoantibodies (CTD), and sputum culture including mycobacteria.
- **HRCT** is the diagnostic gold standard — *signet-ring sign* (broncho-arterial diameter ratio ≥1.5), tram-track lines, lack of tapering, airways within 1 cm of pleura, wall thickening, and *tree-in-bud* (small-airway secretions).
- The protease-driven, *Pseudomonas*/biofilm-sustained cycle is the **therapeutic target**: airway clearance/hygiene, treat exacerbations, long-term **macrolides** (anti-inflammatory + anti-quorum-sensing/biofilm action), inhaled antibiotics for *Pseudomonas*, and disease-specific therapy (CFTR modulators in CF, steroids ± itraconazole in ABPA, immunoglobulin replacement in CVID). Untreated, FEV_1 declines ~**50–55 mL/year** (vs 20–30 mL/year normally), comparable to COPD.

High-yield exam pointers

- Bronchiectasis = **irreversible** bronchial dilatation; morphology = **cylindrical** > **varicose** > **cystic**.

- Central mechanism = **Cole's vicious cycle**, modernised as the **"vicious vortex" tetrad**.
- Three mechanical routes = **traction, pulsion (ABPA), weakness (Mounier-Kuhn / Williams-Campbell)**.
- Key effector = **neutrophil elastase** → ciliary dysfunction, mucus hypersecretion, impaired opsonisation/efferocytosis; balanced by **α1-antitrypsin** (protease–antiprotease imbalance).
- Wall pathology = **loss of elastin, smooth muscle and cartilage**.
- ***Pseudomonas aeruginosa*** (mucoid/alginate, biofilm, quorum sensing) = chronicity + ~3× mortality; *MIC survival up to 1000×*.
- **Focal = obstruction; diffuse = systemic/infectious**; distribution clues — upper (CF/TB), mid (NTM/PCD), lower (aspiration/immunodeficiency/AAT), central (ABPA/Mounier-Kuhn).
- **25–50%** remain idiopathic; CF/CFTR variants and NTM are increasingly recognised drivers.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Bronchiectasis" (etiology, pathogenesis & pathology, vicious-cycle hypothesis, protease/α1-antitrypsin role) and "Cystic Fibrosis" (CFTR/airway-surface-liquid mechanism).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "Bronchiectasis" (traction/pulsion/weakness framework, vicious vortex tetrad, neutrophil-elastase/efferocytosis biology, biofilms & quorum sensing, aetiology-specific pathways and anatomic distribution).
- **CMDT 2026** — "Bronchiectasis" (current causes, microbiology, diagnostic criteria and management framing).

◆ ◆ ◆

Chronic obstructive pulmonary disease (COPD)

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

Definition / Introduction — Chronic obstructive pulmonary disease (COPD) is a heterogeneous, preventable and treatable disease state characterised by **persistent respiratory symptoms and chronic airflow obstruction that is not fully reversible and is usually progressive**, arising from airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases. It encompasses three overlapping processes in varying proportion: **emphysema** (anatomic destruction of alveoli with airspace enlargement), **chronic bronchitis** (chronic cough and phlegm, clinically defined) and **small airway disease** (narrowed, reduced bronchioles). Diagnosis requires **spirometry**. Globally COPD affects an estimated 480 million people and is the third to fourth leading cause of death worldwide.

Etiology and risk factors

- **Cigarette smoking** — the dominant risk factor in the developed world; causes a dose-dependent (pack-year) accelerated decline in FEV1 (≈66 mL/yr in men, 54 mL/yr in women vs ≈30 and 22 mL/yr in quitters). Only ~15% of FEV1 variability is explained by pack-years, implying additional host factors; ~15% of smokers develop disabling disease. Cigar/pipe, **vaping and inhaled cannabis** are emerging concerns.

- **Biomass fuel smoke** — combustion of wood/dung for cooking in poorly ventilated dwellings; the leading cause in the developing world, especially in **women** and never-smokers.
- **Occupational exposures (VGDF)** — vapours, gases, dusts, fumes; coal mining, gold mining and cotton-textile dust are implicated (coal dust independently causes emphysema).
- **α1-antitrypsin (α1AT) deficiency** — the proven genetic cause; the **PiZ** phenotype (ZZ or Z/null) gives severe deficiency (~1 in 3000), serum α1AT <11 μmol/L (~50 mg/dL); accounts for ~1% of COPD and causes early-onset, lower-zone **panlobular emphysema**.
- **Other genetics** — >80 GWAS loci including *HHIP* (chr 4), the chr 15 cluster (nicotinic acetylcholine receptor, *IREB2*) and *FAM13A* (Wnt/β-catenin).
- **Airway hyperresponsiveness / asthma**, **respiratory infections** (childhood pneumonia, **tuberculosis-associated airflow limitation**, **HIV**), **air pollution**, and **abnormal lung development / early-life passive smoke exposure** (maternal smoking, low maximal attained lung function).

Pathology and pathogenesis

- **Large airways** — mucus-gland enlargement, goblet-cell hyperplasia and squamous metaplasia → cough and sputum (chronic bronchitis).
- **Small airways (≤2 mm)** — goblet-cell metaplasia, smooth-muscle hypertrophy, fibrosis, mucus plugging and luminal narrowing; this is the **major site of increased airflow resistance** and the earliest lesion.
- **Parenchyma (emphysema)** — destruction of respiratory bronchioles, alveolar ducts and alveoli. Pathologic types: **centrilobular** (upper-lobe, smoking-related), **panlobular** (lower-lobe, α1AT deficiency) and **paraseptal** (subpleural).
- **Disease mechanisms** — four interrelated events: chronic inhalational injury in susceptible hosts → inflammatory/immune cell recruitment → **protease–antiprotease imbalance** (the *elastase:antielastase* hypothesis; neutrophil elastase, MMP-12) and **oxidant–antioxidant imbalance** (oxidant inactivation of **HDAC2**, NRF2/SOD3 dysfunction) → structural cell death (ceramide, mTOR/Rtp801, senescence) → **ineffective repair** of elastin and matrix → airspace enlargement.

Pathophysiology

- **Airflow obstruction** — chronically reduced FEV1 and **FEV1/FVC ratio** that does not normalise after bronchodilator (fixed obstruction).
- **Hyperinflation** — air trapping (↑residual volume, ↑RV/TLC), then ↑TLC; flattens the diaphragm, shortening fibres and increasing work of breathing.
- **Gas exchange — V/Q mismatch** causes hypoxaemia (shunt minimal, hence corrected by modest O2). Pao2 usually stays near normal until FEV1 <50% predicted; Paco2 rises only when FEV1 <25% predicted. Sustained pulmonary hypertension → **cor pulmonale** typically when FEV1 <25% and Pao2 <55 mmHg.

Clinical features

- **Symptoms** — the classic triad of **chronic cough, sputum production and progressive exertional dyspnoea**; symptoms often precede presentation by years. Arm work above shoulder level is poorly tolerated.
- **Signs** — early examination may be normal. Advanced: prolonged expiration, expiratory wheeze, **barrel chest**, poor diaphragmatic excursion, accessory-muscle use, **tripod posture**, pursed-lip breathing, cyanosis, cachexia (poor prognostic sign) and signs of cor pulmonale (raised JVP, pedal oedema). **Digital clubbing is NOT a feature** of COPD and mandates a search for another cause (especially lung cancer).
- **Two classic phenotypes** (most patients overlap):

Feature	Type A — "Pink Puffer" (emphysema-predominant)	Type B — "Blue Bloater" (bronchitis-predominant)
Main symptom	Severe dyspnoea, onset after ~50 yr; scant cough	Chronic productive cough, frequent infective exacerbations; onset 30s–40s
Build	Thin, recent weight loss, distressed, accessory-muscle use	Overweight, cyanotic, comfortable at rest, peripheral oedema
Chest	Quiet, no adventitious sounds	Noisy — rhonchi, wheezes
Pao2 / Paco2	Near normal (65–75 / 35–40 mmHg)	↓Pao2 (45–60), ↑Paco2 (50–60 mmHg)
Haemoglobin	Normal	Elevated (secondary polycythaemia)
CXR	Hyperinflation, flat diaphragms, ↓vascular markings	"Dirty lungs", ↑interstitial markings, diaphragms not flat
Dlco / cor pulmonale	Reduced Dlco; late cor pulmonale	Normal Dlco; early, marked cor pulmonale

Diagnosis and GOLD criteria

- **Diagnostic requirement — post-bronchodilator FEV1/FVC <0.70** on spirometry confirms persistent airflow obstruction (some authorities prefer the lower limit of normal / Z-score to reduce mis-classification).
- **GOLD spirometric grades** (severity of obstruction, all require FEV1/FVC <0.70):

Grade	Severity	Post-bronchodilator FEV1 (% predicted)
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50–79%
GOLD 3	Severe	30–49%
GOLD 4	Very severe	<30%

- **GOLD "ABE" assessment tool** — combines symptom burden with exacerbation risk to guide therapy. **Symptoms**: mMRC ≥2 or **CAT ≥10** = high; **Exacerbation risk**: ≥2 moderate exacerbations or ≥1 leading to hospitalisation in the past year = high.
  - **Group A** — low symptoms, low risk → a bronchodilator.
  - **Group B** — high symptoms, low risk → **LABA + LAMA**.

- **Group E** — high exacerbation risk (any symptoms) → **LABA + LAMA**; add **ICS if blood eosinophils ≥300/µL**.

- **mMRC dyspnoea scale**: 0 (breathless only on strenuous exertion) to 4 (too breathless to leave the house/dress).
- **Other assessment** — ABG (ventilatory failure = Paco2 >45 mmHg), Dlco (reduced in emphysema), CBC (eosinophils guide ICS; raised Hct = chronic hypoxaemia), chest CT (defines emphysema pattern, screens for cancer), serum α1AT in all COPD/early-onset disease, 6-minute walk and the multidimensional **BODE index** (Body-mass index, Obstruction, Dyspnoea, Exercise capacity) — a better predictor of mortality than FEV1 alone.

Treatment of COPD exacerbation

- **Definition** — an acute worsening of respiratory symptoms (increased dyspnoea, cough, sputum volume/purulence) beyond day-to-day variation, usually over <14 days. Strongest predictor = a prior exacerbation.
- **Precipitants** — respiratory infection (viral in >50%; bacteria — *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*), air pollution, non-adherence; consider **pulmonary embolism** (increased incidence) and pneumothorax mimics.
- **Indications for hospital admission** — respiratory acidosis/hypercapnia, new or worsening hypoxaemia, severe underlying COPD, serious comorbidity (e.g. heart failure), frequent-exacerbator phenotype, inadequate home support.
- **Management:**
  - **Controlled oxygen** — target **SpO2 88–92%**; recheck ABG at 30–60 min for CO2 retention. Hypoxaemia is more dangerous than hypercapnia — never withhold needed O2.
  - **Bronchodilators** — aggressive **short-acting β2-agonist (salbutamol) + short-acting muscarinic antagonist (ipratropium)**, usually nebulised initially.
  - **Systemic glucocorticoids — prednisone 40 mg orally for 5 days** (0.5 mg/kg/day; 5 days non-inferior to 10–14 days) — shortens recovery, improves lung function and reduces relapse; watch for hyperglycaemia.
  - **Antibiotics** — for **moderate/severe exacerbations**, guided by the **Anthonisen criteria** (increased dyspnoea + increased sputum volume + increased sputum purulence; greatest benefit when all three present, or when ventilated), for **5–7 days**. Choice per local susceptibility; cover *Pseudomonas* (e.g. piperacillin-tazobactam, levofloxacin) when risk factors present.
  - **Non-invasive positive-pressure ventilation (NIPPV)** — first-line for **acute respiratory acidosis (Paco2 >45 mmHg and pH ≤7.35)**; reduces mortality, need for intubation, complications and length of stay.
  - **Invasive mechanical ventilation** — for severe distress, refractory hypoxaemia/hypercapnia or acidosis despite NIPPV, impaired consciousness, respiratory arrest or haemodynamic instability; beware **auto-PEEP** — allow adequate expiratory time.
- **Prognosis** — mechanical ventilation in an exacerbation carries 17–49% in-hospital mortality; ~20% are re-hospitalised within 30 days, 45% within a year, and ~20% die within the year after

discharge. Influenza, pneumococcal, COVID-19 and RSV vaccination plus smoking cessation reduce future exacerbations.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Emphysema subtypes / CT patterns** — three labelled lung-acinus panels: **(A) Centrilobular** — dilated airspaces around the respiratory bronchiole, *upper-lobe, smoking*; **(B) Panlobular** — uniform acinar destruction, *lower-lobe, α1AT deficiency*; **(C) Paraseptal** — subpleural airspaces along pleural margins. Label respiratory bronchiole, alveolar duct, alveolus, pleura.
- **GOLD ABE assessment grid** — Y-axis "Exacerbation history" (≥2 moderate or ≥1 hospitalisation = high), X-axis "Symptoms" (mMRC/CAT). Boxes labelled **A, B, E**; side column labelled **GOLD 1–4 with FEV1 thresholds (≥80, 50–79, 30–49, <30)**.

Clinical / Diagnostic significance

- **Spirometry (post-bronchodilator FEV1/FVC <0.70) is mandatory** — clinical features alone over- and under-diagnose COPD.
- Distinguish from **asthma** (reversible obstruction), **bronchiectasis** (recurrent pneumonia, clubbing, hemoptysis), **cystic fibrosis** and central airway obstruction.
- **Three interventions improve survival** — smoking cessation, long-term oxygen in chronic hypoxaemia (Pao2 ≤55 mmHg, or ≤59 with cor pulmonale/erythrocytosis; ≥15 h/day), and lung volume reduction (surgical/endobronchial valve) in selected upper-lobe emphysema; triple inhaled therapy reduces mortality in selected patients.
- **Blood eosinophil count** individualises ICS use; clubbing or hemoptysis should prompt evaluation for **lung cancer**.

High-yield exam pointers

- COPD = **persistent symptoms + non-fully-reversible airflow obstruction**; diagnosis needs **post-bronchodilator FEV1/FVC <0.70**.
- **GOLD grades 1–4** by FEV1 %predicted (≥80 / 50–79 / 30–49 / <30); management by **ABE** groups using mMRC/CAT + exacerbation history.
- **α1AT deficiency** → early-onset **panlobular, lower-zone** emphysema; serum <11 µmol/L (~50 mg/dL), PiZ; IV augmentation ~60 mg/kg weekly.
- **Centrilobular = upper-lobe, smoking; panlobular = lower-lobe, α1AT**.
- **Pink puffer** (emphysema, thin, normal gases) vs **blue bloater** (bronchitis, cyanotic, hypercapnic, cor pulmonale).
- Exacerbation: **prednisone 40 mg × 5 days**, antibiotics 5–7 days by **Anthonisen criteria**, O2 target **88–92%**, **NIPPV when pH ≤7.35 & Paco2 >45**.
- **Clubbing is NOT part of COPD** — investigate for malignancy.
- **BODE index** predicts mortality better than FEV1 alone.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Chronic Obstructive Pulmonary Disease" (definition, pathology/pathogenesis, GOLD spirometric grades [Table 303-1] and ABE tool, exacerbation management).
- Murray & Nadel's Textbook of Respiratory Medicine, 7e — "COPD: Pathogenesis and Natural History" and "COPD: Diagnosis and Management" (GOLD classification figure, Anthonisen criteria, corticosteroid/antibiotic dosing, LTOT thresholds, BODE).
- CMDT 2026 — "Pulmonary Disorders" (pink puffer/blue bloater Table 9–7, diagnostic tests, hospitalised-exacerbation regimen, NIPPV).

◆ ◆ ◆

Pulmonary rehabilitation post severe COVID-19 pneumonia

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

Definition / Introduction — *Pulmonary rehabilitation (PR)* is a comprehensive, multidisciplinary, patient-centred intervention—built on a thorough assessment followed by patient-tailored therapies that include, but are not limited to, **exercise training, education and behaviour change**—designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote long-term adherence to health-enhancing behaviours (ATS/ERS definition). Survivors of **severe COVID-19 pneumonia** frequently leave hospital with prolonged dyspnoea, profound deconditioning, ICU-acquired weakness, impaired exercise capacity and psychological morbidity, so they constitute a logical—though relatively new—indication for PR. Although disease-specific COVID PR protocols are still evolving and largely expert-opinion based, the well-validated framework of PR (derived chiefly from COPD and post-exacerbation/post-ICU rehabilitation) is directly applicable.

Rationale — the systemic legacy of severe COVID pneumonia

- **Pulmonary**: severe COVID pneumonia causes ARDS with bilateral ground-glass opacities/consolidation; survivors of severe acute pulmonary injury may have **persisting respiratory impairment** (residual fibrosis, reduced diffusing capacity, exertional hypoxaemia and breathlessness).
- **Critical-illness sequelae**: prolonged mechanical ventilation, sedation and immobility produce **ICU-acquired weakness, skeletal-muscle deconditioning and debility related to hospitalisation and critical illness**, which explicitly warrant rehabilitation.
- **Recovery is slow**: ~80% of symptomatic infections resolve within 2 weeks, but **severe disease often needs several months** for recovery, and a subset develop persisting/recurring symptoms.
- **Long COVID** (a chronic condition present ≥3 months after infection): commonest features are **fatigue (32%), smell/taste disorder (22%), dyspnoea (16%), headache (12%), memory impairment (11%), hair loss (10%) and sleep disorder (10%)** — fatigue, cognitive deficits, cough, dyspnoea and chest pain dominate.

- **Extrapulmonary**: persisting cardiac injury, thromboembolic risk (PE/DVT), encephalopathy/ICU delirium, and high rates of anxiety, depression, post-traumatic symptoms and sleep disturbance — all of which PR is designed to address.

Definition, goals and evidence base of PR

- PR provides improvements in dyspnoea, exercise tolerance and health status **exceeding those of any other therapy for COPD, despite no direct effect on lung function** — explained by treating the *systemic* manifestations (limb-muscle dysfunction, deconditioning, fear of dyspnoea-producing activity, poor pacing/coping). The same systemic-illness logic applies after severe COVID pneumonia.
- **Goals**: increase exercise tolerance, reduce dyspnoea and fatigue, reduce anxiety/depression, increase self-efficacy and self-management, improve health-related quality of life (QOL), and reduce health-care utilisation.
- **Proven benefits of PR (RCT/Cochrane level)**:

Improved	Reduced
Exercise capacity (endurance, strength, peak workload), balance	Dyspnoea
Functional/ADL & physical-activity performance	Fatigue
Self-efficacy, self-management, disease knowledge	Anxiety / depression
Quality of life	Urgent health-care use & hospitalisations
Survival (when delivered after hospitalisation for COPD exacerbation)	Health-care costs

- Cochrane data (COPD): exercise training increased **6-minute walk distance by 43.9 m** (95% CI 32.6–55.6), increased maximal exercise capacity by 6.8 W, and improved SGRQ by a mean of −6.9 units (exceeding the 4-unit MCID). Following a hospitalised COPD exacerbation, post-discharge PR reduces mortality (~42% relative reduction; Lindenauer *JAMA* 2020 — PR within 90 days of discharge, HR 0.63) — the evidence template for offering early PR to severe-COVID-pneumonia survivors.

Patient assessment, candidacy and pre-rehab screening

- **Referral triggers** relevant after severe COVID: severe dyspnoea/fatigue, decreased exercise tolerance/low physical-activity levels, difficulty with ADLs, impaired health status, and **recovery from an acute event requiring hospitalisation**.
- **Pre-enrolment evaluation**: medical history, examination, record review, and baseline assessment of exercise capacity, symptoms and health status; screen specifically for **persisting cardiac injury, arrhythmia, residual VTE/anticoagulation status, and exertional desaturation** (pulse oximetry) before prescribing exercise.
- **Absolute contraindications**: unstable angina or arrhythmia; unstable bone fracture; **communicable infectious disease** (i.e. the patient must be past the infectious period for COVID-19 before joining group/centre-based PR); unstable psychiatric condition posing harm.

- **Relative contraindications**: severe cognitive impairment, lack of motivation, severe progressive neurological disease, severe anaemia, and severe debilitating fatigue that would prevent participation.
- Patients with a **wide range of impairment benefit**, including those needing supplemental oxygen — so even oxygen-dependent COVID survivors are candidates.

Core components of the programme

Component	Content
Exercise training (*cornerstone*)	Lower- & upper-limb **aerobic** (cycling/walking), **resistance** (weights/bands/machines), **interval** training; **balance** training; adjuncts — neuromuscular electrical stimulation (NMES), whole-body vibration, yoga/Tai Chi
Education / self-management	Disease & medication/inhaler education, oxygen and (where relevant) NIV use, exacerbation recognition + **written action plan**, pacing & energy conservation
Psychosocial support	Coping/relaxation, anxiety & depression management, cognitive-behavioural techniques; refer significant psychiatric illness onward
Nutritional support	Assessment of body composition/BMI; supplementation (esp. if low fat-free mass) combined with resistance training to rebuild muscle
Breathing training & airway clearance	**Pursed-lip breathing** (inhale through nose, exhale over 4–6 s through pursed lips), body-forward positioning, inspiratory-muscle training (selected cases), chest physiotherapy/PEP devices for sputum
Physical-activity promotion	Coaching, pedometers/accelerometers, tele-coaching to translate gains into daily activity and sustain long-term behaviour change

- Exercise is the cornerstone because severe respiratory illness causes **skeletal-muscle dysfunction** (loss of muscle mass/strength, reduced type-I fibres, mitochondrial/capillary loss) that is *reversible with training* — the key therapeutic target after a deconditioning ICU stay.
- Education beyond exercise has not been shown to add to traditional outcomes, but improves engagement, completion and self-management — important in this anxious, symptom-burdened group.

Exercise prescription and delivery settings

- **Prescription (typical, individualised to baseline field-test capacity)**:

Modality	Frequency	Intensity	Duration
Endurance (aerobic)	3–5×/week (ideal)	60–80% of maximal work rate	20–60 min/session
Interval training	3–4×/week	80–100% of maximal work rate	45–60 min total
Resistance training	2–3×/week	Fraction of 1-repetition maximum	progressed as tolerated

- **Interval training** (e.g. 20–30 s high-intensity alternating with 30–40 s low-intensity/rest) gives gains comparable to continuous training and **suits patients with severe dyspnoea or markedly limited capacity** — a practical option for the most deconditioned COVID survivors.

- **Supplemental oxygen** for resting/exertional hypoxaemia maintains safety and allows higher training intensity; optimise any bronchodilator therapy first.
- Most programmes run **8–12 weeks**. **Settings**: outpatient/community (most evidence; usually 2–3 sessions/week over 6–8 weeks), **inpatient** (for complex/nursing-dependent patients; 5–6 days/week for 2–6 weeks), and **home-based/tele-rehabilitation**.
- **COVID-specific delivery**: interest in **home-based PR and tele-rehabilitation rose during the pandemic** because most centre-based programmes were suspended (inability to maintain social distancing); home confinement itself worsened functional status. **Optimal rehabilitation strategy for COVID-19 survivors is not yet defined**, but expert-panel physiotherapy recommendations (e.g. Thomas *et al*, acute-hospital physiotherapy management of COVID-19) and home-exercise recommendations have been published, supporting a staged, individualised, symptom-titrated approach with monitoring for **post-exertional symptom worsening**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Flow diagram — "From severe COVID pneumonia to recovery via PR"**: boxes/labels — *Severe COVID pneumonia (ARDS) → ICU / mechanical ventilation → ICU-acquired weakness + deconditioning + persisting dyspnoea/hypoxaemia + long-COVID fatigue/cognitive symptoms → Referral & baseline assessment (6MWT, mMRC, SpO_2, HADS, screen cardiac/VTE) → Multidisciplinary PR (Exercise training [aerobic/resistance/interval] + Education/self-management + Psychosocial + Nutrition + Breathing/airway clearance + Physical-activity promotion) → Outcomes: ↑exercise capacity & QOL, ↓dyspnoea/anxiety, ↑self-efficacy → Long-term maintenance (home/tele-rehab).*
- **"Wheel of PR components"**: central hub labelled *Pulmonary Rehabilitation*, six spokes labelled — *Exercise training (cornerstone)*, *Education / self-management*, *Psychosocial support*, *Nutritional support*, *Breathing training & airway clearance*, *Physical-activity promotion*.

Clinical / Diagnostic significance

- **Outcome assessment** (mandatory minimum domains = exercise capacity, dyspnoea, health status): field tests — **6-minute walk test (6MWT)** and **incremental shuttle walk test**; **cardiopulmonary exercise testing** where available; exertional dyspnoea by **Borg/VAS**; symptom burden by **modified MRC (mMRC)** score; QOL by **Chronic Respiratory Questionnaire (CRQ), St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT)**; mood by **Hospital Anxiety and Depression Scale (HADS)**; plus muscle strength (dynamometry), timed up-and-go and sit-to-stand tests, and body composition.
- **Safety/monitoring** during exercise: continuous pulse oximetry for desaturation, heart-rate/Borg-guided intensity, and vigilance for cardiac symptoms (given COVID myocardial injury) and post-exertional fatigue.
- **Investigations that guide rehab** in severe-COVID survivors: serial spirometry and **DLCO** (restrictive/diffusion defects), HRCT for residual fibrosis/ground-glass change, echocardiography/troponin if cardiac injury suspected, and D-dimer/imaging for residual VTE.

- **Maintenance**: short-term gains decline after the programme unless exercise continues; home-based and "booster" PR, tele-rehabilitation, activity diaries and pedometers help sustain benefit.

High-yield exam pointers

- **ATS/ERS definition** of PR (comprehensive intervention: assessment → tailored therapies including exercise training, education, behaviour change) — write it verbatim.
- **Exercise training is the cornerstone**; PR improves dyspnoea/exercise/QOL **despite no change in FEV_1** because it treats systemic/skeletal-muscle dysfunction.
- **Prescription numbers**: endurance 3–5×/week at **60–80% max work rate, 20–60 min**; resistance **2–3×/week**; programme **8–12 weeks**.
- **6MWD improves by ~44 m** with PR (Cochrane); post-hospitalisation PR **improves survival** (Lindenauer *JAMA* 2020, HR 0.63) — rationale for early post-COVID rehab.
- **Six core components**: exercise, education/self-management, psychosocial, nutrition, breathing/airway clearance, physical-activity promotion.
- **Long COVID** = symptoms ≥3 months; commonest = **fatigue 32%, smell/taste 22%, dyspnoea 16%**.
- **Absolute contraindications**: unstable angina/arrhythmia, unstable fracture, **communicable infectious disease** (wait out the COVID infectious period), unstable psychiatric illness.
- Settings: outpatient (most evidence), inpatient (complex), **home/tele-rehabilitation (expanded during COVID)**; optimal COVID-specific protocol still expert-opinion based.
- Outcome tools: **6MWT, mMRC/Borg, CRQ/SGRQ/CAT, HADS**.

SOURCE & COVERAGE

- **Murray & Nadel's Textbook of Respiratory Medicine** — "Pulmonary Rehabilitation" (definition/ATS-ERS, components, exercise prescription, settings, outcomes, COVID-19 home-based/tele-rehabilitation and post-critical-illness rehabilitation; post-exacerbation PR survival).
- **Harrison's Principles of Internal Medicine, 22e** — "SARS-CoV-2 and COVID-19" (severe disease/ARDS, mechanical ventilation, recovery timeline, persisting respiratory/cardiac impairment, long COVID, neuropsychiatric sequelae).
- **CMDT 2026** — "Viral & Rickettsial Infections" (COVID-19: long COVID prevalence and symptom frequencies, convalescent management).

Coverage note: As flagged in the spec, the corpus does not contain a dedicated *post-severe-COVID* PR protocol; COVID-specific guidance in the sources is limited and expressly described as **expert-opinion based with "optimal strategies unknown."** This answer therefore applies the validated PR framework (Murray, COPD/post-exacerbation/post-ICU and non-COPD evidence) to the severe-COVID survivor, using COVID-specific epidemiology and sequelae from Harrison/CMDT. Exercise-prescription numbers, the proven-benefit data and contraindications are COPD-derived (the established evidence base) and are extrapolated to the COVID context; the caution regarding post-exertional symptom worsening reflects standard current practice rather than a corpus-quoted COVID protocol.

◆ ◆ ◆

Hospital-acquired pneumonia

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

Definition / Introduction — Hospital-acquired pneumonia (HAP) is an infection of the pulmonary parenchyma that becomes clinically and radiographically apparent **more than 48 hours after admission** in a patient who was **not intubated** at the time pneumonia developed, and which was neither present nor incubating on admission. The 2016 IDSA/ATS guidelines re-defined HAP and **ventilator-associated pneumonia (VAP)** as *mutually exclusive* entities — VAP is pneumonia arising >48 h after endotracheal intubation, so HAP by current usage refers to the **non-ventilated** patient. The older umbrella term *health care–associated pneumonia (HCAP)* has been **discontinued** because it neither reliably predicted resistant pathogens nor improved outcomes, while encouraging overuse of broad-spectrum antibiotics. HAP is among the most common and most lethal nosocomial infections.

Epidemiology and burden

- HAP is the **third most prevalent hospital-acquired infection** after surgical-site and gastrointestinal infections; roughly **96,000–110,000 cases per year** in the United States, affecting about **0.5–2% of all hospitalised patients** (~0.6% point prevalence among non-ventilated inpatients).
- It is **two- to threefold more frequent than VAP**; ~70% of all nosocomial pneumonia is acquired *outside* the ICU.

- Risk is highly condition-dependent: ~**13%** of non-ICU stroke patients and ~**1%** of surgical patients (up to **5.8%** after lobar pulmonary resection, ~3% after major abdominal surgery) develop HAP/postoperative pneumonia. *Cardiothoracic and upper-abdominal surgery* carry the greatest risk.
- HAP carries substantial attributable burden: **excess mortality ~2–14%**, **excess length of stay ~2.5–15.9 days**, and **excess cost ~$30,000–40,000 per case**.

Pathogenesis and risk factors

Three sequential mechanisms are required (each maps to a prevention target):

- **Oropharyngeal colonisation** with pathogenic organisms — hospitalised patients rapidly replace normal flora with **gram-negative bacilli**; driven chiefly by **antibiotic selection pressure**, cross-infection, severe illness and malnutrition.
- **Aspiration (microaspiration)** of these contaminated secretions into the lower respiratory tract — favoured by impaired consciousness (anaesthesia, opioids, sedatives), dysphagia, stroke, and impaired cough from pain/sedation.
- **Compromise of host defences** — failure of laryngeal protection, mucociliary clearance, secretory IgA/lysozyme/lactoferrin, alveolar macrophages and surfactant proteins; aggravated by immune senescence and malnutrition.
- Less common routes: **large-volume gastric aspiration**, **haematogenous spread**, and **inhalation of contaminated aerosols** (the usual route for nosocomial *Legionella*).
- Key modifiable risks: **gastric acid suppression** (PPIs/H_2-blockers promote gastric bacterial overgrowth), nasogastric/endotracheal tubes, supine positioning, prolonged or broad-spectrum antibiotics, COPD, advanced age, diabetes and cerebrovascular disease.

Microbiology

HAP pathogens resemble those of VAP far more than CAP (atypicals are rare), with a higher proportion of **multidrug-resistant (MDR)** organisms than CAP but slightly lower than VAP. Pathogens are unidentified in **50–90%** of cases because adequate lower-respiratory samples are hard to obtain in non-intubated patients.

Group	Approx. share	Representative organisms
Gram-negative bacilli (total)	~35%	—
• Non-fermenters	~20%	*Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*
• Enteric GNB	~15%	*E. coli*, *Klebsiella*, *Proteus*, *Enterobacter* (incl. ESBL/carbapenemase producers)
Staphylococcus aureus	~15%	MSSA ~10%, **MRSA ~6%**
Other bacteria	—	*Streptococcus* spp., *H. influenzae*, rarely *S. pneumoniae*; *Legionella* (water-supply clusters)
Respiratory viruses	>20%	Rhinovirus, influenza, parainfluenza (often co-infection)

Group	Approx. share	Representative organisms
Fungi	Uncommon	*Aspergillus* (severely immunocompromised)

- **Anaerobes** (*Prevotella*, *Peptostreptococcus*, *Fusobacterium*, *Bacteroides*) are *more* common in non-ventilated HAP than VAP due to macroaspiration, but usually as part of polymicrobial infection; specific anti-anaerobe therapy is seldom needed.
- *Candida* recovered from respiratory secretions of non-ventilated patients represents colonisation, **not** a true pathogen.

Diagnosis

- **Clinical/radiographic criteria (2016 IDSA/ATS):** a **new or progressive radiographic opacity** *plus* clinical evidence of infection — typically **≥2 of**: fever/hypothermia, leukocytosis/leukopenia, **purulent secretions**, and **decline in oxygenation**; with cough, dyspnoea or new delirium.
- HAP is frequently **over-diagnosed** — fever, infiltrate and abnormal sounds may instead reflect heart failure, atelectasis, ARDS, pulmonary embolism, pulmonary haemorrhage, or drug reaction. A **good frontal + lateral film** (or **CT**, the most sensitive) outperforms a portable radiograph; ~35% labelled HAP lack confirmatory radiographic findings.
- **Microbiological work-up:** obtain **blood cultures from two sites** (positive in **15–20%**) and a respiratory sample to allow targeted therapy and de-escalation. The **non-invasive** route (expectorated/induced sputum, nasotracheal or endotracheal aspirate) is preferred over invasive bronchoscopy, which adds risk in a non-intubated, hypoxic patient.
- **Quantitative culture thresholds** (mainly extrapolated from VAP): endotracheal aspirate **10^6 CFU/mL**, BAL **<10^4 CFU/mL** and protected-specimen brush / blind bronchial sampling **<10^3 CFU/mL** indicate colonisation → antibiotics may be withheld below threshold.
- **Adjuncts:** rapid **nasal MRSA PCR** (high negative predictive value) helps *de-escalate* anti-MRSA cover; **procalcitonin/CRP** are *not* recommended to establish the diagnosis but can guide *duration*; the **CPIS** is not recommended.

Treatment

Therapy is **empirical first**, started promptly (delay increases mortality), then **de-escalated/targeted** once cultures return. Empirical choice rests on **three factors** (time of onset alone does *not* predict MDR risk): **(1) IV antibiotic use within 90 days, (2) the local unit antibiogram, and (3) disease severity** (need for ventilation or septic shock = "high mortality risk").

Clinical category	Empirical regimen
Not high mortality risk, **no** MRSA risk	**One** anti-pseudomonal agent — piperacillin–tazobactam 4.5 g IV q6h *or* cefepime 2 g IV q8h *or* levofloxacin 750 mg IV daily *or* imipenem 500 mg q6h / meropenem 1 g q8h
Not high risk, **with** MRSA risk	Above anti-pseudomonal + anti-MRSA: **vancomycin** 15 mg/kg q8–12h (trough 15–20) *or* **linezolid** 600 mg q12h

Clinical category	Empirical regimen
High mortality risk / IV antibiotics in prior 90 days	**Two** anti-pseudomonal agents from *different classes* (β-lactam + aminoglycoside [amikacin 15–20 mg/kg, or gentamicin/tobramycin 5–7 mg/kg] or fluoroquinolone; add polymyxin B/**colistin** for carbapenem-resistant GNB) + anti-MRSA agent

- **MRSA cover** is indicated for prior MRSA, IV antibiotics in 90 days, or treatment in a unit where >**20%** of *S. aureus* are MRSA (or rate unknown). **Double gram-negative cover** is favoured where >**10%** of GNB resist the candidate monotherapy, or with structural lung disease (bronchiectasis, cystic fibrosis).
- **Drug pearls: Daptomycin must NOT be used** for pneumonia (inactivated by surfactant); **linezolid** is preferred over vancomycin for high-MIC MRSA/renal impairment; **oxacillin/nafcillin/cefazolin** are definitive for MSSA. Newer agents (ceftazidime–avibactam, ceftolozane–tazobactam, imipenem–relebactam, meropenem–vaborbactam, cefiderocol) extend cover against resistant *Pseudomonas*, carbapenem-resistant Enterobacterales and *Acinetobacter*.
- **PK/PD optimisation** (extended/continuous infusion of β-lactams, weight-based dosing, therapeutic drug monitoring) improves survival. **Inhaled antibiotics** are reserved as adjuncts for MDR gram-negatives susceptible only to aminoglycosides or polymyxins.
- **Duration:** a **7-day course** is standard and as effective as longer regimens (even for non-fermenting GNB), lengthened only for complications (empyema, necrotising pneumonia) or inadequate initial therapy; procalcitonin trends can guide stopping.

Prevention

- **General:** rigorous **hand hygiene** (alcohol-based rubs), antibiotic stewardship, oral care/dysphagia screening (especially stroke patients), avoiding unnecessary **PPIs/H_2-blockers**, minimising sedating opioids/benzodiazepines, optimal pain control, and **early mobilisation**.
- **VAP-specific (also applicable to ventilated HAP), bundled** for ≥95% compliance: **avoid intubation / use NIV**; minimise ventilation duration via **daily sedation interruption and weaning protocols**; **head-of-bed elevation 30–45°**; **subglottic secretion drainage** with specialised tubes; maintain **cuff pressure >20 cm H_2O**; avoid reintubation; drain ventilator-circuit condensate.
- **Selective oral / digestive decontamination (SOD/SDD)** reduces VAP and (SDD) mortality in low-resistance ICUs but risks selecting resistant flora; routine **chlorhexidine oral care** is now questioned (no mortality benefit, possible harm).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis schematic of HAP:** a vertical arrow chain — *Hospital admission → Oropharyngeal colonisation with gram-negative bacilli / S. aureus → Microaspiration past glottis (supine, sedation, dysphagia, NG/ET tube) → Impaired host defence (cough, mucociliary clearance, IgA, macrophages, surfactant) → Bacterial proliferation in alveoli → Pneumonia*. Side-branches labelled: *gastric overgrowth (raised pH/PPI)*, *contaminated aerosols → Legionella*, *haematogenous spread*. Annotate matching prevention at each step (oral care, head-up 30–45°, sedation holds, hand hygiene).
- **Empirical antibiotic decision tree:** root *Suspected HAP* → branch on **MRSA risk** and **mortality/MDR risk** into the three boxes — labels: *"One anti-pseudomonal"*, *"Anti-pseudomonal + Vancomycin/Linezolid"*, *"Two anti-pseudomonal + anti-MRSA"*; footnote labels *MRSA threshold >20%*, *GNB resistance >10%*, *de-escalate at 48–72 h on cultures*, *duration 7 days*.

Clinical / Diagnostic significance

- Distinguishing HAP from its mimics (heart failure, atelectasis, ARDS, PE) prevents unnecessary broad-spectrum antibiotics and resistance amplification.
- **Inappropriate initial empirical therapy** is a major driver of excess mortality — hence early, antibiogram-guided broad cover, followed by **disciplined de-escalation** once susceptibilities (and a negative nasal MRSA PCR) are available.
- Non-ventilated HAP has **better host immunity, fewer MDR pathogens and lower mortality** than VAP, permitting **monotherapy in a larger proportion** of cases.
- Knowledge of the **unit-specific antibiogram** is the single most useful tool for rational empirical prescribing.

High-yield exam pointers

- HAP = pneumonia **>48 h after admission in a non-ventilated patient**; VAP = **>48 h after intubation**; the two are **mutually exclusive** (2016 IDSA/ATS); **HCAP is obsolete**.
- **Third commonest nosocomial infection**; 2–3× more frequent than VAP; pathogens unidentified in 50–90%.
- Triad of pathogenesis: **colonisation → aspiration → impaired host defence**; commonest mechanism is **microaspiration of contaminated oropharyngeal secretions**.
- Core pathogens: **P. aeruginosa, S. aureus (MSSA/MRSA), enteric & non-fermenting GNB**; viruses >20%; atypicals rare.
- Diagnose by **new infiltrate + ≥2 clinical criteria**; obtain **blood cultures (positive 15–20%)** and a respiratory sample; **non-invasive sampling preferred**.
- Empirical therapy keyed to **(1) prior IV antibiotics ≤90 d, (2) local antibiogram, (3) severity**; **MRSA cover if unit MRSA >20%**, double GNB cover if resistance >10%.
- **Vancomycin trough 15–20 / linezolid 600 mg q12h** for MRSA; **never daptomycin** (surfactant-inactivated); **treat for 7 days**.

- Prevention: **head-up 30–45°, sedation holds, weaning protocols, subglottic drainage, hand hygiene, oral care, avoid unnecessary PPIs** — delivered as **care bundles**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Pneumonia"* (HAP/VAP sections, including IDSA/ATS empirical-therapy tables and quantitative-culture thresholds) and *"Infections Acquired in Health Care Facilities"*.
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — *"Hospital-Acquired Pneumonia"* (epidemiology, microbiology, diagnosis, empirical-therapy table, prevention) and *"Ventilator-Associated Pneumonia"* (prevention bundles, SDD/SOD).
- **CMDT 2026** — *"Pulmonary Disorders: Nosocomial Pneumonia (Hospital-Acquired & Ventilator-Associated)"* (MDR/MRSA/Pseudomonas risk-factor tables and current empirical regimens).

◆ ◆ ◆

Hypersensitivity pneumonitis

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

Definition / Introduction — Hypersensitivity pneumonitis (**HP**), also called **extrinsic allergic alveolitis**, is an immunologically-mediated inflammatory and/or fibrotic interstitial lung disease (ILD) caused, in susceptible individuals, by repeated **inhalation of organic antigens or low-molecular-weight chemical sensitizers** that are small enough to deposit in distal airways and alveoli. Sensitization, manifest as specific circulating **IgG** (precipitins), is *necessary but not sufficient* — many heavily exposed people are sensitized yet never develop disease. It is one of the commonest diagnoses at ILD referral centres, and — paradoxically — smokers are at *reduced* risk of developing HP (though smoking worsens prognosis once disease exists).

Etiology — Offending Antigens

More than 200 inciting exposures are described, grouped into **microbes, animal proteins and chemical sensitizers**; named after the setting of exposure (e.g. "farmer's lung"). Despite exhaustive search, **no antigen is identified in up to 50% of chronic HP** at tertiary centres.

Category	Disease (eponym)	Antigen / source
Microbial	Farmer's lung	Thermophilic actinomycetes (*Saccharopolyspora rectivirgula*, *Thermoactinomyces vulgaris*); moldy hay, silage, grain
	Bagassosis	Thermophilic actinomycetes; moldy sugarcane (bagasse)
	Humidifier / air-conditioner lung	Actinomycetes, *Aureobasidium*, *Candida*, *Klebsiella*; contaminated water reservoirs
	Hot-tub lung	*Mycobacterium avium* complex; contaminated hot-tub water/mold

Category	Disease (eponym)	Antigen / source
	Summer-type HP (Japan)	*Trichosporon cutaneum*; residential mold
	Suberosis	*Penicillium glabrum*; moldy cork dust
	Malt/mushroom/cheese-washer's lung	*Aspergillus*, *Penicillium*; barley, compost, cheese
Animal protein	Bird fancier's / pigeon breeder's lung	Avian "bloom", droppings, feathers, serum proteins; also **duvet/feather-bedding lung**
	Poultry / laboratory worker's lung	Chicken serum proteins; rat urine, serum, fur
Chemical	Chemical worker's lung	Isocyanates (toluene/diphenylmethane diisocyanate); polyurethane foam, paints, varnish
	Detergent worker's lung	*Bacillus subtilis* enzymes

Pathogenesis

- HP is an **immune-mediated** response to inhaled antigen, dominated by dysregulated **TH1 and TH17** responses; granuloma formation is driven by Th1/macrophage cytokines (**IFN-γ, TNF-α, IL-18**).
- A combination of **type III (immune-complex; precipitating IgG)** and, predominantly, **type IV (cell-mediated, delayed-type) hypersensitivity** operates. In acute disease BAL shows a **neutrophil influx peaking ~48 h** after exposure, followed by a $CD4^+$-then-$CD8^+$ **lymphocytic alveolitis**.
- **Innate immunity** also contributes — Toll-like receptors and **MyD88** signalling drive neutrophil recruitment.
- **Host susceptibility / genetics**: only a minority of exposed persons fall ill. Associations include polymorphisms in **TAP1** and **MHC class II** (antigen processing/presentation). Chronic (fibrotic) HP shares genetic overlap with IPF — the **MUC5B promoter variant (rs35705950)** and **short telomeres / telomere-related gene mutations** predict fibrosis and reduced survival.
- **Fibrotic HP** reflects a shift toward a profibrotic Th2 phenotype with loss of effector-T-cell function; bone-marrow–derived fibrocytes contribute.

Classification

- **Traditional (now discouraged):** acute / subacute / chronic — a *time-based* scheme that lacks prognostic precision (subacute overlaps both).
- **Current (ATS/JRS/ALAT 2020):** stratified by fibrosis on HRCT/histology into **nonfibrotic (inflammatory)** vs **fibrotic** HP — because radiographic fibrosis (reticulation, traction bronchiectasis, honeycombing) consistently predicts poor outcome. Each is further coded by whether the antigen is identifiable, indeterminate or unidentifiable.

Clinical Features

Feature	Nonfibrotic (acute) HP	Fibrotic (chronic) HP
Onset vs exposure	Symptoms **4–8 h after exposure**; resolve in 24–48 h, recur on re-exposure	Insidious; temporal link to exposure often lost
Symptoms	Flu-like — fever, chills, malaise, myalgia + cough, dyspnoea	Progressive exertional dyspnoea, dry cough, weight loss, fatigue, **clubbing**
Examination	May be normal; bibasilar crackles, **inspiratory "squeaks/squawks"** (bronchiolitis), tachypnoea	**Velcro inspiratory crackles**, squawks, hypoxaemia, signs of right-heart strain
Reversibility	Usually fully reversible with antigen removal	Often **irreversible**, may progress despite avoidance (mirrors IPF)

Diagnosis & Investigations

No single test confirms HP; diagnosis integrates clinical, radiologic and histopathologic data in a **multidisciplinary discussion (MDD)** — now the gold standard (histology alone is not). **A compatible exposure history is the single strongest predictor.**

- **HRCT (essential)** — *nonfibrotic*: diffuse **ground-glass opacities**, poorly-defined **centrilobular nodules**, mid–upper zone, with **mosaic attenuation and expiratory air-trapping** (small-airway disease). Coexisting infiltrative + obstructive lobules produce the **"headcheese" sign** (highly specific). *Fibrotic*: reticulation, traction bronchiectasis, honeycombing — but with **relative basal sparing** (unlike IPF).
- **PFT** — restrictive, obstructive or mixed pattern (so pattern is not diagnostic); **reduced DL_CO**, especially in fibrotic disease; isolated exertional desaturation may be the earliest sign. Used to monitor progression.
- **Serum precipitins / specific IgG** — supportive but neither sensitive nor specific (high false-positives in exposed-but-healthy people; e.g. 87% of control bird fanciers positive — so *not* a screening test; false-negatives if the panel omits the relevant antigen).
- **Bronchoalveolar lavage (BAL)** — a marked **lymphocytosis (>30%, classically >50%)** is characteristic of HP; less prominent in fibrotic disease and in smokers. The **CD4:CD8 ratio is variable** — classically described as low/<1 (CD8 predominance) in contrast to sarcoidosis, but it is inconsistent and of limited diagnostic value.
- **Lung biopsy** (transbronchial, **cryobiopsy**, or surgical/VATS) — reserved for diagnostic uncertainty. Classic histology is the **"triad of four"**: ① bronchiolocentric **lymphoplasmacytic interstitial infiltrate**, ② **poorly-formed, loose non-caseating granulomas** (cf. the well-formed granulomas of sarcoidosis), ③ foci of **organizing pneumonia**; multinucleate giant cells ± cholesterol clefts.
- **HP Study Group clinical prediction rule — 6 predictors:** (1) exposure to a known HP antigen *(strongest)*, (2) positive serum precipitins, (3) recurrent symptoms, (4) symptoms **4–8 h after exposure**, (5) inspiratory crackles, (6) weight loss.

Differential Diagnosis

- **Nonfibrotic HP** ↔ viral/atypical pneumonia, **organic dust toxic syndrome (ODTS)** — ODTS follows heavy organic-dust exposure but needs *no* prior sensitization and lacks specific IgG; asthma; drug reaction; inhalational fever.
- **Fibrotic HP** ↔ **IPF**, **NSIP**, connective-tissue-disease ILD, **sarcoidosis** (well-formed granulomas, hilar adenopathy, multi-organ), pleuroparenchymal fibroelastosis.

Treatment

- **Antigen avoidance is the mainstay** and the only intervention shown to improve clinical course and survival — remove birds/mold, improve ventilation, source-control of water systems (humidity <60%), respirators/ventilated helmets (may be inadequate in the sensitized), and occupational change where needed. Identifying *and* avoiding the antigen improves survival (median **8.8 vs 4.9 years**).
- **Glucocorticoids** — for severe nonfibrotic or symptomatic disease: **prednisone 0.5–1 mg/kg/day** (max 60 mg/day) for ~1–2 weeks (CMDT: ~2 weeks), then taper over weeks (total ~3 months). They *accelerate symptom resolution* but do not alter long-term outcome.
- **Steroid-sparing immunosuppressants** — **azathioprine** or **mycophenolate mofetil** in progressive/fibrotic disease (reduce steroid dose; fewer adverse events); **rituximab** in refractory cases.
- **Antifibrotics** — **nintedanib** (INBUILD trial: slowed FVC decline in progressive fibrosing ILDs including HP) and **pirfenidone** for progressive fibrotic HP.
- **Supportive & advanced** — supplemental O_2, pulmonary rehabilitation, vaccination, smoking cessation; **lung transplantation** for end-stage fibrotic disease (outcomes better than IPF, low recurrence risk).

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **HRCT axial section of nonfibrotic HP** — label: *diffuse ground-glass opacity*, *centrilobular nodules*, *mosaic attenuation / air-trapping*, *"headcheese" sign*, *mid–upper zone predominance*.
> - **Pathogenesis flow diagram** — label: *Inhaled antigen → deposition in distal airways/alveoli → sensitization (specific IgG) → Type III immune complex + Type IV (TH1/TH17) delayed hypersensitivity → neutrophilic then lymphocytic alveolitis → poorly-formed non-caseating granulomas* → (with persistent exposure / Th2 shift, MUC5B, short telomeres) → *fibrosis (honeycombing)*.

Clinical / Diagnostic significance

- **Occupational/avocational history is decisive** — HP cannot be managed without identifying and removing the source; recognition of an index case is a *sentinel event* signalling others at risk (outbreak investigation).
- **Distinguish from IPF** — bronchiolocentric fibrosis, upper/mid-zone predominance with basal sparing, BAL lymphocytosis and mosaic attenuation favour HP; this matters because antifibrotic and avoidance strategies, and transplant outcomes, differ.

- **Prognostic markers of poor outcome**: older age, male sex, baseline crackles, low FVC and DL_CO, HRCT fibrosis/honeycombing, MUC5B variant, short telomeres, smoking, no identifiable antigen, pulmonary hypertension; the **ILD-GAP index** and a **≥10% FVC decline over 6–12 months** predict mortality.

High-yield exam pointers

- HP = **extrinsic allergic alveolitis**; antigen-induced ILD of alveoli + small airways; **IgG sensitization necessary but not sufficient**.
- **Smokers have lower risk** of developing HP but worse prognosis once it develops.
- Classic eponyms: **Farmer's lung** (*S. rectivirgula*), **Bird fancier's/pigeon breeder's lung** (avian proteins), **Hot-tub lung** (*MAC*), **Bagassosis**, **Summer-type HP** (*Trichosporon*, Japan), **Suberosis** (cork).
- New classification: **nonfibrotic vs fibrotic** (replaces acute/subacute/chronic).
- Mechanism: **Type III + Type IV** hypersensitivity; **TH1/TH17**; symptoms **4–8 h** post-exposure.
- HRCT: **centrilobular nodules + GGO + mosaic air-trapping**; **"headcheese" sign**; fibrotic HP spares lung bases (unlike IPF).
- BAL: **lymphocytosis** (often >50%); histology = **"triad of four"** with **poorly-formed non-caseating granulomas**.
- HP Study Group rule strongest predictor = **known antigen exposure**.
- Treatment: **antigen avoidance** (mainstay) > glucocorticoids (**prednisone 0.5–1 mg/kg/day**) > azathioprine/MMF > **nintedanib/pirfenidone** > transplant.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia" (Akuthota & Wechsler); and "Occupational and Environmental Lung Disease".
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "Hypersensitivity Pneumonitis" (Johannson & Fernández Pérez) — classification, immunopathogenesis/genetics, "triad of four" histology, headcheese sign, ILD-GAP prognostication, ATS/JRS/ALAT 2020 diagnostic algorithm and management.
- **CMDT 2026** — "Pulmonary Disorders: Hypersensitivity Pneumonitis" — causes table, clinical findings and corticosteroid regimen.
- *Coverage note:* sources differ on BAL **CD4:CD8 ratio** (Harrison: typically <1; Murray: variable/often elevated and not recommended) — answered as "variable, of limited value," which is faithful to both.

◆ ◆ ◆

Airway inflammation in bronchial asthma

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

Definition / Introduction — Asthma is a disease characterised by **episodic airway obstruction** and **airway hyperresponsiveness (AHR)** that is usually accompanied by **airway inflammation**. In most cases the obstruction is reversible, but in a subset a component becomes irreversible owing to **airway remodeling**. In a large proportion of patients the inflammation is **eosinophilic**, though some have differing inflammatory profiles (neutrophilic, mixed, or pauci-granulocytic) and a minority have no obvious inflammation. Airway inflammation is driven by an orchestrated network of **inflammatory cells** and the **chemical mediators** they release, which together produce the structural and functional changes responsible for symptoms.

Inflammatory cells in the asthmatic airway

Most asthmatics have evidence of **chronic** airway inflammation; while it can be precipitated acutely by inhalant exposure, it usually persists. Both recruited leucocytes and resident structural cells participate.

Cell	Role / products in asthma
Eosinophils	Predominant cell in most asthma; release **oxidative radicals** and **major basic protein** (disrupt epithelium, induce AHR), produce **cysteinyl-leukotrienes**; aggregates contribute to mucus plugs
Mast cells / basophils	Activated by **IgE cross-linking** by allergen; release type 2 cytokines, direct smooth-muscle constrictors, **PGD2**, and edema-producing mediators
Neutrophils	Predominate in some severe, non–type 2 / corticosteroid-resistant asthma; source of **LTB4**
Type 2 innate lymphoid cells (ILC2)	Activated by epithelial **alarmins**; produce IL-5 and IL-13 → link "nonallergic" triggers to eosinophilia
CD4+ T-helper 2 (TH2) cells	Produce IL-4, IL-5, IL-13 — the adaptive arm of type 2 inflammation
Airway epithelium	Disrupted (columnar-from-basal separation); source of **alarmins** and cytokines that drive the inflammatory cascade
Airway smooth muscle	Hyperresponsive; undergoes hypertrophy/hyperplasia; secretes chemokines/cytokines that promote inflammation and mast-cell survival

Classification of airway inflammation (Type 2 vs Non–Type 2)

The older atopic (extrinsic) vs nonatopic (intrinsic) division has been superseded by an **immunologic nosology** based on whether inflammation is type 2 or non–type 2 — a classification driven by mechanism and by the development of mediator-targeted biologics.

Feature	Type 2 inflammation	Non–type 2 inflammation
Key cells	Eosinophils, mast cells, TH2, ILC2	Neutrophils
Key cytokines	**IL-4, IL-5, IL-13**; alarmins TSLP, IL-25, IL-33; IL-9	IL-6, **IL-17**, **TNF-α**, IL-1β, IL-8

Feature	Type 2 inflammation	Non–type 2 inflammation
Triggers	Allergens (adaptive) **and** irritants/pollutants/fungi/viruses via alarmins→ILC2	Severe disease, atypical infection (*Mycoplasma*), RADS
Corticosteroid response	Usually suppressed by corticosteroids	Often corticosteroid-resistant; may respond to macrolides
Biomarkers	↑ Eosinophils, ↑ FeNO, ↑ IgE	None reliable

Pauci-granulocytic asthma shows the structural changes without inflammatory-cell infiltration (etiology unclear).

Inflammatory mediators

"Many chemical substances or signaling factors contribute to the pathobiology of asthma," several of which have been successfully drug-targeted.

Cytokines

- **IL-4** — induces B-cell isotype switching to **IgE** production; IgE then binds mast cells/basophils, conferring environmental sensitivity.
- **IL-5** — critical regulator of eosinophils: controls their **formation, recruitment and survival**.
- **IL-13** — induces **airway hyperresponsiveness, mucus hypersecretion and goblet-cell metaplasia**; also drives FeNO.
- **Alarmins** — **TSLP, IL-25, IL-33** are epithelial-derived "proximal" cytokines released after allergic and nonallergic exposures; they activate ILC2 (→ IL-5/IL-13).
- **Non–type 2 cytokines** — IL-6, IL-17, TNF-α, IL-1β, IL-8 mediate neutrophilic inflammation.

Fatty-acid (arachidonic-acid–derived) mediators

- **Cysteinyl-leukotrienes (LTC4, LTD4, LTE4)** — produced by eosinophils and mast cells; **potent smooth-muscle constrictors** that also stimulate mucus secretion, recruit allergic inflammatory cells, cause microvascular leakage, modulate cytokine production and influence neural transmission.
- **LTB4** (non-cysteinyl) — from neutrophils (also macrophages/epithelium); potent **neutrophil chemoattractant**.
- **Prostaglandins** — largely proinflammatory; **PGD2** from mast cells acts via **CRTH2** receptors on TH2/ILC2/mast cells/eosinophils to **upregulate type 2 inflammation**.
- **Pro-resolution lipids** — **resolvins and lipoxins** drive resolution of inflammation; their deficiency may underlie persistent inflammation in severe asthma.

Other mediators

- **Nitric oxide (NO)** — vasodilator; increases mucus production and smooth-muscle proliferation; basis of the **FeNO** breath test (an indicator of IL-13–induced type 2 inflammation).
- **Reactive oxygen species (ROS)** — released in respiratory bursts on cell activation; cause **oxidative stress** → ↑ smooth-muscle contraction, ↑ mucus, AHR and epithelial shedding.

- **Chemokines — eotaxin** (eosinophil chemoattractant), **TARC and MDC** (attract TH2 cells), **RANTES** (pluripotent pro-phlogistic).
- **IgE** — central to allergen sensitivity through mast-cell/basophil cross-linking.

Effects of airway inflammation (structure–function consequences)

Sustained mediator action produces both acute reversible narrowing and chronic remodeling (Fig. 298-2):

- **Airway hyperresponsiveness** — the hallmark; exaggerated narrowing to stimuli (e.g., histamine, methacholine, cold/dry air) that do not affect normal subjects.
- **Bronchoconstriction** — direct smooth-muscle contraction (cysteinyl-leukotrienes, histamine) invaginates the mucosa and narrows the lumen.
- **Airway (submucosal) edema** — acute and chronic; from microvascular leakage of postcapillary venules.
- **Mucus hypersecretion & goblet-cell metaplasia** — chronic inflammation proliferates mucus cells; **mucus plugs** (often containing eosinophil aggregates) obstruct medium and small airways and cause persistent obstruction.
- **Epithelial denudation/shedding** — disruption forms a trophic unit with mesenchyme that elaborates growth factors driving remodeling.
- **Subepithelial fibrosis / basement-membrane thickening** — deposition of repair collagens, tenascin, periostin, fibronectin, osteopontin from myofibroblasts; **stiffens the airway**, exaggerates responses to wall tension and impairs relaxation → fixed obstruction.
- **Smooth-muscle hypertrophy and hyperplasia** — thickens the wall and amplifies hyperresponsiveness.
- **Vascular proliferation (angiogenesis)** and **neuronal proliferation** (neurotrophin-driven) — add to wall thickening and to abnormal regulation of tone and mucus.

The net result is **airway-wall thickening** (correlating with disease severity and duration) producing a tendency to **narrow disproportionately**, episodic exacerbations and, when remodeling supervenes, partly irreversible obstruction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Normal vs asthmatic airway cross-section (Fig. 298-2).** Labels: *Smooth muscle* (and *smooth-muscle hypertrophy and proliferation*), *invagination of mucosa due to smooth-muscle constriction*, *airway edema*, *mucus production / mucus plug*, *cellular infiltration*, *collagen deposition and thickening of the basement membrane*, *epithelial denudation and shedding*, *vascular proliferation*, *neuronal proliferation*, *lumen*, *submucosa*, *epithelium*, *adventitia*, *thin mucus layer*.
- **Type 2 / non–type 2 mediator cascade (Fig. 298-3).** Labels: *Allergens / nonallergic stimuli* → *epithelium* → *alarmins (TSLP, IL-25, IL-33)*; *ILC2* and *TH2* → **IL-4, IL-5, IL-13**; *mast cell* (IgE, PGD2/CRTH2), *eosinophil* (cysteinyl-leukotrienes, MBP), *neutrophil* (LTB4, IL-8/IL-17, TNF-α); outputs → *smooth-muscle hyperresponsiveness & proliferation*, *fibroblast proliferation & matrix deposition*.

Clinical / Diagnostic significance

- **Biomarkers of type 2 inflammation guide therapy:** blood **eosinophils ≥300/μL** indicate likely response to type 2–targeted drugs; **FeNO >35–40 ppb** (untreated) reflects IL-13–driven inflammation and falls with inhaled corticosteroids (also a marker of adherence); **total IgE >1000 IU/mL** prompts consideration of ABPA.
- **Mediator-targeted controller (biologic) therapy** for severe type 2 asthma: **anti-IgE — omalizumab** (SC, reduces exacerbations 25–50%); **anti–IL-5 / IL-5R — mepolizumab, reslizumab (bind IL-5), benralizumab (binds IL-5 receptor)** (rapidly deplete eosinophils, halve exacerbations when eosinophils ≥300/μL); **anti–IL-4Rα — dupilumab** (blocks IL-4 and IL-13 signalling, exacerbations ↓ ≥50%); **anti-TSLP — tezepelumab** (proximal alarmin blockade, broad effect, exacerbations ↓ 50–70%, works even without elevated FeNO/eosinophils).
- **Leukotriene modifiers** — CysLT1 antagonists (**montelukast, zafirlukast**) and 5-lipoxygenase inhibition; moderately effective, particularly useful in **aspirin-exacerbated respiratory disease** (leukotriene overproduction) and to prevent exercise-induced bronchoconstriction; montelukast favoured in children to avoid corticosteroid growth suppression (note neuropsychiatric warning).
- **Inhaled corticosteroids** remain the cornerstone anti-inflammatory controller suppressing type 2 inflammation; neutrophilic/non–type 2 disease is relatively steroid-resistant and may respond to **macrolides**.

High-yield exam pointers

- Asthma = **episodic airway obstruction + AHR + airway inflammation**; obstruction usually reversible, partly fixed with remodeling.
- **IL-4 → IgE switch; IL-5 → eosinophils; IL-13 → AHR, mucus, goblet-cell metaplasia, FeNO** — memorise this triad.
- **Alarmins = TSLP, IL-25, IL-33** (epithelial, proximal) activate **ILC2**, linking nonallergic triggers to eosinophilia.

- **Cysteinyl-leukotrienes = LTC4, LTD4, LTE4** (eosinophils/mast cells) — potent bronchoconstrictors; **LTB4** = neutrophil chemoattractant.
- **PGD2 acts via CRTH2**; **eotaxin** recruits eosinophils; **MBP** and ROS damage epithelium.
- **FeNO** = NO/IL-13–driven marker; **eosinophils ≥300/μL** and **IgE** guide biologic selection.
- Remodeling = subepithelial fibrosis + smooth-muscle hypertrophy + mucus metaplasia + vascular/neuronal proliferation → fixed obstruction.
- Each major type 2 mediator now has a **biologic** (omalizumab, mepolizumab/reslizumab/benralizumab, dupilumab, tezepelumab).
- **Resolvins/lipoxins** = pro-resolution lipids; their deficiency perpetuates severe asthma.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 298 "Asthma" (Elliot Israel): sections on *Mechanisms Leading to Acute and Chronic Airway Obstruction*, *Airway Inflammation (Type 2 and Non–Type 2)*, *Mediators*, biomarkers and biologic therapy; Figs 298-2 and 298-3. Coverage note: Zileuton is named here as the standard 5-lipoxygenase inhibitor and montelukast's neuropsychiatric (suicidality) caution as universally accepted textbook points; the provided text describes "inhibition of 5-lipoxygenase" and "ideation associated with montelukast" without elaboration.

◆ ◆ ◆

Interstitial lung diseases

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

Definition / Introduction — The interstitial lung diseases (ILDs), or diffuse parenchymal lung diseases, comprise a heterogeneous group of **>200 conditions** that injure the lung parenchyma with varying degrees of **inflammation and fibrosis**. Although the *interstitium* (the space between the alveolar epithelium and the capillary endothelium) is the dominant site of involvement, the alveolar epithelium, airways, and vessels also play a key pathogenic role. Most patients present with **progressive exertional dyspnoea** and/or a **persistent dry cough**, though some are detected incidentally or via non-respiratory features of a multisystem disorder. ILDs carry high morbidity and mortality, so timely, precise diagnosis is essential.

Classification (known vs unknown cause)

A classic, examination-friendly scheme divides ILDs into those of **known** and **unknown** cause (Harrison Fig. 304-1); genetic studies increasingly blur this divide.

Group	Subcategory	Representative disorders
Known cause	Occupational/environmental exposure	Asbestosis, silicosis
	Treatment-related	Radiation; drugs — **methotrexate, amiodarone, nitrofurantoin, bleomycin/chemotherapeutics**

Group	Subcategory	Representative disorders
	Systemic / connective tissue disease	RA, scleroderma (SSc), polymyositis/dermatomyositis, Sjögren's, SLE
	Granulomatous (with vasculitis)	Granulomatosis with polyangiitis (GPA), eosinophilic GPA (Churg-Strauss)
	Granulomatous lung disease	**Hypersensitivity pneumonitis (HP)** (bird-fancier's lung)
Unknown cause	Idiopathic interstitial pneumonias (**IIPs**)	IPF, NSIP, RB-ILD, DIP, COP, AIP, lymphocytic interstitial pneumonia (LIP)
	Granulomatous (unknown)	**Sarcoidosis**
	Other	Lymphangioleiomyomatosis (LAM), pulmonary alveolar proteinosis, Langerhans cell histiocytosis (PLCH), pleural-parenchymal fibroelastosis

- The **IIPs** were precisely defined by the *2002 ATS/ERS consensus statement* (Am J Respir Crit Care Med 165:277, 2002).
- **IPF, sarcoidosis, and CTD-associated ILD** are collectively the most common forms of ILD.

Diagnostic approach — the multidisciplinary principle

- **Central tenet:** No single test is diagnostic alone. The **combined weight** of clinical data, laboratory studies, pulmonary function tests (PFTs), imaging, and (when obtained) histopathology is *jointly* required. A UIP biopsy supports IPF but also occurs in RA-associated ILD.
- Most centres use a **multidisciplinary discussion** — pulmonologist, rheumatologist, radiologist, pathologist — to reach a confident diagnosis.
- **History — discriminating clues:**
  - *Age:* IPF is most common >60 yr and rare <50 yr; sarcoidosis, CTD-ILD, LAM and PLCH typically present at **20–40 yr**.
  - *Sex:* LAM/tuberous sclerosis — young women; most CTD-ILDs commoner in women **except RA-ILD** (commoner in men); IPF and occupational ILD commoner in men.
  - *Duration:* **Acute (days–weeks)** — eosinophilic pneumonia, AIP, HP, GPA, acute exacerbation of IPF; **chronic indolent (months–years)** — typified by IPF; **subacute (weeks–months)** — sarcoidosis, CTD-ILD, drug-induced ILD, COP.
  - *Respiratory symptoms:* dyspnoea and dry cough predominate; **haemoptysis** is rare and suggests diffuse alveolar haemorrhage (**Goodpasture's**, GPA) or LAM.
  - *Drugs:* methotrexate, azathioprine, rituximab, TNF-α blockers, nitrofurantoin, amiodarone, bleomycin.
  - *Family history:* up to **20%** of pulmonary fibrosis is familial; a relative with an IIP is among the strongest risk factors for IPF.
  - *Social/exposure:* smoking is causative in RB-ILD/DIP and present in ~**75%** of IPF; asbestos and pigeon/bird exposure (pigeon breeder's lung → HP).

- **Physical examination:** end-inspiratory fine *"Velcro"* basal **crackles/rales** (often the earliest IPF sign); **digital clubbing**; wheeze is uncommon but may occur in sarcoidosis, HP, eosinophilic GPA; advanced disease → cyanosis, cor pulmonale.
- **Laboratory studies:** autoimmune serology for an underlying CTD (e.g. **anti-CCP** for RA), even when systemic features are absent.
- **Pulmonary function tests:** classically a **restrictive** pattern — reduced TLC, symmetric reduction of FEV1 and FVC, with a **normal/raised FEV1/FVC ratio** — and a reduced **DLCO** (may precede volume loss). Airway-involving ILDs (sarcoidosis, HP, LAM) may add obstruction. **Serial FVC decline correlates with increased mortality.**
- **Imaging:**
  - *CXR* — hilar adenopathy with upper-zone central nodular opacities suggests sarcoidosis; a basilar reticular pattern suggests IPF.
  - **HRCT** is the **standard of care** in initial evaluation; can be diagnostic for IPF in the right context and may obviate biopsy, and defines disease extent and complications.
- **Lung biopsy:**
  - *Fibreoptic bronchoscopy with BAL* — supports DAH, **eosinophilia >25%** (chronic eosinophilic pneumonia), fat globules (lipoid pneumonia); transbronchial biopsy useful for granulomatous disease (sarcoidosis, HP); cryobiopsy role is still being defined.
  - *Surgical (VATS) biopsy* — highest yield (pre-treatment) but carries up to **5% short-term mortality**, higher in IPF and acute presentations.

Major idiopathic interstitial pneumonias

Entity	Typical patient	HRCT	Histopathology	Treatment / prognosis
IPF	>60 yr, male, smoker	Subpleural reticulation, **posterior-basal** predominance, honeycombing, traction bronchiectasis = **UIP pattern**	**UIP** — fibroblast foci, temporal & spatial heterogeneity, honeycombing	**Antifibrotics — pirfenidone, nintedanib** (slow FVC decline; from 2014 trials); immunosuppression is *harmful*; O2, pulmonary rehab; transplant. **50% 3–5 yr survival**
NSIP	Non-smoking female, ~50 yr; often CTD	Diffuse subpleural symmetric **ground-glass** + reticular, traction bronchiectasis	Uniform inflammation/fibrosis; honeycombing absent, fibroblast foci rare; **cellular vs fibrotic**	Steroids ± mycophenolate/azathioprine/cyclophosphamide; rituximab, tocilizumab; antifibrotics if progressive. **5-yr survival >80%** (cellular better)
COP	50–60 yr, subacute flu-like illness	Patchy migratory subpleural consolidation; **reversed halo / atoll sign**	Organizing pneumonia — granulation tissue in small airways/alveoli	**Corticosteroids ≥6 months** (high relapse); mycophenolate/cyclophosphamide/rituximab

Entity	Typical patient	HRCT	Histopathology	Treatment / prognosis
RB-ILD / DIP (smoking -related)	Heavy smoker, 40–50 yr	Centrilobular nodules, ground-glass, bronchial-wall thickening	Pigment-laden macrophages in respiratory bronchioles (RB-ILD) / diffuse (DIP)	**Smoking cessation** is primary; <10% of IIPs; generally good prognosis
AIP (Hamma n-Rich)	Acute respiratory distress + hypoxaemia	Patchy bilateral ground-glass + dependent consolidation	**Diffuse alveolar damage (DAD)**	Supportive ± ventilation; no proven drug; **>50% mortality at 6 months**

- **Acute exacerbation of ILD:** an accelerated phase of injury (onset <30 days) without alternate cause; commonest/most severe in IPF, with **>85% mortality**; histology is DAD; nintedanib may reduce exacerbation frequency in IPF.

ILD associated with connective tissue disease

- **Systemic sclerosis (SSc):** ILD is the **commonest pulmonary manifestation** — ~**50%** of diffuse and ~**30%** of limited SSc; NSIP/UIP patterns; clues = dilated oesophagus, PA enlargement. Treat with **cyclophosphamide or mycophenolate**, ± tocilizumab/nintedanib; **high-dose PPI** for reflux-related injury.
- **Rheumatoid arthritis:** clinically evident ILD in ~**10%**, but radiological abnormalities in **40–50%**; commoner in men/smokers; **UIP** pattern predominates (worse survival) > NSIP.
- **Dermatomyositis/polymyositis: anti-synthetase syndrome** = anti-synthetase (e.g. **anti-Jo-1**) antibodies, myositis, fever, Raynaud's, **mechanic's hands**, arthritis, progressive ILD; NSIP ± COP, sometimes UIP; treat with steroids + cytotoxics; rapidly progressive DAD carries a poor outcome.

Granulomatous ILDs and genetics

- **Sarcoidosis** — commonest granulomatous ILD; **noncaseating granulomas** (caseation should prompt search for infection); multisystem (see Ch. 379).
- **Hypersensitivity pneumonitis** — granulomatous reaction to inhaled organic (bird-fancier's lung) or inorganic dusts (see Ch. 299).
- **Granulomatous vasculitides** — **GPA** (Wegener's): lung nodules, ENT and glomerulonephritis, **haemoptysis**; **eosinophilic GPA** (Churg-Strauss): asthma, chronic sinusitis, peripheral eosinophilia.
- **Genetics:** the **MUC5B** promoter variant is present in ~20% of Caucasians and **35–45% of IPF** patients (~**sixfold** risk); telomere-related genes (**TERT, TERC, RTEL1**) and surfactant genes (**SFTPA2**); sarcoidosis — HLA, IL12B, BTNL2; LAM — **TSC1/TSC2**; Hermansky-Pudlak syndrome (autosomal recessive: pulmonary fibrosis + oculocutaneous albinism + bleeding diathesis + nystagmus).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Classification algorithm of ILD** (Fig. 304-1): a branching tree with the trunk *"ILD"* splitting into **"Known cause"** (branches: *Occupational — asbestosis, silicosis*; *Treatment-related — radiation, methotrexate, amiodarone, nitrofurantoin, chemotherapeutics*; *Systemic/CTD — RA, scleroderma, polymyositis/dermatomyositis*; *Granulomatous with vasculitis — GPA, Churg-Strauss*; *HP*) and **"Unknown cause"** (branches: *IIPs — IPF, NSIP, RB-ILD, DIP, COP, AIP, LIP*; *Sarcoidosis*; *Other — LAM, alveolar proteinosis, Langerhans cell histiocytosis, pleural-parenchymal fibroelastosis*).
- **UIP-pattern HRCT chest** (lower-zone slice): label *subpleural reticulation*, *posterior-basal predominance*, *honeycombing*, *traction bronchiectasis*.

Clinical / Diagnostic significance

- **Pattern-recognition decides therapy and prognosis:** a **UIP/IPF** diagnosis mandates **antifibrotics** and *avoidance of immunosuppression* (proven harmful), whereas **cellular NSIP** and **COP** respond well to immunosuppression — misclassification is dangerous.
- **HRCT + multidisciplinary review** can confidently diagnose IPF and spare a high-risk surgical biopsy.
- **Serial FVC and DLCO** are the practical tools for monitoring progression and predicting mortality.
- Always **screen for an occult CTD** (serology, examination) — ILD may be its first manifestation by years.
- **Lung transplantation** remains the standard of care for advanced/rapidly progressive ILD in eligible patients.

High-yield exam pointers

- ILD = >200 disorders; hallmark = restrictive PFT (↓TLC, ↓FVC, normal/↑ FEV1/FVC) with reduced DLCO.
- **UIP pattern** (subpleural, basal, honeycombing, traction bronchiectasis, fibroblast foci, temporal/spatial heterogeneity) = IPF — but also seen in RA.
- **IPF:** >60 yr, male, smoker; prevalence 50–200/100,000; 50% 3–5-yr survival; treat with **pirfenidone/nintedanib**.
- **NSIP:** non-smoking woman, CTD-associated, ground-glass dominant, honeycombing absent, 5-yr survival >80%.
- **COP:** subacute flu-like, **reversed halo (atoll) sign**, steroid-responsive ≥6 months.
- **AIP = Hamman-Rich** = idiopathic DAD, ARDS-like, >50% 6-month mortality.
- **Acute exacerbation of IPF:** onset <30 days, DAD, mortality >85%.
- **Anti-synthetase syndrome:** anti-Jo-1, myositis, fever, Raynaud's, **mechanic's hands**, ILD.
- **MUC5B** promoter variant — strongest common genetic risk factor for IPF (~6-fold).

SOURCE & COVERAGE

Harrison 22e — Ch 304 "Interstitial Lung Disease." (Cross-references within the chapter: sarcoidosis Ch 379, hypersensitivity pneumonitis Ch 299, systemic sclerosis Ch 372, RA Ch 370, inflammatory myopathies Ch 377.) Coverage note: All classification, patterns, drugs, eponyms and numbers above are drawn from Ch 304; sarcoidosis and HP are only summarised here as Ch 304 defers their detail to Chs 379 and 299 (not provided), so granuloma-staging/specific sarcoid management is intentionally brief. The descriptor *"Velcro crackles"* is standard textbook terminology added for emphasis (Ch 304 states "end-inspiratory fine crackles, or rales").

◆ ◆ ◆

Lung abscess

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

Definition / Introduction — A **lung abscess** is localised **necrosis and cavitation of lung parenchyma following microbial infection**, producing a pus-filled cavity. Abscesses may be single or multiple but are usually marked by a **single dominant cavity >2 cm in diameter**, classically containing an **air–fluid level**. Most are a consequence of **aspiration of oropharyngeal anaerobes** in a susceptible host, and although their incidence has fallen sharply in the antibiotic era they remain an important cause of morbidity and mortality.

Classification

- **By origin:**
  - **Primary (~80%)** — arises from **aspiration**, predominantly **anaerobic**, in a host with **no underlying pulmonary/systemic disease**; occurs in immunocompetent individuals.
  - **Secondary** — develops on a background of an **underlying condition**: a **post-obstructive process** (bronchial tumour, foreign body) or a **systemic/immunocompromising state** (HIV, transplant, malignancy). Microbiology is broader and outcomes worse.
- **By chronicity: Acute (<4–6 weeks)** vs **chronic (~40% of cases; symptoms >1 month)**.
- **By microbiology:** defined by the isolate (e.g., *Pseudomonas* abscess); when **no pathogen is recovered (~40%)** it is termed a **nonspecific lung abscess** (anaerobes presumed). A **putrid lung abscess** = foul-smelling breath/sputum/empyema and is **virtually diagnostic of anaerobic infection**.
- **Special form: Necrotising pneumonia** = multiple small (<2 cm) cavities within an area of consolidation; lies on the same pathological continuum.

Etiology, Risk Factors and Microbiology

- **Cardinal risk factor = aspiration.** Predisposing states (CMDT/Harrison):
  - **Impaired consciousness / depressed gag** — alcoholism, drug overdose, sedatives, seizures, general anaesthesia, head trauma, stroke/CNS disease.
  - **Impaired deglutition** — bulbar dysfunction, neuromuscular disease, oesophageal dysmotility, strictures or tumours.

- **Gastric distension / GERD**, the **recumbent position**, and **tracheal or nasogastric tubes** that breach airway defences.

- **Poor oral hygiene is pivotal:** colonisation of **gingival crevices** by anaerobes and microaerophilic streptococci (gingivitis, periodontal disease) supplies the inoculum. Abscess is considered **rare in the edentulous patient** — if it occurs without teeth, **suspect an obstructing bronchial lesion (malignancy)**.

Clinical setting	Typical pathogens
Primary (aspiration)	Anaerobes — *Peptostreptococcus*, *Prevotella* (incl. *P. melaninogenica*), *Bacteroides* (usually **not** *B. fragilis*), *Fusobacterium nucleatum*, *milleri*-group streptococci; **microaerophilic streptococci**
Secondary / immunocompromised	*Staphylococcus aureus*, gram-negative rods (*Pseudomonas aeruginosa*, Enterobacteriaceae, *Klebsiella pneumoniae*), *Nocardia*, *Aspergillus*, Mucorales, *Cryptococcus*, *Legionella*, *Rhodococcus equi*, *Pneumocystis jirovecii*
Embolic	*S. aureus* (tricuspid endocarditis); *Fusobacterium necrophorum* (**Lemierre's syndrome**)
Endemic	*M. tuberculosis*, *M. avium*, *M. kansasii*; *Coccidioides*, *Histoplasma*, *Blastomyces*; parasites (*Entamoeba histolytica*, *Paragonimus westermani*, *Strongyloides*)
Miscellaneous	*S. aureus* post-influenza/viral infection; *Actinomyces*

- Primary abscesses are typically **polymicrobial**; with optimal anaerobic technique, isolate recovery is reported as high as **78%**.

Pathogenesis

- **Primary abscess:** aspirated **anaerobes/microaerophilic streptococci** from the gingival crevices reach the parenchyma in a host with a large aspirated burden or poor clearance → **pneumonitis** (aggravated by gastric-acid injury) → over **7–14 days** the bacteria produce **parenchymal necrosis and cavitation**. Anaerobes act **synergistically** in polymicrobial infection to amplify tissue destruction.
- **Secondary abscess:** a **bronchial obstruction** (tumour, foreign body) blocks clearance of secretions distally; or **impaired host defence** allows opportunists to cavitate.
- **Septic embolic abscess:** seeding from **right-sided (tricuspid) endocarditis** (*S. aureus*), or **Lemierre's syndrome** — oropharyngeal *F. necrophorum* infection spreads to the **carotid sheath** → **septic thrombophlebitis of the internal jugular vein** with showering of septic pulmonary emboli.
- **Location reflects gravity:** the **dependent segments — posterior segments of the upper lobes and superior segments of the lower lobes** — are most affected; the **right lung > left** because the **right main bronchus is wider, shorter and less angulated**.

Clinical Features

- **Anaerobic (typical primary) abscess — indolent, subacute**: low-grade fever, cough, sputum over weeks, with **night sweats, fatigue, weight loss and anaemia**; a subset expectorate **foul-tasting / foul-smelling (putrid) sputum**, occasionally pleuritic pain or haemoptysis.

- **Non-anaerobic (e.g., *S. aureus*, *Klebsiella*) abscess** — more **fulminant** course with high fever and rapid progression.
- **Examination:** fever, **poor dentition / gingival disease**, **amphoric or cavernous breath sounds**, **digital clubbing** (chronic), an **absent gag reflex**; crackles, egophony or dullness if an effusion coexists.

Investigations and Diagnosis

- **Imaging is the cornerstone.**
  - **Chest radiograph — thick-walled cavity with an air–fluid level** and surrounding consolidation in a dependent segment.
  - **CT chest** — superior definition, detects cavitation early, **distinguishes a peripheral abscess from empyema** (a treatment-critical distinction), and screens for an **underlying obstructing lesion/malignancy**.

Feature	Lung abscess	Empyema	Malignant cavity	Septic emboli
Shape	Round (equal in all views)	Oblong/lenticular	Variable, often nodular	Multiple nodules 1–3 cm
Inner wall	Ragged/"shaggy", irregular	Smooth lining	Nodular, thick (**≥16 mm**)	Cavities at differing stages
Effect on lung	Destroys parenchyma; no compression	**Compresses** adjacent lung	—	Subpleural wedge infarcts
Air–fluid level	Present	May split pleura	Variable	—

- **Microbiology:** expectorated **sputum Gram stain + aerobic, mycobacterial and fungal culture** (anaerobic cultures often falsely negative unless rapidly transported/plated). **Thoracentesis** if effusion present (uncontaminated specimen + excludes empyema). **Blood cultures + echocardiography** when septic emboli/endocarditis suspected. **Molecular methods** (e.g., **16S rRNA gene amplification**) may improve pathogen identification.
- **Bronchoscopy** — performed **early** when **bronchial obstruction (tumour/foreign body)** is suspected, in non-responders, and in immunocompromised hosts (BAL for opportunists); also therapeutic. Risk: spillage of pus into the contralateral lung.
- **CT-guided transthoracic needle aspiration** — clean culture specimen, considered early for abscesses **>4 cm**; risks pneumothorax and bronchopleural fistula.
- **Endemic/HIV settings:** examine **induced sputum for TB** early. **ANCA** if a vasculitis (granulomatosis with polyangiitis) is suspected.

Treatment

- **Empirical antibiotics must cover anaerobes AND microaerophilic streptococci:**
  - **Clindamycin** 600 mg IV TID → 300 mg PO QID — **superior to penicillin** in trials (oral anaerobes elaborate **β-lactamase**); or

- A **β-lactam/β-lactamase inhibitor** (ampicillin-sulbactam, piperacillin-tazobactam) IV → oral **amoxicillin-clavulanate** on stabilisation; or a **carbapenem**.
- **Metronidazole alone fails** — it misses the microaerophilic streptococci of the mixed flora. **Meropenem monotherapy** also lacks reliable streptococcal cover. **Moxifloxacin 400 mg/day PO** is as effective as ampicillin-sulbactam in small trials. CMDT second-line: **3rd-generation cephalosporin + metronidazole**, or a fluoroquinolone.
- **Targeted cover for monomicrobial isolates:** MSSA — cefazolin/nafcillin/oxacillin; **MRSA — linezolid** (alternative vancomycin; **avoid daptomycin** — inactivated by surfactant/poor lung penetration).

- **Duration:** prolonged — commonly **4–6 weeks**, ranging up to **14 weeks**; continue **until the cavity has cleared or regressed to a small stable scar** on imaging (≥6 weeks linked to better outcomes).
- **Response:** clinical improvement by **3–4 days**, defervescence by **7–10 days**. **10–20% fail to respond**; an abscess **>6–8 cm** is less likely to respond to antibiotics alone.
- **Drainage / surgery (~10% of cases):** indicated for failure of medical therapy, **massive/life-threatening haemoptysis**, bronchopleural fistula, empyema, **large cavity (>6 cm)**, or an obstructed bronchus.
  - **Percutaneous (CT/US-guided) catheter drainage** — for abscess **>4 cm**, peripheral, or poorly draining lesions, and in poor surgical candidates; place the **affected lung dependent** to limit spillage. Risks: pneumothorax, haemothorax, pleural seeding/empyema.
  - **Endoscopic (bronchoscopic pigtail) drainage** — for **central** lesions or coagulopathy.
  - **Surgical resection — lobectomy preferred** to segmentectomy (avoids residual necrotic tissue/re-infection); **VATS** for peripheral lesions; a **double-lumen endotracheal tube** protects the contralateral lung.
- **Relieve the obstruction** and treat the predisposing condition in secondary abscess.

Complications and Prognosis

- **Complications: massive/life-threatening haemoptysis** (from hypertrophied **bronchial arteries**), **empyema** and **bronchopleural fistula**, **pneumatoceles**, **bronchiectasis**, mediastinitis, recurrence, massive aspiration of cavity contents, and **metastatic infection — brain abscess / stroke** (clots bypass the pulmonary filter; brain-abscess risk markedly raised, adjusted OR ≈ 8.2).
- **Prognosis:** mortality of **primary** abscess is **as low as 2%** (overall 15–20% historically); **secondary** abscess mortality reaches **~75%**. **Poor prognostic markers:** age **>60 years**, malignancy-related abscess, aerobic organisms, **sepsis at presentation**, symptom duration **>8 weeks**, and **abscess size >6 cm**.
- **Prevention:** airway protection, **oral hygiene/dental care**, minimised sedation with **head-of-bed elevation** in aspiration-prone patients, and pathogen-specific prophylaxis in selected immunocompromised hosts.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled chest CT / radiograph of a lung abscess:** cavity wall, **air–fluid level**, surrounding consolidation/ground-glass opacity, ragged inner lining, dependent location (posterior segment right upper lobe). Labels: *Cavity*, *Air–fluid level*, *Thick irregular wall*, *Surrounding consolidation*, *Right upper lobe (posterior segment)*.
- **Pathogenesis flow diagram:** *Aspiration of gingival anaerobes → Pneumonitis (7–14 days) → Parenchymal necrosis → Cavitation with air–fluid level → Complications (empyema, haemoptysis, brain abscess)*.

Clinical / Diagnostic significance

- **Distinguishing abscess from empyema on CT is treatment-defining** — a tube thoracostomy placed inadvertently into an abscess can create a **bronchopleural fistula**; empyema mandates drainage.
- **A lung abscess in an edentulous patient, or one failing therapy, demands bronchoscopy to exclude an obstructing carcinoma or foreign body.**
- **Putrid sputum** at the bedside is essentially pathognomonic of **anaerobic** infection and guides empirical therapy.
- **Multiple/peripheral cavities at different stages** point to **septic emboli** — look for tricuspid endocarditis or Lemierre's syndrome; obtain blood cultures and echocardiography.

High-yield exam pointers

- Cavity **>2 cm with air–fluid level**; **primary ~80%, chronic ~40%, nonspecific (culture-negative) ~40%.**
- **Right lung > left**; **posterior upper / superior lower** segments (dependent).
- **Anaerobes + microaerophilic streptococci → clindamycin (or β-lactam/β-lactamase inhibitor) preferred; penicillin/metronidazole monotherapy inadequate**.
- **Putrid sputum = anaerobic; edentulous abscess = suspect tumour.**
- **Lemierre's syndrome** = *Fusobacterium necrophorum*, internal-jugular septic thrombophlebitis.
- Antibiotics **4–6 weeks (up to ~14)**; treat **until radiographic resolution/scar**.
- **Surgery/drainage** if failure, **>6 cm**, massive haemoptysis, empyema, BPF, obstruction.
- Mortality: **primary ~2%, secondary up to ~75%**; poor signs — age >60, sepsis, aerobes, >8 weeks, >6 cm.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Lung Abscess" (definition, classification, Table 132-1 microbial causes, pathogenesis, Lemierre's syndrome, antibiotic regimens and durations, prognosis, prevention).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "Lung Abscess" (radiographic differentiation from empyema/malignancy/septic emboli, microbiology, targeted MSSA/MRSA therapy, percutaneous and endoscopic drainage, surgical indications, brain-abscess association).
- **CMDT 2026** — "Pulmonary Disorders / Anaerobic Pleuropulmonary Infection" (essentials of diagnosis, predisposing factors, empirical regimens, abscess-vs-empyema drainage caveat).

◆ ◆ ◆

Non-resolving pneumonia

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

Definition / Introduction — *Non-resolving (non-responding) pneumonia* describes a clinical scenario in which a patient treated empirically for pneumonia fails to show the **expected clinical and/or radiographic improvement** within the anticipated time-frame. Two overlapping patterns are recognised: **non-responding pneumonia** (clinical improvement is not achieved — persistent fever and symptoms despite therapy) and **progressive pneumonia** (clinical deterioration to respiratory failure or septic shock). Radiographically, the term also covers *slowly resolving pneumonia*, where infiltrates persist beyond the expected resolution period despite adequate antibiotics. It is best regarded not as a single disease but as a **clinical syndrome** mandating a systematic search for resistant organisms, sequestered infection, an unexpected pathogen, or a non-infectious mimic.

Defining the problem — timelines and patterns

- **Expected normal response (CAP):** with appropriate antibiotics a clinical response is usually evident within **24–48 h** (pneumococcus, *Legionella*); fever and leukocytosis settle in **2–4 days** in otherwise healthy patients; physical signs persist longer.
- **Radiographic clearance is the slowest variable — 4–12 weeks**, and is slower in the elderly, in underlying lung disease, and with certain pathogens (e.g. *Legionella* infiltrates may progress despite clinical improvement and take months to clear).
- A widely used working definition of *non-resolving pneumonia* is **failure of the infiltrate to clear by ≥50% at 2 weeks or to clear completely by 4 weeks** despite ≥10 days of antibiotics (standard internal medicine; the corpus supports the 4–12-week clearance window).
- **Timing of reassessment:** evaluate the slow responder at **~72 h (day 3)** — or sooner if deteriorating. Earlier escalation is reserved for severe clinical deterioration or dramatic radiologic progression.

Pattern	Defining feature	Typical timing
Early treatment failure	Progressive deterioration / no response	< 72 h of therapy
Non-responding pneumonia	Persistent fever and symptoms, no improvement	Assessed at ≥ 72 h
Progressive pneumonia	Clinical deterioration → respiratory failure / septic shock	Any time
Slowly resolving pneumonia	Clinical improvement but infiltrate persists	Beyond 4–12 weeks

Causes / differential diagnosis (the core of the answer)

Causes are classified as **infectious, non-infectious, and of unknown origin**. In hospitalised CAP a specific infection is found in ~**40%** of non-responders, a non-infectious cause in ~**22%**, and **no cause is identified in ~30%** despite adequate treatment.

Category	Mechanism	Examples
Resistant / wrong-spectrum organism	Pathogen not covered or resistant to empirical drug	Drug-resistant *S. pneumoniae*; **MRSA / CA-MRSA**; *P. aeruginosa* (~10% of non-responding CAP, not covered unless a fluoroquinolone used); *Acinetobacter*; carbapenemase-producing *Klebsiella*
Unexpected / unusual pathogen	Outside the CAP empirical spectrum	*M. tuberculosis*, *Nocardia*, endemic fungi, *Pneumocystis jirovecii*, anaerobes, protozoa, viruses
Sequestered / complicated focus	Antibiotic cannot reach organism	**Empyema / complicated parapneumonic effusion**, **lung abscess**, necrotizing pneumonia
Metastatic / extrapulmonary infection	Seeding (commoner if bacteraemic)	Endocarditis, brain abscess, septic arthritis, pericarditis, meningitis; nosocomial superinfection
Inadequate therapy	Right diagnosis, wrong execution	Wrong drug, wrong dose/frequency, poor absorption/compliance
Host factors	Impaired response	Immunodeficiency (HIV), age, comorbidity, exaggerated or blunted inflammatory response
Non-infectious mimics	Disease that simulates pneumonia	Pulmonary **embolism/infarction**, pulmonary **oedema**, **malignancy** (esp. lepidic/"alveolar-cell" adenocarcinoma), bronchial obstruction, **organizing pneumonia (COP/BOOP)**, eosinophilic pneumonia, hypersensitivity pneumonitis, drug-induced lung disease, pulmonary **haemorrhage/vasculitis** (e.g. granulomatosis with polyangiitis), sarcoidosis, radiation pneumonitis, connective-tissue disease, ARDS

The most frequent organisms in proven infectious non-response are ***S. pneumoniae*, *Legionella*, *P. aeruginosa*** **and** ***S. aureus*.**

Stepwise approach to evaluation

- **Re-take history and examine again** — epidemiologic clues (travel, occupational/animal exposure, TB contact, aspiration risk, immunosuppression, drug history) and reconsider the *original* diagnosis.
- **Biomarkers:** failure of **procalcitonin (PCT)** to fall after 3–4 days suggests inadequate response; high baseline PCT/CRP (and IL-6) independently predict poor response.
- **Repeat & extend microbiology:** new blood and sputum cultures; urinary antigens (pneumococcus, *Legionella*); respiratory-virus and SARS-CoV-2 testing; sputum AFB/molecular TB testing early in endemic settings or HIV.
- **Cross-sectional imaging — chest CT** is pivotal: detects empyema, abscess, cavitation, endobronchial obstruction, lymphadenopathy, and patterns suggesting a specific aetiology —
  - *halo sign* (nodule + ground-glass rim) → **invasive aspergillosis / mucormycosis**;
  - diffuse ground-glass → **PJP**;
  - nodules/masses ± cavitation → **Nocardia, TB, Q fever**;
  - consider **CT-pulmonary angiography** to exclude pulmonary embolism and endobronchial lesions.
- **Bronchoscopy** with **BAL + protected specimen brush** (sensitivity ~40% in non-responding CAP) for culture, DFA and nucleic-acid testing; allows direct airway inspection for **obstruction (tumour, foreign body)** and **transbronchial / endobronchial biopsy** when a non-infectious cause (malignancy, COP, vasculitis) is suspected.
- **Thoracentesis** for any significant pleural effusion — drainage is indicated if fluid **pH < 7.2, glucose < 2.2 mmol/L, LDH > 1000 U/L**, or organisms are seen/cultured (complicated effusion / empyema).
- **Escalate antibiotics** only after re-sampling — broaden to cover resistant pneumococcus, *P. aeruginosa*, MRSA and anaerobes as dictated by risk; add antifungal/anti-TB cover when the clinical scenario supports it; transfer to higher-level care if deteriorating.

Key complicating entities to exclude

- **Lung abscess** — necrosis/cavitation (dominant cavity >2 cm). **Primary (~80%)** from aspiration of anaerobes/microaerophilic streptococci, favouring **dependent segments (posterior segments of upper lobes, superior segments of lower lobes), right > left**; *putrid* (foul) sputum ≈ anaerobic. **Secondary** abscess implies post-obstructive (tumour, foreign body) or immunocompromise. Treat with **clindamycin** (600 mg IV tds → 300 mg PO qds) or a **β-lactam/β-lactamase inhibitor** for 3–4 up to ~14 weeks; *metronidazole alone is inadequate*. Cavities **>6–8 cm**, or non-response, may need drainage/surgery.
- **Pulmonary tuberculosis** — a classic "great mimic" of non-resolving consolidation; obtain sputum AFB, NAAT (e.g. cartridge-based) and culture early, especially with weight loss, upper-lobe disease, cavitation or HIV.
- **Bronchogenic carcinoma / post-obstructive pneumonia** — suspect strongly with **recurrence in the same segment**, in smokers, or non-clearing infiltrate; bronchoscopy ± CT mandatory.

- **Lemierre's syndrome** — *Fusobacterium necrophorum* oropharyngeal infection with septic jugular thrombophlebitis and cavitating septic emboli.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Algorithm — "Approach to the non-resolving pneumonia"** (vertical flowchart). Labels: *Empirical Rx for pneumonia* → *Reassess at 72 h (day 3)* → branch into **Non-responding** vs **Progressive** → *Re-history & examine + reconsider diagnosis* → *Repeat cultures, PCT/CRP, urinary antigens, TB/viral tests* → *Chest CT* → *Bronchoscopy (BAL + PSB ± biopsy) / Thoracentesis* → outcome boxes: **Resistant/unexpected organism**, **Empyema/abscess (drain)**, **Non-infectious mimic (PE, malignancy, COP, vasculitis)**, **Inadequate therapy**.
- **Labelled chest CT of a lung abscess:** thick-walled cavity, **air–fluid level**, surrounding consolidation, located in a dependent (posterior upper / superior lower lobe) segment — with a small inset contrasting **abscess vs empyema** (lenticular pleural collection, split-pleura sign).

Clinical / Diagnostic significance

- Re-labelling a "treatment failure" correctly prevents both **antibiotic over-escalation** and **missed malignancy/TB/PE** — the commonest avoidable errors.
- **Empyema and abscess** are the most frequent infectious complications requiring a *procedure*, not just a drug change — always image the pleura and tap significant effusions.
- A **follow-up chest radiograph at ~4–6 weeks** is recommended after hospitalised CAP; **relapse or recurrence in the same bronchopulmonary segment** demands exclusion of an underlying **neoplasm or focal bronchiectasis**.
- Older patients and those with COPD, diabetes, alcoholism, multilobar disease or bacteraemia resolve more slowly — a *slowly resolving* course in this group may still be benign and need only observation with serial imaging rather than invasive work-up.

High-yield exam pointers

- **Reassess the non-responder at 72 h (day 3)**; wait that long unless rapidly deteriorating.
- Causes = **infectious (40%) / non-infectious (22%) / unknown (≈30%)**.
- Commonest infectious culprits: **pneumococcus, *Legionella*, *P. aeruginosa*, *S. aureus***; *P. aeruginosa* ≈ **10%** of non-responders.
- Must-exclude non-infectious mimics: **PE, malignancy, organizing pneumonia, eosinophilic pneumonia, vasculitis, pulmonary oedema**.
- **CT chest + bronchoscopy (BAL/PSB)** are the key escalation investigations; BAL sensitivity ~40%.
- Drain a parapneumonic effusion if **pH < 7.2, glucose < 2.2 mmol/L, LDH > 1000 U/L** or organisms present.
- **Lung abscess:** anaerobic, dependent segments, right > left; **clindamycin** first-line, **metronidazole alone fails**; cavity **>6–8 cm** → consider drainage/surgery.
- **Recurrence in the same segment → think carcinoma / focal bronchiectasis.** TB and HIV must be actively excluded.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Pneumonia"* (Failure to Improve, Complications, Follow-up) and *"Lung Abscess."*
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — *"Community-Acquired Pneumonia"* (Nonresponding Pneumonia / Treatment Failure; infectious vs non-infectious causes; diagnostic evaluation, biomarkers, imaging and bronchoscopy).
- **CMDT 2026** — *"Pulmonary Disorders"* (Pneumonia; Anaerobic Pneumonia & Lung Abscess — drainage and surgical indications).

Coverage note: The corpus richly covers the syndrome, its causes, evaluation and the abscess/empyema complications. The quantitative radiographic criterion ("<50% clearance at 2 weeks / clearance by 4 weeks") is stated as standard internal medicine; the corpus directly supports the 4–12-week clearance window and the ≥72-h reassessment point rather than that exact percentage cut-off.

◆ ◆ ◆

Obesity and obstructive sleep apnoea

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

Definition / Introduction — **Obesity** is a chronic, heterogeneous disorder of excess body fat conventionally graded by **body mass index (BMI = weight kg / height m^2)**, leading to multiple metabolic, mechanical and cardiovascular complications. **Obstructive sleep apnoea (OSA)** is a sleep-related breathing disorder defined by recurrent episodes of pharyngeal collapse during sleep causing apnoeas/hypopnoeas, intermittent hypoxaemia and arousals, with daytime sleepiness and impaired function. The two are tightly linked: obesity is the single most important modifiable risk factor for OSA, and OSA in turn amplifies obesity's cardio-metabolic harm — hence they are best understood and answered together.

Classification of obesity (WHO / BMI) and abdominal adiposity

- BMI correlates with body fat and disease risk and is the standard screening/population tool; its limitation is that it measures **size, not composition or fat distribution**. Lower thresholds apply to the **Asia-Pacific (South Asian)** population, who are metabolically at risk at lower weights.

Classification	BMI (kg/m^2)	Obesity class	Disease risk
Underweight	<18.5	—	—
Healthy weight	18.5–24.9	—	—
Overweight	25.0–29.9	—	Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme obesity	≥40	III	Extremely high

- **Waist circumference** (surrogate for visceral fat, measured horizontally above the iliac crest in those with BMI ≤35) independently predicts metabolic syndrome, diabetes and CVD. Ethnic cut-points: **Europeans** men >94 cm / women >80 cm; **South Asians & Chinese** men >90 cm / women >80 cm.
- **Functional/clinical staging:** the **AACE/ACE** system stages by BMI *plus* adiposity-related complications — Stage 0 (no complication), Stage 1 (mild–moderate complication, e.g. *OSA with AHI 5–30 and mild symptoms*), Stage 2 (severe complication, e.g. *OSA with symptoms or AHI >30*). The **Edmonton Obesity Staging System (EOSS)** grades 0–4 across medical, functional and psychological domains independent of BMI.

Obesity → OSA: pathophysiological link

- During inspiration intraluminal pharyngeal pressure becomes negative (a "suction" force); because the pharynx has **no bony/cartilaginous support**, patency depends on **pharyngeal dilator muscle** tone, which falls at sleep onset — producing transient collapse (**apnoea**) or near-collapse (**hypopnoea**).
- **Obesity narrows and collapses the airway by several mechanisms:** (1) deposition of upper-airway/parapharyngeal **fat** narrowing the pharyngeal lumen; (2) reduced **chest-wall compliance** and lower **lung volumes**, causing loss of caudal tracheal traction on the pharynx (worst when supine and obese); (3) **android (central) obesity** depositing abdominal and upper-airway fat.
- Quantitatively: **≈40–60% of OSA is attributable to excess weight**; obese individuals carry a **fourfold or greater risk** of OSA; a **10% weight gain raises the AHI by >30%**, and weight loss (notably after bariatric surgery) can markedly reduce severity.
- Collapse sites: **soft palate (most common)**, tongue base, lateral pharyngeal walls and/or epiglottis. Contributory factors include high **nasal resistance**, **retrognathia/micrognathia**, an unstable ventilatory control loop (high CO_2 sensitivity), and a low or high **arousal threshold**.
- Other (non-obesity) risk factors: **male sex** (twofold higher prevalence), **older age**, post-**menopause**, family history, adenotonsillar hypertrophy (children), and endocrine disease (**acromegaly, hypothyroidism**).

Definition, severity grading and clinical features of OSA

- **Diagnosis** requires either (1) symptoms of nocturnal breathing disturbance (snoring, snorting, gasping, witnessed pauses) impairing quality of life, OR unexplained daytime sleepiness/fatigue — **plus ≥5 obstructive events/hour** on a sleep study; OR (2) an **AHI ≥15/h even without symptoms**.
- Each event is a ≥10 s reduction in breathing: **Apnea** = cessation of airflow ≥10 s; **Hypopnoea** = ≥30% airflow reduction ≥10 s with a ≥3% desaturation or arousal; **RERA** = increased respiratory effort terminated by arousal without meeting hypopnoea criteria.

Severity (AHI = apnoeas + hypopnoeas per hour of sleep)	Grade
5–14 events/h	Mild OSAHS
15–29 events/h	Moderate OSAHS

Severity (AHI = apnoeas + hypopnoeas per hour of sleep)	Grade
≥30 events/h	Severe OSAHS

- **Symptoms:** loud habitual **snoring** (commonest; its absence does not exclude OSA), gasping/choking arousals, **excessive daytime sleepiness** (men) or **fatigue** (women preferentially), unrefreshing sleep, nocturia, morning headache, dry mouth, poor concentration, irritability and mood disturbance.
- **Signs:** central (visceral) obesity with large **neck and waist circumference**, hypertension, crowded oropharynx (enlarged tongue, low bulky soft palate/uvula, large tonsils, high-arched palate), retro-/micrognathia, nasal obstruction. *Cor pulmonale suggests a coexisting cardiopulmonary disorder — OSA alone does not cause right-heart failure.*

Diagnosis and investigations

- **In-laboratory polysomnography (PSG)** is the **gold standard**; a negative in-lab PSG usually rules out OSA. **Home sleep apnoea testing** (respiratory + cardiac channels) is a cost-effective alternative, but a negative home study with high pretest probability should be followed by PSG.
- Screening questionnaires (e.g. **STOP-Bang**) evaluating snoring, observed apnoeas and sleepiness aid case-finding, enhanced by considering male sex, obesity and hypertension.
- Supportive findings: **"non-dipping"** overnight blood-pressure pattern; secondary erythrocytosis (elevated haemoglobin) with severe nocturnal hypoxaemia; waking hypoxaemia/hypercarbia points to coexisting cardiopulmonary disease or **hypoventilation syndrome**. A **multiple sleep latency test / maintenance of wakefulness test** quantifies sleepiness and helps separate OSA from narcolepsy.
- In obesity, baseline work-up: **fasting lipid profile, fasting glucose/HbA1c, chemistry panel, blood pressure**, and screening for secondary causes (hypothyroidism, Cushing's, PCOS, hypothalamic disease) and obesogenic drugs.

Health consequences and comorbidities (overlapping burden)

- **Cardiovascular/metabolic (OSA):** resistant and nocturnal **hypertension** (sympathetic + RAAS activation, non-dipping), coronary artery disease, **heart failure** (HFrEF and HFpEF), **atrial and ventricular arrhythmias / AF**, stroke, type 2 diabetes/insulin resistance, premature death and increased cancer risk. CPAP lowers 24-h ambulatory BP modestly (**~2–4 mmHg**, greater if high AHI, sleepy or resistant hypertension).
- **Obesity complications** (shared): type 2 diabetes, dyslipidaemia, metabolic syndrome, hypertension, HFpEF/diastolic dysfunction, AF, **MASLD/NASH→cirrhosis**, GERD, gallstones, **PCOS** and male central **hypogonadism**, osteoarthritis and gout, obesity-related glomerulopathy, **obstructive sleep apnoea and obesity-hypoventilation (Pickwickian) syndrome**, idiopathic intracranial hypertension, and several cancers (a 5 kg/m^2 rise in BMI raises cancer mortality ~10%).
- **Functional:** OSA causes a two-fold rise in occupational accidents and a two- to three-fold rise in motor-vehicle crashes — counsel against **drowsy driving**.

Management

- **Weight loss is the unifying first-line intervention** — even modest loss reduces AHI and metabolic risk; OSA may improve substantially after bariatric surgery.
- **Obesity — lifestyle:** caloric deficit **500–750 kcal/d** (≈1200–1500 kcal/d women, 1500–1800 kcal/d men) for ~1–2 lb/week; realistic target **8–10% loss over 6 months**; **≥150 min/week moderate (or 75 min vigorous)** aerobic activity (>300 min to sustain loss); plus behavioural therapy (self-monitoring, stimulus control, cognitive restructuring).
- **Obesity — pharmacotherapy** (BMI ≥30, or ≥27 with comorbidity). Placebo-subtracted 1-year weight loss:

Drug	Mechanism	Weight loss (placebo-subtracted)
Orlistat 120 mg tid	GI lipase inhibitor (blocks ~30% dietary fat absorption)	~4.4%
Phentermine/topiramate	Sympathomimetic + GABA modulation	~8.0%
Naltrexone SR/bupropion SR	Opioid antagonist + DA/NE reuptake inhibitor (POMC activation)	~5.1%
Liraglutide 3.0 mg SC daily	GLP-1 receptor agonist	~5.4%
Semaglutide 2.4 mg SC weekly	GLP-1 receptor agonist (2nd-generation)	~12.5%
Tirzepatide up to 15 mg SC weekly	Dual GLP-1/GIP receptor agonist	~17.8%

- *GLP-1/dual agonists are contraindicated with personal/family history of medullary thyroid cancer or MEN-2; semaglutide also reduced major adverse cardiovascular events by 20% (SELECT) and improved HFpEF symptoms (STEP-HFpEF).*
- **Bariatric surgery:** for **BMI ≥40**, or **≥35 with comorbidities**. Procedures — restrictive (adjustable gastric banding, **sleeve gastrectomy**) and restrictive-malabsorptive (**Roux-en-Y gastric bypass**, biliopancreatic diversion ± duodenal switch); bypass yields ~28–33% total body-weight loss and reduces overall mortality (OR 0.55) and cardiovascular death (OR 0.58), with marked improvement in OSA and type 2 diabetes.
- **OSA-specific therapy:**
  - **General/behavioural:** weight loss, optimise sleep (7–9 h) and schedule, avoid the **supine position**, treat nasal allergy, eliminate **alcohol within 3 h of bedtime**, minimise **opioids/sedatives**.
  - **CPAP** — *the standard therapy with the highest level of evidence*; a pneumatic splint maintaining airway patency; auto-titrating (APAP) devices avoid titration studies; adherence ~50–80% and is the key determinant of benefit (improves sleepiness, mood, quality of life, BP, insulin sensitivity). Side-effects (nasal congestion, claustrophobia, aerophagia) are managed by humidification, mask change and pressure adjustment.
  - **Oral appliances** (**mandibular advancement devices**) — reduce AHI by ≥50% in two-thirds; best for mild–moderate OSA or CPAP intolerance (caution: TMJ pain, tooth movement).

- **Surgery — uvulopalatopharyngoplasty (UPPP)** (commonest, limited as a standalone procedure, often "multilevel"), and **bariatric surgery** for obese patients; less efficacious than CPAP.
- **Upper-airway (hypoglossal nerve) neurostimulation** — for CPAP failure; inclusion AHI 15–65 and **BMI <35**.
- **Positional therapy**, and **GLP-1 agonists/weight-loss drugs** under active investigation (liraglutide shows small AHI effect; tirzepatide in trials). **No FDA-approved drug for OSA currently.**

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Sagittal upper-airway diagram (OSA collapse sites):** label **Soft palate (most common site)**, **Uvula**, **Tongue base**, **Lateral pharyngeal walls**, **Epiglottis**, **Pharyngeal dilator muscle**, **Nasal passage (resistance)** — show collapse during sleep.
- **Polysomnography apnoea tracing:** label channels **Nasal/thermistor airflow (flat = apnoea)**, **Chest** and **Abdomen** effort showing **paradoxical (out-of-phase) movement**, **SaO_2 desaturation**, **EEG arousal**, with a bracket marking ≥10 s event.

Clinical / Diagnostic significance

- Suspect and screen OSA in every obese patient with snoring, daytime sleepiness, hypertension (especially resistant/non-dipping), type 2 diabetes, AF or stroke — a large fraction of OSA remains undiagnosed.
- AHI defines and grades disease; PSG is confirmatory; STOP-Bang stratifies pretest probability.
- Weight loss is disease-modifying for both conditions; CPAP plus weight reduction is the cornerstone of moderate–severe OSA.
- Pre-operative recognition matters: obese OSA patients are at higher peri-operative and sedation-related risk.

High-yield exam pointers

- **AHI** = apnoeas + hypopnoeas per hour; **Mild 5–14, Moderate 15–29, Severe ≥30**.
- Diagnose OSA at **AHI ≥5 with symptoms** or **AHI ≥15 without symptoms**.
- **40–60%** of OSA is due to excess weight; obese persons have **≥4×** risk; **10% weight gain → >30% rise in AHI**.
- **Soft palate** is the commonest collapse site; **PSG** is the gold-standard test.
- **CPAP** = highest-evidence therapy; lowers ambulatory BP by **~2–4 mmHg**; adherence ~50–80%.
- Obesity classes: **I 30–34.9, II 35–39.9, III (extreme) ≥40**; South Asian waist cut-offs **men >90 / women >80 cm**.
- **Bariatric surgery:** BMI **≥40**, or **≥35 with comorbidity**; reduces all-cause mortality (OR 0.70).
- Weight-loss drug efficacy ranking: **tirzepatide (≈18%) > semaglutide (≈12.5%) > Phen/TPM (≈8%) > liraglutide/Nal-Bup ≈ orlistat**.
- OSA independently increases hypertension, AF, HF, stroke, diabetes and motor-vehicle crash risk.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 308 "Sleep Apnea" (Wellman, Gottlieb, Redline) and Ch 414 "Evaluation and Management of Obesity" (Kushner). Coverage note: STOP-Bang and the Epworth Sleepiness Scale, and the obesity-hypoventilation/Pickwickian and "non-dipping BP" terms, are standard textbook internal medicine — STOP-Bang and non-dipping pattern are referenced in Ch 308; the Epworth scale itself is not named in the provided text but is universally accepted. Drug doses/efficacy and bariatric data are taken verbatim from Ch 414 Table 414-5 and text.

◆ ◆ ◆

Obesity hypoventilation syndrome

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

Definition / Introduction — Obesity hypoventilation syndrome (**OHS**), historically the *Pickwickian syndrome*, is defined by the triad of (1) **obesity** (body mass index, BMI **≥30 kg/m²**), (2) **chronic daytime alveolar hypoventilation** — awake arterial $PaCO_2$ **≥45 mmHg** at sea level — and (3) **sleep-disordered breathing**, *after exclusion of other causes of hypercapnia* (severe COPD, restrictive chest-wall/neuromuscular disease, hypothyroidism, drug-induced hypoventilation). It is therefore a **diagnosis of exclusion** in an obese hypercapnic patient. In the normal lung $PaCO_2$ is held between **37–43 mmHg**; OHS represents a failure of alveolar ventilation to keep pace with CO_2 production despite an *intrinsically normal lung*.

Epidemiology and risk factors

- No population-based prevalence study exists, but estimates suggest OHS affects up to **~0.4% of US adults (≈1 in 263)**, and the burden is rising in parallel with the global obesity epidemic.
- **Obstructive sleep apnoea (OSA) coexists in ~90%** of OHS patients, and close to **70% have severe OSA** (apnoea–hypopnoea index, AHI >30/h). A minority (~10%) hypoventilate *without* significant OSA (pure "sleep hypoventilation" phenotype).
- Recognised risk factors: **severe obesity (BMI >40 kg/m²)** and **severe OSA (AHI >30/h)**; greater waist/neck circumference; the syndrome is frequently *under-recognised* and often first diagnosed during an episode of acute-on-chronic hypercapnic respiratory failure.

Pathophysiology — a multifactorial "load–drive" imbalance

OHS arises when the **mechanical load** on the respiratory pump outstrips both **respiratory muscle capacity** and a **blunted central drive**. Three interacting mechanisms operate:

Domain	Derangement in OHS
Excess mechanical load	Mass loading of chest wall and abdomen ↓ respiratory-system compliance; **FRC reset to a lower, stiffer part of the volume–pressure curve**; ↑ airway resistance and **expiratory flow limitation** (worse supine). **Work of breathing up to ~250% of normal** (vs ~60% in simple obesity); **oxygen cost of breathing rises ~10-fold** (vs 5-fold in simple obesity).

Domain	Derangement in OHS
Blunted central drive	Unlike *eucapnic* obesity (where drive is normal/increased to overcome the load), in OHS the **ventilatory and occlusion-pressure (P0.1) responses to hypoxia and hypercapnia are reduced**. Drive is *not* genetically low (responses are normal in first-degree relatives) — chemoreceptors appear "**reset**" by chronic hypercapnia/hypoxaemia and by **leptin resistance**.
Leptin / neurohumoral	Leptin (an adipocyte hormone) normally stimulates ventilation; serum leptin is *high* in obesity, so **central leptin resistance** is proposed as a key contributor to the diminished ventilatory responsiveness and CO_2 retention.

- **Rapid, shallow breathing pattern** (higher frequency, lower tidal volume than simple obesity) minimises elastic work but **increases dead-space fraction**, worsening alveolar hypoventilation and CO_2 retention.
- **Gas exchange:** hypoventilation alone causes hypoxaemia with a *normal* A–a gradient; superimposed **V/Q mismatch and shunt from premature airway closure** widen the A–a gradient and deepen hypoxaemia, which is **worse supine**.
- **Renal compensation:** chronic respiratory acidosis drives **bicarbonate retention** (metabolic compensation) — an elevated serum HCO_3^- is the bedside footprint of chronic hypoventilation.
- *Reversibility:* central drive defects **improve once sleep-disordered breathing is treated** (CPAP/NIV) or weight is lost — confirming that blunted responsiveness is a **consequence, not the primary cause**, of OHS.

Clinical features

- **Sleep-related:** loud habitual snoring, witnessed apnoeas, **excessive daytime somnolence**, poor-quality unrefreshing sleep, **early-morning headaches** (from nocturnal CO_2 retention).
- **Cardiorespiratory:** exertional **dyspnoea**, orthopnoea, fatigue; signs of **cor pulmonale** — raised JVP, peripheral oedema, loud P_2 (chronic hypoxaemia/hypercapnia → pulmonary vasoconstriction → **pulmonary hypertension and right heart failure**).
- **Examination:** central obesity, plethora/**cyanosis**, possible secondary erythrocytosis (polycythaemia from chronic hypoxaemia), features of metabolic syndrome.
- **Acute presentation:** decompensated **acute-on-chronic hypercapnic respiratory failure** with CO_2 narcosis (drowsiness, asterixis, papilloedema), often precipitated by sedatives, infection or an acute cardiac event.

Diagnosis and investigations

Diagnosis follows a stepwise evaluation of daytime hypercapnia (history/exam → PFTs + chest imaging → BMI → polysomnography), excluding parenchymal, chest-wall, neuromuscular and drive disorders first.

Test	Expected finding / role
Arterial blood gas (ABG)	**Diagnostic hallmark — $PaCO_2$ ≥45 mmHg with near-normal pH** (compensated chronic respiratory acidosis); hypoxaemia common. A *normal* pH distinguishes chronic from acute hypoventilation.

Test	Expected finding / role
Serum bicarbonate	**Sensitive screen:** HCO_3^- **<27 mmol/L makes OHS very unlikely**; HCO_3^- **≥27 mmol/L should trigger an ABG** to confirm hypercapnia.
Polysomnography (PSG)	Confirms and grades **OSA** (AHI) and detects **nocturnal hypoventilation**; essential as ~90% have OSA.
Pulmonary function tests	**Restrictive pattern** with reduced ERV/FRC, *normal* FEV_1/FVC; used to exclude obstructive/restrictive lung disease as the cause of hypercapnia.
CXR / CT, ECG, echocardiography	Exclude parenchymal disease; assess for RV hypertrophy / pulmonary hypertension / cor pulmonale.
TFTs, drug history	Exclude **hypothyroidism** and **sedative/opioid**-induced hypoventilation.
FBC	Secondary **erythrocytosis** supports chronic hypoxaemia.

- **Screening questionnaires** for OSA (Epworth Sleepiness Scale, *Berlin*, **STOP-Bang**) raise suspicion but are insufficiently specific — PSG remains the standard.
- *Distinguish from* **congenital central hypoventilation syndrome (Ondine's curse, PHOX2B mutation)** and primary alveolar hypoventilation, where the lungs and habitus are normal and drive is absent.

Management

Treatment targets *all* contributors — sleep-disordered breathing, the mechanical load (weight), and comorbidities.

Modality	Detail
Positive airway pressure (first line)	**CPAP** is first-line for OHS **with concomitant severe OSA** — it corrects upper-airway obstruction and improves daytime $PaCO_2/PaO_2$ in >half of patients. **RCT evidence (e.g. *Pickwick*/Masa, Lancet 2019)** shows **CPAP and NIV are broadly equivalent** for long-term $PaCO_2$, symptoms, cardiovascular and overall mortality in OHS + severe OSA.
Non-invasive ventilation / BiPAP	Preferred when **hypoventilation predominates** or there is **no significant OSA**, in **acute decompensated OHS**, and when **hypercapnia persists despite adherent CPAP** or obstructive events persist at maximum CPAP (20 cmH_2O). Use **BiPAP with a backup rate (ST mode)** or **volume-assured pressure support**; BiPAP-spontaneous (no backup) is reserved for CPAP-intolerant patients.
Weight reduction	**Substantial weight loss (≈20–25% of body weight) can normalise $PaCO_2$.** Diet, activity, behavioural therapy; **bariatric surgery** gives the most durable loss (indicated BMI ≥40, or ≥35 with serious comorbidity) and improves comorbidities. PaO_2 rises ~**1 mmHg per 5 kg** lost.
Supplemental oxygen	Use cautiously for persistent hypoxaemia/pulmonary hypertension — **may worsen hypercapnia** even at low flow; *not* a substitute for ventilatory support.
Avoid respiratory depressants	**Sedative-hypnotics, opioids and alcohol** are contraindicated/avoided.
Respiratory stimulants	**Medroxyprogesterone, acetazolamide** improve $PaCO_2/PaO_2$ but are **poorly evidenced, carry side-effects, and must not replace PAP or weight loss.**

Modality	Detail
Comorbidities / perioperative	Aggressively treat decompensating events (ACS, PE, pneumonia, heart failure). OHS patients have **high perioperative risk** (respiratory failure, re-intubation, heart failure) — recognition is a key safety measure.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Load vs Strength" balance diagram (Harrison Fig 307-1B):** a beam/see-saw labelled — *Respiratory load* (chest-wall elastic load, **Obesity**, abdominal distension, lung resistive load) on one side **greater than** *Respiratory muscle strength + Respiratory drive*; arrow to "**Alveolar hypoventilation → ↑$PaCO_2$**". Add the three OHS contributors as input arrows: **OSA, blunted central drive (leptin resistance), increased work of breathing**.
- **Obesity volume–pressure curve (Murray Fig 131.13):** label axes **Volume (y)** vs **Pressure cmH_2O (x)**; show **CW, L, RS** curves; mark **FRC reset to a lower, less compliant point** and **TLC**, illustrating tidal breathing on the stiff portion of the curve.

Clinical / Diagnostic significance

- OHS confers **higher morbidity and mortality** than equally obese eucapnic patients — driven by pulmonary hypertension, cor pulmonale, cardiovascular disease and recurrent respiratory failure; effective PAP therapy reduces this.
- Always **measure an ABG in an obese, sleepy, hypercapnic-appearing patient** with a raised serum bicarbonate — OHS is frequently missed until a crisis.
- In acute decompensation, **NIV is the cornerstone**; intubate for failure, but plan early NIV weaning because these patients are difficult to extubate.
- **Treating OSA/hypoventilation can reverse the "blunted drive"** — demonstrating the syndrome's potential reversibility and the priority of CPAP/NIV plus weight loss.

High-yield exam pointers

- **Definition triad:** BMI ≥30 + awake $PaCO_2$ ≥45 mmHg + sleep-disordered breathing, **excluding other causes** = OHS (Pickwickian).
- **~90% have OSA, ~70% severe OSA;** severe obesity (BMI >40) and AHI >30/h are risk factors.
- **Serum HCO_3^- <27 mmol/L makes OHS unlikely; ≥27 mmol/L → do an ABG.**
- ABG shows **chronic compensated respiratory acidosis** (↑$PaCO_2$, near-normal pH, ↑HCO_3^-).
- Pathophysiology = **↑mechanical load + blunted central drive + leptin resistance + OSA**; work of breathing up to ~250% of normal.
- **CPAP first-line if severe OSA; NIV (BiPAP-ST/VAPS) if hypoventilation predominates, no OSA, or acute decompensation.** CPAP and NIV broadly equivalent (*Pickwick* trial).
- **Weight loss of 20–25% can normalise $PaCO_2$;** bariatric surgery most durable.
- **Oxygen can worsen hypercapnia;** avoid sedatives/opioids/alcohol; respiratory stimulants are adjuncts only.

- **Complications:** pulmonary hypertension, cor pulmonale, secondary polycythaemia, high perioperative risk.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of Ventilation" (Hypoventilation; Obesity Hypoventilation Syndrome; diagnostic algorithm Fig 307-2) and "Sleep Apnea."
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "The Respiratory System and Chest Wall Diseases" (obesity respiratory mechanics, work/oxygen cost of breathing, control of breathing, leptin, gas exchange, treatment).
- **CMDT 2026** — "Pulmonary Disorders: Obesity-Hypoventilation Syndrome (Pickwickian Syndrome)" — diagnostic criteria and current management.

◆ ◆ ◆

Pneumothorax

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

Definition / Introduction — Pneumothorax is the presence of air (gas) in the pleural space, with consequent partial or complete collapse of the underlying lung. The normal pleural space is a potential space holding only a thin film of fluid at a sub-atmospheric pressure of about **−3 to −5 cmH_2O**, generated by the balance between the inward elastic recoil of the lung and the outward recoil of the chest wall; entry of air abolishes this negative pressure and the lung recoils inward. It is classified by mechanism into **spontaneous** (primary or secondary), **traumatic**, and **iatrogenic**, with **tension pneumothorax** being a life-threatening physiological emergency in any category.

Classification

Type	Definition / Setting	Typical patient & common causes
Primary spontaneous (PSP)	Occurs *without* antecedent trauma and *without* clinically apparent lung disease	Tall, thin, young (<45 y), male, smoker; rupture of apical subpleural **blebs/bullae** + "pleural porosity"
Secondary spontaneous (SSP)	Spontaneous but on a background of known lung disease; BTS labels pneumothorax in patients >50 y or with significant smoking history as SSP	**COPD** (commonest in the West), **pulmonary TB** (commonest worldwide), cystic fibrosis, lung cancer, necrotizing pneumonia, *Pneumocystis jirovecii*, ILD (IPF, sarcoid), **LAM** and pulmonary **Langerhans cell histiocytosis**
Traumatic	Penetrating or blunt (non-penetrating) chest injury; air enters via chest-wall wound or visceral pleural laceration	Rib-fracture laceration, or alveolar rupture from sudden chest compression; often a **hemopneumothorax**
Iatrogenic	A subset of traumatic, from an invasive procedure	Transthoracic/CT-guided needle biopsy (leading cause), thoracentesis, subclavian/IJ central line, transbronchial biopsy, **barotrauma** of positive-pressure ventilation, CPR

Type	Definition / Setting	Typical patient & common causes
Tension	Pleural pressure positive throughout the respiratory cycle via a one-way (check) valve	Usually during **mechanical ventilation, resuscitation, or trauma**
Catamenial	Pneumothorax temporally linked to menstruation	Women of childbearing age; thoracic/diaphragmatic **endometriosis**

Pathogenesis

- **Blebs vs bullae (Miller 1947):** a **bleb** is an outpouching of the *visceral pleura* caused by air dissecting between the **lamina elastica interna and externa**, typically **<1 cm** diameter; a **bulla** is an air space **>1 cm** sharply demarcated by a thin wall (**≤1 mm**). *Reid (1967)* subdivided bullae into **type I** (narrow/pedunculated, no parenchyma), **type II** (broad/sessile), and **type III** (broad-based, extending to the hilum with minimal parenchyma).
- **PSP — "pleural porosity":** the historical view that bleb/bulla rupture creates an alveolar–pleural communication is challenged. *Noppen's* fluorescein-enhanced autofluorescence thoracoscopy showed air leakage from areas of **porosity** (disrupted mesothelium replaced by an inflammatory fibroelastic layer) rather than from the visible blebs themselves. PSP lungs are therefore **not truly "normal"** — they show distal airway inflammation (respiratory bronchiolitis), emphysema-like change and over-expression of **matrix metalloproteinases (MMP-2, MMP-9)**.
- **Familial / genetic causes (~10%):** *Marfan syndrome* (**FBN1** / fibrillin-1), *Birt-Hogg-Dubé syndrome* (**FLCN** / folliculin — skin fibrofolliculomas, lung cysts, renal cancer), *α_1-antitrypsin deficiency*, *homocystinuria*, *Ehlers-Danlos syndrome*. A strong family history warrants genetic referral and surveillance.
- **Tension physiology:** the visceral defect acts as a **one-way valve** — air enters on inspiration but cannot escape; rising intrapleural pressure progressively collapses the lung, shifts the mediastinum, and **reduces venous return**, lowering left-ventricular filling and cardiac output → obstructive shock.

Clinical features

- **Symptoms:** acute, usually unilateral, **pleuritic chest pain** and **dyspnoea** in nearly all; cough is common. Magnitude of symptoms correlates poorly with radiographic size.
- **Signs (affected hemithorax):** reduced movement/expansion, **hyperresonant (tympanitic) percussion**, **diminished breath sounds**, decreased tactile/vocal fremitus, and ipsilateral chest enlargement. Findings may be subtle in small pneumothoraces or against a background of emphysema.
- **Tension pneumothorax (emergency):** enlarged hemithorax with **no breath sounds**, **hyperresonance**, **tracheal/mediastinal shift to the contralateral side**, severe **tachycardia, hypotension, distended neck veins and cyanosis**. High peak inspiratory pressures (volume-cycled) or falling tidal volume (pressure-cycled) on a ventilator strongly suggest it. *Diagnosis is clinical — treatment must NOT await a chest X-ray.*

Investigations

- **Erect frontal CXR (first-line):** a **visceral pleural line** with absence of lung markings peripheral to it; the line has air on both sides, no vessels beyond it, and runs continuous and sharply demarcated — distinguishing it from a **skin-fold** (edge, lucent on one side only, vessels traceable across it).
- **Supine film (trauma/ICU):** look for the **deep sulcus sign** (abnormally deep, lucent costophrenic angle as air collects anteriorly).
- **Chest CT:** most accurate; clarifies size, detects **occult pneumothorax** (~40% of traumatic, seen on CT not CXR), distinguishes pneumothorax from **giant bullae** (avoids inadvertent intubation of a bulla and bronchopleural fistula), and screens for SSP causes (cystic lung disease/LAM).
- **Thoracic ultrasound:** absence of **lung sliding** and **B-lines** (with a "lung point") diagnoses pneumothorax with high sensitivity/specificity in the supine trauma patient; beware false positives over emphysematous bullae.
- **ABG/ECG:** ABG usually unnecessary but may show hypoxaemia and respiratory alkalosis; left-sided PSP can mimic **acute MI** with QRS-axis/precordial T-wave changes.
- **Size estimation (no global consensus): BTS** "large" = **>2 cm** interpleural distance at the level of the **hilum** (≈50% hemithorax volume by the *Light index*); **ACCP** "large" = **≥3 cm** from apex to cupola. Size guides—but does not dictate—the decision to intervene.

Management

- **General principle:** decide first *whether* intervention is needed (symptoms, size, underlying lung disease, ventilation status), then *how*.
- **PSP:** stable, small, minimally symptomatic patients → **observation** (many resolve as air is reabsorbed; the 2020 *Brown et al.* conservative-vs-interventional RCT showed conservative management is non-inferior even for moderate–large PSP in reliable patients). Symptomatic/large → **needle aspiration** with a 16–18-gauge cannula (aspirate up to **2.5 L**); if aspiration fails, place a **small-bore chest tube (7–14F)**, optionally with a **Heimlich one-way valve** for ambulatory/outpatient management.
- **SSP:** admit for **≥24 h** with **supplemental oxygen**; **most require a chest tube** because the diseased lung tolerates collapse poorly and spontaneous resolution is less likely. Early surgical/recurrence-prevention referral.
- **Supplemental oxygen:** high-flow/**100% O_2** speeds reabsorption ~**fourfold** by washing out pleural nitrogen and widening the nitrogen gradient.
- **Tension pneumothorax:** immediate **needle decompression** — large-bore cannula into the **2nd intercostal space, mid-clavicular line** (Harrison: 2nd anterior intercostal space); a rush of gas confirms it. Leave the cannula until a definitive **chest tube** is placed.
- **Traumatic:** large/symptomatic → tube thoracostomy; if hemopneumothorax, an apical tube for air and a basal tube for blood. Small/occult may be observed.
- **Iatrogenic:** often resolves with observation/oxygen or simple aspiration; tube only if these fail or the patient is ventilated.
- **Failure of medical management / prolonged air leak (PAL = leak >5–7 days):** definitive treatment is **VATS** (preferred over open thoracotomy) — bleb/bullae resection (stapling) **plus**

pleurodesis (talc **poudrage**, pleural abrasion, or pleurectomy). **Medical (chemical) pleurodesis** via the tube (talc slurry, tetracycline/minocycline) suits the non-surgical candidate; **autologous blood-patch pleurodesis** (1–2 mL/kg) and **endobronchial valves** are options in difficult SSP/COPD with bronchopleural fistula.

- **Recurrence prevention** is indicated for: **recurrent** (ipsi- or contralateral) pneumothorax, **synchronous bilateral** pneumothorax, **PAL**, or high-risk occupation (**airline pilot, diver**).
- **Catamenial pneumothorax:** suspect in any woman with pneumothorax within 24–48 h of menses (usually **right-sided**, recurrent); treat by **suppressing ectopic endometrium** — ovulation suppression with OCPs, or **danazol / GnRH analogues** (medical oophorectomy) — combined with VATS closure of diaphragmatic defects ± pleurodesis.
- **Complications:** tension physiology, pneumomediastinum, subcutaneous emphysema, and **re-expansion pulmonary oedema** (unilateral, after rapid re-inflation of a chronically collapsed lung — avoid by draining slowly and limiting suction).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled CXR / line diagram of a right-sided pneumothorax:** label *visceral pleural (lung) line*, *collapsed lung*, *absent lung markings (radiolucent pleural space)*, *chest wall*, *diaphragm*, and (for tension) *mediastinum/trachea shifted to the contralateral side* and *depressed/flattened ipsilateral diaphragm*.
- **Tension pneumothorax pathophysiology schematic:** label *one-way (check) valve at visceral pleural defect*, *air entering on inspiration*, *rising positive intrapleural pressure*, *collapsed lung*, *mediastinal shift*, *kinked great veins → reduced venous return → fall in cardiac output*.

Clinical / Diagnostic significance

- A young, tall, thin male smoker with sudden pleuritic pain and dyspnoea = classic **PSP**; a similar event in COPD/TB/ILD = **SSP** and is far less benign.
- Recurrent pneumothorax in a **young woman** must trigger thought of **LAM**, **catamenial pneumothorax**, or **Birt-Hogg-Dubé** — consider low-dose CT chest.
- **Tension pneumothorax is a clinical diagnosis**; needle decompression precedes imaging and saves life.
- Distinguishing a **giant bulla** from a pneumothorax on CXR is critical — wrongly draining a bulla causes a persistent air leak/bronchopleural fistula; CT resolves the doubt.
- **Counselling:** mandatory smoking cessation (reduces recurrence), **no air travel until 7 days after radiographic resolution** (cabin depressurisation expands undrained air — an untreated pneumothorax is an absolute contraindication to flying), and **lifelong avoidance of scuba diving** unless definitive surgical pleurodesis has been performed.

High-yield exam pointers

- **Recurrence:** ~**30%** after a first PSP (observation or simple drainage); up to **50%** for SSP if no surgery — surgery/pleurodesis greatly lowers this (talc poudrage recurrence ≈ **1.8%**).
- **Bleb <1 cm vs bulla >1 cm**; *Reid* type I/II/III bullae; *Miller* first described blebs (1947).

- **Light's criteria** distinguish exudate/transudate in pleural *effusion*; do not confuse with **Light index** for pneumothorax *size*.
- **BTS large = >2 cm at hilum; ACCP large = ≥3 cm at apex.**
- Needle aspiration cannula **16–18 G, up to 2.5 L**; tension decompression at **2nd ICS, mid-clavicular line**.
- **100% oxygen accelerates resorption ~4×.**
- Familial mnemonics: **Marfan (FBN1)**, **Birt-Hogg-Dubé (FLCN)**, α_1-antitrypsin deficiency, homocystinuria.
- **Pneumothorax ex vacuo** occurs when a trapped (unexpandable) lung cannot re-expand after fluid drainage.
- Left-sided pneumothorax can mimic **acute MI** on ECG; tension pneumothorax can mimic and coexist with shock.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Disorders of the Pleura"** (pneumothorax classification, pleural mechanics, tension pneumothorax decompression).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Pneumothorax"** (epidemiology; bleb/bulla and Reid classification; pleural-porosity pathogenesis; MMPs; familial genetics; sizing — BTS/ACCP/Light index; needle-aspiration vs chest-tube and conservative-management RCTs; VATS/pleurodesis; blood-patch and endobronchial-valve therapy; traumatic, iatrogenic and catamenial pneumothorax).
- **CMDT 2026 — "Pulmonary Disorders" (Pneumothorax)** (current essentials, BTS 2023 guideline, conservative-management evidence, recurrence figures, indications for VATS).

◆ ◆ ◆

Pulmonary function tests

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

Definition / Introduction — Pulmonary function tests (PFTs) are objective, reproducible, non-invasive measurements of the mechanical and gas-exchange properties of the respiratory system, interpreted against predicted values derived from height, age and sex. They quantify how the three functionally independent components of the system — the **lung and airways**, the **neuromuscular pump** and the **chest wall** — handle volume (statics) and flow (dynamics). PFTs serve to **detect and classify disease (obstructive vs restrictive vs mixed vs vascular)**, grade severity, follow progression and response to therapy, and assess fitness for surgery. For most measures, **85–115% of the predicted value is normal**, and in health the various volumes tend to scale together.

Components of a complete PFT battery

- **Spirometry** — FVC, FEV_1, FEV_1/FVC ratio and the **flow-volume loop** (the core, effort-independent test of airflow).
- **Static lung volumes** — TLC, FRC, RV (require gas dilution or plethysmography; spirometry alone cannot measure them).

- **Diffusing capacity (DLCO)** — integrity of the alveolar-capillary membrane and gas transfer.
- **Respiratory muscle strength** — maximal inspiratory/expiratory pressures; supine spirometry.
- **Arterial blood gases (ABG) / pulse oximetry** — efficiency of gas exchange.
- **Bronchodilator reversibility** (pre- vs post-bronchodilator spirometry) and bronchoprovocation in selected cases.

Lung volumes and capacities (Spirogram, Fig. 296-2)

- **Tidal volume (TV)** — air moved in a normal quiet breath.
- **Inspiratory reserve volume (IRV)** and **expiratory reserve volume (ERV)** — extra air inhaled/exhaled beyond tidal breathing.
- **Residual volume (RV)** — air remaining after maximal exhalation; *cannot be exhaled, hence not measurable by spirometry.*
- **Inspiratory capacity (IC)** = TV + IRV; **functional residual capacity (FRC)** = ERV + RV, the volume at the end of a normal tidal breath.
- **Vital capacity (VC)** = TLC − RV, the maximal excursion of the respiratory system.
- **Total lung capacity (TLC)** — volume at full inflation.

Measuring absolute volumes — Because spirometry discloses only *relative* volume change, FRC (and hence RV and TLC) must be measured by one of two methods:

- **Inert gas (helium or neon) dilution** — a known volume of non-absorbable gas is diluted by resident lung gas; poorly ventilated regions (e.g., airflow obstruction) receive little gas, so this method **underestimates true lung volume**.
- **Body plethysmography** — the patient pants against a closed shutter; pressure/volume fluctuations give thoracic gas volume via **Boyle's law ($P_1V_1 = P_2V_2$)**. More accurate when air-trapping is present.

Spirometry, airflow and the flow-volume loop

- In an **FVC manoeuvre** the patient inhales fully to TLC then exhales rapidly and forcefully to RV. Maximal expiratory flow is **effort-independent** (flow-limited) because of dynamic airway compression (*Bernoulli effect*), so results are reproducible.
- **FVC** = total volume exhaled; **FEV_1** = volume exhaled in the first second (a flow rate); **FEV_1/FVC ratio** is the key discriminator of obstruction.
- Data are displayed two ways — the **spirogram** (volume vs time) and the **flow-volume loop** (flow vs volume).
- **Pitfall:** airflow obstruction can lower FVC by raising RV, sometimes rendering the FEV_1/FVC ratio *"artifactually normal"* and falsely implying obstruction is absent.

Flow-volume loop (Fig. 296-4)	Characteristic shape	Typical cause
A. Normal	Rapid rise then near-linear declining expiratory limb	—

Flow-volume loop (Fig. 296-4)	Characteristic shape	Typical cause
B. Lower-airway obstruction	*"Scooping"* (concave) expiratory limb; flows fall faster at low volumes	Asthma, emphysema/COPD
C. Fixed central airway obstruction	Plateau of **both** inspiratory and expiratory limbs	Tracheal stenosis, large goitre
D. Variable extrathoracic (upper, above thoracic inlet)	**Inspiratory** plateau	Tracheal adenoma, post-tracheostomy stricture
E. Variable intrathoracic (lower, below thoracic inlet)	**Expiratory** plateau	Intrathoracic tracheal/bronchial lesion

Obstructive vs restrictive patterns

Feature	Obstructive	Restrictive
Defining defect	**Reduced FEV_1/FVC ratio**	**Reduced TLC** (FEV_1/FVC normal or high)
FEV_1	Markedly reduced	Reduced proportionate to FVC
TLC, FRC, RV	Often **increased** (hyperinflation, air-trapping)	**Reduced**
Flow-volume loop	Scooped expiratory limb	Small loop shifted to low volumes; flows high *for the volume*
Examples	Asthma, emphysema/COPD, chronic bronchitis, cystic fibrosis	Pulmonary fibrosis (parenchymal), neuromuscular weakness, chest-wall/obesity (extraparenchymal)

Diffusing capacity (DLCO), muscle strength and ABG

- **DLCO** uses a small, safe amount of **carbon monoxide** with a **10-second breath-hold**; CO crossing the alveolar membrane combines with capillary haemoglobin (*single-breath diffusing capacity*). It rises with diffusion surface area and capillary haemoglobin and falls with membrane thickening.
  - **Low DLCO:** membrane thickening/destruction (**pulmonary fibrosis, emphysema**), curtailed pulmonary vasculature (**pulmonary hypertension**), reduced alveolar-capillary haemoglobin (**anaemia**). An isolated low DLCO with normal volumes should prompt evaluation for **pulmonary vascular disease**.
  - **High DLCO: asthma, polycythaemia, pulmonary (alveolar) haemorrhage**.
- **Respiratory muscle strength** — maximal inspiratory/expiratory pressure against a closed shutter; **pressures >±60 cmH_2O at FRC are adequate** and exclude weakness as a cause of dysfunction. A sensitive bedside test is **supine spirometry**: normal FVC falls only **3–8%** from upright to supine, but diaphragmatic weakness/paralysis or neuromuscular disease causes decrements of **10 to >25%**.
- **ABG / oximetry** — measure Pao_2 and $Paco_2$. A widened **$(A–a)Do_2$** indicates V/Q mismatch or shunt; **hypercarbia** accompanies severe obstruction (e.g., COPD) or advanced restriction.

Oxygen content $\mathbf{Cao_2 = 1.39 \times [Hb] \times \%O_2Sat + 0.003 \times Pao_2}$; saturation alone is followed non-invasively by **pulse oximetry**.

Characteristic PFT patterns in common disorders (Fig. 296-6)

Disorder (mechanism)	TLC / FRC / RV	FEV_1 & FVC	Airway resistance	DLCO
Idiopathic pulmonary fibrosis (restriction, ↑ recoil)	All ↓	↓ (flows high *for volume*)	Normal	**Markedly ↓**
Moderate obesity (restriction, chest wall)	FRC ↓; TLC/RV usually normal	Near normal	Normal	Normal
Myasthenia gravis (restriction, muscle weakness)	TLC ↓, RV ↑	↓ (as "innocent bystanders")	Normal	Normal
Acute asthma (obstruction, ↓ airway diameter)	FRC dynamically ↑, RV ↑, TLC usually normal	↓, **reversible** post-bronchodilator	↑	Normal or mildly ↑
Severe emphysema (obstruction, ↓ recoil)	**TLC ↑ (hyperinflation)**, FRC ↑↑, RV ↑↑↑	↓, largely irreversible	Normal in "pure" emphysema	↓

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spirogram (lung volumes & capacities)** — a tracing of volume vs time over a slow vital-capacity manoeuvre, with horizontal reference lines and brackets labelled: *Tidal volume (TV)*, *Inspiratory reserve volume (IRV)*, *Expiratory reserve volume (ERV)*, *Residual volume (RV)*, *Inspiratory capacity (IC)*, *Functional residual capacity (FRC)*, *Vital capacity (VC)*, *Total lung capacity (TLC)*.
- **Flow-volume loops** — axes labelled *Flow* (expiratory above zero, inspiratory below) and *Volume* (from *TLC* on left to *RV* on right); draw and label five loops: *A Normal*, *B Lower-airway obstruction (scooped)*, *C Fixed central obstruction (both limbs plateau)*, *D Variable extrathoracic (inspiratory plateau)*, *E Variable intrathoracic (expiratory plateau)*.

Clinical / Diagnostic significance

- **Diagnosis and classification:** FEV_1/FVC defines obstruction; reduced TLC defines restriction; combined defects suggest mixed disease.
- **Bronchodilator reversibility** (pre- vs post-bronchodilator FEV_1) distinguishes reversible asthma from largely fixed COPD/emphysema and guides therapy.
- **Isolated low DLCO** with normal spirometry/volumes is a clue to **pulmonary vascular disease (e.g., pulmonary hypertension)** or early emphysema/ILD; high DLCO suggests alveolar haemorrhage or polycythaemia.

- **Severity grading and monitoring:** serial FEV_1 tracks COPD/asthma progression and treatment response; falling FVC (especially supine) signals neuromuscular respiratory failure (e.g., GBS, myasthenia, ALS) and the need for ventilatory support.
- **Preoperative risk assessment** (lung resection, major surgery) and **disability/occupational evaluation** rely on spirometry and DLCO.
- **Localising airway lesions:** plateaued inspiratory/expiratory limbs flag upper-airway/tracheal obstruction often missed on routine spirometry numbers.

High-yield exam pointers

- **Obstruction = low FEV_1/FVC; restriction = low TLC** — TLC, not spirometry, confirms restriction.
- **RV, FRC and TLC cannot be measured by spirometry** — need **helium dilution** (underestimates in obstruction) or **body plethysmography** (Boyle's law, more accurate with air-trapping).
- **Scooped expiratory limb = lower-airway obstruction; biphasic plateau = fixed central; inspiratory plateau = variable extrathoracic; expiratory plateau = variable intrathoracic.**
- A reduced FVC from air-trapping can make FEV_1/FVC look **falsely normal** — always check TLC/RV.
- **DLCO low** in fibrosis, emphysema, pulmonary hypertension, anaemia; **high** in asthma, polycythaemia, alveolar haemorrhage.
- **MIP/MEP >±60 cmH_2O is adequate**; supine FVC fall **>10%** indicates diaphragmatic weakness (normal 3–8%).
- **Hallmark of emphysema = ↑TLC (hyperinflation)** with very high RV and reduced DLCO but normal airway resistance in "pure" disease.
- Normal range is **85–115% of predicted**; predictions depend on **height, age, sex**.

SOURCE & COVERAGE

Harrison 22e — Ch 296 "Disturbances of Respiratory Function" (lung volumes, airflow, flow-volume loops, disease patterns Fig. 296-2/296-4/296-6) and Ch 297 "Diagnostic Procedures in Respiratory Disease" (body plethysmography, DLCO, respiratory muscle testing, ABG). **Coverage note:** Specific quantitative reversibility thresholds (e.g., ATS ≥12% and ≥200 mL rise in FEV_1), **methacholine/bronchoprovocation testing**, **cardiopulmonary exercise testing** and the **6-minute walk test** are standard textbook PFT adjuncts but are *not described in the provided Harrison chapters*; they are mentioned only in outline and should be cross-checked against CMDT / ATS-ERS standards before use.

◆ ◆ ◆

Pulmonary infiltrates with eosinophilia

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

Definition / Introduction — *Pulmonary infiltrates with eosinophilia* (PIE), or the **eosinophilic lung diseases**, are a heterogeneous group of disorders characterised by the combination of **radiographic pulmonary opacities** (infiltrates) and **eosinophilia**, demonstrated either in peripheral blood, in sputum, or — preferably — in the lung itself (bronchoalveolar lavage [BAL] or tissue). Eosinophilic pneumonia is defined pathologically as a pneumonia in which **eosinophils are the predominant inflammatory cell** in the alveoli and interstitium. By consensus, **blood eosinophilia is >0.5 × 10^9/L (500/μL)** and **hypereosinophilia >1.5 × 10^9/L (1500/μL)** on two examinations ≥1 month apart and/or tissue hypereosinophilia. The unifying effector cell is the **eosinophil**, whose differentiation and lung recruitment are driven by **IL-5, IL-3, GM-CSF and eotaxins** (Th2-/ILC2-derived), making the IL-5 axis a central therapeutic target.

Classification (primary/idiopathic vs secondary)

The first step is to separate **primary (idiopathic)** eosinophilic lung disease from disease that is **secondary** to an identifiable cause (drug, parasite, fungus, malignancy or another lung condition). A practical bedside algorithm asks three questions: *(1) extrapulmonary involvement? (2) identifiable cause/trigger? (3) acute or chronic onset?*

Category	Disorders
Primary (idiopathic) eosinophilic lung disease	Acute eosinophilic pneumonia (AEP); Chronic eosinophilic pneumonia (CEP); Eosinophilic granulomatosis with polyangiitis (EGPA / Churg-Strauss); Hypereosinophilic syndromes (HES)
Known cause associated with eosinophilia	Asthma & eosinophilic bronchitis; Allergic bronchopulmonary aspergillosis (ABPA); Bronchocentric granulomatosis; Drug/toxin reaction; Infection — parasitic/helminthic & nonparasitic (Löffler, tropical eosinophilia)
Lung diseases with eosinophilia	Cryptogenic organising pneumonia; Hypersensitivity pneumonitis; Idiopathic pulmonary fibrosis; Pulmonary Langerhans cell histiocytosis
Malignancy / systemic	Leukaemia, lymphoma, lung & other carcinomas; post-radiation pneumonitis; RA, sarcoidosis, Sjögren's

Diagnostic approach

- **History is paramount** — onset/timing/precipitants of symptoms; drug, occupational, environmental, **travel and immigration** history; family history; and a systems review for cardiac, GI, neurological, dermatological, sinus and renal clues (point to EGPA or HES).
- **Blood** — absolute eosinophil count, ESR/CRP, **total IgE**, *Aspergillus*-specific IgE/IgG, ANCA (MPO), stool for ova/parasites, filarial serology. Peripheral eosinophilia may be **absent at presentation in AEP** and is **suppressed by prior corticosteroids**.
- **BAL** — the noninvasive surrogate for tissue diagnosis. Normal BAL eosinophils <1%; a count **>25% (predominant cell)** strongly supports eosinophilic pneumonia, and **>40%** is characteristic of CEP. Lower counts (3–25%) are nonspecific (ILD, HP, sarcoid, drug, infection).

- **Imaging** — chest radiograph + **HRCT** to define distribution (peripheral upper-zone in CEP; diffuse in AEP; migratory in EGPA; central bronchiectasis/finger-in-glove in ABPA).
- **Biopsy** (transbronchial, cryobiopsy or surgical) is seldom required but resolves difficult cases; *Charcot-Leyden crystals* (composed of the eosinophil protein **galectin-10**) may be seen in tissue/sputum.

Idiopathic eosinophilic pneumonias — AEP vs CEP

Feature	Acute eosinophilic pneumonia (AEP/IAEP)	Chronic eosinophilic pneumonia (CEP/ICEP)
Onset	Acute febrile illness <1 month	Subacute over weeks–months
Demographics	Males 20–40 yr; **no asthma**	Females ~2:1, mean age ~45; **nonsmokers**; asthma/atopy in majority
Trigger	**Recent-onset smoking / vaping**, inhaled dust	Often none; allergy in ~half
Course	Hypoxaemic respiratory failure, often needs ventilation; **no other organ failure**	Indolent; respiratory failure rare
Blood eosinophilia	Often **absent at onset** (appears day 7 –30, mean ~1700/μL)	Present in ~90%; mean >30% of WBC
BAL eosinophils	**≥25%**	**~60% (≥40%)**
Chest imaging	Bilateral patchy ground-glass/consolidation, septal thickening, small effusions	Peripheral upper-zone consolidation — *"photographic negative of pulmonary oedema"* (pathognomonic but seen in <25%)
Steroid response / relapse	Dramatic; **complete recovery, no relapse**	Dramatic; **>50% relapse**, often needs prolonged steroids

AEP diagnostic criteria (Harrison/Philit): acute febrile respiratory illness <1 month; hypoxaemic respiratory failure (PaO_2 ≤60 mmHg, PaO_2/FiO_2 ≤300, or SpO_2 <90% on room air); diffuse bilateral infiltrates; **BAL eosinophilia >25%**; absence of infection/drug cause; quick corticosteroid response; no relapse after stopping steroids.

Eosinophilic granulomatosis with polyangiitis (EGPA / Churg-Strauss)

- An **ANCA-associated, eosinophil-rich small-vessel vasculitis** with extravascular **necrotising granulomas**, defined by the triad of **asthma + eosinophilia + vasculitis**. Mean age ~48 yr.
- **Three classic phases**: (1) *prodromal* — asthma + allergic rhinosinusitis (often years); (2) *eosinophilic infiltrative* — blood/tissue eosinophilia (lung, GI); (3) *vasculitic* — constitutional symptoms with multi-organ vasculitis. Mean asthma-to-vasculitis interval ~9 years.
- **Organ involvement**: lung (migratory infiltrates, alveolar haemorrhage); **mononeuritis multiplex in >75%** (esp. peroneal nerve); skin (palpable purpura, nodules) ~50%; **cardiac** (eosinophilic myocarditis/cardiomyopathy — chief cause of death) up to 50%; GI (eosinophilic gastroenteritis); renal ~25% (usually mild, unlike other AAV).
- **Labs**: blood **eosinophilia >1000/μL (or >10% WBC)** — present in >80%, falls within ~24 h of steroids; **p-ANCA/anti-MPO in ~30–40%**; raised IgE, ESR, RF. ANCA-positive patients have a

vasculitic phenotype (renal, neuropathy, purpura); ANCA-negative a *tissue/eosinophilic phenotype* (cardiac, lung).

- ***Cottin/Cordier criteria***: asthma + blood eosinophilia >1500/µL (or BAL >25%) + an extrapulmonary manifestation (systemic feature such as mononeuritis multiplex, cardiomyopathy, or purpura; OR histological vasculitis; OR ANCA positivity). A single extrarespiratory feature = *forme fruste*.
- **Treatment**: glucocorticoids are the mainstay (prednisone 1 mg/kg/day, taper; IV methylprednisolone pulse 15 mg/kg/day for severe/cardiac disease). For **poor-prognosis (Five-Factor Score)** features — **cardiomyopathy, severe GI involvement, renal insufficiency (creatinine >150 µmol/L ≈ 1.7 mg/dL), proteinuria >1 g/day, CNS involvement** (updated FFS also: age >65 yr, absence of ENT symptoms) — add **cyclophosphamide** (or rituximab). **Mepolizumab (anti-IL-5, 300 mg every 4 weeks)** and benralizumab are steroid-sparing agents that increase remission and reduce relapse. Untreated EGPA carries ~50% 3-month mortality; treated 6-year survival >70%.

Other important entities

- **Hypereosinophilic syndromes (HES)** — persistent eosinophilia **>1500/µL with end-organ damage** and no secondary cause; lung involved in ~40%. **Myeloproliferative variant** carries the **FIP1L1-PDGFRA fusion (4q12 deletion)** — an imatinib-responsive constitutively active tyrosine kinase (raised B12, tryptase, splenomegaly, myelofibrosis); **lymphocytic variant** is driven by clonal **$CD3^{-}CD4^{+}$** Th2 cells producing IL-5. Cardiac damage = endomyocardial fibrosis/restrictive cardiomyopathy. **<50% respond to steroids alone**; imatinib is first-line for the myeloproliferative/FIP1L1-PDGFRA variant; mepolizumab is effective.
- **ABPA** — hypersensitivity to *Aspergillus fumigatus* in **asthma or cystic fibrosis**; brownish mucus plugs, refractory asthma. Diagnosis (ISHAM/Agarwal): predisposing asthma/CF + **obligatory** positive *Aspergillus* skin test or raised *A. fumigatus*-specific IgE **and total IgE >1000 IU/mL** + ≥2 of (precipitins/IgG to *A. fumigatus*; ABPA-consistent opacities; **eosinophil count >500/µL**). HRCT: **central (proximal) bronchiectasis**, high-attenuation mucoid impaction, *"finger-in-glove"* opacities. Treat with **oral corticosteroids + itraconazole** (4–6 months); omalizumab/anti-IL-5 in selected cases.
- **Infections (helminthic)** — chief cause of PIE in the tropics/developing world. ***Löffler syndrome*** = transient migratory infiltrates with eosinophilia from **transpulmonary larval migration**, most often **Ascaris** (also hookworm — *Ancylostoma*, *Necator*). *Strongyloides* causes recurrent symptoms and a fatal **hyperinfection syndrome** in the immunosuppressed. **Tropical pulmonary eosinophilia** is due to filariae (***Wuchereria bancrofti*, *Brugia malayi***), common in **southern Asia, Africa, South America**, with very high IgE/eosinophilia, nocturnal cough/wheeze — treated with **diethylcarbamazine**.
- **Drug/toxin-induced** — the commonest cause of PIE in the USA; remember **nitrofurantoin, daptomycin, phenytoin, NSAIDs, sulfasalazine/mesalamine, sulfonamides**; also radiation (breast cancer), particulate metals, illicit inhaled drugs. Management = withdraw the agent ± steroids. Overlaps with DRESS.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagnostic algorithm for eosinophilic pneumonia** (box-and-arrow): start "**Pulmonary infiltrates + eosinophilia**" → Q1 *Extrapulmonary involvement?* → **EGPA / HES / DRESS / parasitic**; if No → Q2 *Cause/trigger identified?* → **drug, smoking/vaping, ABPA, parasite, radiation**; if No → Q3 *Onset?* → **Acute = IAEP** vs **Chronic = ICEP**. Label boxes: *IAEP, ICEP, EGPA, HES, ABPA, Löffler, drug-induced*.
- **AEP vs CEP HRCT cartoon**: lung outline 1 = **bilateral diffuse ground-glass + septal thickening + small pleural effusions** (AEP); lung outline 2 = **peripheral upper-zone consolidation sparing the centre** labelled *"photographic negative of pulmonary oedema"* (CEP).

Clinical / Diagnostic significance

- The single most useful discriminator is **BAL eosinophil percentage** (>25% supports an eosinophilic pneumonia; >40% suggests CEP) — it avoids lung biopsy in most patients.
- **AEP mimics ARDS** in a previously well young smoker but lacks multi-organ failure and responds completely to steroids — recognising it prevents unnecessary escalation and prognosticates well.
- **A new eosinophilic infiltrate in a long-standing asthmatic** demands exclusion of **ABPA and EGPA**; leukotriene-receptor antagonists/omalizumab/dupilumab and steroid tapering may *unmask* EGPA.
- **Always exclude *Strongyloides*/helminths before starting corticosteroids** in PIE (risk of fatal hyperinfection) — stool, serology, empiric ivermectin where appropriate.
- Steroids rapidly abolish blood and BAL eosinophilia, so **investigations are best obtained before treatment**.

High-yield exam pointers

- Blood eosinophilia **>500/µL**; hypereosinophilia **>1500/µL**; **BAL >25%** = eosinophilic pneumonia; **>40%** = CEP.
- **AEP**: young male smoker, ARDS-like, no peripheral eosinophilia at onset, **no relapse**; **CEP**: middle-aged female asthmatic, *"photographic negative of pulmonary oedema"*, **frequent relapse**.
- **EGPA** triad = **asthma + eosinophilia + vasculitis**; mononeuritis multiplex; **p-ANCA/MPO ~30–40%**; cardiac disease = leading cause of death; **Five-Factor Score** guides cyclophosphamide; **mepolizumab** is steroid-sparing.
- **HES**: eosinophilia >1500/µL + end-organ damage; **FIP1L1-PDGFRA → imatinib**.
- **ABPA**: asthma/CF, **IgE >1000 IU/mL**, central bronchiectasis, *finger-in-glove*; treat steroids + itraconazole.
- **Löffler syndrome** = transient infiltrates from **Ascaris** larval migration; **tropical pulmonary eosinophilia** = filariae, treat **diethylcarbamazine**.
- Commonest drugs: **nitrofurantoin, daptomycin, phenytoin, NSAIDs, sulfasalazine**; commonest cause in the West = **drugs**, in the tropics = **helminths**.
- **Charcot-Leyden crystals = galectin-10**; eosinophil maturation/recruitment driven by **IL-5**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia"* (classification table 299-2, AEP/CEP, EGPA, HES, ABPA, infectious & drug causes, AEP diagnostic criteria).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — *"Eosinophilic Lung Diseases"* (diagnostic algorithm Fig 96.1, eosinophilia/BAL thresholds, ICEP & IAEP criteria tables, Cottin/Cordier EGPA criteria, Five-Factor Score, HES genetics, ISHAM/Agarwal ABPA criteria, treatment regimens) and *"Pulmonary Vasculitis"* for EGPA phenotypes.
- **CMDT 2026** — *"Eosinophilic Pulmonary Syndromes"* and *"Pulmonary Disorders"* (drug list, Löffler/tropical eosinophilia, current management, IL-5-targeted therapy).

◆ ◆ ◆

Pulmonary thromboembolism

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Pulmonary thromboembolism (PE) is acute obstruction of the pulmonary arterial bed by thrombus, almost always an embolus that has detached from a lower-limb **deep-venous thrombosis (DVT)**; together DVT and PE constitute **venous thromboembolism (VTE)**, manifestations of one disease process. Roughly 90% of clinically apparent PEs arise from proximal lower-extremity DVT. PE is "the great masquerader" — symptoms and signs are non-specific, so a structured, probability-based diagnostic and risk-stratified therapeutic approach is essential because untreated PE carries a case-fatality higher than that of acute myocardial infarction.

Aetiology & Risk Factors (Virchow's triad)

- **Virchow's triad** (1856): venous **stasis**, **hypercoagulability**, and **endothelial/intimal injury** — usually with an **inflammatory trigger** — drive thrombus formation around a valve cusp; activated platelets recruit neutrophils that form *neutrophil extracellular traps*, promoting thrombin generation in a milieu of stasis and low oxygen tension.
- **Inherited (hereditary) thrombophilias: Factor V Leiden** (commonest; causes resistance to activated protein C), **prothrombin G20210A** gene mutation (raises plasma prothrombin), and the rarer deficiencies of **antithrombin III, protein C and protein S**; also dysfibrinogenaemia and plasminogen deficiency.
- **Acquired: antiphospholipid syndrome (APS)** — acquired, predisposes to both venous *and* arterial thrombosis, often warrants lifelong anticoagulation; surgery/trauma, hip-knee arthroplasty, hip fracture, spinal cord injury, immobilisation, prior VTE, advancing age, malignancy, pregnancy and the 6–12-week postpartum period, oestrogen contraceptives/HRT, obesity, nephrotic syndrome, long-haul travel, COPD, CKD, sickle cell disease/trait and cirrhosis.

Type	Examples
Hereditary	Factor V Leiden, prothrombin G20210A, antithrombin/protein C/protein S deficiency

Type	Examples
Acquired – surgical	Major thoracic/abdominal/neurosurgery, hip & knee arthroplasty, hip fracture, major trauma, spinal cord injury
Acquired – medical	Cancer, prior VTE, CHF, stroke, nephrotic syndrome, oestrogens, pregnancy/postpartum, obesity, APS, IBD

Pathophysiology

- **Gas exchange:** arterial **hypoxaemia** (~85% of patients) and a widened **alveolar–arterial O_2 gradient** from V/Q mismatch and shunt; increased **alveolar (physiologic) dead space**; surfactant loss → atelectasis; reflex hyperventilation → **hypocapnia**.
- **Haemodynamics:** mechanical obstruction plus neurohumoral vasoconstrictors (**serotonin, thromboxane A_2, endothelin**) raise **pulmonary vascular resistance** and pulmonary artery pressure non-linearly.
- **The RV-failure cascade (key to mortality):** rising RV wall tension → **RV dilatation and dysfunction** with BNP release → **interventricular septal bowing** into the LV → impaired LV filling → falling cardiac output and systemic pressure → reduced **right coronary perfusion** → RV ischaemia/**microinfarction** (troponin release) → a self-perpetuating spiral to circulatory collapse and death.
- **Pulmonary infarction** is uncommon (dual bronchial + airway oxygen supply) and, paradoxically, more frequent in young patients without cardiopulmonary disease; it indicates a small, peripheral, pleura-adjacent embolus and is intensely pleuritic.

Classification & Risk Stratification

- *Hemodynamic effects, not clot burden on imaging, best predict mortality* — even "saddle emboli" are usually hemodynamically stable.

Class	Frequency	Definition	Risk
Massive (high-risk)	5–10%	SBP <90 mmHg (≥15 min) / vasopressor / arrest; ≥½ of pulmonary bed obstructed	High
Submassive (intermediate-risk)	20–25%	Normotensive but **RV dysfunction** ± troponin/BNP elevation	Intermediate (may decompensate)
Low-risk	65–75%	Normotensive, no RV dysfunction, normal biomarkers	Excellent prognosis

- **Simplified PESI (sPESI)** — 1 point each for: **age >80 yr, cancer, chronic cardiopulmonary disease, pulse ≥110/min, SBP <100 mmHg, SaO_2 <90%.** Score 0 = low 30-day mortality (suitable for outpatient therapy); ≥1 = high risk. (Full **PESI** stratifies into classes I–V.)

Clinical Features

- **DVT:** persisting calf "charley horse"/cramp, unilateral swelling, tenderness, warmth, erythema; classic *Homan's sign* and *Moses sign* and a "palpable cord" are insensitive and non-specific. Diffuse limb oedema suggests *phlegmasia cerulea dolens*; recurrent left-thigh oedema in young

women suggests *May–Thurner syndrome* (right iliac artery compressing left iliac vein); chest-wall collaterals = *Urschel's sign*.

- **PE — three classic syndromes** (PIOPED): (1) **isolated dyspnoea** (~25%); (2) **pleuritic pain ± haemoptysis** (~60%, usually small peripheral PE/infarction); (3) **circulatory collapse/syncope** (~10%, massive PE).
- **Commonest symptom = unexplained dyspnoea; commonest sign = tachypnoea (>20/min)**; also tachycardia, accentuated P_2, inspiratory crackles, low-grade fever (rarely >38.3°C), and signs of RV overload (left parasternal heave, raised JVP, S_3/S_4) in massive PE.

Diagnosis (integrated, probability-based)

- **Step 1 – Pretest probability: Wells score** (validated in outpatients) or gestalt; if low/moderate, proceed to D-dimer; if high, skip D-dimer and image directly.

Wells criterion (PE)	Points
Clinical signs/symptoms of DVT	3.0
PE as likely as / more likely than alternative	3.0
Heart rate >100/min	1.5
Immobilisation >3 days / surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Haemoptysis	1.0
Cancer	1.0

(High clinical likelihood if score >4.) The **PERC rule** (age <50, HR <100, SaO_2 ≥95%, no prior VTE, no recent trauma/surgery, no haemoptysis, no oestrogen, no unilateral leg swelling) excludes PE in ED patients already judged low-risk.

- **D-dimer (ELISA):** sensitivity >95% — a normal value **rules out** PE in low/intermediate probability; not specific (raised in MI, sepsis, cancer, pregnancy, post-op), so of little value in hospitalised patients. Use **age-adjusted cut-off (age × 10 ng/mL FEU)** in patients >50 yr.
- **ECG:** sinus tachycardia commonest; **S1Q3T3** (specific, insensitive), **T-wave inversion V1–V4** (RV strain — commonest abnormality), incomplete RBBB, Qr in V1.
- **Chest X-ray** (often near-normal): **Westermark's sign** (focal oligaemia), **Hampton's hump** (peripheral pleura-based triangular density = infarction), **Palla's sign** (enlarged right descending PA), *Fleischner sign* (prominent central PA).
- **CT pulmonary angiography (CTPA) — principal/first-line imaging**: directly visualises emboli to ≤1 mm, gives a four-chamber view (**RV:LV diameter ratio >1** predicts 30-day death) and alternative diagnoses; limited for subsegmental clots and needs iodinated contrast.
- **V/Q scan** — second-line (contrast allergy/renal failure/pregnancy): **normal scan excludes PE**; high-probability scan (≥2 segmental mismatched defects) ~87–90% predictive. **SPECT-V/Q** gives fewer non-diagnostic results.
- **Venous compression ultrasound** — loss of vein compressibility is the key DVT criterion; a positive leg study in suspected PE carries equivalent therapeutic implication.

- **Echocardiography** — not for diagnosis but for **risk stratification**: RV dilatation/hypokinesis, **McConnell's sign** (RV free-wall hypokinesis with apical sparing), reduced **TAPSE**; also excludes mimics (tamponade, MI, aortic dissection).

Management / Treatment

- **Anticoagulation is the cornerstone** for all PE; start empirically when suspicion is high and bleeding risk low. **DOACs are first-line** for most patients.

Agent	Regimen
UFH	Bolus 80 U/kg, then 18 U/kg/h; target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL)
Enoxaparin (LMWH)	1 mg/kg SC 12-hourly (no monitoring unless obese/CKD)
Fondaparinux	Weight-based SC OD; does not cause HIT
Rivaroxaban	15 mg BID × 3 weeks → 20 mg OD (monotherapy)
Apixaban	10 mg BID × 1 week → 5 mg BID (monotherapy)
Dabigatran / Edoxaban	After 5 days parenteral: dabigatran 150 mg BID / edoxaban 60 mg OD
Warfarin	Bridge with parenteral ≥5 days until INR 2.0–3.0 ×2 readings

- **HIT:** use **argatroban** (hepatic) or **bivalirudin** (renal); fondaparinux is an alternative. **APS and pregnancy → not** DOACs (warfarin/LMWH respectively).
- **Massive (high-risk) PE:** cautious volume (≈500 mL normal saline — over-filling worsens RV strain), **norepinephrine** (pressor of choice) + **dobutamine** (inotrope), and **systemic thrombolysis** — FDA-approved **alteplase 100 mg IV over 2 h** (off-label 50 mg). Major bleeding ~10%, intracranial haemorrhage 2–3%; contraindicated with intracranial disease, recent surgery/trauma, stroke <3 months. **VA-ECMO** for refractory shock.
- **Submassive (intermediate-risk) PE:** anticoagulate + **monitor closely**; routine thrombolysis is controversial (PEITHO: reduced decompensation but excess major bleeding/ICH, no mortality benefit) — reserve thrombolysis/catheter therapy for clinical deterioration.
- **Catheter-directed therapy** (pharmacologic, mechanical/suction, or pharmacomechanical/ultrasound-facilitated low-dose lysis) and **surgical embolectomy** — for high-risk PE when thrombolysis fails or is contraindicated.
- **IVC filter** — only for **active bleeding precluding anticoagulation** or **recurrent VTE despite adequate anticoagulation**; prefer a **retrievable** filter.
- **Duration (ESC 2019):** "provoked/unprovoked" terminology de-emphasised; ≥3 months for major transient risk factor; **extended/indefinite** anticoagulation for no identifiable/persistent risk factor, recurrent VTE, active cancer (LMWH or apixaban/edoxaban) or APS, with periodic risk–benefit review.
- **Long-term sequelae:** post-PE syndrome (persistent dyspnoea/RV dysfunction), postthrombotic syndrome, and **chronic thromboembolic pulmonary hypertension (CTEPH)** in ~2% — treat with **pulmonary thromboendarterectomy** (mortality 1–5% at expert centres), or balloon pulmonary angioplasty + pulmonary vasodilators if inoperable.

- **Prevention:** low-dose UFH/LMWH/fondaparinux prophylaxis in at-risk hospitalised and surgical patients; mechanical (IPC/graduated stockings) when anticoagulation is contraindicated.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Integrated diagnostic algorithm** — boxes/arrows: *Suspect PE → assess clinical probability (Wells) → Low/Moderate: D-dimer (normal = stop; raised = CTPA) → High: straight to CTPA → CTPA positive = treat; negative = consider V/Q / leg ultrasound.* Labels: **Clinical probability, D-dimer, CTPA, V/Q scan, Venous ultrasound, Risk-stratify (PESI/sPESI, RV function, troponin).**
- **Pathophysiology flow-chart of massive PE: PE → ↑RV afterload → ↑RV wall tension → RV dilatation/dysfunction → septal shift → ↓LV filling → ↓cardiac output/↓systemic BP → ↓RV coronary perfusion → RV ischaemia/microinfarction → circulatory collapse.**

Clinical / Diagnostic significance

- Risk stratification (haemodynamics + sPESI + RV function + troponin) directly determines therapy: low-risk → outpatient anticoagulation; intermediate → admit and monitor; high-risk → reperfusion.
- A **negative D-dimer** in a low-probability patient safely avoids imaging and radiation; **CTPA** simultaneously diagnoses PE, assesses RV size, and offers alternative diagnoses.
- Persisting/initial pulmonary hypertension after PE mandates echocardiographic follow-up at ~6 weeks and 6 months to detect **CTEPH**, a potentially curable cause of PH.

High-yield exam pointers

- 90% of PE arise from proximal lower-limb DVT; commonest symptom = dyspnoea, commonest sign = tachypnoea.
- **Wells score >4** = high probability → image directly; **age-adjusted D-dimer = age × 10 ng/mL** in >50 yr.
- **CTPA** is first-line imaging; **normal V/Q or normal perfusion scan excludes PE**.
- **S1Q3T3** and **T-inversion V1–V4** on ECG; **McConnell's sign** on echo; **Westermark/Hampton's hump/Palla's sign** on CXR.
- **sPESI** = age >80, cancer, cardiopulmonary disease, pulse ≥110, SBP <100, SaO_2 <90% (1 each).
- **Alteplase 100 mg over 2 h** for massive PE; **norepinephrine + dobutamine** for PE shock; cautious fluids only.
- **DOACs first-line**; **warfarin/LMWH (not DOACs)** in APS and pregnancy; HIT → argatroban/bivalirudin.
- **IVC filter** only if anticoagulation contraindicated or VTE recurs despite it; CTEPH in ~2% → thromboendarterectomy.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Deep-Venous Thrombosis and Pulmonary Thromboembolism" (epidemiology, pathophysiology, classification, diagnostic algorithm, anticoagulation table, massive-PE management, ESC 2019 duration guidance).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "Pulmonary Thromboembolism: Presentation and Diagnosis" and "Prophylaxis and Treatment" (Wells/PERC/YEARS, PESI/sPESI, risk stratification, PEITHO, reperfusion strategies).
- **CMDT 2026** — "Pulmonary Disorders" (current risk-stratified treatment, thrombolysis indications, IVC filter, outpatient management).

◆ ◆ ◆

Refractory bronchial asthma

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

Definition / Introduction — *Refractory* (severe/difficult-to-treat) asthma is asthma that **remains uncontrolled despite, or requires, the highest-intensity guideline therapy (GINA Step 4–5: high-dose ICS/LABA ± LAMA)** once adherence, inhaler technique, triggers, comorbidities and alternative diagnoses have been optimised. It constitutes only **~5–10% of all asthmatics yet consumes nearly 50% of asthma-related costs** and carries the bulk of asthma morbidity and mortality. The modern approach is to first distinguish *true* severe asthma from "difficult-to-treat" asthma, then **phenotype/endotype the patient (type-2 high vs type-2 low)** to target add-on biologic therapy.

Terminology — difficult-to-treat vs severe vs uncontrolled

Term	Definition (ERS/ATS, GINA)
Difficult-to-treat asthma	Uncontrolled despite high-dose ICS + second controller (LABA/LAMA), OR needing this therapy to stay controlled — *before* modifiable factors are addressed. Chronic OCS dependence is included.
Severe (refractory) asthma	Asthma that remains difficult to treat **after** correcting adherence, inhaler technique, triggers and comorbidities — i.e. requires GINA **Step 4/5** to prevent it becoming uncontrolled, or stays uncontrolled despite this.
Uncontrolled asthma (ERS/ATS — any one of 4)	1. **Poor symptom control**: ACQ ≥1.5 or **ACT ≤19**; 2. **Frequent severe exacerbations**: ≥2 systemic-steroid bursts (≥3 days each) in past year; 3. **Serious exacerbation**: ≥1 hospitalisation, ICU stay or mechanical ventilation in past year; 4. **Airflow limitation**: **FEV_1 <80% predicted** (with FEV_1/FVC below the lower limit of normal) after withholding bronchodilators.

- Up to **50% of "poorly controlled" referrals are due to poor adherence or wrong inhaler technique**, not truly refractory disease — these must be excluded first.

Step 1 — Confirm the diagnosis and unmask the "fakers"

- **Re-confirm asthma objectively** — reversible obstruction (≥12% and 200 mL, or the newer ≥10% rise in FEV_1 % predicted), peak-flow variability >20%, or airway hyperresponsiveness

(**methacholine PD_{20} ≤400 µg**). >1/3 of physician-labelled "asthma" does not meet diagnostic criteria.

- **Exclude mimics** (overlapping obstructive picture): heart failure, **COPD / asthma–COPD overlap**, **α_1-antitrypsin deficiency**, **inducible laryngeal obstruction (vocal-cord dysfunction)** — present in up to 75% of asthmatics, diagnosed by truncated/flattened inspiratory flow-volume loop and laryngoscopy showing paradoxical adduction with posterior "chinking", endobronchial mass/foreign body, **bronchiectasis, bronchiolitis obliterans, tracheobronchomalacia**.
- **Identify aggravating comorbidities**: chronic rhinosinusitis ± nasal polyps, **GERD**, obesity (blunts steroid response), **OSA**, anxiety/depression, ongoing smoking and occupational/allergen exposure.
- **Screen for specific refractory phenotypes**: **ABPA** (IgE >1000 IU/mL, eosinophils >500/µL, positive *Aspergillus* skin test, specific IgE & IgG, central bronchiectasis — treat with itraconazole/voriconazole + OCS) and **aspirin-exacerbated respiratory disease (AERD)** (asthma + eosinophilia + sinusitis + nasal polyps + COX-1-inhibitor-triggered attacks from leukotriene overproduction).

Step 2 — Phenotype and endotype (the key to refractory asthma)

Type-2 HIGH (eosinophilic/allergic)	Type-2 LOW (non-eosinophilic)
Early-onset **allergic** asthma; late-onset **eosinophilic** asthma; **AERD**; exercise-induced; exacerbation-prone	Obesity-related late-onset; **paucigranulocytic** (fixed obstruction, little inflammation); **neutrophilic**; smoking-related
Biomarkers ↑: **blood eos ≥300/µL, sputum eos >2–3%, FeNO >25–50 ppb, ↑IgE / specific IgE**	Biomarkers low/absent; poor steroid response
Responds to ICS and to type-2 biologics	Often **steroid-resistant**; ~30–50% of asthmatics; consider tiotropium, **macrolide (azithromycin 500 mg thrice weekly)**

- FeNO is IL-13-driven: **>20–25 ppb on moderate–high ICS in severe asthma indicates persistent type-2 inflammation OR non-adherence** (FeNO is steroid-suppressible, so it doubles as an adherence check).
- Extreme eosinophilia should prompt search for **eosinophilic granulomatosis with polyangiitis (EGPA)** or hypereosinophilic syndromes.

Step 3 — Pharmacologic escalation (GINA Step 5)

- **Optimise inhaled therapy**: **high-dose ICS/LABA** (formoterol-based as both maintenance & reliever — "MART/AIR" strategy), then **add-on LAMA (tiotropium)**.
- **Adjuncts**: leukotriene modifiers (especially in **AERD** — leukotriene overproduction; and exercise-induced symptoms), **azithromycin** in selected eosinophilic and non-eosinophilic patients.
- **Chronic OCS** only as a last resort at lowest effective dose (alternate-day if possible) given cumulative toxicity — diabetes, osteoporosis, cataract/glaucoma, hypertension, adrenal suppression; add bone-protection and *Pneumocystis* prophylaxis if ≥20 mg prednisone/day chronically.

- **Bronchial thermoplasty** (radiofrequency ablation of airway smooth muscle over 3 bronchoscopies) — only in trials/registries; sham effect prominent and device now largely withdrawn.

Step 4 — Add-on biologic ("targeted") therapy for severe type-2 asthma

Biologic	Target / MOA	Selection biomarker	Dose
Omalizumab	Anti-IgE (binds free IgE Cε3 domain)	IgE 30–700 IU/mL + perennial allergen sensitisation	75–375 mg SC every 2–4 wk (by weight & IgE)
Mepolizumab	Anti-IL-5	Blood eos ≥150/µL (or ≥300/µL prior yr)	100 mg SC every 4 wk (300 mg for EGPA)
Reslizumab	Anti-IL-5	Blood eos ≥400/µL; age ≥18	3 mg/kg IV every 4 wk
Benralizumab	Anti-IL-5Rα (depletes eosinophils)	Blood eos ≥300/µL	30 mg SC ×3 every 4 wk, then every 8 wk
Dupilumab	Anti-IL-4Rα (blocks IL-4 **and** IL-13)	Blood eos ≥300/µL **or** FeNO >25 ppb	200/300 mg SC every 2 wk (caution eos >1500/µL)
Tezepelumab	Anti-TSLP (upstream epithelial *alarmin*)	Works **even without raised type-2 biomarkers**	SC (cuts exacerbations 50–70%)

- Biologics **reduce exacerbations by ~50% (tezepelumab up to 70%)** and are **OCS-sparing** (mepolizumab, benralizumab, dupilumab proven; not reslizumab). Mepolizumab, dupilumab and benralizumab also treat coexisting **nasal polyposis**; mepolizumab is the only one approved for **EGPA**.
- Assess response at **~4 months**: most have a partial response, **10–15% are non-responders** (switch biologic), a few achieve complete response (then wean OCS/ICS, watch for adrenal insufficiency).

Step 5 — Acute severe asthma / status asthmaticus

- **Recognise impending failure**: silent chest, exhaustion, altered sensorium, and a **normal or rising $PaCO_2$ in a distressed, tachypnoeic patient** (most present with hypocapnia — normocapnia = danger).
- **Oxygen** to keep SpO_2 >90%; **high-dose nebulised SABA** (≥3 in first hour, then frequent/continuous) + **ipratropium**; **systemic corticosteroid early** (prednisone 40–60 mg/day or methylprednisolone 1.5–2 mg/kg IV).
- **IV magnesium sulfate 2 g over 20 min** (40 mg/kg in children, max 2 g) for severe exacerbation (FEV_1 <25% predicted or non-responders).
- **NIV** in alert, cooperative patients; **heliox** and inhaled volatile anaesthetics (isoflurane/halothane) for refractory bronchospasm.
- **Mechanical ventilation** if respiratory arrest/impending arrest: **low minute ventilation (RR 12–14, V_t 6–8 mL/kg), high inspiratory flow, minimal/no PEEP, permissive hypercapnia** to avoid dynamic hyperinflation/barotrauma; deep sedation ± short-term paralysis. Avoid sedatives/mucolytics outside ventilation; antibiotics only for proven infection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Asthmatic vs normal airway cross-section** — label: *epithelial denudation/shedding, basement-membrane (subepithelial collagen) thickening, smooth-muscle hypertrophy & hyperplasia, submucosal oedema, mucus plug/goblet-cell metaplasia, eosinophil/cellular infiltrate, vascular & neuronal proliferation, narrowed lumen*.
- **Type-2 inflammatory cascade with biologic targets** — label: *allergen/alarmins (TSLP, IL-33, IL-25) → epithelium → ILC2 / Th2 → IL-4, IL-5, IL-13 → IgE, eosinophils, mucus/AHR*, with arrows naming **omalizumab (IgE), mepolizumab/reslizumab/benralizumab (IL-5/IL-5R), dupilumab (IL-4Rα), tezepelumab (TSLP)**.

Clinical / Diagnostic significance

- A structured **"confirm–exclude–phenotype–target"** pathway converts unselected "difficult" asthma into treatable subgroups and is the single highest-yield concept.
- **Biomarkers (eos, FeNO, IgE) are predictive, not merely diagnostic** — they select biologic responders and monitor type-2 activity and adherence.
- Recognising **AERD and ABPA** changes management (leukotriene modifiers/aspirin desensitisation; antifungal + steroid respectively).
- In acute care, **response to the first hour of therapy predicts need for admission better than presentation severity**.

High-yield exam pointers

- Severe asthma = **GINA Step 4–5; ~5–10% of asthmatics, ~50% of cost**.
- **ERS/ATS uncontrolled = any of**: ACT ≤19/ACQ ≥1.5; ≥2 OCS bursts/yr; ≥1 hospitalisation-ICU-ventilation/yr; FEV_1 <80% predicted.
- **First step is always adherence + inhaler technique** (cause in up to 50%).
- **Type-2 high** (eos ≥300, FeNO ≥25, ↑IgE) responds to ICS + biologics; **type-2 low** is steroid-resistant.
- **6 biologics**: anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL-4Rα (dupilumab), anti-TSLP (tezepelumab); **tezepelumab works in biomarker-low disease**.
- **ABPA**: IgE >1000 IU/mL + eos >500 + central bronchiectasis → itraconazole + steroid.
- **AERD**: asthma + nasal polyps + aspirin sensitivity → leukotriene modifier / aspirin desensitisation / anti-IL-5 / dupilumab.
- **Status asthmaticus**: normalising $PaCO_2$ = impending failure; ventilate with permissive hypercapnia, low rate/V_t, minimal PEEP.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Asthma"** (definitions of severe/difficult-to-treat asthma, pathophysiology, type-2/non-type-2 inflammation, biologics incl. tezepelumab, AERD, ABPA, acute attack/status asthmaticus management, high-risk-death features).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Asthma: Diagnosis and Management"** (ERS/ATS severe-asthma and uncontrolled-asthma criteria, phenotype/endotype & biomarker tables, FDA-approved biologics table with doses, difficult-to-treat vs severe definitions, acute asthma & mechanical-ventilation strategy, vocal-cord dysfunction).
- **CMDT 2026 — "Pulmonary Disorders" (Asthma)** (current stepwise/add-on management, IV magnesium indication, acute-exacerbation severity & antibiotic guidance).

◆ ◆ ◆

Glucocorticoids in management of COPD

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

Definition / Introduction — Chronic obstructive pulmonary disease (COPD) is a common, preventable, treatable disorder characterised by persistent, incompletely reversible airflow limitation arising from chronic airway and systemic inflammation driven by noxious particles/gases (chiefly cigarette smoke and biomass fuel). Because inflammation is central to its pathogenesis, **glucocorticoids** — with their broad anti-inflammatory action — are an attractive intervention. However, the inflammation of COPD is relatively *steroid-resistant*, so glucocorticoids occupy a **selective, eosinophil- and exacerbation-guided** role rather than being universal therapy. Their utility differs sharply by route (inhaled vs systemic) and by setting (stable disease vs acute exacerbation).

Rationale and why COPD is relatively steroid-resistant

- Airway and systemic inflammation are critical to COPD pathogenesis; glucocorticoids suppress transcription of pro-inflammatory cytokine genes, and **inhaled corticosteroids (ICS)** offer this benefit while minimising systemic exposure.
- Unlike asthma, COPD inflammation responds **poorly** to steroids. The molecular basis is *oxidative/nitrosative inactivation of histone deacetylase-2 (HDAC-2)* — cigarette-smoke-derived reactive oxygen species and peroxynitrite nitrate and inactivate HDAC-2, the enzyme normally recruited by the glucocorticoid receptor to switch off activated inflammatory genes.
- Consequently steroid efficacy is blunted; *low-dose theophylline* can partially **restore HDAC-2 activity and steroid responsiveness** (basis for theophylline as an add-on, though limited by its narrow therapeutic window).
- This explains the cardinal clinical rule: **ICS are never used as monotherapy in COPD** and the response is best in patients with an *eosinophilic/asthma-like* inflammatory signature.

Inhaled corticosteroids (ICS) in stable COPD

- **Main role = reduction of exacerbations**, especially in those with FEV_1 ≤60% predicted and a frequent-exacerbator phenotype; exacerbation reduction (~20–25%) is comparable to that of a LABA or LAMA.
- Effect on lung function is **modest** — improvement in FEV_1 of only ~50–100 mL, less than achieved with bronchodilators; four large 3–5-year trials failed to show that ICS slow the long-term decline in lung function.
- **Little symptomatic benefit alone**, so ICS are always combined with a long-acting bronchodilator: **ICS + LABA**, or as **triple therapy ICS + LABA + LAMA** (single-inhaler triple therapy improves adherence).
- Landmark trials shaping practice:
  - *TORCH* (6112 patients, 3 years; placebo vs fluticasone vs salmeterol vs combination) — fluticasone–salmeterol improved lung function, health status and exacerbations more than either agent alone; a post-hoc analysis suggested a reduced rate of FEV_1 decline.
  - *IMPACT* — triple therapy (ICS/LABA/LAMA) and ICS/LABA reduced **all-cause mortality** versus LABA/LAMA in an on-treatment analysis (strongest signal for an ICS mortality benefit, in fairly severe disease: mean FEV_1 ≈45%, CAT ≈20).
  - *FLAME* — in exacerbators, LABA/LAMA (indacaterol–glycopyrronium) was **superior** to ICS/LABA (fluticasone–salmeterol) for exacerbation reduction (0.98 vs 1.19/year), reinforcing that ICS are not first-line for all exacerbators.
- Common ICS molecules: **fluticasone (propionate/furoate), budesonide, mometasone, beclomethasone**, combined with LABAs (salmeterol, formoterol, vilanterol).

Eosinophil-guided ICS use and GOLD placement

The blood eosinophil count is the key biomarker predicting ICS benefit and is built into GOLD recommendations.

Blood eosinophil count	Likelihood of ICS benefit	Practical implication
< 100 cells/µL	Low — little/no exacerbation reduction	ICS generally **not** favoured; consider withdrawal
100–300 cells/µL	Intermediate zone	ICS may be **tried** and response assessed (add if exacerbations persist on dual bronchodilators)
≥ 300 cells/µL	Greatest likelihood of benefit	ICS **supported** as part of initial/escalation therapy; ICS withdrawal risks more exacerbations

GOLD (2024) initial pharmacological therapy — ICS placement:

Group	Definition	Recommended start	Role of ICS
A	≤1 exacerbation (no admission); low symptoms (mMRC 0–1 / CAT <10)	A bronchodilator	No

Group	Definition	Recommended start	Role of ICS
B	≤1 exacerbation; more symptoms (mMRC ≥2 / CAT ≥10)	LABA + LAMA	No
E	≥2 moderate exacerbations or ≥1 leading to hospitalisation	LABA + LAMA	**Consider adding ICS if blood eos ≥300**

- On **follow-up**, ICS is **added** to dual bronchodilator therapy if exacerbations persist and eos ≥100; in stable patients without exacerbations, **ICS withdrawal** may be considered (withdrawal does not increase exacerbations overall but may cause a small fall in FEV_1; de-escalation is riskier if eos ≥300).
- Other favourable factors for ICS: **concomitant asthma/ACO, history of hospitalised exacerbations**.

Systemic (oral) glucocorticoids in stable COPD

- **Chronic oral glucocorticoids are NOT recommended** for stable COPD because of an unfavourable benefit/risk ratio — and chronic systemic steroid use is associated with **increased mortality**.
- Tapering patients off chronic low-dose prednisone (~10 mg/day) does **not** worsen exacerbation frequency, quality of life or lung function — supporting withdrawal.
- A rare exception: in exacerbation-prone patients requiring repeated high-dose courses, the *lowest possible* maintenance dose may occasionally reduce total annual steroid exposure, but this is discouraged.

Glucocorticoids in acute exacerbations of COPD (AECOPD)

This is the **strongest, evidence-based indication** for glucocorticoids in COPD.

- **Benefits in hospitalised exacerbations:** shorten length of stay, **hasten recovery** (faster improvement in FEV_1 and oxygenation), and **reduce the chance of relapse / subsequent exacerbation**.
- **Regimen:**
  - *Harrison 22e / GOLD:* **prednisone 40 mg orally (or equivalent) once daily for 5 days** — a short course is as effective as longer courses (REDUCE-trial principle).
  - *CMDT 2026:* **prednisone ~0.5 mg/kg/day orally for 7–10 days** in hospitalised patients, with even 5 days often adequate.
  - Oral and IV routes are equivalent in most patients; IV methylprednisolone is reserved for those unable to take oral or critically ill.
- **Key acute complication: hyperglycaemia**, most frequent in patients with pre-existing diabetes — requires glucose monitoring.
- Combined with the rest of AECOPD therapy: short-acting bronchodilators (SABA ± SAMA), **antibiotics** (for increased sputum purulence/volume + dyspnoea, typically 5–7 days), controlled **oxygen** (target SpO_2 88–92%) and **NIV** for respiratory acidosis ($PaCO_2$ >45 mmHg, pH ≤7.35).

Adverse effects of glucocorticoids in COPD

Inhaled corticosteroids (ICS)	Systemic / oral glucocorticoids
Oral/oropharyngeal **candidiasis (thrush)**	Hyperglycaemia / glucose intolerance (commonest acute AE)
Dysphonia (hoarseness)	**Osteoporosis** and fractures
Pneumonia (increased incidence, esp. severe COPD)	Weight gain, fluid retention, cushingoid features
Easy bruising / skin capillary fragility	**Cataracts**, glaucoma
Reduced bone density, cataracts (with prolonged use)	Increased risk of **infection**; myopathy; HPA-axis suppression; increased mortality with chronic use

Mitigation: spacer use, mouth rinsing/gargling after ICS, lowest effective dose, ICS withdrawal when stable, and short steroid courses for exacerbations.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **GOLD 2024 ABE initial-therapy + eosinophil decision tree (showing where glucocorticoids fit).** Labels: *Groups A / B / E*; *Group A → a bronchodilator*; *Group B → LABA + LAMA*; *Group E → LABA + LAMA, consider + ICS if eos ≥300*; eosinophil ladder boxes — *<100 (no ICS), 100–300 (intermediate, trial ICS), ≥300 (ICS favoured)*; arrows for *escalation (add ICS)* and *de-escalation (withdraw ICS)*.
- **HDAC-2 mechanism of steroid resistance.** Labels: *cigarette smoke → oxidative/nitrosative stress (ROS, peroxynitrite) → inactivation/nitration of HDAC-2 → failure to switch off pro-inflammatory genes → relative steroid resistance*; side-arrow *theophylline → restores HDAC-2 activity*.

Clinical / Diagnostic significance

- **Phenotype-directed therapy:** measure the **blood eosinophil count** before committing a patient to long-term ICS — it predicts who benefits and limits unnecessary pneumonia/steroid risk.
- ICS reduce exacerbations but do **not** alter the relentless FEV_1 decline or (mostly) mortality — set patient expectations accordingly.
- **Pneumonia vigilance:** in a patient on ICS who develops recurrent pneumonia, consider ICS de-escalation, especially if eos <100.
- For an **acute exacerbation**, give a short systemic steroid course early — it is one of the few interventions that shortens admission and prevents relapse; monitor capillary glucose.
- Avoid **chronic oral steroids** for stable COPD; if a patient is steroid-dependent, attempt a structured taper.

High-yield exam pointers

- Glucocorticoid role in COPD is **selective**, NOT universal — driven by **exacerbation risk + blood eosinophils**.
- **ICS are never used as monotherapy** — always with LABA (± LAMA = triple therapy).

- ICS **reduce exacerbations** (~20–25%) but give only ~**50–100 mL FEV_1** gain and do not slow lung-function decline.
- **Eosinophil thresholds: <100 = no benefit; ≥300 = favour ICS;** 100–300 = trial and assess.
- Key ICS adverse effects: **oral candidiasis, dysphonia, pneumonia**, reduced bone density, cataracts.
- **Chronic oral glucocorticoids are NOT recommended** (unfavourable risk/benefit; increased mortality).
- **AECOPD:** prednisone **40 mg/day × 5 days** (GOLD/Harrison) or **0.5 mg/kg/day × 7–10 days** (CMDT) — shortens stay, hastens recovery, cuts relapse; **hyperglycaemia** is the commonest acute complication.
- Trials to quote: **TORCH** (fluticasone–salmeterol), **IMPACT** (triple therapy → lower all-cause mortality), **FLAME** (LABA/LAMA > ICS/LABA in exacerbators).
- Mechanism of steroid resistance = **oxidative inactivation of HDAC-2**; theophylline restores it.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Chronic Obstructive Pulmonary Disease" (inhaled and oral glucocorticoids in stable disease, eosinophil-guided ICS, GOLD ABE initial therapy, systemic glucocorticoids in exacerbations — prednisone 40 mg × 5 days).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "COPD: Diagnosis and Management" (ICS efficacy/FEV_1 50–100 mL, ~20–25% exacerbation reduction, TORCH/IMPACT/FLAME, eosinophil thresholds, adverse effects, chronic systemic steroids and mortality) and "COPD: Pathogenesis and Natural History" (HDAC-2 inactivation and steroid resistance; theophylline restoring HDAC-2).
- **CMDT 2026** — "Pulmonary Disorders / COPD" (judicious ICS in severe COPD with frequent exacerbations / eos ≥300 / concomitant asthma; ICS withdrawal after 2 years stable; oral corticosteroids not for long-term use; hospitalised exacerbation prednisone 0.5 mg/kg/day for 7–10 days).

◆ ◆ ◆

Sarcoidosis

Asked in: Paper III Jun 2024 · Paper III Nov 2022 (2×) — RGUHS MD General Medicine

Definition / Introduction — Sarcoidosis is a **multisystem inflammatory disease of unknown aetiology** characterised by the formation of **nonnecrotizing (noncaseating) epithelioid-cell granulomas** in affected organs. It involves the **lung and intrathoracic lymph nodes in >90%** of cases but can afflict almost any organ. It is presumed to result from an **exaggerated TH1 immune response to an undetermined antigen in a genetically susceptible host**. The skin lesions were first described by *Jonathan Hutchinson* (lupus pernio, Mortimer's malady) and termed "*sarkoid*" by *Caesar Boeck* (1899) because they resembled sarcoma yet were benign. Course is highly variable — spontaneous remission in just over half, chronic organ-threatening disease in the rest.

Epidemiology & Etiopathogenesis

- **Incidence/prevalence:** highest in **African Americans (~35.5/100,000)** and **Northern Europeans/Swedes (~24/100,000)**; US Black Women's Health Study noted prevalence ~2%. Female preponderance (ratio usually <2:1). **Peak age 35–45 years**, though a significant proportion present after 55.
- **Risk factors:** familial clustering, certain occupational/environmental exposures (firefighters; post-9/11 World Trade Center responders had markedly raised "sarcoid-like" disease), mould/musty environments, raised BMI. *Smoking is consistently associated with reduced odds (negative predictor).*
- **Putative antigens:** mycobacterial proteins (*mKatG, ESAT-6, superoxide dismutase A, antigen 85A, heat-shock proteins*) and *Cutibacterium (Propionibacterium) acnes*; transmissibility supported by the historical **Kveim–Siltzbach reagent** (splenic homogenate inducing granulomas) and donor-derived sarcoid-like disease in transplant recipients.
- **Genetics:** HLA class II haplotypes determine acute vs chronic phenotype; risk/prognosis variants include **BTNL2 (butyrophilin-like 2), TNF-α and ANXA11 (annexin A11)**.
- **Pathogenesis:** poorly degradable antigen presented by macrophages/dendritic cells via **MHC** to **$CD4^+$ T cells → highly polarized TH1 response** (IFN-γ, IL-2, IL-12/15/18, CXCR3) → activated macrophages aggregate into tightly formed granulomas. Dysregulated **T-regulatory and TH17** responses underlie failure of resolution and progression to fibrosis.

Clinical Features & Organ Involvement

- **Constitutional:** fever, malaise, night sweats, weight loss, multifactorial fatigue (up to 80%).
- **Acute syndromes (excellent prognosis, often spontaneous remission ~80%):**
  - **Löfgren syndrome** — *fever + erythema nodosum + bilateral hilar lymphadenopathy + ankle arthritis/peri-arthralgia*; common in Northern Europeans (20–30% of Caucasians), rare in Asians/African Americans.
  - **Heerfordt (uveoparotid fever) syndrome** — *anterior uveitis + parotid enlargement + fever + facial (VII) nerve palsy.* Both are clinically diagnostic and may obviate biopsy.

Organ	Approx. frequency	Key features
Lungs/thoracic nodes	~95%	Upper-lobe predominant; perilymphatic nodules, BHL; restriction ± obstruction
Skin	~16%	Erythema nodosum (non-granulomatous); **lupus pernio** (chronic, poor prognosis)
Peripheral lymph nodes	~15%	Discrete, mobile, nontender
Eyes	~12%	**Uveitis** (commonest), optic neuropathy (vision-threatening)
Liver	~12%	Granulomas common; ↑alkaline phosphatase; usually subclinical
Spleen	~7%	Splenomegaly, usually silent
Nervous system	~5%	Cranial neuropathy (VII, optic), basal meningitis, hypothalamic-pituitary dysfunction, small-fibre neuropathy
Salivary/parotid	~4%	Heerfordt; Sjögren-like
Heart	~2% clinical	AV block, VT, cardiomyopathy, sudden death
Kidney	~1%	Interstitial nephritis; nephrocalcinosis from hypercalciuria

- **Hypercalcaemia (10–20%) / hypercalciuria (up to 50%):** unregulated **1-α-hydroxylase (CYP27B1)** activity in macrophages converts vitamin D to **calcitriol (1,25-$(OH)_2D_3$)** *despite suppressed PTH* → ↑gut absorption + bone resorption → nephrocalcinosis.
- **Cardiac sarcoidosis:** ventricular tachycardia is the commonest arrhythmia; **sudden cardiac death is the commonest cause of death** in cardiac involvement and may be the presenting event.
- **Pulmonary hypertension:** a **WHO Group 5** cause; consider when symptoms/desaturation are disproportionate to parenchymal disease or DLCO is low.

Diagnosis & Investigations

- **Three diagnostic criteria** (the diagnosis is never absolutely secure): (1) **compatible clinical/radiological picture**, (2) **histological nonnecrotizing granuloma** in ≥1 tissue, and (3) **exclusion of alternative causes** (TB/atypical mycobacteria, fungi, berylliosis, hypersensitivity pneumonitis, lymphoma, IgG4-RD, vasculitis, drug/checkpoint-inhibitor reactions).
- **Biopsy:** least-invasive accessible site (skin, conjunctiva, peripheral node). For mediastinal/hilar disease, **EBUS-guided TBNA** has high yield with low risk; **transbronchial lung biopsy yield ~75–90%**. Airway granulomas give a *cobblestone* mucosa. Surgical biopsy/mediastinoscopy reserved for nondiagnostic cases.
- **Histology:** tightly formed granuloma of epithelioid cells + **multinucleated giant cells**, rimmed by lymphocytes/fibroblasts; **$CD4^+$** cells central, **$CD8^+$/B cells** peripheral. Inclusions: **asteroid bodies, Schaumann bodies, Hamazaki-Wesenberg bodies**, birefringent calcium oxalate/carbonate crystals (all non-specific).

- **BAL:** lymphocytosis with **CD4:CD8 ratio >3.5** supports the diagnosis (specificity ~95% in some series); a normal ratio does not exclude it. Also excludes infection.
- **Baseline workup (all patients):** history/examination, **PFTs**, **chest imaging**, **ophthalmologic exam** (silent uveitis), **ECG**, serum creatinine, alkaline phosphatase, **calcium**, CBC, and 25-/1,25-vitamin D.
- **Chest radiograph — Scadding stages** (predict resolution, *not* activity):

Stage	Radiographic finding	Spontaneous resolution
0	Normal chest X-ray	—
I	Bilateral hilar lymphadenopathy alone	55–90%
II	BHL + parenchymal infiltrates	40–70%
III	Parenchymal infiltrates without BHL	10–20%
IV	Pulmonary fibrosis, volume loss, architectural distortion	~0%

- **HRCT:** perilymphatic micronodules along bronchovascular bundles and subpleural surfaces, beaded interlobular septa, mediastinal/hilar nodes; advanced → honeycombing, traction bronchiectasis, cavitation.
- **Cardiac:** ECG screening in all; **cardiac MRI with late gadolinium enhancement is the preferred test** (FDG-PET if MRI unavailable/contraindicated), largely replacing endomyocardial biopsy (low sensitivity owing to patchy involvement); perfusion shows *reverse redistribution*.
- **Serum markers: ACE** (from epithelioid cells) is *neither sensitive nor specific* — roughly tracks granuloma burden, not diagnostic; soluble IL-2 receptor correlates with activity/relapse. Hypercalcaemia, ↑ESR and ↑alkaline phosphatase are supportive.

Treatment

- **Principle:** there is **no cure**; aim is to suppress granulomatous inflammation, prevent irreversible fibrosis and relieve symptoms. **Treat only when indicated** — asymptomatic Stage I and mild disease are observed (high spontaneous remission). Treat for significant/progressive pulmonary impairment or dangerous extrapulmonary disease (cardiac, neuro, ocular/vision-threatening, symptomatic hypercalcaemia, disfiguring skin).

Line	Agent(s)	Dose / note
First-line	**Oral corticosteroids** (prednisone/prednisolone)	0.5 mg/kg/day or ~20–40 mg/day × 4 wk, taper to maintenance <10 mg/day; *SARCORT* (India) — 20 mg ≈ 40 mg starting dose
Second-line (steroid-sparing)	**Methotrexate** (most recommended)	7.5–20 mg/week + folic acid; monitor LFT/CBC; avoid in alcohol use
	Azathioprine / Leflunomide / Mycophenolate	alternatives; azathioprine has higher infection/malignancy risk
	Hydroxychloroquine	200–400 mg/day — useful for **skin & hypercalcaemia**, not pulmonary

Line	Agent(s)	Dose / note
Refractory / steroid-dependent	**Infliximab** (TNF-α mAb, best evidence) / Adalimumab	screen for TB first; avoid in heart failure
Ineffective	**Etanercept**	TNF-receptor antagonist — *not effective, do not use*
Topical/local	Inhaled or injected/topical steroids	mild airway cough, skin lesions

- **Refractory** = failure to respond to the equivalent of **prednisone 40 mg/day**. **Duration ~1 year** (shorter courses → higher relapse). Bisphosphonates to prevent steroid-induced osteoporosis; periodic eye exams on steroids/hydroxychloroquine. **Organ transplantation** (lung/heart/liver/kidney) for end-stage disease; granulomas may recur in the graft but rarely cause graft failure.
- **Supportive / parasarcoidosis syndromes:** fatigue, small-fibre neuropathy, pain, depression and cognitive impairment often respond poorly to immunosuppression — manage with exercise training, sleep/pain/neuropsychiatric care.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Immunopathogenesis schematic:** Unknown antigen → APC/macrophage with **MHC** → **TCR on CD4⁺ T cell (activated)** → **TH1 response (IFN-γ, IL-2)** with **TH17** → **noncaseating granuloma** → branch to **Resolution** vs **Fibrosis** (modulated by **Treg**). Labels: *Unknown antigen, MHC, TCR, CD4⁺ T cell, TH1, TH17, Treg, Granuloma, Resolution, Fibrosis.*
- **Sarcoid granuloma vs comparators:** (A) **Sarcoidosis** — tightly formed, **nonnecrotizing**; (B) **Tuberculosis/fungal** — tight with **caseous necrotic centre**; (C) **Hypersensitivity pneumonitis** — loosely formed, non-necrotizing. Label central **epithelioid + multinucleated giant cells**, peripheral **lymphocyte rim**, and inclusions (**asteroid / Schaumann bodies**).

Clinical / Diagnostic significance

- A diagnosis of **exclusion** — always rule out TB (critical in India) and lymphoma before labelling; necrosis on biopsy argues strongly against sarcoidosis.
- Every patient needs **baseline ophthalmology, ECG, calcium and PFTs** because silent uveitis, conduction disease and hypercalcaemia are organ/sight/life-threatening.
- **Scadding stage predicts resolution rate, not disease activity** — do not use it alone to decide treatment.
- **Pulmonary fibrosis is the leading cause of sarcoid death** (Western populations); **cardiac involvement predominates as cause of death in Japanese** patients.
- Steroid-sparing agents should be introduced early when prolonged (>1 year) therapy is anticipated to limit cumulative steroid toxicity.

High-yield exam pointers

- **Noncaseating granuloma** + lung/intrathoracic nodes in **>90%**; histology of **exclusion**.
- **Löfgren** = EN + BHL + ankle arthritis + fever (good prognosis); **Heerfordt** = uveoparotid fever + VII palsy.
- **BAL CD4:CD8 > 3.5**; **EBUS-TBNA** preferred for mediastinal nodes; **TBLB yield 75–90%**.
- **Scadding stages I–IV**: I 55–90%, II 40–70%, III 10–20%, IV ~0% resolution.
- **Hypercalcaemia** from macrophage **1-α-hydroxylase → calcitriol with low PTH**.
- **ACE is neither sensitive nor specific** — for activity monitoring, not diagnosis.
- **Cardiac MRI (LGE)** preferred for cardiac sarcoid; **VT** commonest arrhythmia, **sudden death** commonest cardiac death.
- **First-line steroids**; **methotrexate** second-line; **infliximab** refractory; **etanercept ineffective**.
- Poor-prognosis markers: **lupus pernio, chronic uveitis, neuro/cardiac involvement, chronic hypercalcaemia/nephrocalcinosis, pulmonary hypertension, fibrotic (Stage IV) disease, African origin.**
- **Smoking is protective**; PH in sarcoidosis is **WHO Group 5.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Sarcoidosis"** (Gerke; immunopathogenesis, organ involvement frequencies, Scadding staging with resolution rates, hypercalcaemia mechanism, treatment table including doses, prognosis).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Sarcoidosis"** (Scadding patterns, HRCT perilymphatic distribution, serum ACE from epithelioid cells, BAL CD4:CD8 specificity, Löfgren/Heerfordt definitions, refractory = failure of prednisone 40 mg/day, corticosteroid-sparing rationale, parasarcoidosis syndromes).
- **CMDT 2026 — "Sarcoidosis" (Pulmonary Disorders)** (essentials, staging, transbronchial-biopsy yield, prednisone 0.5–1.0 mg/kg/day, SARCORT 20 vs 40 mg trial, cardiac MRI over PET, prognosis figures).

◆ ◆ ◆

Obstructive sleep apnoea

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

Definition / Introduction — Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, characterised by recurrent episodes of complete (apnea) or partial (hypopnea) collapse of the **pharyngeal airway during sleep**, occurring despite persistent respiratory effort. Each event terminates in arousal and/or oxyhemoglobin desaturation, producing sleep fragmentation, intermittent hypoxemia and sympathetic surges. The term **obstructive sleep apnea/hypopnea syndrome (OSAHS)** denotes OSA accompanied by symptoms, classically excessive daytime sleepiness (EDS). Diagnosis rests on objective sleep study quantification using the **apnea-hypopnea index (AHI)**: ≥5 events/h with symptoms, or ≥15 events/h irrespective of symptoms.

Pathophysiology

- The pharynx lacks rigid bony/cartilaginous support, so patency depends on **pharyngeal dilator muscle** tone (genioglossus the principal). During inspiration, intraluminal pressure becomes negative ("suction"); dilator activation must counteract this.
- At **sleep onset**, neuromuscular output to dilators falls. In a person with an anatomically narrow/collapsible airway, this transient loss of compensation causes pharyngeal collapse (apnea) or near-collapse (hypopnea). Common collapse sites: **soft palate (most common), tongue base, lateral pharyngeal walls, and epiglottis**.
- Collapse is worst in **REM sleep** (lowest skeletal-muscle tone) and in the **supine position** (gravity). Low lung volume in recumbency/obesity reduces caudal tracheal traction, decreasing pharyngeal-wall stiffness.
- **Starling resistor model** — collapsibility is expressed as the **critical closing pressure (Pcrit)**; a more negative Pcrit = less collapsible airway: normal <−10 cmH_2O, non-apneic snoring −10 to −5, obstructive hypopnea −5 to 0, obstructive apnea >0 cmH_2O.
- **Non-anatomic ("ventilatory control") traits** also contribute: high loop gain (oversensitive chemoresponsiveness to CO_2 causing unstable breathing), a low arousal threshold (premature awakening prevents dilator compensation), and poor dilator muscle responsiveness. These define individual **OSA endotypes/phenotypes**.

Predisposing risk factors

- **Obesity** — the dominant modifiable factor; accounts for ~40–60% of cases. A 10% weight gain raises AHI by ~30% and confers a sixfold risk of developing AHI ≥15; obese persons have ≥4-fold risk.
- **Male sex** (2–3× more prevalent; android fat distribution, longer/more collapsible pharynx); **older age**; **postmenopausal** state in women (loss of protective sex-hormone effect on ventilatory drive).
- **Craniofacial**: retrognathia, micrognathia, high-arched palate; genetic syndromes — *Down syndrome*, *Treacher-Collins*, *Pierre-Robin sequence*.
- **Adenotonsillar hypertrophy** (chief cause in children, peak age 3–8 yr), **macroglossia**, nasal obstruction (septal deviation, polyps).

- **Endocrine**: hypothyroidism (25–35%), acromegaly (~70% have SDB), PCOS; also **family history** (first-degree relative risk ~2×), East-Asian ancestry (craniofacial), alcohol, sedative-hypnotics and opioids, and smoking.

Clinical features

Nocturnal symptoms	Daytime symptoms
Loud habitual **snoring**, witnessed apneas, gasping/choking, nocturnal restlessness/diaphoresis, **nocturia**, GERD, morning headache, unrefreshing sleep, insomnia (more in women)	**Excessive daytime sleepiness** (cardinal), fatigue, impaired concentration/memory, irritability, mood/depressive symptoms, reduced libido/impotence

- **Physical findings**: central obesity, large **neck circumference**, hypertension; crowded oropharynx with **Mallampati class III–IV**, low-lying soft palate, bulky uvula, enlarged tonsils, macroglossia, retro-/micrognathia, nasal obstruction.
- Sex differences: women report more insomnia/fatigue/depression and less heavy snoring; apneas shorter and REM-predominant — a cause of under-recognition.

Diagnosis and investigations

- **Screening tools** (estimate pretest probability; sensitive but not specific): **STOP-Bang** (Snoring, Tiredness, Observed apnea, Pressure/HTN, BMI >35, Age >50, Neck >40 cm, male Gender), Berlin and NoSAS questionnaires. The **Epworth Sleepiness Scale** quantifies sleepiness (8 situations, 0–3 each; **score ≥11 = excessive sleepiness**).
- **Polysomnography (PSG)** is the **gold standard** (Level 1, attended, in-laboratory): records EEG, EOG, chin/leg EMG, ECG, oronasal airflow (thermistor + nasal pressure), thoraco-abdominal effort bands, oximetry, body position, snoring. **Home sleep apnea testing (Level 3)** is acceptable for high-pretest-probability patients without major comorbidity; a negative home study in a high-probability patient should be followed by PSG.
- **Respiratory event scoring (AASM):**

Event	Definition
Apnea	≥90% fall in airflow ≥10 s; *obstructive* = effort persists (thoraco-abdominal paradox), *central* = effort absent, *mixed* = central then obstructive
Hypopnea	≥30% airflow reduction ≥10 s with ≥3% desaturation **or** an arousal (def 1A); or ≥4% desaturation (def 1B)
RERA	Increasing effort/flow-limitation terminating in arousal, not meeting hypopnea criteria

- **AHI** = (apneas + hypopneas)/hour of sleep; **RDI** adds RERAs. Severity grading:

Severity	AHI (events/h)
Normal	<5
Mild	5–14
Moderate	15–29
Severe	≥30

- Adjuncts: serum **TSH/FT_4** (exclude hypothyroidism); erythrocytosis from chronic hypoxemia; ABG normal in pure OSA (waking hypercapnia suggests **obesity hypoventilation syndrome [OHS]** — BMI >30 with daytime $PaCO_2$ >45 mmHg; OSA coexists in ~90%). Overnight BP often shows a "**non-dipping**" pattern. MSLT/MWT help distinguish narcolepsy and quantify sleepiness.

Health consequences / complications

- **Hypertension** — OSA is an identifiable secondary cause; produces nocturnal non-dipping, and **resistant/uncontrolled HTN** via sympathetic activation and RAAS/fluid effects. CPAP lowers 24-h BP modestly (~2–4 mmHg, more in sleepy/resistant patients).
- **Cardio-/cerebrovascular**: coronary artery disease, heart failure (HFrEF and HFpEF), **atrial fibrillation** and ventricular arrhythmias, stroke; OSA does not by itself cause right-heart failure (cor pulmonale implies coexisting cardiopulmonary disease).
- **Metabolic**: insulin resistance/type 2 diabetes, pro-inflammatory and prothrombotic state.
- **Neurobehavioural**: EDS, cognitive impairment, depression; **2–3× risk of motor-vehicle and occupational accidents**; reduced quality of life. (Large RCTs of CPAP have not shown reduced cardiovascular event rates, likely from exclusion of sleepy patients and poor adherence.)

Management

- **General / behavioural**: weight reduction (even bariatric surgery), adequate sleep duration (7–9 h), **avoid supine sleep** (positional/vibrotactile therapy can cut AHI ~50% in positional OSA), treat nasal allergy, increase activity, **avoid alcohol within 3 h of bed**, and minimise sedatives/opioids.
- **CPAP** — *standard first-line therapy with the highest evidence*; a pneumatic splint maintaining airway patency. Titrated by sleep study or auto-titrating **APAP** (5–20 cmH_2O). Improves sleepiness, mood, BP and insulin sensitivity; adherence is the limiting factor (~50–80%; ~75% still using at 1 year). Side effects (nasal congestion, claustrophobia, aerophagia) are managed with humidification, mask change, or bilevel PAP.
- **Mandibular advancement (oral) appliances** — advance the mandible/tongue; reduce AHI by ≥50% in two-thirds; best for **mild–moderate OSA** or CPAP-intolerant patients; side effects: TMJ pain, tooth movement.
- **Surgery**: **uvulopalatopharyngoplasty (UPPP)** (removes uvula + ~15 mm of soft-palate margin) helps ~50%, better for snoring than apneas; often part of **multilevel surgery**. Nasal septoplasty aids CPAP tolerance. **Tracheostomy** is definitive but reserved for refractory severe disease. **Bariatric surgery** for obese patients.
- **Hypoglossal (upper-airway) nerve stimulation** — implanted stimulator for CPAP-intolerant moderate–severe OSA (**AHI 15–65**, per CMDT up to 100), **BMI <35**, and **absence of complete concentric collapse at the velum** on drug-induced sleep endoscopy.
- **Pharmacotherapy**: no FDA-approved drug historically; **tirzepatide** (dual GLP-1/GIP agonist) achieved ~16–17% weight loss with reduction in AHI (*NEJM 2024*) — a major recent advance; noradrenergic-antimuscarinic combinations (enhancing dilator tone) are in trials. Supplemental O_2 alone is **not** recommended (may prolong apneas).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Upper-airway sagittal section** showing collapse sites — label: *nasal cavity, soft palate, uvula, tongue base, lateral pharyngeal walls, epiglottis, genioglossus muscle*; arrows for negative inspiratory ("suction") pressure causing collapse.
- **Polysomnography tracing of an obstructive apnea** — label channels: *EEG (arousal), nasal-pressure & thermistor airflow (cessation ≥10 s), chest and abdomen effort bands showing paradoxical/thoraco-abdominal paradox, SaO_2 (desaturation dip)*; contrast with a central apnea (flat effort channels).

Clinical / Diagnostic significance

- Consider OSA in any patient with resistant hypertension, recurrent AF, nocturnal angina/arrhythmia, type 2 diabetes, unexplained pulmonary hypertension, or pre-operative obese patients (use STOP-Bang).
- Pre-operative recognition reduces perioperative airway/cardiac complications; OHS carries the highest risk.
- Confirm with PSG/HSAT and grade by AHI before committing to lifelong CPAP; reassess residual sleepiness and adherence at follow-up.

High-yield exam pointers

- **AHI** defines and grades OSA: mild 5–14, moderate 15–29, severe ≥30; diagnostic threshold ≥5 with symptoms or ≥15 without.
- **Apnea** = ≥90% airflow drop ≥10 s; obstructive = effort present (thoraco-abdominal paradox); **hypopnea** = ≥30% drop with ≥3% desat or arousal.
- Major risk factors: **obesity, male sex, older age**; collapse site most often the **soft palate**; worst in **REM** and **supine**.
- **Epworth ≥11** = excessive sleepiness; **STOP-Bang** for screening; **Mallampati III–IV** on exam.
- **PSG is gold standard**; **CPAP is first-line treatment**; oral appliance for mild–moderate/CPAP-intolerant.
- **Pcrit** (Starling resistor) >0 cmH_2O = frank obstructive apnea.
- OSA is a secondary cause of **resistant hypertension** and is linked to **AF, stroke, CAD, diabetes**.
- Newer options: **hypoglossal nerve stimulation** (AHI 15–65, BMI <35, no concentric velar collapse) and **tirzepatide** for weight-driven OSA.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Sleep Apnea" (definitions, pathophysiology, AHI severity, consequences, treatment including CPAP/oral appliance/UPPP/hypoglossal nerve stimulation/GLP-1 agonists).
- Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Obstructive Sleep Apnea" and "Sleep-Disordered Breathing: A General Approach" (pathogenesis, Pcrit/Starling resistor, AASM event-scoring criteria, Epworth scale, levels of sleep testing, predisposing/endocrine factors, OHS).
- CMDT 2026 — "Pulmonary Disorders: Obstructive Sleep Apnea" (clinical findings, Mallampati, polysomnography, current management, hypoglossal nerve stimulation criteria, tirzepatide).

◆ ◆ ◆

Silicosis

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

Definition / Introduction — Silicosis is a fibrotic interstitial lung disease (a **pneumoconiosis**) caused by inhalation of **free crystalline silica (SiO_2)**, principally as **quartz**. It is one of the oldest known occupational lung hazards and remains a major cause of disease worldwide. Pulmonary fibrosis due to silica characteristically develops in a **dose–response fashion**, usually after many years of exposure, though intense exposure can cause fulminant disease within months. The hallmark lesion is the **upper-zone silicotic nodule**, which may coalesce into **progressive massive fibrosis (PMF)**.

Etiology, sources and pathogenesis

- **Hazardous agent:** free silica (SiO_2), i.e., **crystalline quartz**. Risk relates to the *free silica content* of the inhaled dust.
- **Respirable particle size:** only particles **<10 µm** deposit below the larynx; **coarse-mode (2.5–10 µm)** crustal particles such as silica deposit relatively high in the tracheobronchial tree. Particles >10–15 µm are filtered in the nose/throat.
- **Major occupational exposures: mining; stone-cutting; sand-blasting; glass and cement manufacturing; foundry work; packing of silica flour; quarrying (particularly granite).**
- **Recent outbreaks / emerging high-risk work: sand-blasting of denim jeans** to make them look "used," and the **manufacture and installation of artificial ("faux granite"/engineered quartz) stone kitchen countertops** — a cause of acute silicosis in young workers.
- **Pathogenesis (source-grounded):** inhaled silica is ingested by **alveolar macrophages**; silica is directly cytotoxic and causes **alveolar macrophage dysfunction**. Silica also has **immunoadjuvant properties**, driving a fibrogenic and autoimmune-prone inflammatory response that produces the characteristic nodular fibrosis. The fibrosis may be **progressive even after exposure ceases**.
- **Dose–response and cumulative dose:** the probability and severity of fibrosis rise with **intensity × duration** of respirable-silica exposure; this explains why most chronic disease follows years of work while intense confined-space exposure can cause disease within months.

- **Macrophage defence is impaired**, leaving the silicotic lung vulnerable to intracellular pathogens — a single mechanism that links silicosis to both **tuberculosis** and the autoimmune/carcinogenic complications below.

Clinical–radiological types

Type	Exposure / latency	Key features
Acute silicosis (*silicoproteinosis*)	Very heavy exposure (sand-blasting in **confined spaces**, tunnelling rock of **15–25% quartz**, artificial-stone work) — symptoms within **months**	Clinical & pathological features resemble **pulmonary alveolar proteinosis**; rapidly progressive; severe even after exposure stops
Accelerated silicosis	Heavy exposure over **~5–10 years** (standard textbook category)	Features intermediate between acute and chronic; faster progression to PMF
Chronic simple silicosis	Long-term, less intense exposure — opacities after **15–20 years**	**Small rounded opacities, upper lobes**; usually **without functional impairment**; **"eggshell" hilar node calcification** in up to **20%**
Complicated silicosis / PMF	Coalescence of nodules (may progress *without* further exposure)	Non-segmental **conglomerate masses >1 cm** in upper zones; significant **restrictive + obstructive** impairment

- **Acute silicosis imaging:** chest radiograph may show **profuse miliary infiltration or consolidation**; HRCT shows a **"crazy-paving"** pattern (ground-glass with thickened intralobular/interlobular septa producing polygonal shapes).
- **Complicated silicosis:** silicotic nodules coalesce into **irregular conglomerate masses >1 cm**; when these become large the term **progressive massive fibrosis (PMF)** is applied.

Investigations and radiology

- **Chest radiograph (ILO classification):** the **International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses** grades opacities; **small rounded opacities** are typical of silicosis (and coal-worker's pneumoconiosis), contrasting with the **small linear/irregular opacities** of asbestosis. Useful for epidemiology/screening but limited in the individual worker.
- **HRCT:** more sensitive than plain film for detecting **silicotic nodules** and the **crazy-paving** pattern of acute disease; nodules are often **subpleural** and **upper-zone predominant**.
- **"Eggshell" calcification** of hilar lymph nodes is a classic supportive sign (up to ~20% of cases).
- **Pulmonary function tests:** often normal in **simple** silicosis; **PMF** produces **mixed restrictive and obstructive** deficits with reduced diffusing capacity.
- **Occupational history** is central — quantify type, intensity and duration of exposure; combine work history with any environmental sampling data to estimate cumulative exposure.

Complications and associations

- **Tuberculosis (silicotuberculosis):** because silica causes **alveolar macrophage dysfunction**, patients are at **increased risk of active TB** and other intracellular pathogens (**Mycobacterium**

tuberculosis, atypical mycobacteria, fungi). Because of this risk, **treatment of latent TB is given for a longer duration** in silicotic patients.

- **Autoimmune connective-tissue disease:** silica's **immunoadjuvant** effect predisposes to **rheumatoid arthritis** and **scleroderma**.
- **Caplan syndrome:** combination of **pneumoconiotic nodules and seropositive rheumatoid arthritis** — first described in coal miners but subsequently recognised in silicosis.
- **Lung cancer:** the **International Agency for Research on Cancer (IARC)** lists silica as a **probable lung carcinogen**.
- **COPD / chronic airflow obstruction** may accompany dust exposure.
- **Related silicate/inorganic-dust exposures** to consider: fuller's earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate and cement dusts; **talc and vermiculite** may be **contaminated with asbestos** (risk of fibrosis, lung cancer, mesothelioma).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Chest radiograph of chronic/complicated silicosis (frontal view).** Labels: *upper-zone small rounded nodules*; *"eggshell" calcification of hilar lymph nodes*; *conglomerate mass = progressive massive fibrosis (PMF)*; *relatively spared lower zones*; *retracted hila*.
- **Diagram 2 — Pathogenesis flow.** Labels: *Inhaled crystalline silica (respirable, <10 μm) → Alveolar macrophage ingestion → Macrophage cytotoxicity / dysfunction + immunoadjuvant effect → Release of inflammatory & fibrogenic mediators → Silicotic nodule formation → Fibrosis → coalescence → PMF*; side-branches to *↑TB risk*, *autoimmune disease (RA, scleroderma)*, *probable lung carcinogen*.

Clinical / Diagnostic significance

- **Diagnosis** rests on a triad of **compatible occupational exposure history**, **characteristic chest imaging** (upper-zone rounded nodules ± eggshell nodal calcification ± PMF on radiograph/HRCT), and **exclusion of mimics** (especially TB and sarcoidosis). Lung biopsy is rarely needed and is reserved for atypical presentations.
- **Differential diagnosis: pulmonary tuberculosis** (always exclude active disease before attributing upper-zone change to silicosis), **sarcoidosis** (bilateral hilar adenopathy, granulomas), **coal-worker's pneumoconiosis** and **chronic beryllium disease** (sarcoid-like, occupational), and for acute silicosis, **pulmonary alveolar proteinosis** (which it mimics clinically, radiologically and pathologically).
- **No specific curative therapy** exists; management is **supportive**, as for any diffuse interstitial lung disease — exposure cessation, smoking cessation, oxygen and pulmonary rehabilitation, and vaccination.
- **Whole-lung lavage** may provide **symptomatic relief and slow progression** in **acute silicosis** (mirroring its role in alveolar proteinosis).
- **Active TB surveillance** and **prolonged treatment of latent TB infection** are essential because of the markedly raised tuberculosis risk.

- **Prevention is paramount:** dust control (wet methods, enclosure, ventilation), substitution, respiratory protection, periodic chest imaging/PFT surveillance, and regulatory exposure limits — protection has improved in developed countries but risk persists in developing-country and engineered-stone settings.

High-yield exam pointers

- Causative agent = **free crystalline silica (SiO_2)/quartz**; only **respirable (<10 µm)** particles cause disease.
- **Upper-zone** small rounded nodules + **"eggshell" hilar nodal calcification** = classic silicosis radiology.
- **Acute silicosis = silicoproteinosis** — resembles **pulmonary alveolar proteinosis**, HRCT **"crazy paving,"** treat with **whole-lung lavage**; seen in **artificial-stone/quartz countertop** workers and denim sand-blasting.
- **Simple → complicated → PMF:** PMF = conglomerate masses **>1 cm**; may progress **even after exposure stops**.
- **Silicotuberculosis** — high active-TB risk; give **longer** latent-TB treatment.
- **Caplan syndrome** = pneumoconiotic nodules + **seropositive rheumatoid arthritis**.
- Silica is a **probable lung carcinogen (IARC)** and predisposes to **scleroderma & RA**.
- High-quartz tunnelling = **15–25% quartz**; tunnelling/sand-blasting in **confined spaces** → acute disease in **months**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 300 "Occupational and Environmental Lung Disease" (silicosis section, particle-deposition and ILO-classification sections, Table 300-1; Caplan syndrome cross-ref Ch 370). **Coverage note:** the chapter explicitly describes *acute*, *simple chronic* and *complicated/PMF* silicosis; the intermediate **"accelerated silicosis"** category and the generic **supportive-care/prevention** measures (smoking cessation, vaccination, dust control, surveillance) are universally accepted standard internal medicine added for completeness and are not verbatim subtypes in the provided text. Detailed molecular pathogenesis (e.g., NALP3/inflammasome) is beyond the provided chapter and is therefore not asserted.

◆ ◆ ◆

Systemic manifestations of COPD

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

Definition / Introduction — Chronic obstructive pulmonary disease (COPD) is a disease state characterised by **persistent respiratory symptoms and airflow obstruction**, and encompasses *emphysema* (alveolar destruction with air-space enlargement), *chronic bronchitis* (chronic cough and phlegm) and *small airway disease*. Although defined by spirometric airflow limitation, COPD is now recognised as a **multi-system disorder**: a low-grade systemic inflammatory "spill-over" together with chronic hypoxaemia, physical inactivity and shared smoking-related risk drives extrapulmonary effects and **comorbidities** that independently determine symptoms, exacerbations, quality of life and mortality. Harrison explicitly directs the clinician to seek symptoms of common comorbidities — **cardiovascular disease, gastro-oesophageal reflux, osteoporosis, frailty, depression and anxiety** — in every COPD patient.

Why COPD becomes a systemic disease (mechanistic basis)

- **Systemic inflammation / cytokine spill-over** — the airway inflammatory process is mirrored by raised circulating inflammatory cytokines, notably **tumour necrosis factor-α (TNF-α)**, which mediate wasting and contribute to several extrapulmonary effects.
- **Chronic hypoxaemia** — develops as airflow obstruction worsens; drives secondary **erythrocytosis (elevated haematocrit)**, pulmonary vasoconstriction/pulmonary hypertension and cor pulmonale, and signals the need for long-term oxygen.
- **Autoimmune component** — lymphoid follicles of B and T cells, TH1/TH17 activation and autoantibodies against elastin fragments and pulmonary epithelium perpetuate chronic inflammation even after smoking cessation.
- **Deconditioning & shared exposure** — dyspnoea-limited inactivity plus the common risk factor of tobacco smoke link COPD with cardiovascular disease, lung cancer, osteoporosis and metabolic disturbance.

Systemic manifestations & comorbidities — at a glance

System	Manifestation	Mechanism / note (Harrison)
Nutritional	**Cachexia**, weight loss, loss of subcutaneous fat	Inadequate intake + raised cytokines (TNF-α); **independent poor prognostic factor**
Musculoskeletal	Skeletal-muscle dysfunction, accessory-muscle use, reduced exercise capacity	Deconditioning, hyperinflation; quantified by 6-min walk
Skeletal	**Osteoporosis**	Listed comorbidity; aggravated by inhaled/oral glucocorticoids
Cardiovascular	**Cardiovascular disease**; **cor pulmonale / RV failure**, pulmonary hypertension	Hypoxaemia + pulmonary vascular destruction
Haematological	**Secondary polycythaemia (raised haematocrit)**	Chronic hypoxaemia; *anemia of chronic disease may coexist* (see Coverage note)

System	Manifestation	Mechanism / note (Harrison)
Neuropsychiatric	**Depression, anxiety, frailty**	Common, under-recognised comorbidities
GI / Metabolic	**GERD**; glucose intolerance, weight gain	GERD a comorbidity; metabolic effects largely steroid-related
Neoplastic	**Lung cancer**	Smokers with COPD at high risk; new **clubbing** must prompt work-up
Thrombotic	**Pulmonary embolism**	Incidence increased during exacerbations

Nutritional & musculoskeletal manifestations

- **Cachexia** is a feature of advanced disease — *significant weight loss with diffuse loss of subcutaneous adipose tissue*. It is linked to both **inadequate oral intake** and **elevated inflammatory cytokines (e.g., TNF-α)**.
- Such **wasting is an independent poor prognostic factor** in COPD — i.e., it predicts mortality over and above the degree of airflow obstruction.
- **Body mass index (BMI)** is therefore embedded in the **BODE index** (*B*ody mass index, airflow *O*bstruction, *D*yspnoea, *E*xercise capacity), a multifactorial tool that predicts mortality better than FEV_1 alone.
- **Skeletal-muscle dysfunction & deconditioning** — patients use accessory muscles (sternocleidomastoid, scalene, intercostals) and adopt the **"tripod" position**; exercise capacity is reduced and is quantified by the distance walked in 6 minutes.
- **Osteoporosis** is a listed comorbidity and is compounded by therapy: **inhaled corticosteroids** are associated with loss of bone density (and cataracts, oropharyngeal candidiasis, pneumonia), and **chronic oral glucocorticoids** cause **osteoporosis, weight gain, cataracts, glucose intolerance and increased infection risk** — hence chronic oral steroids are *not recommended*.

Cardiovascular & pulmonary-vascular manifestations

- **Cardiovascular disease** is among the most important comorbidities to screen for in the history.
- **Cor pulmonale** — signs of overt **right heart failure** (raised JVP, lower-extremity oedema). Pulmonary arterial hypertension severe enough to cause cor pulmonale and **right ventricular failure** typically occurs with **FEV_1 <25 % predicted and chronic hypoxaemia (PaO_2 <55 mmHg)**.
- Some patients develop significant **pulmonary arterial hypertension from pulmonary vascular destruction, independent of COPD severity**.
- Cor pulmonale has become *relatively infrequent since supplemental oxygen therapy* became available, but pulmonary hypertension must be considered in any patient with persistent activity limitation or lower-extremity oedema.
- **Right ventricular hypertrophy** signs and an **elevated haematocrit** are clues to chronic hypoxaemia.

Haematological, neuropsychiatric, neoplastic & other systemic effects

- **Secondary polycythaemia / erythrocytosis** — an **elevated haematocrit suggests chronic hypoxaemia**; **erythrocytosis** is itself one of the qualifying signs (with pulmonary arterial hypertension or right heart failure) that lowers the oxygen-saturation threshold for long-term O_2 to **≤89 %** (≤88 % otherwise).
- **Central cyanosis** — visible in the lips and nail beds, reflecting hypoxaemia.
- **Lung cancer** — smokers with COPD are at high risk; annual **low-dose chest CT** screening reduces lung-cancer mortality. **Clubbing is NOT a feature of COPD** — its appearance must trigger a search for another cause, most often **lung cancer**.
- **Depression, anxiety and frailty** — frequent neuropsychiatric/whole-patient comorbidities that should be actively elicited.
- **Gastro-oesophageal reflux disease (GERD)** — a recognised comorbidity and a contributor to exacerbations.
- **Metabolic** — glucose intolerance and weight gain occur chiefly as adverse effects of glucocorticoid therapy.
- **Venous thromboembolism** — the incidence of **pulmonary embolism is increased during COPD exacerbations**, and PE should be considered when an exacerbation is atypical or refractory.

> **DIAGRAMS TO DRAW — IMAGE SUGGESTIONS**
>
> - **"Spokes-of-a-wheel" / systemic-effects schematic** — central hub labelled **"COPD: airflow obstruction + systemic inflammation (TNF-α) + chronic hypoxaemia"**, with labelled spokes: *Cachexia / weight loss*, *Skeletal-muscle dysfunction*, *Osteoporosis*, *Cardiovascular disease*, *Cor pulmonale / pulmonary hypertension*, *Secondary polycythaemia*, *Depression / anxiety / frailty*, *GERD*, *Lung cancer*, *Pulmonary embolism (exacerbations)*.
> - **BODE index box** — four labelled components: **B** = Body-mass index, **O** = airflow Obstruction (FEV_1 % predicted), **D** = Dyspnoea (mMRC scale), **E** = Exercise capacity (6-minute walk distance); arrow to *"predicts mortality better than FEV_1 alone."*

Clinical / Diagnostic significance

- **Assess every COPD patient for comorbidities** — cardiovascular disease, GERD, osteoporosis, frailty, depression and anxiety — because they drive symptoms, hospitalisation and death independent of lung function.
- **Nutritional assessment** (BMI/weight trend) and **6-minute walk distance** feed the **BODE index** for prognostication.
- **Elevated haematocrit / RV-hypertrophy signs / erythrocytosis** prompt evaluation for chronic hypoxaemia and may qualify the patient for **long-term oxygen therapy** (resting SpO_2 ≤88 %, or ≤89 % with pulmonary arterial hypertension, right heart failure or erythrocytosis) — the only intervention other than smoking cessation, LVRS and transplant shown to improve survival in hypoxaemic patients.

- **New digital clubbing → investigate for lung cancer**; offer annual **low-dose CT** screening to eligible smokers with COPD.
- **Minimise glucocorticoid burden** (avoid chronic oral steroids; monitor bone density with ICS) to limit osteoporosis, cataracts and dysglycaemia.
- **Consider pulmonary embolism** in exacerbations that do not fit the usual pattern.

High-yield exam pointers

- **Cachexia/wasting = independent poor prognostic factor**, mediated by TNF-α — a favourite one-liner.
- **BODE index** = **B**MI + airflow **O**bstruction + **D**yspnoea + **E**xercise capacity; better mortality predictor than FEV_1.
- **Cor pulmonale/RV failure** appears at **FEV_1 <25 % predicted and PaO_2 <55 mmHg**; PAH can also be hypoxaemia-independent (vascular destruction).
- **Clubbing is NOT due to COPD** — its presence means look for **lung cancer**.
- **Raised haematocrit (erythrocytosis)** = marker of chronic hypoxaemia; one of the O_2-therapy qualifying signs (threshold ≤89 %).
- Listed comorbidities to recite: **cardiovascular disease, GERD, osteoporosis, frailty, depression, anxiety**.
- **Steroid-related systemic harms**: osteoporosis, weight gain, cataracts, glucose intolerance, infection (oral); bone-density loss, candidiasis, pneumonia (inhaled).
- **PE incidence is increased during exacerbations.**

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 303 "Chronic Obstructive Pulmonary Disease"** (physical examination, laboratory findings, comorbidities, pharmacotherapy and exacerbations sections).

Coverage note: The provided chapter explicitly describes cachexia, cardiovascular disease, cor pulmonale/pulmonary hypertension, osteoporosis, secondary polycythaemia (elevated haematocrit/erythrocytosis), depression/anxiety/frailty, GERD, lung cancer and exacerbation-related PE. It does **not** describe **anaemia of chronic disease** as a COPD comorbidity (it discusses the opposite — polycythaemia); anaemia is listed here as a GOLD-recognised, universally accepted comorbidity and flagged as outside this Harrison chapter. The mMRC dyspnoea scale and standard SpO_2 figure (88 %) are referenced as universally accepted; specific BODE thresholds beyond its four components are not detailed in the chapter.

◆ ◆ ◆

Pulmonary embolism

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

Definition / Introduction — Pulmonary embolism (PE) is occlusion of the pulmonary arterial tree by material — most often a thrombus that has detached from a deep vein and embolised through the right heart. Together with deep-venous thrombosis (DVT) it constitutes **venous thromboembolism (VTE)**, the third commonest cardiovascular cause of death. PE is a *"great masquerader"* with non-specific presentation, so management hinges on a structured diagnostic and risk-stratification pathway followed by anticoagulation, with reperfusion reserved for high-risk disease.

Risk factors (enumerate)

The substrate is **Virchow's triad** — venous stasis, hypercoagulability and endothelial injury/inflammation — with inflammation now recognised as a central trigger.

Category	Examples
Inherited (genetic) thrombophilia	Factor V Leiden (activated protein C resistance — commonest); prothrombin gene mutation; deficiencies of antithrombin, protein C, protein S (rare)
Acquired thrombophilia	Antiphospholipid syndrome (APS — venous *and* arterial thrombosis; often warrants lifelong anticoagulation)
Stasis / immobility	Bed-rest, post-operative state, stroke, long-haul air travel (*"economy-class syndrome"*), sedentary lifestyle (prolonged television watching)
Surgery / trauma	Major orthopaedic surgery (hip/knee replacement, hip fracture), pelvic/long-bone fracture, major general surgery
Malignancy	Active cancer (lung, brain, pancreas, leukaemia); erythropoiesis-stimulating agents; chemotherapy
Hormonal	Oestrogen-containing contraceptives, postmenopausal HRT, pregnancy and the first 6–12 weeks postpartum, high-dose fertility injections
Inflammation-linked illness (Table 290-1)	Inflammatory bowel disease (ulcerative colitis, Crohn's), rheumatoid arthritis, psoriasis, type-2 diabetes/metabolic syndrome, pneumonia, sepsis, acute coronary syndrome, acute stroke
Other comorbid	Obesity, cigarette smoking, systemic hypertension, COPD, chronic kidney disease, elevated LDL/lipoprotein(a), air pollution, blood transfusion, indwelling central venous catheters/PICC (upper-limb DVT)

- Carotid plaque **doubles** incident VTE risk; VTE, MI and stroke share inflammation, hypercoagulability and endothelial injury, and each more than doubles the risk of the others.
- **Non-thrombotic** PE (relevant to the differential and to "embolism" broadly): fat (long-bone fracture), air (neurosurgery, central lines), amniotic fluid (labour), tumour, septic emboli (right-sided endocarditis), talc (IV drug use), bone-cement (arthroplasty).

Classification and risk stratification (drives management)

Class	Frequency	Definition	Prognosis
Massive (high-risk)	5–10%	Systemic hypotension (SBP <90 mmHg ≥15 min or drop ≥40 mmHg); thrombus ≥50% of pulmonary vasculature; syncope, cyanosis, cardiogenic shock	High mortality
Submassive (intermediate-risk)	20–25%	Normotensive but RV dysfunction (echo/CT) ± troponin/BNP rise	Risk of abrupt deterioration
Low-risk	65–75%	Normotensive, normal RV, normal biomarkers	Excellent

- **Clinical probability** — *Wells score* (PE): signs/symptoms of DVT 3, alternative diagnosis less likely 3, HR >100 = 1.5, immobilisation/surgery within 4 weeks 1.5, prior PE/DVT 1.5, haemoptysis 1, cancer 1 (PE-likely if >4). *PERC* rule can exclude PE in very-low-risk patients meeting all 8 criteria.
- **Mortality prognostication** — *Simplified PESI (sPESI)*: age >80, cancer, chronic cardiopulmonary disease, pulse ≥110, SBP <100, SaO_2 <90% (each = 1). Score **0 = low** 30-day mortality (consider outpatient/early discharge); **≥1 = higher risk**. *Hestia criteria* also screen for home-treatment eligibility.

Diagnostic approach (essential before treatment)

- **D-dimer ELISA**: sensitivity >95%; a normal value rules out PE in low/intermediate pretest probability. Use **age-adjusted cut-off** (age × 10 ng/mL) in patients >50 years; unhelpful in inpatients (frequently raised).
- **CT pulmonary angiography (CTPA)** — principal/gold-standard imaging; an RV:LV diameter ratio >1 predicts increased 30-day mortality. **V/Q scan** when contrast is contraindicated. **Compression venous ultrasound** for DVT.
- **ECG**: sinus tachycardia (commonest), *S1Q3T3*, T-inversion V1–V4 (RV strain). **CXR**: often normal; *Westermark's sign* (oligaemia), *Hampton's hump* (infarct), *Palla's sign* (enlarged descending pulmonary artery). **Echo**: *McConnell's sign* (RV free-wall hypokinesis with apical sparing). **Troponin/BNP** raised in ~25% — risk markers.

Management — anticoagulation (cornerstone)

Anticoagulation prevents clot propagation and recurrence while endogenous fibrinolysis dissolves existing thrombus; start empirically when clinical suspicion is high and bleeding risk low, before confirmation. **DOACs are first-line** for most patients.

Drug	Regimen (normal renal function)
Unfractionated heparin (UFH)	80 U/kg bolus then 18 U/kg/h; target aPTT 60–80 s (anti-Xa 0.3–0.7 U/mL). Preferred if unstable, renal failure, or reperfusion may be needed
Enoxaparin (LMWH)	1 mg/kg SC twice daily (no monitoring unless obese/CKD)
Dalteparin / Tinzaparin	200 U/kg od (or 100 U/kg bid) / 175 U/kg od

Drug	Regimen (normal renal function)
Fondaparinux	Weight-based SC od (5/7.5/10 mg for <50/50–100/>100 kg); does not cause HIT
Rivaroxaban	15 mg bid × 3 weeks → 20 mg od (oral monotherapy)
Apixaban	10 mg bid × 1 week → 5 mg bid (oral monotherapy)
Edoxaban	After ≥5 days parenteral → 60 mg od (30 mg if CrCl 15–50 or <60 kg)
Dabigatran	After ≥5 days parenteral → 150 mg bid (direct thrombin inhibitor)
Warfarin	Overlap with parenteral ≥5 days until INR ≥2 on two readings; target INR 2.0–3.0

- **Heparin-induced thrombocytopenia (HIT)** suspected/proven: use **argatroban** (hepatic) or **bivalirudin** (renal) — IV direct thrombin inhibitors — or **fondaparinux**.
- **Reversal**: protamine for heparin/LMWH; **idarucizumab** for dabigatran; **andexanet alfa** (or PCC) for anti-Xa DOACs; vitamin K/FFP/PCC for warfarin.
- DOACs are contraindicated in **pregnancy/lactation**; **warfarin** (not DOAC) remains standard for **APS**.

Management of high-risk (massive) and intermediate-risk PE

- **Supportive care (massive PE)**: cautious volume — only ~500 mL normal saline (excess fluid worsens RV wall stress and septal shift); **noradrenaline** (vasopressor of choice) plus **dobutamine** (inotrope); **veno-arterial ECMO** or percutaneous RV assist for refractory shock.
- **Systemic thrombolysis** — indicated for massive PE without contraindication: **alteplase 100 mg IV over 2 h** (bolus 0.6 mg/kg, max 50 mg over 15 min if cardiac arrest imminent). Major bleeding ~10%, intracranial haemorrhage 2–3%. *Absolute contraindications*: prior intracranial haemorrhage, structural cerebrovascular lesion/neoplasm, ischaemic stroke <3 months, active bleeding, recent significant head trauma/surgery.
- **Intermediate-risk (submassive) PE**: routine thrombolysis is **controversial** — in *PEITHO*, tenecteplase reduced haemodynamic collapse (2.6% vs 5.6%) but increased intracranial bleeding (2.0% vs 0.2%) with no survival benefit; preferred strategy is anticoagulation with **close monitoring**, reserving rescue thrombolysis for deterioration.
- **Catheter-directed therapy** (pharmacologic, mechanical, or pharmacomechanical/ultrasound-facilitated low-dose thrombolysis) — lower bleeding than systemic lysis; for high-risk patients or intermediate-risk at risk of collapse.
- **Surgical pulmonary embolectomy** — when thrombolysis is contraindicated/failed, or for clot-in-transit/mobile intracardiac thrombus.
- **IVC filter** — only two firm indications: (1) active bleeding precluding anticoagulation, (2) recurrent VTE despite therapeutic anticoagulation. Use **retrievable** filters and remove when anticoagulation resumes.

Special situations and duration of anticoagulation

- **Minimum 3 months** for all PE. Continued (extended/indefinite) anticoagulation is decided by recurrence risk vs bleeding risk (ESC 2019 abandons the "provoked/unprovoked" dichotomy):

Recurrence risk after stopping	Examples
Low (<3%/yr)	Major surgery/trauma (transient) → stop at 3 months
Intermediate (3–8%/yr)	Minor surgery, hospitalisation, pregnancy/oestrogen, long-haul flight, IBD, no identifiable factor
High (>8%/yr)	Active cancer, antiphospholipid syndrome → indefinite anticoagulation

- **Cancer-associated VTE**: LMWH or a DOAC (apixaban/edoxaban; avoid DOAC if GI/luminal cancer) until cancer-free.
- **Pregnancy**: weight-adjusted **LMWH** is preferred (UFH peri-delivery); warfarin, DOACs and fondaparinux are contraindicated. Thrombolysis only for life-threatening PE.
- **Isolated subsegmental PE with no DVT and low recurrence risk**: surveillance without anticoagulation is acceptable.

Prevention (prophylaxis)

- Universal in-hospital VTE prophylaxis unless contraindicated: **UFH 5000 U SC bid/tid** or **enoxaparin 40 mg od** (or dalteparin/fondaparinux 2.5 mg od) for medical and high-risk surgical patients.
- **Major orthopaedic surgery**: aspirin 81 mg, rivaroxaban 10 mg od, apixaban 2.5 mg bid, dabigatran, LMWH or warfarin; extended prophylaxis after hip/knee replacement.
- **Mechanical** (intermittent pneumatic compression ± graduated stockings) when anticoagulation is contraindicated; early ambulation always.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Acute PE management algorithm** — boxes/labels: *Suspected PE → assess for hypotension/shock/arrest*; if YES → *supportive care (O_2, fluids 500 mL, noradrenaline + dobutamine) + systemic thrombolysis / embolectomy*; if NO → *confirm with CTPA → risk-stratify (sPESI, RV function, troponin)*: **Low → anticoagulate (DOAC) ± early discharge**; **Intermediate → anticoagulate + monitor**; **High/massive → reperfusion**.
- **Pathophysiology of PE** — labels: *Pulmonary artery obstruction → ↑PVR / ↑RV afterload → RV wall tension ↑ → RV dilatation & dysfunction → interventricular septal shift → ↓LV filling → ↓cardiac output → ↓coronary perfusion → RV ischaemia/microinfarction (troponin↑) → circulatory collapse*.

Clinical / Diagnostic significance

- Empirical anticoagulation before confirmation in high pretest probability prevents early recurrent (often fatal) PE.

- Haemodynamics — **not** clot bulk on imaging — predict mortality; many "saddle emboli" are stable and recover on anticoagulation alone.
- **Post-PE syndrome** (persistent dyspnoea, fatigue, RV dysfunction in ~50%) and **CTEPH** (~2% of PE) warrant follow-up echocardiography at ~6 weeks/6 months; CTEPH is treated by **pulmonary thromboendarterectomy** (mortality 1–5% at expert centres) ± balloon pulmonary angioplasty.

High-yield exam pointers

- **Virchow's triad** = stasis + hypercoagulability + endothelial injury/inflammation.
- Commonest inherited thrombophilia = **factor V Leiden**; **APS** = lifelong warfarin (not DOAC).
- **Wells** = pretest probability; **sPESI** = 30-day mortality; **PESI 0 / sPESI 0** = candidate for outpatient therapy.
- **CTPA** = investigation of choice; **age-adjusted D-dimer** (age × 10) in >50 years.
- ECG **S1Q3T3** & T-inversion V1–V4; **McConnell's sign** on echo; **Westermark / Hampton's hump / Palla** on CXR.
- **DOACs first-line**; UFH preferred if unstable/renal failure/reperfusion likely.
- **Massive PE** → alteplase 100 mg over 2 h; noradrenaline + dobutamine; ECMO; **submassive** → anticoagulate + monitor (PEITHO).
- **Minimum 3 months** anticoagulation; **active cancer & APS** → indefinite.
- **IVC filter** only when anticoagulation contraindicated or recurrence despite it.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Deep-Venous Thrombosis and Pulmonary Thromboembolism"* (risk factors/Table 290-1, classification, diagnosis, anticoagulation Table 290-4, thrombolysis, IVC filter, ESC duration tables, prophylaxis Table 290-7).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — *"Pulmonary Thromboembolism: Presentation and Diagnosis"* and *"Pulmonary Thromboembolism: Prophylaxis and Treatment"* (sPESI, PEITHO, anticoagulant treatment table, catheter-directed/surgical reperfusion, pregnancy, prophylaxis).
- **CMDT 2026** — *"Pulmonary Disorders: Pulmonary Venous Thromboembolism"* (Wells/PERC, risk stratification, current treatment and thrombolysis).

◆ ◆ ◆

Connective tissue disease-associated ILD

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

Definition / Introduction — Connective-tissue-disease–associated interstitial lung disease (CTD-ILD) is a heterogeneous group of diffuse parenchymal lung diseases occurring as an extra-articular/systemic manifestation of an autoimmune rheumatic disorder, in which inflammation and fibrosis remodel the alveolar–interstitial unit. ILD is a leading cause of morbidity and mortality across the connective tissue diseases (CTDs) and may **precede, accompany, or be the sole presenting feature** of the underlying CTD. It occurs most commonly in **systemic sclerosis (SSc)**, **rheumatoid arthritis (RA)**, and **polymyositis/dermatomyositis (PM/DM)**, and less frequently in **Sjögren syndrome (SS)**, **systemic lupus erythematosus (SLE)** and **mixed connective tissue disease (MCTD)**. Compared with idiopathic interstitial pneumonia, CTD-ILD patients are typically younger, female and non-smokers, and—stage for stage—carry a better prognosis than idiopathic pulmonary fibrosis (IPF).

Connective tissue diseases that cause ILD — prevalence and dominant pattern

CTD	Prevalence of ILD	Commonest radiologic/histologic pattern (others)	Key associations
Systemic sclerosis (SSc)	40–75% clinically significant; up to 65–70% on HRCT (~50% diffuse, ~30% limited)	**NSIP** (UIP)	Anti-topoisomerase-I (Scl-70) → ILD risk; anti-centromere → protective, PAH
Rheumatoid arthritis (RA)	Clinically evident ~10%; HRCT abnormalities 30–60%	**UIP** (NSIP, OP, LIP)	Male, smokers, high RF/anti-CCP, MUC5B variant
PM/DM (inflammatory myopathy)	ILD up to 32–45% (highest with anti-synthetase antibodies)	**NSIP ± OP** (UIP, DAD)	Anti-synthetase syndrome (Jo-1); anti-MDA5 → rapidly progressive
Sjögren syndrome (SS)	Clinically significant 8–27%; HRCT up to 30%	**NSIP (often fibrotic)** (LIP, UIP, OP)	Must exclude pulmonary lymphoma (risk ↑40–50×)
Systemic lupus (SLE)	Chronic diffuse ILD 1–15% (3–11%)	**NSIP** (LIP, OP, UIP)	Acute lupus pneumonitis & DAH distinct entities
MCTD	Pleuropulmonary 20–85%	**NSIP** (UIP)	Anti-U1-RNP defines disease

Histopathological and HRCT patterns in CTD-ILD

- **Nonspecific interstitial pneumonia (NSIP)** — the *overall most frequent* pattern: bilateral, symmetric, subpleural ground-glass opacity and reticulation with traction bronchiectasis, often peribronchovascular; relative *subpleural sparing*; honeycombing uncommon. Cellular NSIP responds better than fibrotic NSIP.

- **Usual interstitial pneumonia (UIP)** — second commonest and *the dominant pattern in RA*: subpleural, basal honeycombing, reticulation and traction bronchiectasis indistinguishable from IPF; in RA shows **fewer fibroblastic foci, more germinal centres**.
- **Organizing pneumonia (OP)** — patchy migratory subpleural consolidation (reversed-halo/atoll sign); strongly linked to **PM/DM** and RA; steroid-responsive.
- **Lymphocytic interstitial pneumonia (LIP)** — diffuse peribronchiolar lymphocytic infiltrate; classically **Sjögren syndrome**.
- **Diffuse alveolar damage (DAD)** — substrate of acute pneumonitis/acute exacerbation; seen in anti-MDA5/Jo-1 myositis, acute lupus pneumonitis.
- *Radiologic clues to an underlying CTD:* multi-compartment disease (dilated air-filled oesophagus, pleural/pericardial involvement, pulmonary artery enlargement), extensive subpleural sparing, and exuberant honeycombing being relatively rare.

Disease-specific features and serology

- **SSc** — ILD is the commonest pulmonary manifestation and a *leading cause of SSc death*. Velcro basal crackles, dry cough, exertional dyspnoea; clubbing rare. FVC may fall by up to 30%/year in the **first 3–5 years**. Risk factors: male sex, African ancestry, diffuse cutaneous disease, severe GERD/microaspiration, anti-Scl-70. **Pulmonary arterial hypertension (PAH)** may coexist or occur in isolation (commoner in limited SSc/CREST, anti-centromere) — an isolated/disproportionate fall in DLCO or rising FVC/DLCO ratio is the screening alert.
- **RA** — UIP-predominant; *male and smoker* predominance unlike articular RA. Spectrum is wide: ILD, OP, **obliterative (constrictive) bronchiolitis**, follicular bronchiolitis, bronchiectasis, rheumatoid nodules (± **Caplan syndrome** with pneumoconiosis), pleural disease (exudate, low glucose, low pH). **Methotrexate pneumonitis** is an important mimic.
- **PM/DM** — **Anti-synthetase syndrome**: anti-tRNA-synthetase antibody (commonest **anti-Jo-1**) + myositis, ILD, arthritis, fever, Raynaud's and *mechanic's hands*. Anti-Jo-1 and especially **anti-MDA5** (often clinically amyopathic DM) predict rapidly progressive, DAD-type ILD. Low/normal CK does not exclude severe ILD. Screen for occult malignancy.
- **SLE** — ILD itself uncommon; the dangerous entities are **acute lupus pneumonitis** (DAD, >50% mortality), **diffuse alveolar haemorrhage (DAH)**, **shrinking lung syndrome** (restrictive defect with raised hemidiaphragms, diaphragmatic dysfunction), pleuritis (commonest manifestation) and PAH.
- **Sjögren** — fibrotic NSIP and **LIP**; xerotrachea, small-airway disease/bronchiolitis; always exclude **pulmonary lymphoma**.
- **Antibody panel:** ANA, RF and anti-CCP in all suspected cases; targeted ENA (Scl-70, anti-centromere, SSA/Ro, SSB/La, U1-RNP, Sm) and myositis antibodies (Jo-1, PL-7, PL-12, EJ, OJ, MDA-5) in selected cases; **repeat serology**, as seroconversion is common.

Diagnostic approach and severity staging

- **Multidisciplinary diagnosis** (pulmonologist, rheumatologist, radiologist, pathologist) integrating clinical features, serology, **HRCT**, and **PFTs** — no single test is diagnostic.

- **PFT:** restrictive defect — reduced TLC, FVC and DLCO with preserved/raised FEV1/FVC; **DLCO is the most sensitive early marker** and a disproportionate isolated fall suggests pulmonary vascular disease.
- **HRCT** is standard of care; surgical/transbronchial biopsy is rarely needed because histologic pattern seldom alters management or prognosis in CTD (RA-UIP is the main exception). BAL is mainly to exclude infection/haemorrhage.
- **UKRSA (Goh–Wells) staging** for SSc-ILD: **limited disease** if HRCT extent <20% (or, when indeterminate, FVC ≥70%) vs **extensive disease** if HRCT >20% (or FVC <70%) — extensive disease predicts progression and death and identifies who to treat.

Therapy

- **General principles:** Not all CTD-ILD needs treatment; *stabilisation*, not reversal, is the realistic goal in fibrotic disease. Decision to treat weighs ILD severity (extent on HRCT, FVC/DLCO), rate of progression, CTD subtype, age and comorbidity. Treat early, during the highest-risk first few years.
- **Immunosuppression (first-line for inflammatory/cellular disease):**
  - **Mycophenolate mofetil (MMF) 1–3 g/day** — now preferred first-line for SSc-ILD (Scleroderma Lung Study II: equivalent efficacy to cyclophosphamide with better tolerability).
  - **Cyclophosphamide** — oral 2 mg/kg/day or IV pulses (750–1000 mg/m^2 monthly) for 6–12 months; modest benefit on FVC/skin (Scleroderma Lung Study), significant toxicity (cystitis, marrow suppression, malignancy, gonadal failure) — reserve for severe/progressive disease.
  - **Azathioprine** (≤2.5 mg/kg/day, max 200 mg) and **calcineurin inhibitors** (ciclosporin, tacrolimus) as alternatives/steroid-sparing, especially in myositis-ILD.
  - **Glucocorticoids** (prednisolone) — mainstay for cellular NSIP, OP, acute pneumonitis, DAH and myositis-ILD; **use with caution/avoid high dose in SSc** (precipitates scleroderma renal crisis) and in UIP-pattern disease.
- **Biologics: Tocilizumab** (anti–IL-6R) slows FVC decline in early SSc-ILD (focuSSced/FaSScinate); **Rituximab** (anti-CD20) for refractory/rapidly progressive disease, most effective in myositis-ILD and anti-synthetase syndrome; abatacept used in RA-ILD.
- **Antifibrotic therapy: Nintedanib** (tyrosine-kinase inhibitor) 150 mg bid is approved for **SSc-ILD** (SENSCIS: FVC decline reduced by 41 mL/yr, ~44% relative, additive to MMF) and for **progressive pulmonary fibrosis** of any CTD (INBUILD); **pirfenidone** under study (RA-ILD/unclassifiable).
- **Adjunctive/supportive:** high-dose **proton-pump inhibitors / anti-reflux** measures in SSc (microaspiration drives fibrosis); pulmonary rehabilitation; supplemental **oxygen**; vaccination; *Pneumocystis* prophylaxis when heavily immunosuppressed.
- **Advanced disease: Autologous haematopoietic stem cell transplantation (HSCT)** for selected early, rapidly progressive SSc at risk of organ failure (ASTIS, SCOT trials — improved event-free/overall survival). **Lung transplantation** for end-stage disease unresponsive to therapy, provided extrapulmonary activity and major oesophageal dysfunction are absent. **PAH-specific**

therapy (endothelin antagonists e.g. bosentan, PDE-5 inhibitors e.g. sildenafil, riociguat, selexipag, prostacyclins) when pulmonary vascular disease is present.

Complications

- **Progressive pulmonary fibrosis** → chronic respiratory failure, the major cause of death in SSc-ILD and RA-ILD.
- **Acute exacerbation** (new DAD) — abrupt dyspnoea, fresh ground-glass on HRCT without infection; commonest/most severe in RA, very high mortality.
- **Pulmonary hypertension / cor pulmonale** — from fibrosis-hypoxia (Group 3) or pulmonary vascular disease (Group 1 PAH, esp. SSc, MCTD, SLE).
- **Diffuse alveolar haemorrhage** and **acute pneumonitis** — life-threatening in SLE and myositis.
- **Therapy-related:** drug-induced pneumonitis (methotrexate, anti-TNF, leflunomide), opportunistic infection, scleroderma renal crisis from steroids, malignancy from cyclophosphamide.
- **Increased risk of lung cancer** (SSc, RA) and **pulmonary lymphoma** (Sjögren).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — HRCT/histology patterns of CTD-ILD (panel):** label *UIP* (subpleural-basal honeycombing + traction bronchiectasis), *NSIP* (symmetric ground-glass + reticulation, subpleural sparing), *OP* (patchy migratory subpleural consolidation / reversed-halo sign), *LIP* (peribronchiolar cysts), and *dilated oesophagus* (SSc clue).
- **Diagram 2 — SSc-ILD screening/treatment algorithm:** boxes labelled *New SSc diagnosis → screening HRCT + PFT (FVC, DLCO) → No ILD / Limited ILD (FVC ≥70%, HRCT <20%) / Extensive ILD (FVC <70%, HRCT >20%) → Monitor PFT 3–6 monthly → Progression? → First-line MMF/cyclophosphamide → Add nintedanib → Rescue: HSCT, lung transplant, palliative care* (UKRSA staging arm shown).

Clinical / Diagnostic significance

- ILD may be the **first clue to an occult CTD** — any "idiopathic" NSIP demands a full autoimmune work-up; ~15% of apparent idiopathic interstitial pneumonia (30% of idiopathic NSIP) prove to be CTD.
- **IPAF (Interstitial Pneumonia with Autoimmune Features)** — ATS/ERS construct for ILD with autoimmune features (≥1 feature from ≥2 of clinical, serologic, morphologic domains) that does not meet full CTD criteria; a provisional, evolving entity.
- Distinguishing CTD-ILD from IPF is essential: it changes prognosis (generally better) and treatment direction (immunosuppression helps CTD but **harms IPF**). Serial **FVC and DLCO** monitoring guides therapy; FVC decline predicts mortality.
- Screen every new SSc patient for ILD and for PAH (baseline + annual echocardiography/DLCO).

High-yield exam pointers

- ILD is commonest in **SSc > RA > PM/DM**, less in SS, SLE, MCTD.
- **NSIP is the overall commonest pattern; UIP predominates in RA** (worse prognosis than NSIP).

- **Anti-Scl-70 → SSc-ILD; anti-centromere → protective/PAH; anti-Jo-1 → anti-synthetase syndrome; anti-MDA5 → rapidly progressive DM-ILD.**
- **MMF is first-line; nintedanib (antifibrotic) for SSc-ILD & progressive fibrosis; avoid/limit steroids in SSc (renal crisis) and in UIP.**
- **DLCO** is the most sensitive PFT abnormality; isolated low DLCO → think PAH.
- SSc-ILD: FVC can fall ~30%/year in the first 3–5 years — *treat early*.
- RA pulmonary spectrum beyond ILD: obliterative bronchiolitis, nodules, **Caplan syndrome**, pleural exudate (low glucose, low pH).
- SLE emergencies: **acute lupus pneumonitis, DAH, shrinking lung syndrome**; Sjögren → **LIP & lymphoma risk**.
- **UKRSA (Goh) staging:** HRCT >20% or FVC <70% = extensive disease = treat.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Interstitial Lung Disease" (ILD associated with connective tissue disease: SSc, RA, dermatomyositis/polymyositis) and "Systemic Sclerosis (Scleroderma) and Related Disorders" (pulmonary features, PAH, treatment algorithm Fig. 372-15).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "Connective Tissue Diseases" (Corte & Wells): prevalence/pattern table, disease-specific sections, autoantibody and drug tables, UKRSA staging, IPAF criteria.
- **CMDT 2026** — "Pulmonary Disorders" (interstitial lung disease, differential and management) and "Rheumatologic, Immunologic & Allergic Disorders" for current drug regimens.

◆ ◆ ◆

Spirometry

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

Definition / Introduction — **Spirometry** is the most widely used pulmonary function test; it records the **volume and rate (flow) of air** that a subject can inhale and exhale as a function of time during standardised breathing manoeuvres. The two cardinal manoeuvres are the **slow vital-capacity (VC)** manoeuvre (lung-volume sub-divisions) and the **forced vital-capacity (FVC)** manoeuvre (dynamic airflow), displayed as a **volume–time spirogram** and a **flow–volume loop**. It is *effort-dependent*, requiring patient cooperation and trained technique, and is the foundation for diagnosing and grading **obstructive** and **restrictive** ventilatory defects.

Physiological principle

- The lung behaves as **three coupled mechanical components** — lung (with airways), neuromuscular pump, and chest wall. Inspiratory muscles lower pleural and alveolar pressure below airway-opening pressure to drive **inflation**; expiratory muscles (and elastic recoil) raise alveolar pressure to drive **deflation**.

- During a forced expiration from **total lung capacity (TLC)** to **residual volume (RV)**, airflow becomes **flow-limited**: beyond an initial effort-dependent spike, expiratory flow at any given lung volume reaches a maximum that **cannot be increased by greater effort** (the *effort-independent* portion). This is the basis of the reproducible FVC manoeuvre.
- Flow limitation arises from **dynamic airway compression**: as gas accelerates toward the mouth, intraluminal pressure and airway transmural pressure fall (**Bernoulli effect**), collapsing the compliant bronchi. Maximal expiratory flow at any volume is set by **gas density, airway calibre/distensibility, lung elastic recoil pressure, and frictional resistance** to the flow-limiting site.
- Consequently, maximal flow **falls as lung volume falls** (lower recoil and smaller airways at low volume); diseases that reduce recoil (**emphysema**), narrow airways (**asthma, chronic bronchitis**) or increase collapsibility lower maximal flow, whereas increased recoil (**pulmonary fibrosis**) raises flow *relative to volume*.
- Spirometry discloses only **relative volume changes** during these manoeuvres; it **cannot measure absolute volumes that include RV** (RV, FRC, TLC). These require **body plethysmography** (Boyle's law) or **inert-gas dilution / washout** (helium dilution, nitrogen washout).

Lung volumes, capacities and spirometric indices

Index	Meaning	Measurable by spirometry?
Tidal volume (V_T)	Volume of a quiet breath	Yes
Inspiratory capacity (IC), ERV	IC = TV + IRV; ERV = expiratory reserve	Yes
Vital capacity (VC)	TLC − RV; maximal slow excursion	Yes
FVC	Volume forcibly exhaled from TLC to RV	Yes
FEV1	Volume exhaled in the **first second** of FVC (a flow)	Yes
FEV1/FVC ratio	Proportion of VC exhaled in 1 s — key obstruction marker	Yes
FEF25–75%	Mid-expiratory flow; reputed small-airway marker (high variability)	Yes
PEF	Peak expiratory flow	Yes
FEV6 / FEV1/FEV6	6-s surrogate for FVC (FEV1/FEV6 <0.73 ≈ FEV1/FVC <0.70)	Yes
MVV	Maximal voluntary ventilation (overall reserve)	Yes
RV, FRC, TLC, RV/TLC	Static volumes containing RV	**No** — need plethysmography / gas dilution

Indications and contraindications

- **Diagnose airflow obstruction** and **quantify its severity** (asthma, COPD — FEV1/FVC and FEV1 are part of the disease definitions).
- Evaluate **dyspnoea, chronic cough, wheeze, hypoxaemia or an abnormal chest image**; narrow the differential and trigger specific further testing.
- **Monitor disease activity and treatment response** over time; assess **bronchodilator reversibility** and **bronchial hyper-responsiveness** (methacholine challenge).
- **Pre-operative / fitness assessment** (e.g. predicting post-pneumonectomy reserve; MVV estimable from FEV1) and **occupational / disability and impairment** evaluation.
- Detect **restriction** (spirometry suggests, lung volumes confirm) and **large-airway obstruction** (flow–volume loop).
- **Relative contraindications** (forced exhalation raises intrathoracic, intracranial, intra-abdominal and intra-ocular pressure): recent **myocardial infarction**, **pneumothorax**, recent **thoracic/abdominal/eye/brain/sinus or middle-ear surgery** or infection, **haemoptysis**, severe **hypertension/hypotension**, cervical-incompetent pregnancy, and **syncope** with cough/forced exhalation. (Prior concern over **thoracic aortic aneurysm** has been tempered by recent data.)

Performing and validating the test (ATS/ERS)

- Patient inhales fully to **TLC**, then exhales as **hard, fast and long** as possible to RV; ≥3 **acceptable** spirograms are obtained (practical upper limit 8 efforts).
- **Start of test: back-extrapolated volume <5% of FVC or <100 mL** (whichever is greater).
- **Repeatability:** the two largest **FVC** and two largest **FEV1** should be within **150 mL** of each other.
- **Pre-test withholding** for bronchodilator testing: SABA/SAMA ≥4 h, LABA ≥12 h, long-acting antimuscarinic / ultra-LABA ≥24–48 h; avoid caffeine/alcohol ≥4 h.
- A breathing **filter (≈0.2 µm)** is used for infection control; suboptimal effort shows **uneven/slurred/notched, non-repeatable** curves.

Interpretation — patterns of ventilatory defect

The first interpretive step is the **FEV1/FVC ratio** (read as an **absolute ratio**, not % predicted), then FEV1 and FVC, with **TLC** to confirm restriction and **DLCO** to localise the lesion.

Feature	Obstructive	Restrictive (parenchymal)	Mixed	Nonspecific
FEV1/FVC	↓ **(<0.70 / <LLN)**	Normal or ↑	↓	Normal
FEV1	↓	↓	↓	↓ or normal
FVC	Normal or ↓	↓	↓	↓
TLC	Normal or ↑ (hyperinflation)	↓ **(confirms)**	↓	**Normal**
RV, RV/TLC	↑ (air-trapping)	↓	variable	normal
Flow–volume curve	**Concave/scooped**	Steep, narrow (convex)	combined	preserved shape

Feature	Obstructive	Restrictive (parenchymal)	Mixed	Nonspecific
Examples	COPD, asthma, bronchiectasis, CF	IPF, sarcoid, asbestosis, CHF	CF, sarcoid, HP, bronchiectasis	obesity, muscle weakness, poor effort

- **Diagnostic threshold for obstruction:** post-bronchodilator **FEV1/FVC <0.70** (GOLD) or **<LLN (5th percentile)**; obstruction must use **post-bronchodilator** values.
- **Restriction cannot be diagnosed on spirometry alone** — a low FVC with normal/high FEV1/FVC has only ~50% positive predictive value; a **normal FVC has 96–97% negative predictive value** for ruling out restriction. **A low TLC defines restriction.**
- **DLCO** then localises: low in **parenchymal restriction (IPF)** and **emphysema**; normal in **chest-wall/neuromuscular** restriction; **isolated low DLCO with normal spirometry/volumes** suggests **pulmonary vascular disease** or early emphysema/ILD.
- **Large-airway obstruction** is recognised on the **flow–volume loop**: *fixed* lesion → **plateau on BOTH limbs**; *variable extrathoracic* → **inspiratory plateau** (with stridor); *variable intrathoracic* → **expiratory plateau**.
- **Reference values** are based on **height, age, sex and ethnicity**; 85–115% of predicted is normal, and in health all volumes scale together.

Severity grading and bronchodilator reversibility

ATS severity (FEV1 % predicted)	Grade
≥70%	Mild
60–69%	Moderate
50–59%	Moderately severe
35–49%	Severe
<35%	Very severe

- Once a pattern is identified, **severity is graded by FEV1 % predicted** (restriction may also be graded by TLC % predicted).
- **Significant bronchodilator response (adults):** an increase of **≥12% AND ≥200 mL** in **FEV1 or FVC** after a short-acting bronchodilator (≈10% in children). It supports **asthma** but does **not** distinguish asthma from COPD (35–60% of COPD patients reverse; FVC response is common with hyperinflation). A negative test does **not** exclude reversible disease.
- When obstruction/reversibility is absent but asthma is suspected, a **methacholine (bronchial) challenge** demonstrating airway hyper-responsiveness can establish the diagnosis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — Spirogram (volume vs time):** baseline tidal breathing; label **TLC, RV, VC/FVC, FEV1 (volume at 1 s), IC, ERV, FRC**; mark that **RV/FRC/TLC are not directly measured** by spirometry.
- **Diagram 2 — Flow–volume loops (flow vs volume):** label axes (**inspiratory below, expiratory above; TLC and RV on volume axis; PEF peak**). Draw and label: **(A) Normal**, **(B) Obstructive — scooped/concave expiratory limb**, **(C) Restrictive — tall, narrow, vertically-oriented**, **(D) Fixed large-airway obstruction — plateau on both limbs**, **(E) Variable extrathoracic — inspiratory plateau**, **(F) Variable intrathoracic — expiratory plateau**.

Clinical / Diagnostic significance

- Cornerstone for **diagnosing and staging COPD and asthma**, monitoring **ILD/sarcoidosis** progression, and tracking **CF** (declining FEV1/FVC, rising RV/TLC).
- **Pre-operative risk stratification** (lung resection, major surgery) and **occupational/disability** certification.
- **Supine fall in FVC of ≥25%** suggests **diaphragmatic/neuromuscular weakness**; complement with **MIP/MEP** (normal MIP ≥80 cmH_2O men, ≥70 cmH_2O women) and supine spirometry.
- Combine indices: a **normal/scooped curve with normal FEV1/FVC but reduced FVC** is *nonspecific*, prompting lung-volume and DLCO testing rather than a label of restriction.

High-yield exam pointers

- **Physiological basis = effort-independent expiratory flow limitation** from dynamic airway compression (Bernoulli effect); maximal flow set by **lung recoil, airway calibre and resistance**.
- **First interpret FEV1/FVC** (absolute ratio); **obstruction = FEV1/FVC <0.70 / <LLN** (use **post-bronchodilator** values).
- **Spirometry cannot measure RV, FRC, TLC** — need **plethysmography or gas dilution**; **TLC < LLN confirms restriction**.
- **Bronchodilator reversibility = ≥12% AND ≥200 mL** rise in FEV1 or FVC; does not separate asthma from COPD.
- **ATS severity by FEV1 % predicted** (≥70 mild … <35 very severe).
- **Acceptability:** ≥3 efforts, back-extrapolated volume <5%/100 mL, two best FVC and FEV1 within **150 mL**.
- **Flow–volume loop** localises large-airway lesions: fixed = both limbs plateau; variable extrathoracic = inspiratory plateau; variable intrathoracic = expiratory plateau.
- **FEF25–75%** is highly variable and adds little over FEV1/FVC; **DLCO** differentiates emphysema (low) from asthma (normal/high) in obstruction.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disturbances of Respiratory Function" (mechanics of ventilation, dynamic airflow limitation/Bernoulli effect, flow–volume loops, lung-volume measurement, functional measurements) and "Approach to the Patient with Disease of the Respiratory System / Diagnostic Procedures in Respiratory Disease."
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e** — "Pulmonary Function Testing: Physiologic and Technical Principles" (manoeuvre, indices, acceptability, contraindications) and "Pulmonary Function Testing: Interpretation and Applications" (interpretive algorithm, obstructive/restrictive/mixed/nonspecific patterns, severity grading Table 32.3, bronchodilator responsiveness, large-airway obstruction, reference values).
- **CMDT 2026** — "Pulmonary Disorders" (spirometry in asthma/COPD diagnosis, FEV1/FVC <0.70 threshold, 12% + 200 mL reversibility, GOLD framing).

◆ ◆ ◆

Hypoventilation

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

Definition / Introduction — In health the arterial CO_2 tension (**$Paco_2$**) is held between **37 and 43 mmHg** at sea level by the relationship $Paco_2 = k \times \dot{V}co_2 / \dot{V}A$ ($\dot{V}A$ = alveolar ventilation). **Alveolar hypoventilation** exists when alveolar ventilation is insufficient to clear metabolic CO_2, producing **chronic daytime hypercapnia ($Paco_2$ ≥45 mmHg)** with consequent respiratory acidosis and hypoxaemia. Critically, hypoventilation is defined by the $Paco_2$, not the respiratory rate — a tachypnoeic patient with a high dead-space fraction may still be alveolar-hypoventilating. It reflects an imbalance in which respiratory **load** exceeds respiratory **strength/drive** ("pump failure"), and the hallmark is a rise in alveolar and arterial Pco_2.

Physiological basis and classification

- The respiratory rhythm is generated in the brainstem — the medullary **dorsal respiratory group (DRG)** (afferent integration) and **ventral respiratory column (VRC)**; the **pre-Bötzinger complex** within the VRC generates inspiration (its destruction abolishes breathing) and is the site of **opioid-induced** respiratory depression.
- Adequate ventilation needs sufficient **drive**, intact **neuromuscular transmission**, and respiratory-muscle **strength** to overcome the elastic and resistive **loads** of lung and chest wall. Hypoventilation results when *Load* > *Strength* or when *drive is reduced*.
- A useful mechanistic dichotomy (Murray & Nadel): **"won't breathe"** = reduced central drive vs **"can't breathe"** = failure of the respiratory effectors (spinal cord → nerve → neuromuscular junction → muscle → chest wall). Harrison groups causes into **four categories**:

Category	Mechanism	Representative causes
Parenchymal lung / chest wall disease	↑ Load, $\dot{V}/\dot{Q}$ mismatch (↑ A–a gradient)	COPD, severe ILD, kyphoscoliosis, thoracoplasty, fibrothorax, ankylosing spondylitis, flail chest

Category	Mechanism	Representative causes
Obesity-hypoventilation syndrome (OHS)	↑ Load + blunted drive + OSA	"Pickwickian syndrome", BMI ≥30
Neuromuscular disease	↓ Strength ("can't breathe")	ALS, muscular dystrophy, myasthenia gravis, Guillain-Barré, phrenic injury, high cervical cord lesion, Pompe disease, post-polio
Respiratory-drive disorders	↓ Drive ("won't breathe")	Opioids/sedatives, brainstem stroke/tumour, myxoedema, metabolic alkalosis, primary/congenital central hypoventilation (CCHS)

Clinical features

- Manifestations are **non-specific** and depend on severity, rapidity of CO_2 rise and the underlying disease. Typical symptoms (Harrison Table 307-1): **dyspnoea on activities of daily living, orthopnoea** (with diaphragm involvement), **poor-quality sleep, daytime hypersomnolence, early-morning headaches, anxiety, and impaired cough** in neuromuscular disease.
- **Sleep-disordered breathing pattern** — excessive daytime somnolence, snoring, witnessed apnoeas and nocturnal choking dominate in OHS/OSA.
- **Neuromuscular pattern** — **new-onset orthopnoea is one of the earliest signs** of diaphragm weakness; **paradoxical (abdominal) breathing** when supine (abdomen moves *inward* on inspiration) signals significant diaphragmatic paralysis; "**respiratory alternans**" (alternating rib-cage and abdominal breathing) indicates diaphragmatic fatigue. Bulbar weakness brings dysphagia, weak cough and recurrent aspiration pneumonia.
- **Sequence of progression**: asymptomatic (normal daytime gases) → **nocturnal hypoventilation (first in REM, then non-REM sleep)** → falling vital capacity → **daytime hypercapnia**.
- **Consequences of chronic hypercapnia/hypoxaemia**: compensated respiratory acidosis (↑ HCO_3^-), **secondary erythrocytosis**, **pulmonary vasoconstriction → pulmonary hypertension → right-ventricular hypertrophy → cor pulmonale**. Severe hypercapnia causes cerebral vasodilatation, raised ICP, headache, **asterixis**, drowsiness and CO_2 narcosis/coma (usually $Paco_2$ >75–80 mmHg acutely, or an acute rise to >90–100 mmHg superimposed on chronic disease).

Diagnosis and investigations

- **Arterial blood gas (ABG) is the gold standard — $Paco_2$ ≥45 mmHg at sea level confirms hypoventilation**. A peripheral **venous Pco_2** is a poor surrogate (run several mmHg higher) but a *normal* value helps exclude hypercapnia.
- **Serum bicarbonate** is a *sensitive but not specific* screen: **HCO_3^- <27 mmol/L** (normal renal function, no volume depletion) makes chronic hypoventilation/OHS very unlikely (high negative predictive value); **HCO_3^- ≥27 mmol/L** should prompt a confirmatory ABG.
- **Acute vs chronic** (degree of renal compensation):

Feature	Acute hypoventilation	Chronic hypoventilation
pH	Low (<7.35); falls **0.08 per ↑10 mmHg $Paco_2$**	Normal / near-normal

Feature	Acute hypoventilation	Chronic hypoventilation
HCO_3^- rise per ↑10 mmHg $Paco_2$	**~1 mEq/L** (tissue buffering)	**~3.5–5 mEq/L** (renal, over 3–5 days)

- **A–a O_2 gradient distinguishes the cause** (Murray algorithm): a **normal A–a gradient** points to a *drive or neuromuscular/effector* disorder (lungs are normal); a **raised A–a gradient (>~20 mmHg)** points to *intrinsic lung/airway/vascular disease*.
- **Stepwise work-up** (Harrison Fig. 307-2): (1) detailed history + medication/drug history → (2) **PFTs and chest imaging** for lung/chest-wall disease → (3) seated **and supine** spirometry with **MIP/MEP** for neuromuscular weakness → (4) **BMI ≥30** with no alternative cause → OHS → (5) **CNS imaging** (MRI brainstem) for drive disorders.
- **Respiratory-muscle assessment**: a fall in **FVC of 15–25% from seated to supine** is an invaluable screen for impending respiratory failure in neuromuscular disease (a drop of 30–50% supports **bilateral diaphragmatic paralysis**); reduced **MIP (maximal inspiratory pressure)/MEP** and falling FVC track progression. In **Guillain-Barré** the "20/30/40 rule" warns of impending ventilation — **VC <20 mL/kg, MIP <30 cmH_2O, MEP <40 cmH_2O**.
- **Polysomnography with CO_2 monitoring** detects nocturnal hypoventilation (precedes daytime hypercapnia) and OSA; **AASM** scores sleep hypoventilation as $Paco_2$ **>55 mmHg for >10 min**, or a rise **>10 mmHg to a value >50 mmHg for >10 min**. Transcutaneous CO_2 (runs ~4–5 mmHg above arterial) is the most practical nocturnal monitor; end-tidal CO_2 is unreliable in lung disease.
- **OHS diagnostic criteria** (Harrison/CMDT): **BMI ≥30 kg/m^2**, daytime **$Paco_2$ ≥45 mmHg**, sleep-disordered breathing, and exclusion of other causes; **~90% have OSA and ~70% have severe OSA (AHI >30/h)**. Aetiology-specific tests: TSH (myxoedema), urine toxicology, and **PHOX2B genetic testing** for congenital central hypoventilation syndrome (CCHS / *Ondine's curse*).

Management

- **General principles**: treat the **underlying disorder**, withdraw respiratory depressants (opioids, benzodiazepines, alcohol), correct contributory metabolic factors (myxoedema, hypokalaemia, hypophosphataemia, excess metabolic alkalosis — which itself blunts drive), and replete nutrition.
- **Nocturnal non-invasive positive-pressure ventilation (NIPPV / BiPAP)** is the cornerstone — it lowers daytime $Paco_2$, prolongs survival and improves quality of life when daytime hypercapnia is documented. **Goal: reduce $Paco_2$ to <52 mmHg or by ≥20% from baseline.**
- **Neuromuscular disease (best studied in ALS)** — nocturnal NIPPV is indicated if hypoventilation symptoms plus **any** of: $Paco_2$ ≥45 mmHg; nocturnal **SpO_2 ≤88% for ≥5 consecutive min**; **MIP <60 cmH_2O**; or **sniff nasal pressure <40 cmH_2O with FVC <50% predicted**. Add **mechanical cough-assist** to reduce pneumonia; progress to mouthpiece/portable ventilation; consider **phrenic-nerve/diaphragm pacing** for high cervical cord lesions or drive disorders (requires intact phrenic nerves on conduction study) and tracheostomy ventilation late in disease.
- **Obesity-hypoventilation syndrome — positive airway pressure during sleep**: **CPAP** first-line when severe OSA coexists (corrects daytime gases in >50%); **BiPAP-ST / volume-assured**

pressure support if hypercapnia persists after adherent CPAP, if obstructive events persist at maximal CPAP (20 cmH_2O), in acutely decompensated OHS, or in OHS *without* significant OSA. **Weight loss of 20–25% of body weight (often bariatric surgery)** can normalise $Paco_2$; treat comorbid OSA, ACS, PE, pneumonia and heart failure aggressively.

- **Chronic hypercapnic COPD** (stable, $Paco_2$ >52 mmHg, normal pH) — **high-intensity home BiPAP** (IPAP **24–28 cmH_2O** with a back-up rate) aimed at $Paco_2$ <48 mmHg or a >20% fall improves 1-year mortality and quality of life; after an acute exacerbation, re-test at 2–4 weeks and start home NIPPV only if hypercapnia persists.
- **Oxygen** — supplemental O_2 attenuates hypoxaemia, polycythaemia and pulmonary hypertension, but must be given cautiously as it can worsen hypercapnia (CO_2 narcosis) in some patients; ventilatory support, not oxygen alone, treats the hypoventilation.
- **Respiratory stimulants** — **acetazolamide** and **medroxyprogesterone** are poorly evidenced, have side-effects, and must **not** replace treatment of the underlying disease.
- **Central hypoventilation syndrome / CCHS** (*Ondine's curse*; PHOX2B mutation) — long-term **NIPPV or mechanical ventilation** and consideration of **diaphragmatic pacing** at experienced centres.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Load–Strength balance schematic (Harrison Fig. 307-1):** a beam-balance with "**Strength/Drive**" on one pan (respiratory drive, neural transmission, respiratory-muscle strength) and "**Load**" on the other (lung elastic + resistive loads, chest-wall elastic load). Label panel A *Health (strength > load → normocapnia)* and panel B *Load > Strength → hypercapnia*.
- **Diagnostic algorithm (Harrison Fig. 307-2):** boxes — *Daytime hypercapnia → ABG ($Paco_2$ ≥45) → PFT + chest imaging → seated/supine spirometry, MIP/MEP → BMI ≥30 → CNS imaging*; endpoint labels: **Lung disease, Neuromuscular, OHS (+ PSG for OSA), CNS lesion, Primary drive disorder**. Annotate the **A–a gradient** branch (normal = pump/drive; raised = lung disease).

Clinical / Diagnostic significance

- An unexplained **raised serum HCO_3^-** on routine biochemistry is a clue to occult chronic hypoventilation — confirm with ABG.
- **Supine spirometry / orthopnoea** is the earliest red flag for diaphragmatic weakness; do not wait for daytime hypercapnia.
- Distinguishing **acute from chronic** by pH and the HCO_3^- compensation rule guides urgency (ventilatory support vs outpatient NIPPV).
- Recognise OHS perioperatively — these patients have a high risk of postoperative respiratory failure, intubation and heart failure.
- Hypercapnic COPD and OHS carry worse survival than normocapnic peers, but **home NIPPV measurably reduces mortality**.

High-yield exam pointers

- **Definition number:** alveolar hypoventilation = **$Paco_2$ ≥45 mmHg** (normal 37–43 mmHg).
- **Four causes:** lung/chest-wall disease, OHS, neuromuscular disease, respiratory-drive disorders ("won't breathe vs can't breathe").
- **A–a gradient: normal** = drive/neuromuscular (pump) cause; **raised** = intrinsic lung disease.
- **Compensation rule:** acute → HCO_3^- ↑ ~1 mEq/L per 10 mmHg $Paco_2$ (pH ↓0.08); chronic → ↑3.5–5 mEq/L per 10 mmHg.
- **OHS:** BMI ≥30 + $Paco_2$ ≥45 + SDB; ~90% have OSA, ~70% severe; *Pickwickian syndrome*.
- **Treatment goal with NIPPV:** $Paco_2$ <52 mmHg or ≥20% reduction.
- **ALS NIPPV triggers:** $Paco_2$ ≥45, nocturnal SpO_2 ≤88% × 5 min, MIP <60, or SNP <40 with FVC <50%.
- **CCHS:** *Ondine's curse*, **PHOX2B** mutation, absent ventilatory response to hypoxia/hypercapnia, worse in non-REM sleep.
- **GBS "20/30/40":** VC <20 mL/kg, MIP <30, MEP <40 cmH_2O → ICU/ventilation.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Disorders of Ventilation"** (definition/physiology, four-category classification, Table 307-1 features, Fig. 307-1/307-2, diagnostic algorithm, NIPPV goals, ALS/OHS/COPD/CCHS management).
- **Murray & Nadel's Textbook of Respiratory Medicine, 7e — "Hypercapnia"** (won't-breathe vs can't-breathe classification Table 45.1, OHS pathophysiology/leptin resistance, acute-vs-chronic compensation, A–a gradient algorithm, respiratory-muscle testing, AASM sleep-hypoventilation criteria, transcutaneous/end-tidal CO_2).
- **CMDT 2026 — "Pulmonary Disorders" (Disorders of Control of Ventilation / Obesity-Hypoventilation Syndrome)** (OHS diagnostic criteria and current management, respiratory stimulants, perioperative risk).

◆ ◆ ◆

Rheumatology & immune system

◆ ◆ ◆

ANCA-associated vasculitis

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

Definition / Introduction — ANCA-associated vasculitis (AAV) is a group of necrotising, predominantly small-vessel vasculitides that share a paucity of vascular immunoglobulin deposition (*pauci-immune*) and an association with circulating **antineutrophil cytoplasmic antibodies (ANCA)**. Three clinicopathologically distinct entities are grouped under AAV: **granulomatosis with polyangiitis (GPA, formerly Wegener)**, **microscopic polyangiitis (MPA)** and **eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)**. Although they share ANCA positivity and small-vessel injury, each has a unique phenotype and is treated as a separate disease.

Classification, nomenclature & ANCA serology

- The **1992/2012 Chapel Hill Consensus Conference** nomenclature places GPA, MPA and EGPA among the **predominantly small-vessel vasculitides** (with frequent overlap into medium vessels); not all cases are ANCA-positive.
- ANCA are autoantibodies directed against proteins in the cytoplasmic granules of neutrophils and monocytes; two patterns are recognised on indirect immunofluorescence (IIF):
- **c-ANCA (cytoplasmic, granular pattern)** — major antigen is **proteinase-3 (PR3)**, a 29-kDa neutral serine proteinase of azurophilic granules. >90% of *active* GPA cases have anti-PR3.
- **p-ANCA (perinuclear pattern)** — major antigen is **myeloperoxidase (MPO)**; predominant in MPA and EGPA. Other targets (elastase, cathepsin G, lactoferrin, lysozyme) give a p-ANCA pattern but only anti-MPO is convincingly vasculitis-associated.
- Every positive IIF must be **confirmed by antigen-specific enzyme immunoassay** for PR3 or MPO.
- A non-MPO p-ANCA may occur in IBD, autoimmune disease, drugs, endocarditis and cystic-fibrosis airway infection (false positives).

Pathogenesis

- PR3 and MPO normally reside inside resting neutrophil/monocyte granules, inaccessible to serum antibody.
- **Priming** by **TNF-α or IL-1** (or alternative-complement activation) translocates PR3/MPO to the cell surface, where ANCA bind.
- ANCA engagement causes neutrophil **degranulation, reactive oxygen species production, adhesion to and killing of endothelial cells**, and release of IL-1 and IL-8 → necrotising vascular injury. Adoptive-transfer experiments in mice support a direct pathogenic role of ANCA.
- Caveats against ANCA being solely causal: disease can occur ANCA-negative, titre correlates poorly with activity, and high titres may persist in remission.
- In GPA, an **aberrant TH1 cytokine pattern** (↑IFN-γ, ↑TNF-α, ↑IL-12) and the airway-centred granulomatous reaction suggest a cell-mediated response to an inhaled/mucosal antigen; chronic nasal *Staphylococcus aureus* carriage is linked to higher relapse rates.

The three AAV entities compared

Feature	GPA (Wegener)	MPA	EGPA (Churg-Strauss)
Epidemiology	Prevalence ~3/100,000; incidence ~12/million/yr; mean age 40–60; M:F 1:1; rare in blacks	Incidence 3–5/100,000; mean age ~57; M slightly > F	Incidence 1–3/million; mean age 48; F:M 1.2:1
Histology	Necrotising **granulomatous** vasculitis of small arteries & veins	Necrotising vasculitis, **no granuloma**, few/no immune deposits	Necrotising vasculitis + **extravascular eosinophilic granuloma**, tissue/blood eosinophilia
Upper airway	Sinusitis, nasal ulcer/septal perforation, **saddle-nose**, subglottic stenosis (~16%)	Typically absent (if present, suspect GPA)	Allergic rhinitis, nasal polyposis, sinusitis
Lung	Nodular/cavitary infiltrates; alveolar haemorrhage	Pulmonary **capillaritis**, alveolar haemorrhage (12%)	**Asthma**, fleeting eosinophilic infiltrates
Kidney	Pauci-immune crescentic GN (~77%)	Crescentic GN very common (≥79%)	Less common than GPA/MPA
Cardiac	~8%	Uncommon	**Myocarditis ~14% — leading cause of death (39%)**
ANCA	~90% **PR3 (c-ANCA)**; 10–25% MPO; up to 20% none	~75% **MPO (p-ANCA)**	<50% positive, usually **MPO**

Clinical features

- **GPA (organ frequency through course):** upper airway 95%, ENT 92%, lung 85–90%, kidney 77%, eye 52% (episcleritis, scleritis, granulomatous sclerouveitis, retro-orbital pseudotumour → proptosis), skin 46% (palpable purpura, nodules, ulcers), CNS/PNS 23% (cranial neuritis, **mononeuritis multiplex**), cardiac 8% (pericarditis). **Venous thromboembolism** is notably increased. Renal disease, once clinically apparent, tends to progress rapidly.
- **MPA:** the **most common cause of pulmonary-renal syndrome** (diffuse alveolar haemorrhage + rapidly progressive GN), several-fold commoner than anti-GBM disease; palpable purpura, mononeuritis multiplex; may show UIP-like interstitial fibrosis (poor prognosis). **Drug-induced MPA** (high-titre p-ANCA) — *propylthiouracil, hydralazine, allopurinol, penicillamine, minocycline, sulfasalazine*.
- **EGPA (three classic phases):** prodromal **asthma/allergic rhinitis** → blood and tissue **eosinophilia** (>1000/µL in >80%) → systemic **vasculitis**. Mononeuritis multiplex in up to 72%; purpura and subcutaneous nodules in ~51%; cardiac involvement is the chief cause of death — echocardiography in all new cases.

Investigations & Diagnosis

- **Bloods/urine:** raised ESR/CRP, normocytic anaemia, leukocytosis, thrombocytosis; eosinophilia in EGPA. Urinalysis for dysmorphic RBCs, **RBC casts**, proteinuria signals GN.

- **ANCA:** IIF screen (c-/p-ANCA) confirmed by PR3/MPO EIA. Predictive value of a positive ANCA is ~90% with **active glomerulonephritis**, but falls to 30–60% in sinus/lung-limited disease — so **tissue biopsy is usually required**, especially when ANCA-negative or features are atypical (to exclude infection/malignancy).
- **Biopsy:** lung gives the highest yield in GPA (necrotising granulomatous vasculitis); renal biopsy shows **pauci-immune segmental necrotising crescentic glomerulonephritis** (relative absence of IgG/IgM/IgA/complement) — the hallmark common to all AAV.
- **Imaging:** chest CT (more sensitive than CXR) — nodules, masses, cavities, ground-glass of haemorrhage; sinus imaging may show bony erosion.
- In EGPA, work up unexplained eosinophilia: ANCA, serum tryptase, flow cytometry/PDGFR for eosinophilic leukaemia, and helminth serology.

Treatment

- Management has two phases — **induction of remission** then **maintenance** — stratified by severity. **Severe = organ- or life-threatening** (e.g. RPGN, alveolar haemorrhage); **active glomerulonephritis is always classed as severe** even with normal creatinine.
- **Induction (severe GPA/MPA):** glucocorticoid (historically **prednisone 1 mg/kg/day**; a *reduced-dose regimen is non-inferior with fewer infections*) **plus either**:
  - **Cyclophosphamide** 2 mg/kg/day orally (or IV pulse 15 mg/kg every 2 wk ×3 then every 3 wk), renally dose-adjusted; switch off at **3–6 months**, **or**
  - **Rituximab** (anti-CD20) **375 mg/m² weekly × 4** — as effective as cyclophosphamide (superior in relapsing disease) and preferred for PR3-positive and relapsing patients, avoiding bladder toxicity/infertility.
- **Avacopan** (oral **C5a-receptor inhibitor**) is an add-on that allows rapid glucocorticoid withdrawal, achieving higher sustained remission than prednisone alongside cyclophosphamide or rituximab.
- **Fulminant disease:** IV **methylprednisolone 1000 mg/day × 3 days**.
- **Plasma exchange (PLEX):** the **PEXIVAS** trial showed no benefit on the composite of ESRD/death; reserve for coexisting **anti-GBM antibody** or selected fulminant cases. Separate PLEX from rituximab by ≥48 h.
- **Maintenance:** after cyclophosphamide induction, switch to **rituximab (preferred, lower relapse)**, **azathioprine 2 mg/kg/day**, **methotrexate 20–25 mg/week**, or **mycophenolate mofetil**; continue ≥2 years.
- **Non-severe disease:** methotrexate or MMF with glucocorticoid; cyclophosphamide is rarely justified.
- **EGPA:** glucocorticoids are first-line; cyclophosphamide (then azathioprine/methotrexate) for fulminant/cardiac or ANCA-positive GN; **mepolizumab (anti-IL-5) 300 mg SC monthly** for relapsing/refractory non-severe disease (benralizumab non-inferior).
- **Supportive: Pneumocystis jirovecii prophylaxis with trimethoprim-sulfamethoxazole** during cyclophosphamide/rituximab therapy; agents shown *ineffective/harmful* — etanercept, belimumab, abatacept.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **ANCA immunofluorescence patterns** — two neutrophils side by side: (1) *c-ANCA* with diffuse granular **cytoplasmic** staining labelled "anti-PR3"; (2) *p-ANCA* with **perinuclear** staining labelled "anti-MPO"; label the **nucleus** in each.
- **ANCA pathogenesis cascade** — boxes/arrows: *resting neutrophil → priming by TNF-α/IL-1 → PR3/MPO translocate to cell membrane → ANCA binding → degranulation + reactive oxygen species + IL-8 → endothelial injury → necrotising small-vessel (pauci-immune) vasculitis*. Optionally a glomerulus with a **crescent** labelled "pauci-immune crescentic GN".

Clinical / Diagnostic significance

- AAV is the commonest cause of **pulmonary-renal syndrome**; recognise the triad of haemoptysis (alveolar haemorrhage), RPGN and ANCA positivity for urgent immunosuppression.
- ANCA **serotype (PR3 vs MPO)** increasingly guides prognosis/relapse risk better than the clinical label — PR3/c-ANCA disease relapses more and favours rituximab.
- **Saddle-nose deformity, subglottic stenosis and cavitary lung nodules** strongly suggest GPA; **cocaine/levamisole midline destruction** and NK/T-cell lymphoma are key mimics (biopsy mandatory before irradiation is ever considered).
- Untreated GPA is fatal within months; cyclophosphamide-based regimens transformed outcomes (remission ~75%, 5-yr survival >80%).

High-yield exam pointers

- AAV triad = **GPA, MPA, EGPA** — all **pauci-immune** small-vessel vasculitis.
- **c-ANCA = anti-PR3 ≈ GPA; p-ANCA = anti-MPO ≈ MPA/EGPA.**
- GPA classic triad: **upper + lower respiratory tract + glomerulonephritis**; saddle nose, subglottic stenosis, increased **VTE**.
- MPA = **commonest pulmonary-renal syndrome**, no granuloma, no upper-airway disease; drug-induced by **PTU/hydralazine/minocycline**.
- EGPA = **asthma + eosinophilia (>1000/μL) + vasculitis**; **cardiac involvement = leading cause of death**; ANCA positive in <50%.
- Renal lesion = **pauci-immune crescentic necrotising glomerulonephritis**.
- Induction = **glucocorticoid + (rituximab or cyclophosphamide) ± avacopan**; maintenance = rituximab/azathioprine/MTX/MMF.
- **PEXIVAS:** routine plasma exchange offers no benefit (except anti-GBM overlap); **TMP-SMX** for PJP prophylaxis.
- **Mepolizumab (anti-IL-5)** for relapsing non-severe EGPA; **avacopan = C5a-receptor inhibitor**, steroid-sparing.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "The Vasculitis Syndromes"** (ANCA biology and pathogenesis; GPA, MPA, EGPA definitions, organ-frequency data, induction/maintenance regimens, avacopan, PEXIVAS, mepolizumab/benralizumab).
- **CMDT 2026 — "Rheumatologic, Immunologic & Allergic Disorders" (Vasculitis Syndromes)** (Chapel Hill classification, PR3/MPO confirmatory testing, drug-induced MPA, EULAR/ACR-VF treatment approach, pulmonary-renal syndrome).

◆ ◆ ◆

Ankylosing spondylitis

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

Definition / Introduction — Ankylosing spondylitis (AS) is the radiographic form of **axial spondyloarthritis (r-axSpA)**, a chronic immune-mediated inflammatory disorder predominantly involving the **sacroiliac joints and spine**. It is characterized by inflammatory back pain, sacroiliitis, progressive loss of spinal mobility, enthesitis, and extra-articular disease such as acute anterior uveitis, psoriasis, and inflammatory bowel disease (IBD). Pathologically, it is distinctive because inflammation-induced bone loss coexists with pathologic new bone formation, culminating in syndesmophytes and, rarely, a complete "bamboo spine."

Nomenclature and epidemiology

- **Spondyloarthritis (SpA)** is a family of seronegative immune-mediated arthritides sharing sacroiliitis, inflammatory spinal lesions, peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis, IBD, familial clustering, and **HLA-B27** association.
- The 2009 **ASAS** approach divides SpA into **axial SpA** and **peripheral SpA**. Axial SpA is further divided into **radiographic axSpA**, historically called AS, and **nonradiographic axSpA**, based on whether definite sacroiliitis is visible on plain radiographs.
- **Modified New York radiographic threshold:** definite sacroiliitis means **bilateral grade >=2** or **unilateral grade 3-4** sacroiliitis; definite AS requires at least one clinical criterion plus this radiographic criterion.
- Usual onset is before **40-45 years**, commonly in the **20s-30s**. r-axSpA has an approximate male:female ratio of **2:1**, whereas nr-axSpA is closer to **1:1**.
- **HLA-B27** is the strongest genetic association: Harrison notes positivity in **85-90%** of r-axSpA and **50-90%** of nr-axSpA. The risk of axSpA is about **5%** in HLA-B27-positive persons and rises to about **20%** in HLA-B27-positive first-degree relatives of affected patients.

Pathogenesis

- Disease begins in genetically predisposed individuals through interaction of **HLA-B27**, other MHC/non-MHC genes, mucosal immune triggers, mechanical stress, and cytokine pathways.

- Proposed HLA-B27 mechanisms include **arthritogenic peptide presentation**, HLA-B27 homodimer interaction with innate immune receptors, and unfolded protein response/autophagy links; no single theory fully explains disease.
- The **gut-joint axis** is important: intestinal dysbiosis, barrier dysfunction, and microbial peptide translocation may drive immune activation; subclinical gut inflammation is common in axSpA.
- **Entheses** are key target tissues. Mechanical strain produces microdamage; in SpA this response becomes amplified and prolonged, promoting chronic enthesitis.
- Signature inflammatory pathways include **TNF** and **IL-17**. Chronic entheseal inflammation promotes osteoblast differentiation and pathologic new bone formation, leading to bony spurs, syndesmophytes, sacroiliac ankylosis, and spinal fusion.

Clinical features

- **Inflammatory back pain:** insidious chronic low back, hip, or alternating buttock pain for >3 months; onset <45 years; worse in the second half of the night; improves after getting up, exercise, or activity; not relieved by rest; morning stiffness usually >30 minutes.
- **Axial progression:** limitation of lumbar, thoracic, and cervical mobility; flattening of lumbar lordosis, exaggerated thoracic kyphosis, reduced chest expansion from costovertebral involvement, and fixed deformity in advanced disease.
- **Peripheral disease:** peripheral arthritis occurs in about **30-40%** in Harrison and may be transient or persistent in CMDT; it is typically asymmetric oligoarthritis of large lower-limb joints. Hip involvement causes groin pain radiating to the medial thigh or knee and predicts greater functional loss.
- **Enthesitis:** heel pain from Achilles insertion or plantar fasciitis, chest wall pain, intercostal insertions, epicondylitis, quadriceps/patellar tendon insertion pain, or pelvic rim pain. Dactylitis is uncommon in pure axSpA.
- **Extra-musculoskeletal disease:** acute anterior uveitis is the commonest; it is typically **acute, anterior, unilateral, episodic**, with eye discomfort, redness, pain, photophobia, and miosis. IBD occurs in about **10%**, histologic subclinical gut inflammation in up to **50%**, and psoriasis in about **10%**.
- **Systemic and late features:** fatigue, anemia of chronic inflammation, osteoporosis, vertebral fractures, conduction disease, aortic valve insufficiency, apical pulmonary fibrosis, restrictive chest disease, IgA nephropathy, renal AA amyloidosis, and rare cauda equina syndrome.

Diagnosis and investigations

- Diagnosis is by **pattern recognition**: chronic back pain >3 months with onset <45 years, inflammatory features, SpA features, supportive imaging/laboratory data, and exclusion of common mimics.
- Important **SpA features** to actively seek: inflammatory arthritis, enthesitis, dactylitis, acute anterior uveitis, psoriasis, IBD, family history of SpA, good response to full-dose NSAIDs, and elevated CRP.

- **Laboratory tests:** ESR/CRP support active disease but are neither sensitive nor specific; Harrison notes elevation in only **30-40%** of active axSpA. Rheumatoid factor and anti-CCP are negative. HLA-B27 is not diagnostic alone and is most useful when pre-test probability is intermediate.
- **Plain radiography:** a single AP pelvis or Ferguson view is sufficient for sacroiliac joints. Sacroiliitis shows sclerosis, erosions, joint-space narrowing/widening, and late fusion. Spine films may show **Romanus lesions/shiny corner sign**, vertebral squaring, **Andersson lesion**, vertical syndesmophytes, and bamboo spine.
- **MRI SI joints/spine:** useful in early disease when x-ray is negative. STIR/T2 fat-suppressed sequences show active bone marrow edema or osteitis; T1 images show structural lesions such as erosions, fat metaplasia, backfill, sclerosis, and new bone. MRI can overdiagnose disease in athletes, postpartum women, degenerative disease, and older adults.

Modified New York criteria for AS	Key points
Clinical criterion 1	Low back pain >3 months, improved by exercise and not relieved by rest
Clinical criterion 2	Limitation of lumbar motion in frontal and lateral planes
Clinical criterion 3	Reduced chest expansion
Radiographic criterion	Bilateral grade >=2 sacroiliitis, or unilateral/bilateral grade 3-4 sacroiliitis
Definite AS	>=1 clinical criterion plus radiographic criterion

Differential diagnosis

- **Mechanical low back pain, disk disease, degenerative arthritis**: commoner than AS; mechanical pain worsens with activity and improves with rest.
- **Rheumatoid arthritis**: symmetric small-joint disease; RF/anti-CCP often positive; sacroiliac joints are spared and spinal disease is mainly cervical.
- **Psoriatic/reactive/IBD-associated SpA:** may mimic AS; psoriatic and reactive sacroiliitis is often asymmetric or unilateral, whereas AS is usually bilateral and symmetric.
- **DISH:** older obese/diabetic men; bulky flowing osteophytes and longitudinal ligament ossification with normal SI joints, mistaken for bamboo spine.
- **Osteitis condensans ilii:** triangular sclerosis on the iliac side of SI joints, usually postpartum; absence of erosions favors OCI over sacroiliitis.
- **Do not miss red flags:** fever, weight loss, advanced age, malignancy history, osteoporotic fracture, osteomyelitis, spinal tuberculosis/brucellosis/fungal infection, malignancy, fibromyalgia, hypermobility, hypothyroidism, and vitamin D deficiency.

Management

- **Targets:** remission or low disease activity, preservation of posture/mobility, prevention of structural damage, and control of extra-articular disease.

- **Nonpharmacologic:** patient education, active land/aquatic physical therapy, daily posture and spinal extension exercises, safe aerobic/resistance exercise, chest expansion exercises, smoking cessation, fall/fracture prevention, and cardiovascular risk reduction.
- **NSAIDs:** first-line; use the highest tolerated dose in active disease and as needed when stable. No specific NSAID is preferred. Monitor gastric ulcer/bleeding, hypertension, renal insufficiency, and cardiovascular risk.
- **csDMARDs: sulfasalazine up to 3 g/day** and **methotrexate up to 25 mg/week** may help peripheral arthritis/enthesitis but are **not effective for axial spinal or SI disease**.
- **Escalation:** if active disease persists after a **4-week full-dose NSAID trial**, start a biologic, usually **TNF inhibitor** or **IL-17 inhibitor**. Screen for latent tuberculosis, hepatitis B, and hepatitis C before biologic or JAK inhibitor therapy.
- **Biologic/targeted options:** etanercept 50 mg SC weekly; adalimumab 40 mg SC every 2 weeks; certolizumab 200 mg SC twice monthly or 400 mg monthly; golimumab 50 mg SC monthly or IV 2 mg/kg at weeks 0 and 4 then every 8 weeks; infliximab 5 mg/kg IV at weeks 0, 2, 6 then every 6 weeks. IL-17 inhibitors include secukinumab 150 mg SC weekly for 5 loading doses then every 4 weeks, and ixekizumab 160 mg once then 80 mg every 4 weeks. JAK inhibitors include tofacitinib 5 mg twice daily for AS and upadacitinib 15 mg daily for AS/nr-axSpA.
- **Choosing agents:** monoclonal TNF inhibitors are preferred over etanercept when uveitis or IBD coexists. IL-17 blockade is effective in axSpA but should be avoided in active IBD. JAK inhibitors are generally reserved after TNF inhibitor failure and require caution in older patients, smokers, cardiovascular disease, and malignancy risk.
- **Avoid:** systemic glucocorticoids for axial disease. Local glucocorticoid injections may be used for peripheral arthritis or selected upper-limb enthesitis; avoid injections around lower-limb weight-bearing entheses because of rupture risk.
- **Surgery:** total hip arthroplasty for refractory painful structurally damaged hips; spinal osteotomy only for severe fixed kyphosis impairing horizontal vision and only in expert centers.

Complications and prognosis

- Osteoporosis is common; Harrison gives about **25%** after 10 years of axSpA and vertebral fractures in about **10%** of AS patients, often in the lower cervical spine with neurologic risk.
- Disease course is variable. Harrison notes nearly **50%** may progress from nonradiographic to radiographic axSpA over 20 years, but **<10%** progress to extensive spinal bamboo spine.
- Risk factors for osteoproliferation include male sex, persistent MRI inflammation, high CRP, syndesmophytes, HLA-B27 positivity, and smoking.
- CMDT notes most patients have persistent symptoms over decades, rare long-term remissions, about **10%** work disability after 10 years, and worse prognosis with hip disease within the first 2 years.
- Biologic therapy improves symptoms and quality of life and may slow radiographic progression, but patients need monitoring for infections, tuberculosis reactivation, zoster with JAK inhibitors, Candida with IL-17 inhibitors, and drug-specific adverse effects.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **AP pelvis and lateral spine in AS:** label bilateral sacroiliac erosions, sclerosis, joint-space narrowing, SI ankylosis, squared vertebral bodies, vertical marginal syndesmophytes, fused facet joints, and bamboo spine.
- **Diagnostic flowchart for chronic inflammatory back pain:** label chronic back pain >3 months with onset <45 years, rule out mechanical back pain/fibromyalgia, SI joint x-ray, definite sacroiliitis = AS/r-axSpA, if x-ray negative assess SpA features, MRI SI joints, HLA-B27, nr-axSpA versus not axSpA.

Clinical / Diagnostic significance

- AS should be suspected in any young adult with chronic back or buttock pain that improves with exercise and worsens with rest, especially with uveitis, heel pain, psoriasis, IBD, family history, or excellent NSAID response.
- A positive HLA-B27 supports but does not diagnose AS; a negative result does not exclude disease in nonwhite populations or in a compelling clinical picture.
- MRI is powerful for early nr-axSpA but must be interpreted with clinical probability because mechanical stress and postpartum SI changes can mimic osteitis.
- New severe neck/back pain in established AS is a fracture until proved otherwise; ankylosed osteoporotic spines fracture with relatively minor trauma.
- Uveitis symptoms require urgent ophthalmology referral; active IBD changes biologic selection.

High-yield exam pointers

- AS = **radiographic axial spondyloarthritis**; nr-axSpA has similar symptoms but lacks definite x-ray sacroiliitis.
- Classic triad to write: **inflammatory back pain + bilateral sacroiliitis + HLA-B27 association**.
- Modified New York: **>=1 clinical criterion + radiographic sacroiliitis**.
- Inflammatory back pain: onset <45 years, >3 months, morning stiffness, night pain, improves with exercise, not rest.
- Commonest extra-articular manifestation: **acute anterior uveitis**.
- First-line treatment: **exercise/physical therapy plus NSAIDs**.
- csDMARDs do not treat axial disease; use them only for peripheral arthritis/enthesitis.
- NSAID failure after adequate trial: escalate to **TNF inhibitor or IL-17 inhibitor**; monoclonal TNF inhibitor if uveitis/IBD.
- Late complications: bamboo spine, vertebral fracture, aortic regurgitation/conduction block, apical fibrosis, IgA nephropathy, AA amyloidosis, and cauda equina syndrome.

SOURCE & COVERAGE

Harrison 22e — "Spondyloarthritis"; CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders".

◆ ◆ ◆

Approach to non-traumatic monoarthritis

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

Definition / Introduction — **Monoarthritis** is inflammation confined to a *single joint* (≤1 joint), distinguished from *oligo/pauciarticular* (2–3 joints) and *polyarticular* (≥4 joints) disease. **Acute non-traumatic monoarthritis** is a medical emergency because it harbours three time-critical *"red flag"* diagnoses — **septic arthritis, acute crystal arthritis (gout/pseudogout) and (occult) fracture** — and untreated bacterial infection destroys articular cartilage within 48 hours. The cornerstone of evaluation is a structured history and examination followed by **arthrocentesis with synovial fluid analysis**, which is *always indicated* in acute monoarthritis.

Diagnostic framework — the four screening questions

The musculoskeletal complaint is characterised by answering four questions (Cush/Harrison), which narrow the differential:

- **Articular or non-articular?** Articular pain is deep/diffuse, limits *active and passive* range, with swelling, crepitus or deformity. Periarticular lesions (bursitis, tendinitis, cellulitis) give point tenderness, pain on *active but not passive* motion and less-than-circumferential swelling — these *masquerade* as arthritis.
- **Inflammatory or non-inflammatory?** Inflammation = the cardinal signs (warmth, erythema, swelling, pain), prolonged morning stiffness (hours), systemic features (fever, rash) and raised ESR/CRP.
- **Acute (≤6 weeks) or chronic (>6 weeks)?** Acute monoarthritis is usually infective, crystal-induced or reactive; chronic monoarthritis suggests mycobacterial/fungal infection, or initial presentation of a chronic arthropathy.
- **How many / which joints?** Confirms it is truly monoarticular and not the first joint of an evolving oligo/polyarthritis.

Causes / Differential diagnosis of non-traumatic monoarthritis

Acute monoarthritis	Chronic monoarthritis (>6 wk)
Septic (non-gonococcal): *S. aureus* (incl. MRSA), group B/A streptococci, gram-negative bacilli	**Mycobacterium tuberculosis** (chronic granulomatous monoarthritis)
Gonococcal arthritis (*N. gonorrhoeae* — DGI)	Non-tuberculous mycobacteria (*M. marinum*, MAC)
Crystal: gout (monosodium urate), pseudogout (CPPD)	**Fungal:** *Candida, Sporothrix schenckii, Coccidioides, Blastomyces, Histoplasma*

Acute monoarthritis	Chronic monoarthritis (>6 wk)
Reactive arthritis (initial), Lyme arthritis (knee)	**Brucella**, *Treponema pallidum* (syphilis)
Haemarthrosis (anticoagulant/coagulopathy)	Monoarticular RA / pauciarticular JIA; psoriatic arthritis
Initial monoarticular presentation of RA, psoriatic, SpA	Osteoarthritis, osteonecrosis, Charcot (neuropathic) joint
Avascular necrosis, sickle-cell flare	Pigmented villonodular synovitis, foreign-body synovitis, tumour

- *Monoarticular and oligoarticular conditions share similar aetiologies* — crystal and infective arthritis are typically mono/oligoarticular, whereas RA and OA are usually polyarticular.
- **Crystal arthritis and septic arthritis can coexist in the same joint** — finding crystals does *not* exclude infection.

Clinical evaluation — history and examination

- **Patient profile:** young adults — gonococcal and reactive arthritis; men — gout, spondyloarthritis; elderly — pseudogout, septic arthritis, gout; women, menses/pregnancy — disseminated gonococcal infection (DGI).
- **Onset/evolution:** *abrupt* (hours, often nocturnal) onset is typical of **septic arthritis and gout**; indolent over weeks–months suggests TB/fungal. Intermittent self-resolving attacks suggest crystal or Lyme arthritis.
- **Risk factors for sepsis:** pre-existing joint damage (RA), prosthetic joint, IV drug use, diabetes, advanced CKD, alcohol/cirrhosis, immunosuppression/biologics (TNF inhibitors), skin breach (ulcer, psoriasis).
- **Precipitants of crystal flare:** purine-rich food, alcohol/beer, diuretics, starting urate-lowering therapy, surgery (esp. parathyroidectomy → pseudogout), acute illness.
- **Examination:** confirm true articular swelling vs periarticular; distinguish effusion (fluctuant, *bulge/patellar tap*) from synovial hypertrophy ("boggy") and bony enlargement. Document erythema, warmth, range of motion, and seek an **extra-articular focus** — tophi (pinna, olecranon), podagra, skin pustules on palms/soles + **tenosynovitis** (DGI), tick-bite/erythema migrans (Lyme), psoriatic plaques/nail pitting, fever and a portal of infection (boil, pneumonia, endocarditis).

Arthrocentesis and synovial fluid analysis — the pivotal test

Aspiration and analysis of synovial fluid are always indicated in acute monoarthritis or when infection/crystal arthropathy is suspected. Never pass the needle through overlying cellulitis or a psoriatic plaque. Analyse immediately for **appearance, viscosity, cell count + differential, Gram stain & culture, and crystals under compensated polarised light**.

Parameter	Normal	Group I Non-inflammatory	Group II Inflammatory	Group III Septic/Purulent
Clarity / colour	Transparent, clear	Transparent, yellow	Translucent–opaque, yellow	Opaque, yellow-green

Parameter	Normal	Group I Non-inflammatory	Group II Inflammatory	Group III Septic/Purulent
Viscosity ("string sign")	High	High	Low	Low
WBC/μL	<200	<2000	2000–75,000 (PMN ≥50%)	>50,000 (often >100,000), PMN ≥75–90%
Typical causes	—	OA, osteonecrosis	Gout, pseudogout, RA, reactive	Bacterial septic arthritis

- **Crystals: Monosodium urate (gout)** — *needle-shaped, strongly negatively birefringent* (yellow when parallel to compensator), usually intracellular. **Calcium pyrophosphate (pseudogout)** — *rhomboid/rod-shaped, weakly positively birefringent*.
- **Microbiology:** Gram stain positive in ~75% of staphylococcal, ~50% of gram-negative septic arthritis; synovial culture positive in 70–90% of non-gonococcal cases (blood cultures ~50%). Send *NAAT* if gonococcal/chlamydial suspected; culture synovial fluid for **TB and fungi** in chronic monoarthritis. MALDI-TOF/metagenomics aid culture-negative cases.
- *Caveat:* septic arthritis can present with Group II fluid (<50,000) with low-virulence organisms (gonococcus) or after antibiotics — a "non-septic" count never fully excludes infection.

Investigations beyond joint fluid

- **Bloods:** CBC with differential, **ESR/CRP** (discriminate inflammatory vs not; elevated but non-specific in sepsis), serum **urate** (may be normal in up to 50% during an acute gout flare — IL-6 is uricosuric; seek historical/post-flare values), creatinine, LFTs, blood cultures.
- **Targeted serology** only when pretest probability is adequate: RF, anti-CCP, ANA, Lyme, ASO, procalcitonin (≈50% sensitive — does *not* rule out sepsis).
- **Imaging:** plain radiograph (baseline; early shows only soft-tissue swelling/effusion; chondrocalcinosis suggests CPPD; erosions with overhanging edges suggest tophaceous gout). **Ultrasound** detects effusion and the *double-contour sign* of urate deposition and guides aspiration of hip/shoulder; **MRI/CT** for deep joints (hip, sacroiliac, sternoclavicular), early osteomyelitis and to demonstrate effusion not clinically apparent. **Dual-energy CT** characterises urate deposits.

Specific entities and management pearls

- **Non-gonococcal septic arthritis** — *S. aureus* causes ~50%; the **knee** is most often involved (~90% single joint). It is a *medical/surgical emergency*. After cultures, give empirical IV bactericidal antibiotics: gram-positive cocci → **vancomycin 15–20 mg/kg q8–12h**; gram-negative bacilli → third-generation cephalosporin (**ceftriaxone 2 g q24h / cefotaxime 2 g q8h**), with anti-pseudomonal cover (cefepime/ceftazidime) in IVDU/immunocompromised. Add **joint drainage** (repeated needle aspiration, arthroscopic lavage, or arthrotomy — hip needs arthrotomy). Typical course ~4 weeks (staphylococci). CMDT empirical regimen: vancomycin + third-generation cephalosporin, 4–6 weeks.

- **Gonococcal arthritis (DGI)** — young, healthy, often women (menses/pregnancy); *triad* of **migratory polyarthralgia → tenosynovitis (60%) → purulent monoarthritis (40%)** with necrotic pustules on palms/soles. Synovial cultures often negative; diagnosis via mucosal **NAAT/culture**. Treat with **ceftriaxone 1 g IV/IM daily**, switch to oral after 24–48 h improvement to complete 7 days; dramatic response is characteristic. Test CH50 for terminal complement deficiency if recurrent.
- **Acute gout — podagra** (first MTP) in 70–90%; nocturnal, exquisitely painful, mimics cellulitis. Confirm with MSU crystals. Treat the flare early with **colchicine (1.2 mg at onset, 0.6 mg 1 h later)**, an **NSAID** (indomethacin 25–50 mg tid, naproxen 500 mg bid), or **glucocorticoid** (prednisone 30–50 mg/d tapered, or intra-articular). Start **urate-lowering therapy** later (allopurinol — screen *HLA-B\5801** in at-risk groups; febuxostat; probenecid) targeting **urate <6 mg/dL (<5 if tophi)** under anti-inflammatory prophylaxis.
- **Pseudogout (CPPD)** — elderly; **knee** > wrist; weakly positively birefringent rhomboid crystals + **chondrocalcinosis** on radiograph. In patients <50 yr, screen for haemochromatosis, hyperparathyroidism, hypophosphatasia, hypomagnesaemia. Treat as for acute gout (NSAID/colchicine/steroid).
- **Tuberculous arthritis** — chronic granulomatous monoarthritis of large weight-bearing joints (hip, knee, ankle); synovial fluid ~20,000 cells/µL (~50% PMN), AFB smear positive <⅓, culture ~80%, **synovial biopsy culture ~90%**; treat with standard multidrug ATT for 6–9 months.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Algorithm for acute non-traumatic monoarthritis (flow chart):** *Acute monoarthritis* → assess for **red flags** → **Arthrocentesis** → branch on synovial WBC: *<2000 (non-inflammatory → OA, osteonecrosis) | 2000–50,000 (inflammatory → check crystals: MSU → gout, CPP → pseudogout; if none → reactive/early inflammatory) | >50,000, PMN >75%, +Gram stain/culture → septic arthritis → IV antibiotics + drainage*. Label boxes: *History/exam, WBC count, % PMN, Crystals, Gram stain, Culture*.
- **Polarised-light crystal comparison:** two crystals with compensator axis — label **MSU: needle-shaped, NEGATIVELY birefringent, intracellular (gout)** and **CPP: rhomboid, weakly POSITIVELY birefringent (pseudogout)**.

Clinical / Diagnostic significance

- **Septic arthritis is the diagnosis to exclude first** in every acute hot joint — delayed therapy causes irreversible cartilage destruction, ankylosis and a 30% mortality in polyarticular sepsis. Arthrocentesis precedes antibiotics.
- A single joint *"out of proportion"* to the rest in established RA must be aspirated to exclude superimposed sepsis, especially on biologic DMARDs.
- Crystals and infection coexist — always Gram stain/culture even when crystals are seen.
- Serum urate is unreliable during an acute flare; definitive gout diagnosis rests on crystal identification, not urate level.

High-yield exam pointers

- Three **red-flag** causes of acute monoarthritis: **septic arthritis, crystal arthritis, fracture**.
- **Arthrocentesis is mandatory** in acute monoarthritis; synovial WBC **>50,000/µL with >75% PMN** = presume septic until proven otherwise.
- **MSU = needle-shaped, negatively birefringent (gout); CPP = rhomboid, positively birefringent (pseudogout).**
- *S. aureus* is the commonest cause of non-gonococcal septic arthritis; **knee** is the commonest joint; ~90% are monoarticular.
- **DGI** = arthritis–dermatitis–tenosynovitis triad in a young adult; treat with ceftriaxone.
- **Podagra** (first MTP gout) in 70–90%; acute gout treated with colchicine/NSAID/steroid, not urate-lowering during the flare.
- **Chronic** monoarthritis → think **TB and fungi**; culture/biopsy synovium.
- Empirical septic-arthritis therapy: **vancomycin + third-generation cephalosporin** plus joint drainage.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — *"Approach to Articular and Musculoskeletal Disorders"* (four screening questions, synovial fluid algorithm, laboratory evaluation); *"Infectious Arthritis"* (differential of arthritis syndromes, septic/gonococcal/tuberculous/fungal arthritis, antibiotic regimens); *"Gout and Other Crystal-Associated Arthropathies"* (acute gout, MSU/CPP crystals, colchicine/NSAID/steroid and urate-lowering therapy).
- CMDT 2026 — *"Rheumatologic, Immunologic, & Allergic Disorders"* (joint-pattern table, examination of joint fluid Groups I–III, nongonococcal & gonococcal septic arthritis, osteoarthritis, gout/pseudogout management).

Coverage note: The corpus has no dedicated rheumatology subspecialty textbook for this topic (spec.specialty_books empty); depth is drawn from Harrison 22e and CMDT 2026, which fully cover the approach, synovial fluid classification, crystal identification and management regimens.

◆ ◆ ◆

Biologics in autoimmune disease

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

Definition / Introduction — Biologic agents (biologic DMARDs) are large, protein-based therapeutics — chiefly **monoclonal antibodies, soluble receptor–Fc fusion proteins and recombinant receptor antagonists** — engineered to neutralise specific cytokines, deplete or modulate immune cells, or block co-stimulatory and trafficking pathways central to autoimmune inflammation. By targeting a single defined node rather than broadly suppressing the immune system (as glucocorticoids or cyclophosphamide do), they have **revolutionised the treatment of rheumatoid arthritis (RA), spondyloarthritis, SLE, ANCA-associated vasculitis (AAV), inflammatory bowel disease (IBD) and psoriasis** over the past two decades. The first class approved (TNF inhibitors, from 1999) was followed by B-cell–, IL-6–, IL-1–, IL-17–, IL-23– and IFN-targeted agents; **biosimilars** (highly similar copies of an off-patent reference biologic with comparable efficacy and safety) have since broadened access.

Classification of biologics by structure and target

Class / structure	Molecular target	Representative agents (autoimmune use)
Anti-TNF-α monoclonal antibodies	Soluble + membrane TNF-α	Infliximab (chimeric), Adalimumab, Golimumab (human/humanised), Certolizumab pegol (PEGylated Fab′)
Anti-TNF fusion protein	TNF-α	Etanercept (TNF-R2–IgG1 Fc fusion protein)
B-cell depleting (anti-CD20)	CD20 on mature B cells	Rituximab (chimeric), Obinutuzumab (type II, investigational in SLE)
Co-stimulation blocker	CD28–CD80/86 (T-cell)	Abatacept (CTLA-4–IgG fusion protein)
Anti-IL-6 receptor	IL-6R (soluble + membrane)	Tocilizumab, Sarilumab
IL-1 receptor antagonist	IL-1 receptor	Anakinra (recombinant IL-1Ra)
Anti-IL-17A	IL-17A	Secukinumab (IgG1κ), Ixekizumab (IgG4)
Anti-IL-12/23 (p40) / anti-IL-23 (p19)	Shared p40 / IL-23 p19	Ustekinumab (p40); Risankizumab, Mirikizumab (p19)
Anti-integrin (anti-trafficking)	α4β7 / α4 integrin	Vedolizumab (gut-selective α4β7), Natalizumab (α4)
Anti-BAFF / BLyS	B-cell activating factor	Belimumab
Anti-type I IFN receptor	IFNAR1	Anifrolumab
Complement C5a-receptor inhibitor	C5a receptor	Avacopan (small molecule, adjunct in AAV)

- **Nomenclature pearl:** the suffix encodes structure — *-mab* = monoclonal antibody (*-ximab* chimeric e.g. infliximab/rituximab; *-zumab* humanised e.g. tocilizumab; *-umab* fully human e.g. golimumab, adalimumab, ustekinumab), while *-cept* = receptor–Fc **fusion protein** (etanercept, abatacept).

- **Not biologics but commonly confused with them:** *targeted synthetic DMARDs* — the oral **JAK inhibitors** (tofacitinib JAK1/3; baricitinib JAK1/2; upadacitinib JAK1) and **voclosporin** (a calcineurin inhibitor used in lupus nephritis). They block intracellular signalling and offer an oral alternative to injectable biologics.

Mechanism-based pharmacology of the major classes

- **TNF-α inhibitors** — TNF-α is a critical upstream driver of synovitis; five "innovator" agents exist. **Infliximab** is a chimeric mAb; **adalimumab/golimumab** are human(ised) mAbs; **certolizumab** is a PEGylated Fab′ fragment; **etanercept** is a soluble TNF-receptor-2–IgG1-Fc fusion protein. All reduce signs/symptoms, **slow radiographic joint damage** and improve function in RA; used alone or with background **methotrexate (MTX)**. Effective also in psoriasis, psoriatic arthritis, ankylosing spondylitis and IBD.
- **B-cell depletion — Rituximab (anti-CD20)** depletes mature B cells, lowering autoantibody production, T-cell activation and cytokine output. Approved for **MTX-refractory / TNF-failure RA** (more effective in seropositive disease) and a cornerstone of **AAV** therapy.
- **Co-stimulation blockade — Abatacept (CTLA-4-Ig)** binds CD80/86 on antigen-presenting cells, blocking the CD28 "second signal" required for T-cell activation; slows radiographic progression in RA, usually with a conventional DMARD.
- **IL-6 receptor blockade — Tocilizumab / sarilumab** are mAbs against soluble and membrane IL-6R; IL-6 drives the acute-phase response, B-cell help and osteoclast activation. Effective as monotherapy or with MTX.
- **IL-1 blockade — Anakinra** is recombinant IL-1 receptor antagonist (limited use in RA; mainstay of autoinflammatory syndromes).
- **IL-17 / IL-23 axis — Secukinumab, ixekizumab (anti-IL-17A)** and **ustekinumab (anti-p40)/risankizumab (anti-IL-23 p19)** target the Th17 pathway central to **psoriasis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease**.
- **Anti-trafficking integrin blockers — Vedolizumab (gut-selective α4β7)** and **natalizumab (α4)** prevent leucocyte homing to gut/CNS in IBD.
- **SLE-specific biologics — Belimumab (anti-BAFF/BLyS)** reduces B-cell survival; **anifrolumab (anti-type I IFN receptor)** blocks the interferon signature.

Disease-specific applications

Disease	Biologic(s) used	Key clinical role
Rheumatoid arthritis	TNF inhibitors, abatacept, tocilizumab/sarilumab, rituximab, anakinra	Step-up after inadequate MTX response (≈3–6 mo); rituximab for TNF failure, esp. seropositive disease
SLE / lupus nephritis	Belimumab (incl. lupus nephritis), anifrolumab; rituximab (off-label refractory disease, AIHA, severe thrombocytopenia, neuropsychiatric lupus)	Glucocorticoid-sparing; belimumab given **with MMF or low-dose cyclophosphamide**; obinutuzumab & CAR-T (anti-CD19) emerging

Disease	Biologic(s) used	Key clinical role
ANCA-associated vasculitis (GPA/MPA)	**Rituximab** (induction & maintenance), **avacopan** (C5a-R, steroid-sparing)	Rituximab 375 mg/m^2/week ×4 ≈ cyclophosphamide for induction; **superior in relapsing disease**
IBD (Crohn / UC)	Anti-TNF (infliximab, adalimumab, golimumab, certolizumab), vedolizumab, ustekinumab, risankizumab, mirikizumab	Moderate–severe disease; vedolizumab/IL-23 agents favoured when TNF risk is high
Psoriasis / PsA / ankylosing spondylitis	TNF inhibitors, secukinumab, ixekizumab, ustekinumab	IL-17/IL-23 agents highly effective for skin and axial disease
Sjögren syndrome	Belimumab → rituximab sequential, ianalumab (investigational)	Promising composite outcomes

Pre-treatment screening and monitoring

- **Latent tuberculosis** — *mandatory before any TNF inhibitor (and most biologics):* tuberculin skin test (PPD) **or** IFN-γ release assay (IGRA) + chest X-ray; if positive, treat LTBI for **≥1 month before** starting the biologic.
- **Viral hepatitis panel** — HBsAg + anti-HCV before rituximab, TNF inhibitors and tocilizumab; risk of **hepatitis B reactivation** (esp. rituximab).
- **CBC, LFTs, renal function and lipids** at baseline and periodically (cytopenias with rituximab/tocilizumab; transaminitis and dyslipidaemia — raised LDL — with tocilizumab).
- **Vaccination** before initiation — *live vaccines are contraindicated* during therapy; rituximab markedly **blunts vaccine responses** (e.g. SARS-CoV-2).
- **Therapeutic drug monitoring** in IBD — target trough levels: infliximab **>7 µg/mL**, adalimumab **>7–10 µg/mL**, golimumab **>1 µg/mL**; scheduled maintenance or co-immunomodulator use reduces anti-drug antibody formation to <10%.

Adverse effects and contraindications

- **Infection** (the dominant risk) — serious bacterial, opportunistic fungal and viral infections; **reactivation of latent TB** (TNF inhibitors), **HBV reactivation** (rituximab), and **Pneumocystis jirovecii** pneumonia with rituximab/cyclophosphamide in AAV (give TMP-SMX prophylaxis).
- **TNF inhibitors specifically contraindicated in:** active infection, hypersensitivity, **chronic hepatitis B**, and **NYHA class III/IV heart failure**; can precipitate **demyelinating/neurologic events** (avoid in multiple sclerosis), **drug-induced lupus** (anti-histone antibodies) and rarely lymphoma (controversial).
- **Rituximab** — infusion reactions (premedicate with methylprednisolone), cytopenias, hypogammaglobulinaemia with prolonged use, and rare **progressive multifocal leukoencephalopathy (PML)** (≈1:25,000 in RA).
- **Tocilizumab/sarilumab** — neutropenia, thrombocytopenia, raised LDL, raised LFTs, and **gastrointestinal perforation** (avoid with diverticulitis/recent peptic ulcer).
- **Natalizumab** — **PML** from JC virus; largely abandoned in Crohn's for this reason (vedolizumab's gut selectivity confers lower PML risk).

- **Abatacept** and rituximab blunt vaccine responses.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Cytokine and cell targets of biologics in the rheumatoid synovium"** — central panel showing macrophage, T cell, B cell, synovial fibroblast and osteoclast. Label arrows for: **TNF-α → infliximab/etanercept/adalimumab/golimumab/certolizumab**; **IL-6/IL-6R → tocilizumab/sarilumab**; **IL-1 → anakinra**; **CD20 (B cell) → rituximab**; **CD28–CD80/86 co-stimulation → abatacept (CTLA-4-Ig)**; **JAK/STAT (intracellular) → tofacitinib (tsDMARD)**.
- **"Site of action ladder by disease"** — vertical bars labelled: *Skin/joints* → IL-17 (secukinumab), IL-23 (risankizumab); *Gut* → α4β7 (vedolizumab); *SLE* → BAFF (belimumab), IFNAR (anifrolumab); *Vasculitis* → CD20 (rituximab) + C5aR (avacopan).

Clinical / Diagnostic significance

- **Treat-to-target / step-up strategy:** in RA, begin with MTX; if inadequate response after 3–6 months, **add a TNF or non-TNF biologic** — combination DMARD therapy is superior to MTX alone.
- **Choice is individualised:** seropositive RA and refractory disease favour rituximab; concomitant psoriatic arthritis favours ustekinumab/IL-17 agents; lupus nephritis favours belimumab/voclosporin-based combinations; relapsing AAV favours rituximab.
- **Steroid-sparing** is a key modern goal — belimumab/anifrolumab in SLE and avacopan in AAV all allow rapid glucocorticoid tapering.
- **Biosimilars** lower cost and improve access without loss of efficacy — important in the Indian/RGUHS context.

High-yield exam pointers

- **First biologic class = TNF inhibitors (1999);** etanercept is a **fusion protein**, the rest are **monoclonal antibodies**; certolizumab is a **PEGylated Fab′**.
- **Always screen for latent TB and HBV** before TNF inhibitors; treat LTBI ≥1 month before starting.
- **Rituximab = anti-CD20**, key in **TNF-refractory seropositive RA and AAV induction (375 mg/m² ×4)**; watch for **PML and HBV reactivation**.
- **Abatacept = CTLA-4-Ig (co-stimulation blocker); tocilizumab = anti-IL-6R (raises LDL, risk of GI perforation); anakinra = IL-1Ra.**
- **SLE biologics: belimumab (anti-BAFF) and anifrolumab (anti-IFNAR);** belimumab also approved for **lupus nephritis** with MMF/cyclophosphamide.
- **IBD: anti-TNF, vedolizumab (α4β7, gut-selective), ustekinumab (IL-12/23 p40), risankizumab (IL-23 p19).**
- **Psoriasis/spondyloarthritis: IL-17 (secukinumab, ixekizumab) and IL-12/23 agents.**
- **TNF inhibitors contraindicated in class III/IV CHF, chronic hepatitis B and demyelinating disease.**

- **JAK inhibitors are oral targeted-synthetic DMARDs, NOT biologics** — carry boxed warnings for thrombosis, MACE and malignancy.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Rheumatoid Arthritis" (biologic DMARD classes, Table 370-2 doses/toxicities, TNF/IL-6/B-cell/co-stimulation mechanisms), "Autoimmunity and Autoimmune Diseases" (cytokine and B-cell targets in autoimmunity), "Systemic Lupus Erythematosus" (belimumab, anifrolumab, rituximab, voclosporin, obinutuzumab, CAR-T), "The Vasculitis Syndromes / Granulomatosis with Polyangiitis" (rituximab induction/maintenance, avacopan, failure of etanercept/abatacept/belimumab in AAV), "Inflammatory Bowel Disease" (anti-TNF, natalizumab/vedolizumab integrin blockers, ustekinumab/risankizumab, trough levels), and the psoriasis/spondyloarthritis chapters (IL-17 and IL-23 agents).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders" (abatacept, rituximab, tocilizumab/sarilumab, Sjögren and vasculitis biologics, drug-induced lupus) and "Gastrointestinal Disorders" (IBD anti-TNF and anti-IL agents, therapeutic drug monitoring).
- *Coverage note:* This corpus has **no single dedicated "biologics" chapter** (as the spec flags); the answer is synthesised from the disease-specific therapy sections across Harrison and CMDT. The *-mab/-cept* nomenclature framework is standard, universally accepted pharmacology added for exam completeness.

◆ ◆ ◆

Calcium pyrophosphate deposition disease

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

Definition / Introduction — Calcium pyrophosphate deposition disease (CPPD) is a crystal-induced arthropathy caused by the deposition of **calcium pyrophosphate (CPP) crystals** in articular hyaline cartilage and fibrocartilage, producing the radiographic hallmark of **chondrocalcinosis**. The acute inflammatory presentation was originally termed *pseudogout* by McCarty and colleagues because it mimics acute gout. CPPD is overwhelmingly a disease of the elderly, with prevalence in articular tissues roughly **doubling with each decade after 60 years** (reaching nearly 50% in those >85 years). It encompasses a spectrum from asymptomatic chondrocalcinosis through acute crystal arthritis to several chronic arthropathies.

Pathogenesis

- The central abnormality is an **increased concentration of inorganic pyrophosphate (PPi) in the cartilage matrix** — pathogenically analogous to hyperuricaemia in gout. PPi combines with calcium to form CPP crystals within **cartilage matrix vesicles** or on collagen fibres.
- Most matrix PPi derives from breakdown of **extracellular ATP**. ATP efflux (and hence PPi levels) is tightly regulated by a multipass membrane transport protein, **ANKH**; mutations in the *ANKH* gene (described in both familial and sporadic disease) increase elaboration and extracellular transport of pyrophosphate.

- PPi production is also augmented by enhanced activity of **ATP pyrophosphohydrolase** and **5′-nucleotidase** (which generate adenosine and pyrophosphate from ATP). **Decreased cartilage glycosaminoglycans** and **increased transglutaminase** activity further favour CPP crystal nucleation.
- Once shed into the joint space, CPP crystals are phagocytosed by **monocyte-macrophages and neutrophils**, which release chemotactic/inflammatory mediators and activate the **NLRP3 inflammasome**, driving **IL-1β**-mediated acute synovitis (shared final pathway with gout).
- Biochemical changes of **ageing or diseased cartilage** are thought to favour crystal nucleation in the common sporadic ("idiopathic") form, where the underlying aetiology remains uncertain.

Associated conditions ("the four H's and beyond")

- A minority of patients have an underlying metabolic or hereditary cause. **CPPD presenting in a patient aged <50 years** must prompt a search for a secondary cause and inherited disease.
- Endocrine-metabolic and other associations (Harrison Table 384-2):

Category	Associations
Degenerative / mechanical	Ageing, osteoarthritis, post-meniscectomy or joint trauma
Hereditary	Familial-genetic CPPD (*ANKH* mutations)
Endocrine-metabolic	**Primary hyperparathyroidism**, **Hemochromatosis**, **Hypophosphatasia**, **Hypomagnesemia**
Renal-tubular / electrolyte	Gitelman's syndrome, X-linked hypophosphatemic rickets, familial hypocalciuric hypercalcemia, malabsorption
Drug-associated	Thiazide and loop diuretics; potentially proton-pump inhibitors
Other crystal	Coexistent gout

- *Useful screening mnemonic*: the classic remediable causes are **H**yperparathyroidism, **H**aemochromatosis, **H**ypophosphatasia and **H**ypomagnesaemia.
- **Work-up of the young patient** should include serum **calcium, phosphorus, alkaline phosphatase, magnesium, iron and transferrin**, plus enquiry for familial aggregation.

Clinical manifestations

- **Acute CPP crystal arthritis (pseudogout)** — an acute, self-limiting mono- or oligoarthritis closely mimicking gout. Distinguishing clinical clues:
  - The **knee is the most commonly affected joint**, followed by the **wrist**; the first metatarsophalangeal joint (*podagra*) is **rarely** involved (in contrast to gout). Shoulder, ankle, elbow and hands may also be affected.
  - **Initial attacks tend to last longer than gout** — often weeks to months.
  - Frequently provoked by **trauma, severe medical illness, or surgery — especially parathyroidectomy**, which causes rapid fall in serum calcium and magnesium, leading to crystal dissolution and shedding. Pseudogout characteristically develops **24–48 h after major surgery**.

- Systemic features (fever, chills, raised acute-phase reactants) occur; in up to **50%** there is low-grade fever, occasionally as high as **40°C (104°F)** — synovial fluid culture is then essential to exclude coexistent sepsis.

- **Chronic CPPD arthropathies** (several patterns):
  - **Pseudo-osteoarthritis** — the *most common* chronic form; a degenerative arthropathy with unusually severe damage in joints atypical for primary OA (**metacarpophalangeal, wrist, elbow, shoulder, glenohumeral, ankle, patellofemoral**).
  - **Pseudo-rheumatoid arthritis** — chronic symmetric synovitis affecting MCP joints and wrists, clinically resembling RA.
  - **Pseudo-neuropathic (pseudo-Charcot)** — severe destructive disease that radiographically mimics neuropathic arthropathy.
  - **Spinal disease** — intervertebral disk and ligament calcification with restricted spinal mobility; **spinal stenosis** (elderly); and the **crowned dens syndrome** — CPP deposition at the atlanto-axial junction with "crown-like" calcification around the odontoid, presenting with severe neck pain, rigidity and high fever that can mimic **meningitis or giant cell arteritis**.
  - Rarely, **tumoral CPP deposits** in soft tissue.

Diagnosis

- **Synovial fluid crystal analysis is definitive.** Under **compensated polarized light microscopy** CPP crystals are **rhomboid or rod-shaped** and **weakly positively birefringent (or non-birefringent)** — contrasting with the needle-shaped, strongly **negatively birefringent** MSU crystals of gout. Crystals may be seen within neutrophils, tissue fragments and fibrin clots; they may coexist with MSU or apatite.
- **Synovial fluid is inflammatory** — leukocyte counts range from several thousand to **100,000 cells/μL** (mean ~24,000/μL), predominantly **neutrophils**. Always **Gram stain and culture** to exclude septic arthritis (which can coexist).
- **Imaging — chondrocalcinosis**: plain radiographs or ultrasound show **punctate and/or linear radiodense deposits** within fibrocartilage (knee menisci, triangular fibrocartilage of the wrist, symphysis pubis) and hyaline articular cartilage. In the absence of a tappable effusion, **chondrocalcinosis is presumptive of CPPD** — a key exception being chondrocalcinosis from **calcium oxalate** in chronic renal failure. Radiographs in pseudo-OA also show asymmetric joint-space narrowing and osteophytes in atypical joints.
- The **2023 ACR/EULAR classification criteria for CPPD** provide a formal weighted scheme (incorporating crystal identification, imaging chondrocalcinosis and clinical features) for research/diagnostic standardisation.

Differential diagnosis

- **Gout** — distinguished by joint distribution (podagra), negatively birefringent needle-shaped MSU crystals, usually elevated serum urate, and erosions with overhanging edges rather than chondrocalcinosis.
- **Septic arthritis** — must always be excluded by synovial fluid Gram stain and culture, particularly when fever is present.

- **Rheumatoid arthritis** (vs pseudo-RA), **osteoarthritis** (vs pseudo-OA), **neuropathic joint** (vs pseudo-neuropathic), **apatite / basic calcium phosphate disease** (e.g. Milwaukee shoulder), and **calcium oxalate arthropathy** in dialysis patients.

Treatment

- **Acute pseudogout** (management largely adapted from acute gout):
  - **Joint aspiration plus intra-articular glucocorticoid** — e.g. *triamcinolone 10–40 mg* depending on joint size; effective and well tolerated for one or a few joints.
  - **NSAIDs** in full anti-inflammatory dose (with gastroprotection where required).
  - **Colchicine** — up to *1.8 mg orally in the first 24 h*, then *0.6 mg once or twice daily* until resolution.
  - **Systemic glucocorticoids** — *oral prednisone 30–50 mg/day tapered over 7–10 days*, useful in polyarticular attacks or where NSAIDs/colchicine are contraindicated.
  - **IL-1β antagonists (anakinra, canakinumab)** for severe polyarticular attacks or when conventional therapy fails/is contraindicated.
  - Adjuncts: ice-pack application and rest of the involved joint.
- **Recurrent attacks (≥3 per year)** — prophylactic **low-dose colchicine 0.6 mg once or twice daily** reduces flare frequency.
- **Chronic CPPD arthritis** — there is **no agent that dissolves or removes CPP crystals** from cartilage (a crucial contrast with urate-lowering therapy in gout). Symptomatic options for chronic synovitis include NSAIDs, colchicine, low-dose glucocorticoids, **hydroxychloroquine** or **methotrexate**. **Treat any underlying metabolic cause** (e.g. iron depletion in haemochromatosis, magnesium repletion). Progressive destructive large-joint arthropathy may require **joint replacement**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Compensated polarized-light comparison of CPP vs MSU crystals**: draw two adjacent panels. *Panel A (CPPD)* — short **rhomboid/rod-shaped** crystals, one lying intracellularly within a neutrophil; label "**weakly POSITIVELY birefringent — blue when parallel to compensator axis**". *Panel B (gout)* — long **needle-shaped** crystals; label "**strongly NEGATIVELY birefringent — yellow when parallel**". Add common axis label "slow axis of red compensator".
- **Knee radiograph showing chondrocalcinosis**: outline the knee joint with **linear/punctate calcific deposits in the meniscal fibrocartilage** and a thin line of **hyaline articular cartilage calcification**. Labels: *menisci (fibrocartilage)*, *hyaline articular cartilage*, *chondrocalcinosis*, *joint-space narrowing/osteophyte (pseudo-OA)*.

Clinical / Diagnostic significance

- CPPD is a leading cause of **acute monoarthritis in the elderly** and a key mimic of **gout and septic arthritis** — every acute hot joint warrants aspiration for crystals, Gram stain and culture.

- **Chondrocalcinosis on imaging in a patient <50 years** is a red flag mandating screening for **haemochromatosis, hyperparathyroidism, hypophosphatasia and hypomagnesaemia** — diagnosing these may avert systemic complications.
- The **crowned dens syndrome** is an important reversible cause of acute neck pain with fever and raised inflammatory markers that can be misdiagnosed as meningitis or giant cell arteritis.
- Recognising **pseudo-OA / pseudo-RA / pseudo-neuropathic** patterns prevents misdiagnosis and inappropriate therapy.

High-yield exam pointers

- CPP crystals = **rhomboid, weakly POSITIVELY birefringent**; MSU = **needle-shaped, strongly NEGATIVELY birefringent** (the single most-tested discriminator).
- **Knee** is the commonest joint in pseudogout; **podagra is characteristically rare** (unlike gout).
- **Chondrocalcinosis** = linear/punctate cartilage calcification; **presumptive of CPPD** when no effusion is obtainable.
- Secondary causes — **4 H's**: **H**yperparathyroidism, **H**aemochromatosis, **H**ypophosphatasia, **H**ypomagnesaemia (± thiazide/loop diuretics).
- **Parathyroidectomy** and **major surgery (24–48 h post-op)** are classic precipitants via abrupt falls in Ca^{2+}/Mg^{2+}.
- Central pathogenesis = **excess inorganic pyrophosphate** from ATP breakdown; *ANKH* gene mutation in familial/sporadic disease.
- Acute attacks: **aspiration + intra-articular steroid, NSAIDs, colchicine, prednisone**; refractory → **anakinra/canakinumab**.
- **No crystal-dissolving (urate-lowering equivalent) therapy exists** for CPPD — management is anti-inflammatory plus treatment of any underlying metabolic cause.
- Up to 50% have **fever** during attacks (up to 40°C) → always exclude **septic arthritis** by culture.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22nd edition** — "Gout and Other Crystal-Associated Arthropathies" (pathogenesis, *ANKH*/pyrophosphate mechanism, Table of associated conditions, clinical patterns, crystal morphology and treatment).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders" — Calcium Pyrophosphate Deposition section (current drug doses — triamcinolone 10–40 mg, colchicine 1.8 mg/24 h, prednisone 30–50 mg, anakinra/canakinumab, prophylaxis; crowned dens syndrome; 2023 ACR/EULAR classification criteria reference, Abhishek A et al, *Arthritis Rheumatol* 2023;75:1703, PMID 37494275).

◆ ◆ ◆

Biological agents in rheumatoid arthritis

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

Definition / Introduction — Rheumatoid arthritis (RA) is a chronic, symmetric, erosive inflammatory polyarthritis driven by dysregulated cytokine and cellular immunity. **Biologic disease-modifying antirheumatic drugs (biologic DMARDs / bDMARDs)** are protein therapeutics engineered to target specific cytokines or cell-surface molecules in this inflammatory cascade. Introduced in 1999, they have revolutionised RA management by reducing signs and symptoms, retarding radiographic joint damage, and improving function. They are typically added when conventional synthetic DMARDs (especially methotrexate) fail to achieve low disease activity, and are usually given **in combination with background methotrexate** within a "treat-to-target" strategy.

Classification of biologic agents used in RA

Biologics are best classified by their molecular target and mechanism of action:

Class (target)	Agents	Molecular nature / mechanism
TNF-α inhibitors (5 innovators)	Infliximab; Adalimumab; Golimumab; Certolizumab pegol; Etanercept	Infliximab = chimeric (mouse–human) anti-TNF mAb; adalimumab & golimumab = human(ized) anti-TNF mAbs; certolizumab = PEGylated Fab′ fragment of a humanized mAb; etanercept = soluble TNF-receptor-2–IgG1 Fc **fusion protein**. All neutralise TNF-α, a pivotal upstream cytokine of synovitis
T-cell co-stimulation blocker	Abatacept	Soluble fusion protein of extracellular **CTLA-4** + modified human IgG Fc; blocks the **CD28–CD80/86** second signal, inhibiting T-cell activation
B-cell depletion (anti-CD20)	Rituximab	Chimeric mAb against **CD20** on mature B lymphocytes → B-cell depletion; approved for RA refractory to a TNF inhibitor; more effective in **seropositive** (RF/ACPA+) disease
IL-6 receptor inhibitors	Tocilizumab; Sarilumab	mAbs against membrane-bound and soluble **IL-6 receptor**; block acute-phase response, osteoclast activation
IL-1 receptor antagonist	Anakinra	Recombinant human **IL-1 receptor antagonist**; limited RA use owing to weaker efficacy than other bDMARDs

Biosimilars — agents with the same active properties as a licensed reference biologic (e.g. of infliximab, etanercept, adalimumab); demonstrate comparable efficacy and safety.

Related but distinct — targeted synthetic DMARDs (tsDMARDs): The oral **JAK inhibitors** *tofacitinib* (JAK1/3), *baricitinib* (JAK1/2) and *upadacitinib* (selective JAK1) target intracellular signalling. They are **not biologics** (they are small molecules), but are often examined alongside them as the modern "targeted" therapy; their adverse-effect profile is summarised below for completeness.

Mechanism and standard adult dosing

Agent	Route & dose (Harrison Table 370-2)
Infliximab	3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks (may ↑ to 10 mg/kg q4 weeks)

Agent	Route & dose (Harrison Table 370-2)
Etanercept	50 mg SC weekly (or 25 mg SC twice weekly)
Adalimumab	40 mg SC every other week
Golimumab	50 mg SC monthly
Certolizumab pegol	400 mg SC at weeks 0, 2, 4, then 200 mg every other week
Abatacept	Weight-based IV (<60 kg: 500 mg; 60–100 kg: 750 mg; >100 kg: 1000 mg) at weeks 0, 2, 4, then q4 weeks; OR 125 mg SC weekly
Rituximab	1000 mg IV × 2 (days 0 and 14); repeat course every ≥24 weeks; premedicate with methylprednisolone 100 mg
Tocilizumab	4–8 mg/kg IV monthly; OR 162 mg SC every other week (<100 kg) / weekly (≥100 kg)
Sarilumab	200 mg SC every other week
Anakinra	100 mg SC daily

Adverse effects

Common to all biologics — increased infection risk is the dominant class effect: serious bacterial infections, opportunistic fungal infection, and **reactivation of latent tuberculosis** (most marked with TNF inhibitors, which characteristically cause granulomatous/TB reactivation). Live-vaccine responses are blunted.

- **TNF-α inhibitors:** ↑ bacterial and fungal infections; **reactivation of latent TB**; infusion reactions (IV infliximab; rarely anaphylaxis) and injection-site reactions (SC agents); raised LFTs; **drug-induced lupus** (induction of anti-dsDNA antibodies); **demyelinating/neurologic deficits** resembling multiple sclerosis (rare); possible ↑ lymphoma risk (controversial — most observational data show no excess malignancy); worsening of moderate–severe heart failure.
- **Abatacept:** ↑ risk of bacterial and viral infection; can **blunt vaccine responses**.
- **Rituximab:** mild–moderate **infusion reactions**; ↑ infection; **hepatitis B reactivation**; cytopenias; rare **progressive multifocal leukoencephalopathy (PML)** (≈1:25,000, mostly with prior immunosuppression); markedly inhibits vaccine response (e.g. to SARS-CoV-2 vaccine).
- **IL-6 receptor inhibitors (tocilizumab, sarilumab):** ↑ infection; **neutropenia and thrombocytopenia** (reversible on stopping); **LFT elevation**; **dyslipidaemia (↑ LDL cholesterol)**; ↑ rate of **gastrointestinal perforation**.
- **Anakinra:** injection-site reactions; ↑ bacterial/viral infection; neutropenia.
- **JAK inhibitors (tsDMARDs):** ↑ infection including **herpes zoster**; raised transaminases; dyslipidaemia; neutropenia; **thrombosis/VTE**; **major adverse cardiovascular events** (MACE) and malignancy — these carry an **FDA black-box warning** (highest risk in the elderly, from the tofacitinib-vs-TNFi safety trial); ↑ creatinine and hypertension.

Contraindications & pre-treatment screening

- **Active infection** of any kind — a contraindication to starting (and reason to suspend) any biologic.

- **Untreated latent TB** — *all* candidates must be screened with a **tuberculin skin test (Mantoux/PPD) or interferon-γ release assay (IGRA)** before therapy; if positive, treat LTBI for at least 1 month before starting.
- **TNF-α inhibitors specifically:** contraindicated in **chronic/active hepatitis B**, **NYHA class III/IV congestive heart failure**, and prior **hypersensitivity**; use cautiously in demyelinating disease (relative).
- **Rituximab:** active hepatitis B (risk of reactivation) — **viral hepatitis screening (HBsAg, anti-HBc, HCV antibody) mandatory** before use.
- **IL-6 receptor inhibitors:** avoid where possible in **diverticulitis** or recent **gastric/duodenal ulcer** (GI perforation risk); pre-existing significant neutropenia/thrombocytopenia or transaminitis.
- **Pregnancy:** anti-TNF agents are generally regarded as acceptable but are **discontinued in the third trimester**; data are insufficient for abatacept, anti-IL-6, rituximab and JAK inhibitors, so these are **stopped at conception**. (The teratogenic conventional DMARDs **methotrexate and leflunomide** are absolutely contraindicated in pregnancy, but are not biologics.)
- **General: live vaccines** should not be given during biologic therapy; combining two biologics is not recommended (no added efficacy, additive toxicity).

Baseline work-up before any biologic: TB screen (PPD/IGRA), viral hepatitis panel (especially for TNF inhibitors and rituximab), CBC and LFTs; with periodic monitoring of CBC, LFTs and lipids thereafter.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Cytokine/cell targets of biologic DMARDs in the rheumatoid synovium":** Draw an antigen-presenting cell (APC) presenting via **MHC-II/peptide–TCR** to a **$CD4^+$ T cell**, with the **CD80/86–CD28** co-stimulation pair, a **B cell/plasma cell** producing RF/ACPA, and a **macrophage/fibroblast** secreting **TNF-α, IL-1, IL-6**, driving an **osteoclast (RANKL)**. Label each biologic at its target: **TNF inhibitors → TNF-α; Abatacept → CD80/86–CD28; Rituximab → CD20 (B cell); Tocilizumab/Sarilumab → IL-6 receptor; Anakinra → IL-1 receptor; JAK inhibitors → intracellular JAK-STAT (label as tsDMARD).**
- **Diagram 2 — "Treat-to-target ladder":** NSAIDs/short glucocorticoid → **Methotrexate** (anchor) → +conventional combination (oral triple therapy) → **add anti-TNF or non-TNF biologic ± MTX** → switch biologic class / JAK inhibitor. Label the goal box: **low disease activity / remission**.

Clinical / Diagnostic significance

- **Sequencing:** methotrexate remains the **anchor/first-choice DMARD**; a biologic (usually anti-TNF) is added on inadequate response after 3–6 months. Combination of methotrexate + anti-TNF is superior to methotrexate alone for both symptoms and radiographic progression.
- **Switching:** patients failing one anti-TNF may respond to a **second anti-TNF** or to a **different mechanism** (abatacept, rituximab, IL-6 inhibitor); some evidence favours switching class (e.g. to abatacept) over a second anti-TNF.
- **Serostatus guides choice:** rituximab is more effective in **RF/ACPA-positive** disease.

- **Monitoring:** vigilance for infection (suspend during febrile illness), serial CBC/LFTs/lipids; IL-6 inhibitors mask CRP/ESR, so acute-phase reactants are unreliable for detecting infection.
- **Comorbidity steering:** avoid TNF inhibitors in advanced heart failure and hepatitis B; avoid IL-6 inhibitors in diverticular disease; reserve JAK inhibitors cautiously in the elderly and those with cardiovascular/thrombotic/malignancy risk.
- **Extra-articular disease:** rituximab is useful for **RA-associated interstitial lung disease** (with corticosteroids ± azathioprine/MMF).

High-yield exam pointers

- Five TNF inhibitors: **infliximab (chimeric mAb), adalimumab, golimumab (human mAbs), certolizumab pegol (PEGylated Fab′), etanercept (TNFR2–Fc fusion protein)**.
- **Abatacept = CTLA-4-Ig** (co-stimulation block); **rituximab = anti-CD20** (B-cell depletion); **tocilizumab/sarilumab = anti-IL-6R**; **anakinra = IL-1Ra**.
- **JAK inhibitors (tofacitinib, baricitinib, upadacitinib) are targeted *synthetic* DMARDs, NOT biologics** — oral, JAK-STAT pathway, carry an **FDA black-box warning** (MACE, malignancy, thrombosis, death).
- Class hazard = **infection + latent TB reactivation** → screen with **PPD/IGRA** in all; treat LTBI before starting.
- TNF inhibitors are contraindicated in **chronic hepatitis B, NYHA III/IV heart failure**; can cause **drug-induced lupus** and **demyelination**.
- **Rituximab:** hepatitis B reactivation, rare **PML**; check viral hepatitis panel first.
- **IL-6 inhibitors:** dyslipidaemia, cytopenias, **GI perforation** (avoid in diverticulitis).
- **Live vaccines contraindicated**; do **not** combine two biologics; anti-TNF stopped in third trimester.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Rheumatoid Arthritis"** (classification, molecular design, dosing Table 370-2, adverse effects and contraindications, treat-to-target approach).
- **CMDT 2026 — "Rheumatologic, Immunologic & Allergic Disorders" (Rheumatoid Arthritis)** (current management framing, TNF-inhibitor/JAK-inhibitor safety, mandatory hepatitis and TB screening, EULAR 2022 update).

◆ ◆ ◆

Vasculitis classification

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

Definition / Introduction — Vasculitis is a clinicopathologic process characterised by **inflammation of and damage to blood vessel walls**, with luminal compromise leading to ischaemia of the tissues supplied. Because *any* type, size and location of vessel may be involved, the result is a broad, heterogeneous and overlapping group of syndromes that may be primary or secondary, single-organ or multisystem. Classification is anchored on the **dominant calibre of vessel involved** (the basis of the *Chapel Hill Consensus Conference, CHCC 2012* nomenclature), refined by the **immunopathological mechanism** (immune-complex deposition, ANCA, or T-cell/granuloma formation) and by features such as granuloma, ANCA status and artery-vs-vein involvement.

Basis of pathological classification

- **Size of predominant vessel** — large, medium or small (the first and most important discriminator).
- **Type of vessel** — artery only, vein, or both.
- **Presence/absence of granulomatous inflammation** on biopsy.
- **Immune mechanism** — immune-complex (with vessel-wall immunoglobulin/complement deposition) versus *pauci-immune* (ANCA-associated, scant immunoglobulin) versus cell-mediated/granulomatous.
- **Demography & associations** — age, sex, ethnicity, smoking, and any underlying trigger (infection, drug, connective-tissue disease, malignancy).

Classification by vessel size (Chapel Hill Consensus Conference 2012)

Predominant vessel	Syndromes	Characteristic pathology
Large vessel (aorta + major branches)	Takayasu arteritis; Giant cell (temporal) arteritis	Granulomatous panarteritis, mononuclear infiltrate, giant cells, fragmentation of internal elastic lamina
Medium vessel (main visceral/muscular arteries)	Polyarteritis nodosa (PAN); Kawasaki disease	Necrotising arteritis, fibrinoid necrosis, micro-aneurysms; *no* glomerulonephritis or granuloma in PAN
Small vessel — ANCA-associated (pauci-immune)	Granulomatosis with polyangiitis (GPA); Microscopic polyangiitis (MPA); Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss)	Necrotising vasculitis of capillaries/venules/arterioles with *few or no* immune deposits; granuloma in GPA & EGPA; eosinophilia in EGPA
Small vessel — immune-complex	IgA vasculitis (Henoch-Schönlein); Cryoglobulinaemic vasculitis; Hypocomplementaemic urticarial (anti-C1q) vasculitis; Anti-GBM disease	Vessel-wall immune-complex/immunoglobulin deposition (e.g. IgA, cryoglobulins)
Variable vessel	Behçet disease; Cogan syndrome	May affect small, medium and large vessels; arteries *and* veins

Predominant vessel	Syndromes	Characteristic pathology
Single-organ	Cutaneous leukocytoclastic angiitis; cutaneous arteritis; primary CNS vasculitis; isolated aortitis	Confined to one organ without systemic spread
Associated with systemic disease	Lupus, rheumatoid, sarcoid vasculitis	Secondary to a defined connective-tissue/systemic illness
Associated with probable aetiology	HBV-associated (PAN-like); HCV-associated cryoglobulinaemic; drug-induced; cancer-associated	Identifiable antigenic trigger

Classification by immunopathogenic mechanism (pathology of vessel injury)

Dominant mechanism	Representative syndromes
Pathogenic immune-complex formation / deposition	IgA vasculitis (HSP); lupus vasculitis; serum-sickness & cutaneous vasculitis; HCV cryoglobulinaemic; HBV-associated
ANCA production (pauci-immune)	GPA (PR3/cANCA), MPA (MPO/pANCA), EGPA (MPO)
Pathogenic T-lymphocyte response & granuloma formation	Giant cell arteritis; Takayasu arteritis; GPA; EGPA

- **ANCA serology** further subdivides small-vessel disease: *cANCA/anti-proteinase-3* in **>90%** of active GPA; *pANCA/anti-myeloperoxidase* in ~**75%** of MPA and ~**48%** of EGPA. Up to 20% of GPA may be ANCA-negative.
- Renal lesion of GPA/MPA is a **pauci-immune crescentic glomerulonephritis** (no immune-complex deposition), distinguishing it from immune-complex small-vessel disease.

ACR classification criteria — Giant Cell (Temporal) Arteritis (1990 ACR criteria — featured example)

Classification criteria are designed to define a homogeneous patient population for study (and to distinguish one vasculitis from another once vasculitis is established) — they are not strict diagnostic criteria.

#	Criterion	Definition
1	**Age at onset ≥50 years**	Development of symptoms/findings beginning at age 50 or older
2	**New headache**	New onset of, or new type of, localised pain in the head
3	**Temporal artery abnormality**	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4	**Elevated ESR**	Erythrocyte sedimentation rate ≥50 mm/h (Westergren method)
5	**Abnormal artery biopsy**	Vasculitis with a predominance of mononuclear-cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

- **Classification** is satisfied when **≥3 of 5** criteria are present → sensitivity **93.5%**, specificity **91.2%**.

- *Alternative example — GPA (1990 ACR):* (1) nasal/oral inflammation (oral ulcers or purulent/bloody nasal discharge); (2) abnormal chest radiograph (nodules, fixed infiltrates or cavities); (3) abnormal urinary sediment (microhaematuria >5 RBC/hpf or red-cell casts); (4) granulomatous inflammation on biopsy. **≥2 of 4** → sensitivity ~88%, specificity ~92%.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Vessel-size "tree" of vasculitis** — three concentric/parallel columns labelled **Large**, **Medium**, **Small**; place under each: Large → *Takayasu, Giant cell arteritis*; Medium → *PAN, Kawasaki*; Small → split into *ANCA-associated (GPA, MPA, EGPA)* and *Immune-complex (IgA vasculitis, cryoglobulinaemic, anti-GBM, urticarial)*; side boxes for *Variable vessel (Behçet, Cogan)* and *Single-organ*. Label overlapping zone "small + medium overlap (ANCA disease, PAN)."
- **Cross-section of an inflamed artery** — label: *lumen, thrombus, fibrinoid necrosis of media, transmural mononuclear/neutrophil infiltrate, fragmented internal elastic lamina, multinucleated giant cell, granuloma, adventitia/vasa vasorum.*

Clinical / Diagnostic significance

- **Vessel size predicts the clinical picture:** large-vessel → limb claudication, asymmetric BP/absent pulses, bruits, aortic dilatation; medium-vessel → cutaneous nodules, livedo reticularis, digital gangrene, mononeuritis multiplex, micro-aneurysms; small-vessel → palpable purpura, glomerulonephritis/haematuria, alveolar haemorrhage, splinter haemorrhages, scleritis.
- **Workup sequence:** consider vasculitis in any unexplained multisystem illness (palpable purpura, pulmonary infiltrates + haematuria, chronic sinusitis, mononeuritis multiplex, glomerulonephritis); **first exclude mimics** (endocarditis, atrial myxoma, cholesterol emboli, antiphospholipid syndrome, drug toxicity e.g. cocaine/levamisole). Confirm by **biopsy of involved tissue**; use **catheter angiography** when PAN, Takayasu or primary CNS vasculitis is suspected (micro-aneurysms / stenoses).
- **Serology directs categorisation:** PR3-ANCA, MPO-ANCA, cryoglobulins, complement, hepatitis B & C serology, eosinophil count.
- **Treatment is category-driven:** GPA/MPA — induction with **cyclophosphamide 2 mg/kg/day** *or* **rituximab 375 mg/m²/week ×4** + glucocorticoids ± **avacopan** (C5a-receptor inhibitor), then azathioprine/methotrexate/rituximab maintenance; GCA — **prednisone 40–60 mg/day** (urgent, to prevent blindness) ± **tocilizumab** (IL-6R); EGPA — glucocorticoids ± **mepolizumab** (anti-IL-5). Always weigh relapse risk and immunosuppression toxicity.

High-yield exam pointers

- First step in classifying vasculitis = **size of the dominant vessel** (large / medium / small) — CHCC 2012.
- **Pauci-immune** = ANCA-associated (GPA, MPA, EGPA); **immune-complex** = IgA vasculitis, cryoglobulinaemic, anti-GBM, urticarial.
- **GPA** = upper + lower airway granulomatous vasculitis + glomerulonephritis; PR3-cANCA >90%; saddle-nose, subglottic stenosis.

- **PAN** = medium-vessel necrotising arteritis, **spares the lungs**, no glomerulonephritis/granuloma, HBV-associated, renal micro-aneurysms; ANCA usually negative; consider **DADA2** in early-onset disease.
- **GCA** = age >50, new headache, jaw claudication, ESR ≥50, temporal artery biopsy giant cells; dreaded complication = **anterior ischaemic optic neuropathy / blindness** — treat *before* biopsy.
- **Takayasu** = "pulseless disease" of young women, aortic arch and branches.
- ACR **classification** criteria define study populations (homogeneity) — they are **not** diagnostic criteria; e.g. GCA **3 of 5**, GPA **2 of 4**.
- EGPA triad = **asthma + eosinophilia (>1000/µL) + vasculitis**; MPO-ANCA in ~48%.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "The Vasculitis Syndromes"** (classification tables, pathogenic mechanisms — immune-complex / ANCA / T-cell granuloma; syndrome-by-syndrome pathology and treatment).
- **CMDT 2026 — "Vasculitis Syndromes / Rheumatologic, Immunologic & Allergic Disorders"** (classification scheme by size of predominant vessel — Table 23–11; clinical manifestations by vessel size — Table 23–12; revised International Chapel Hill Consensus Conference nomenclature, Jennette et al. 2012; current management).
- *Coverage note:* The provided corpus (Harrison 22e, CMDT 2026) tabulates the **vessel-size/CHCC classification** and pathogenic mechanisms fully, and references the **2022 ACR/EULAR** classification criteria for GCA, Takayasu and GPA, but does **not** reproduce the older **1990 ACR item-level classification criteria** as a list. The 1990 ACR criteria for giant cell arteritis (and GPA) given above are **universally accepted standard internal medicine** (Hunder et al., *Arthritis Rheum* 1990) and are supplied to satisfy the "give the ACR criteria" stem; the cut-offs and sensitivity/specificity quoted are the published ACR figures.

◆ ◆ ◆

Behçet's syndrome

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

Definition / Introduction — Behçet's syndrome is a chronic, relapsing **systemic vasculitis** of unknown cause, first described by the Turkish dermatologist *Hulusi Behçet*. It is characterised by recurrent **oral and genital aphthous ulcers**, skin lesions, **uveitis**, arthritis, and variable involvement of major arteries and veins, the gastrointestinal tract and the central nervous system, occurring in differing combinations and sequences over time. Uniquely among the vasculitides it can involve vessels of **any size, on both the arterial and venous side** of the circulation, and is diagnosed clinically as there is no confirmatory laboratory test.

Epidemiology

- Strongly clustered along the ancient *"Silk Road"* — the **Middle East, Mediterranean, and the Far East**. Most prevalent in **Turkey (≈1 in 250 adults)**.

- Onset typically in the **20s–30s**; relatively rare before the late teens and after age 50.
- **Males and females are affected equally**, but **males tend to have more severe disease and a poorer prognosis** (worse ocular, vascular and neurologic outcomes); young age and male sex are adverse prognostic markers.
- **HLA-B∗51** is positive in **50–60%** of patients (regional variation) but is found in ~20% of the normal population, so it is *not* a diagnostic test.

Pathogenesis

- Aetiology unknown; a **genetic predisposition** (family clustering; HLA-B∗51 association) interacts with dysregulated **innate and adaptive immunity** and increased inflammation.
- Underlying pathology is a **leukocytoclastic venulitis**, though vessels of any calibre and any organ may be affected.
- Marked **neutrophil hyperreactivity** is characteristic (primary vs cytokine-driven is unsettled).
- Behçet's occupies a **niche between classic autoimmune and autoinflammatory disease**:
  - *Unlike autoimmune disease* — no autoantibodies, and no association with Raynaud's, Sjögren's, thrombocytopenia, haemolytic anaemia, photosensitivity or serositis.
  - *Unlike autoinflammatory disease* — it tends to **abate with time**, lacks the defining gene mutations (e.g. of familial Mediterranean fever), and is far more prevalent than typical periodic-fever syndromes.

Clinical features

- **Mucocutaneous (the hallmark):**
  - **Oral ulcers** — in virtually all patients (~98%) and usually the **first manifestation**; multiple, painful, canker-sore-like, last ~10 days, recur; only uncommon "major" ulcers scar.
  - **Genital ulcers** — the **most specific** lesion; on scrotum/labia; larger, deeper, slower to heal, and characteristically **scar**.
  - **Skin lesions** — *acne-like / papulopustular* lesions (including atypical sites such as the legs); **erythema nodosum**-like nodules (panniculitis); and **superficial thrombophlebitis** (common in men; flags risk of deep-vein thrombosis and pulmonary artery aneurysm).
- **Ocular** — in ~50% overall and up to **~70% of males**; typically a **bilateral panuveitis**. *Hypopyon* (sterile pus layering in the anterior chamber) occurs in ~10% of those with eye disease and is highly suggestive. Posterior uveitis (retinal vasculitis/venulitis) can silently destroy the retina. Poor ocular prognostic factors: **male sex, posterior involvement, >3 attacks/year, dense vitreous opacity, macular oedema.**
- **Musculoskeletal** — a **non-erosive, non-deforming mono- or oligoarthritis** of the lower limbs (knees, ankles) in about half of patients.
- **Vascular** — in up to **40%**; an intense, relapsing **thrombotic** tendency. Venous: superficial and deep-vein thrombosis, *Budd-Chiari syndrome*, inferior vena cava syndrome, intracardiac thrombosis, and **cerebral venous sinus thrombosis**. Arterial: **pulmonary artery aneurysms** (5-year mortality **20–25%**, may cause fatal haemoptysis).
- **Neurologic (neuro-Behçet)** — in ~5%; two largely non-overlapping forms:

- **Parenchymal (~75%)** — affects the **telencephalic-diencephalic junction, brainstem and spinal cord**; subacute headache, cranial-nerve palsy, dysarthria, ataxia, hemiparesis. Can radiologically mimic *multiple sclerosis*.
- **Cerebral venous sinus thrombosis (~25%)** — headache, raised intracranial pressure.

- **Gastrointestinal** — frequency is markedly regional (up to ~50% in the Far East, ~30% in the US, rare in Turkey/Middle East). Few (usually <5), **deep, round ulcers confined to the ileocaecal area**, prone to **perforation**; perianal/rectal disease rare. Clinically and endoscopically **difficult to distinguish from Crohn's disease** without extra-intestinal clues.

Diagnostic criteria

Behçet's is a **clinical diagnosis of exclusion**. The most validated tool is the **International Study Group (ISG) criteria** (sensitivity ~95%, specificity ~96%):

Criterion	Frequency	Comment
Recurrent oral ulceration (mandatory)	~98%	At least **3 times in a 12-month period**
PLUS any 2 of the following 4:		
Recurrent genital ulceration	~80%	Usually scarring
Skin lesions	~80%	Erythema nodosum, pseudofolliculitis, papulopustular/acneiform nodules (post-adolescent, not on corticosteroids)
Eye lesions	~50%	Anterior/posterior uveitis, vitreous cells, or retinal vasculitis
Positive pathergy test	~50%	Read at **24–48 h** after pricking the skin with a **20–21-gauge needle**

- **Pathergy** = non-specific cutaneous hyperreactivity to trauma; a sterile papule/pustule forms within 24–48 h. Rather unique to Behçet's; more often positive in patients from the Middle/Far East.
- No pathognomonic laboratory finding — **acute-phase reactants** (ESR/CRP) are often raised; **no specific autoantibody**. HLA-B∗51 supports but does not establish the diagnosis.

Differential diagnosis

- **Oral/genital ulcers:** complex aphthosis, inflammatory bowel disease, coeliac disease, IgA deficiency, infections (HIV, herpes, histoplasmosis), and mucosal conditions (pemphigus vulgaris, lichen planus, mucous membrane pemphigoid).
- **GI disease:** *Crohn's disease* (key mimic).
- **Neuro-Behçet:** multiple sclerosis, CNS infection/vasculitis.
- **Uveitis:** sarcoidosis, HLA-B27 spondyloarthropathy, infective uveitis.

Treatment

Treatment is **organ- and severity-directed**, aiming to prevent irreversible damage; young males warrant more aggressive therapy. Most new manifestations appear within the **first 5 years**, after which disease tends to wane — **tapering/stopping drugs may be attempted 2–3 years** after remission, with immunosuppressants usually continued **≥2 years**.

Manifestation	Preferred / first-line	Add-on / severe disease
Oral & genital ulcers, mucocutaneous	Topical glucocorticoids; **colchicine**; **apremilast** (PDE-4 inhibitor; FDA-approved for oral ulcers)	Azathioprine; **TNF-α inhibitor (infliximab)** for resistant disease
Ocular (uveitis)	Brief glucocorticoid courses + **azathioprine** (preferred long-term agent)	**TNF inhibitors (infliximab/adalimumab)**; cyclosporine; interferon-α
Gastrointestinal	Glucocorticoids + **azathioprine**	± **infliximab**
Venous thrombosis	**Immunosuppression** (azathioprine; cyclophosphamide if severe) to control inflammation — *not primarily anticoagulation*	Anticoagulate only if low bleeding risk **and no pulmonary artery aneurysm**
CNS (parenchymal neuro-Behçet)	**Azathioprine + a TNF inhibitor**	Glucocorticoids; cyclophosphamide

- Management follows the **2018 EULAR recommendations** (Hatemi et al). Key principle for vascular disease: thrombosis is **inflammatory**, so suppress inflammation rather than relying on anticoagulants, and **always exclude a pulmonary artery aneurysm before anticoagulating** (risk of catastrophic haemorrhage).
- Recent evidence (*Saadoun et al, 2024*) compared **infliximab vs cyclophosphamide** for severe Behçet's, reflecting the growing role of biologics in major-organ disease.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Figure 1 — "Clinical map of Behçet's syndrome":** a central figure with labelled arrows to: *Oral aphthous ulcer (tongue/buccal mucosa)*; *Genital (scrotal/labial) ulcer — scarring*; *Eye — hypopyon / panuveitis*; *Skin — erythema nodosum, papulopustular lesions, superficial thrombophlebitis*; *Pathergy site (forearm)*; *Vascular — DVT, pulmonary artery aneurysm, Budd-Chiari, cerebral venous sinus thrombosis*; *CNS — brainstem lesion*; *GI — ileocaecal ulcer*.
- **Figure 2 — Pathergy test:** label *20–21-gauge needle prick → sterile papule/pustule at 24–48 h*.

Clinical / Diagnostic significance

- A **young patient with recurrent oral + genital ulceration and uveitis** from a Silk-Road region should prompt consideration of Behçet's.
- **Hypopyon uveitis** and a **positive pathergy test** are the most disease-specific bedside clues.
- **Superficial thrombophlebitis** must trigger a search for occult vascular disease, especially **pulmonary artery aneurysm**, the most lethal complication.

- Distinguishing **GI Behçet's from Crohn's** and **neuro-Behçet's from MS** is a recurring clinical challenge — extra-intestinal/systemic features and lesion distribution guide diagnosis.
- HLA-B∗51 positivity supports the diagnosis and correlates with disease but is **neither necessary nor sufficient**.

High-yield exam pointers

- First described by **Hulusi Behçet (Turkish dermatologist)**; classic triad = **oral ulcers + genital ulcers + uveitis**.
- **Silk Road** distribution; highest prevalence in **Turkey (1 in 250)**; **HLA-B∗51** associated.
- **ISG criteria:** recurrent oral ulcers (≥3×/yr) **plus 2 of 4** (genital ulcers, skin lesions, eye lesions, positive pathergy); sensitivity ~95%, specificity ~96%.
- **Pathergy** = sterile pustule 24–48 h after a 20–21-G needle prick — read at 24–48 h.
- **Hypopyon** + **bilateral panuveitis**; eye disease commoner/severer in **males**.
- **Pulmonary artery aneurysm** = most feared lesion (5-yr mortality 20–25%); **do not anticoagulate** without excluding it.
- Venous thrombosis is **inflammatory** → treat with **immunosuppression**, not anticoagulation alone.
- **Apremilast** (PDE-4 inhibitor) is FDA-approved for oral ulcers; **azathioprine** is the workhorse steroid-sparing agent; **TNF inhibitors** for severe ocular/CNS/GI disease.
- Behçet's **abates with time**, unlike most chronic rheumatic diseases — many patients can taper therapy at 2–3 years.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Behçet Syndrome"* (ISG criteria, clinical features, organ-directed treatment) and *"The Vasculitis Syndromes"* (classification; leukocytoclastic venulitis).
- **CMDT 2026** — *"Behçet Disease"* (Rheumatologic, Immunologic & Allergic Disorders; clinical findings, differential diagnosis, current drug regimens and recent trial data).
- Management framework consistent with the **2018 EULAR recommendations for the management of Behçet's syndrome** (cited in Harrison).

◆ ◆ ◆

Systemic lupus erythematosus (SLE)

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

Definition / Introduction — Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterised by loss of immune tolerance, production of autoantibodies to nuclear antigens (especially nucleic acids and nuclear proteins), and immune-complex–mediated inflammation and tissue damage. There is **no single confirmatory test**; the diagnosis is clinical, integrating a compatible multi-organ presentation with serology and *exclusion of mimics*. Standardised **classification criteria** (2019 EULAR/ACR and 2012 SLICC) were devised to enrol homogeneous patients into clinical trials — they are widely used as a structured diagnostic framework but are **not** a substitute for individualised clinical judgement.

Classification vs diagnosis — the cardinal exam point

- Harrison stresses that classification criteria were **developed for enrolment into clinical trials, not for diagnosis**. For an individual patient, diagnosis is made on the totality of clinical and laboratory features after **excluding other disease entities**, and ultimately rests on **clinical judgement**.
- Two criteria sets are currently in use for trial enrolment: the **2019 EULAR/ACR** classification criteria and the **2012 SLICC** (Systemic Lupus International Collaborating Clinics) criteria.
- Important limitation: because EULAR/ACR criteria mandate ANA positivity, they **exclude the ~5% of SLE patients who are ANA-negative**, as well as patients with *incomplete lupus* — both groups still require clinical recognition and management.

Entry criterion — ANA is the gateway

- The **2019 EULAR/ACR** criteria use a positive **antinuclear antibody (ANA) titre of ≥1:80** (on HEp-2 cells or equivalent) as a **mandatory entry criterion**. If ANA is negative (and was never positive), the patient cannot be classified as SLE by these criteria.
- ANA is present in ~**95%** of SLE patients; a titre of **≥1:80 is considered positive** — highly **sensitive but not specific**. *Repeatedly negative ANA by immunofluorescence makes SLE unlikely*, though rare ANA-negative cases occur.
- Only after the entry criterion is satisfied are the **additive weighted clinical and immunological criteria** applied; **a patient requires ≥10 points** across the domains to be classified as SLE.

2019 EULAR/ACR additive weighted criteria

Criteria are grouped into **7 clinical** and **3 immunological** domains, each item carrying a weight. Scoring rules: a criterion is counted only if there is **no more likely explanation**; it need occur on **only one occasion**; **at least one clinical criterion** is required; and within each domain **only the single highest-weighted item** is counted. Total **≥10 points (with ANA ≥1:80) = classify as SLE**.

Domain	Representative criteria (highest weight in domain)	Weight
Constitutional	Fever	2

Domain	Representative criteria (highest weight in domain)	Weight
Hematologic	Leukopenia (3); Thrombocytopenia (4); Autoimmune haemolysis (4)	up to 4
Neuropsychiatric	Delirium (2); Psychosis (3); Seizure (5)	up to 5
Mucocutaneous	Non-scarring alopecia / oral ulcers (2); Subacute cutaneous or discoid lupus (4); Acute cutaneous lupus / malar rash (6)	up to 6
Serosal	Pleural/pericardial effusion (5); Acute pericarditis (6)	up to 6
Musculoskeletal	Joint involvement (≥2 joints synovitis / tenderness + stiffness)	6
Renal	Proteinuria >0.5 g/24 h (4); biopsy Class II/V LN (8); biopsy **Class III/IV LN (10)**	up to 10
Antiphospholipid antibodies	Anticardiolipin OR anti-β2-glycoprotein-1 OR lupus anticoagulant	2
Complement proteins	Low C3 OR low C4 (3); low C3 **AND** C4 (4)	up to 4
SLE-specific antibodies	**Anti-dsDNA OR anti-Sm**	6

- Harrison highlights the practically important rule: **no single value reaches 10 points except a renal biopsy showing Class III or IV lupus nephritis** — biopsy-proven proliferative nephritis (with a positive ANA) alone satisfies classification.
- **Anti-dsDNA and anti-Sm are the *only* ANA subtypes included** in the EULAR/ACR criteria, reflecting their high specificity.

Other criteria sets — SLICC 2012 and ACR 1997

- **SLICC 2012:** classify as SLE if **≥4 of 17 criteria (11 clinical + 6 immunological)** are met, with **at least one clinical AND one immunological** criterion; **OR biopsy-proven lupus nephritis** in the presence of **ANA or anti-dsDNA**. SLICC improved sensitivity over the older ACR set and formally recognised biopsy-proven nephritis as a stand-alone pathway.
- **ACR 1997 (revised) criteria:** historically, **≥4 of 11** criteria (present serially or simultaneously) classify SLE. The 11 items (mnemonic *SOAP BRAIN MD*): **S**erositis, **O**ral ulcers, **A**rthritis, **P**hotosensitivity, **B**lood disorder (cytopenias), **R**enal disorder, **A**NA, **I**mmunologic (anti-dsDNA/anti-Sm/antiphospholipid), **N**eurologic, **M**alar rash, **D**iscoid rash.

Autoantibody profile supporting the diagnosis

The **immunologic, renal and haematologic domains** form the laboratory backbone. After a positive ANA, test anti-dsDNA and anti-Sm; if ANA-negative but the picture is highly suggestive, **anti-Ro (SS-A)** confers a high likelihood of SLE.

Antibody	Prevalence	Diagnostic value / association
ANA	~95%	Best screening test; sensitive, not specific; ≥1:80 positive

Antibody	Prevalence	Diagnostic value / association
Anti-dsDNA	~70%	Higher titres specific for SLE; **correlate with activity and nephritis**
Anti-Sm	~30%	**Most specific** autoantibody for SLE
Anti-RNP / U1-RNP	~25% / ~13%	Overlap syndromes; pulmonary hypertension; high IFN signature
Anti-Ro (SS-A)	~30%	Often positive in **ANA-negative SLE**; sicca, neonatal lupus, congenital heart block, SCLE
Anti-La (SS-B)	~20%	Associated with anti-Ro
Antiribosomal P	~15%	CNS lupus; specific but not sensitive
Antihistone	~70%	**Drug-induced lupus**
Antiphospholipid (aCL, anti-β2GP-1, lupus anticoagulant)	~50%	Arterial/venous thrombosis, pregnancy loss, thrombocytopenia, Libman–Sacks endocarditis

- **Low C3/C4** falls during high disease activity; **anti-dsDNA + low complement** indicates a propensity to lupus nephritis and is used to track activity.
- Baseline work-up: CBC (leukopenia, lymphopenia, thrombocytopenia, anaemia of chronic inflammation/haemolytic anaemia), eGFR, serum creatinine, and **urine protein-to-creatinine ratio (UPCr)**; **renal biopsy when UPCr exceeds 0.5** to exclude active nephritis. Lupus nephritis is graded by the **ISN/RPS classification** (Class I–VI; Class III focal proliferative, IV diffuse proliferative, V membranous).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Flow algorithm — "EULAR/ACR 2019 classification":** box 1 **Entry criterion: ANA ≥1:80** → *if negative* → *not classified*; *if positive* → box 2 **Apply additive weighted criteria** (label the 7 clinical domains: Constitutional, Hematologic, Neuropsychiatric, Mucocutaneous, Serosal, Musculoskeletal, Renal; and 3 immunology domains: Antiphospholipid, Complement, SLE-specific antibodies) → box 3 **Score (count only highest item per domain; ≥1 clinical required)** → decision diamond **Total ≥10 points?** → **Classify as SLE**.
- **Labelled face/hand sketch:** malar ("butterfly") rash with **nasolabial sparing**; discoid plaques; Jaccoud arthropathy of the hand — label *malar rash*, *nasolabial sparing*, *discoid lesion*, *photosensitive distribution*, *Jaccoud deformity*.

Clinical / Diagnostic significance

- Criteria provide a **structured checklist** that improves diagnostic consistency, but a patient may be unequivocally diagnosed clinically **without** meeting classification points (e.g., early or ANA-negative disease) — never withhold treatment because a patient is "one point short."
- **Biopsy-proven Class III/IV lupus nephritis** is diagnostically decisive (10 points) and dictates aggressive immunosuppression; renal involvement (~35% of patients) drives prognosis.
- **Drug-induced lupus (DIL)** is a key differential: ~6–12% of lupus cases; classic triggers **procainamide** (highest risk, up to 30%) and **hydralazine** (first described, 1954), plus isoniazid,

minocycline, anti-TNF agents, etc.; **antihistone antibodies** typical, dsDNA usually absent; rarely affects kidney/brain; resolves on stopping the drug.

- Differentiate from RA (overlap = *rhupus*), mixed connective tissue disease (anti-U1-RNP), Sjögren's (anti-Ro/La), and primary antiphospholipid syndrome.

High-yield exam pointers

- Classification criteria = **for trials, not diagnosis**; diagnosis = clinical + lab + exclusion + judgement.
- **EULAR/ACR 2019:** mandatory entry **ANA ≥1:80**, then **additive weights, ≥10 points** to classify.
- **No single item = 10 points except renal biopsy Class III/IV LN.**
- **Anti-dsDNA and anti-Sm are the only ANA subtypes in EULAR/ACR criteria**; anti-Sm = most specific; anti-dsDNA tracks activity/nephritis.
- **SLICC 2012:** ≥4 of 17 (≥1 clinical + ≥1 immunologic) **OR** biopsy-proven LN with ANA/anti-dsDNA.
- **ACR 1997:** ≥4 of 11 — mnemonic *SOAP BRAIN MD*.
- **~5% of SLE is ANA-negative** (anti-Ro often positive) and is excluded by EULAR/ACR.
- **Low C3/C4 + rising anti-dsDNA** = flag for active disease/nephritis.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e (2025) — **Ch 368 "Systemic Lupus Erythematosus."** Coverage note: the chapter explicitly supports the entry criterion (ANA ≥1:80), the **≥10-point** threshold, the **renal-biopsy Class III/IV = 10 points** rule, the use of EULAR/ACR 2019 and SLICC 2012, autoantibody prevalences/associations (Table 368-2), and that anti-dsDNA/anti-Sm are the only included ANA subtypes. The **detailed per-item point weights** of the EULAR/ACR table, the **full SLICC ≥4/17 rule**, and the **ACR 1997 11-criteria list (SOAP BRAIN MD)** are **not enumerated in the provided chapter**; they are added here as universally accepted, accurate standard rheumatology to satisfy the exam ask.

◆ ◆ ◆

SLE flares — risk factors and severity classification

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

Definition / Introduction — Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease driven by autoantibodies and immune-complex deposition, with a characteristically **relapsing–remitting course** — roughly 70% of patients follow a pattern of flares and remissions. A **flare** is a measurable increase in disease activity (clinical and/or serological) above the patient's prior stable state that warrants escalation or intensification of therapy. Recognising the triggers of a flare allows preventive counselling, while grading flare severity is the central decision node that dictates whether treatment is purely symptomatic, intensified with steroid-sparing immunosuppression, or escalated to high-dose/pulse glucocorticoids and aggressive immunosuppression.

What constitutes a "flare"

- An *increase* in disease activity over baseline — new organ involvement or worsening of existing involvement — sufficient to require a change in treatment, distinct from chronic irreversible **damage** (which does not respond to immunosuppression).
- Flares may be **clinical** (e.g., arthritis, rash, serositis, nephritis, cytopenia, neuropsychiatric) and/or **serological** (rising anti-dsDNA titre, falling C3/C4).
- Most SLE patients have active disease despite therapy or have frequent flares requiring treatment adjustment; the treatment goal is remission or a low disease-activity state on the least possible therapy.

Risk factors / triggers for disease flares

Grouped by mechanism (all faithful to the source corpus unless flagged):

Category	Specific risk factors
Environmental / physical	**Ultraviolet (UV) light / sun exposure** — induces apoptosis, self-stimulatory nucleic acids, keratinocyte activation and DNA-methylation change (photosensitive patients flare rapidly after first major UV exposure); **crystalline silica**; toxins (mercury, diet)
Infections	Viral infection, especially **Epstein–Barr virus (EBV)**, induces the type-1 interferon response and can precipitate activity
Hormonal / reproductive	**Pregnancy and the postpartum period** — disease can flare in any trimester; **oestrogen-containing** contraceptives/HRT are avoided in active or moderate–severe SLE (thrombosis and flare risk); active disease at conception predicts more flares
Drug / treatment-related	**Non-adherence** to therapy; **discontinuation of hydroxychloroquine (HCQ)**; too-rapid glucocorticoid tapering/withdrawal; **drug-induced** lupus activity from offending agents
Lifestyle	**Cigarette smoking** — causes autoantigen release, worsens disease and interferes with antimalarial efficacy
Serological / disease-intrinsic	**Rising anti-dsDNA** titres and **falling C3/C4** complement herald impending activity, especially nephritis; high prior disease activity; persistently active disease despite therapy

Category	Specific risk factors
Host factors	Non-White ethnicity and low socioeconomic status (worse/more severe disease and poorer access to care)

Key prevention pearls embedded in the corpus: **HCQ prevents flares**, prolongs survival and reduces flares during pregnancy and postpartum — hence it is recommended for *all* patients unless contraindicated; daily sunscreen, smoking cessation and adherence are foundational.

Serological predictors of an impending flare

- **Anti-dsDNA** antibodies are produced by short-lived plasmablasts and track disease activity; a rising titre signals reactivation.
- **C3 and C4** fall during high activity (consumed by immune-complex formation); the **anti-dsDNA↑ / complement↓** combination specifically predicts active lupus **nephritis**.
- Quarterly monitoring of UPCr/eGFR, CBC and complement/anti-dsDNA is advised because renal and haematological flares can be clinically *silent*.
- Caveat (well recognised): a subset of patients have persistently high anti-dsDNA and low complement without clinical flare ("serologically active, clinically quiescent") — treat the patient, not the number alone.

Classification of flare / disease-activity severity

Severity is graded both by **validated composite indices** (for trials and longitudinal monitoring) and by a practical **categorical mild/moderate/severe** scheme that drives therapy.

A. Validated disease-activity instruments

- **SLEDAI / SLEDAI-2K** (SLE Disease Activity Index) — weighted score summing active manifestations across organ systems; underpins treat-to-target targets (LLDAS, DORIS remission).
- **BILAG** (British Isles Lupus Assessment Group) — an organ-by-organ "physician's intention-to-treat" categorical index grading each system: **A = severe** activity (needs high-dose steroids/immunosuppression), **B = moderate**, **C = mild/stable**, **D = previously involved, now inactive**, **E = never involved**.
- **SELENA–SLEDAI Flare Index (SFI)** — purpose-built flare instrument that categorises flares as **mild/moderate vs severe** using the change in SLEDAI plus clinical descriptors and the Physician Global Assessment (see Coverage note).
- Composite trial endpoints derived from these: **SRI** (SLE Responder Index) and **BICLA** (BILAG-based Composite Lupus Assessment); **CLASI** for cutaneous activity; **SLICC/ACR Damage Index** measures accrued damage (not activity).

B. EULAR categorical severity (the bedside, therapy-driving classification)

Severity	Defining features	SLE DAI	BILAG	Typical first-line therapy
Mild	Constitutional symptoms; mild arthritis; rash ≤9% BSA; platelets 50–100 $\times 10^9$/L	**≤6**	BILAG **C** or ≤1 BILAG **B**	HCQ ± short low-dose glucocorticoid; NSAIDs; topicals
Moderate	Moderate–severe ("RA-like") arthritis; rash 9–18% BSA; platelets 20–50 $\times 10^9$/L; serositis	**7–12**	**≥2 BILAG B**	HCQ + GC + steroid-sparing agent (MTX/AZA/MMF); belimumab/anifrolumab add-on
Severe	Major **organ-threatening** disease (cerebritis, myelitis, pneumonitis, mesenteric vasculitis); platelets <20 $\times 10^9$/L; TTP-like / acute haemophagocytic syndrome; rash >18% BSA	**>12**	**≥1 BILAG A**	Pulse/high-dose GC (IV methylprednisolone 125–1000 mg/day ×1–3 d) + MMF or cyclophosphamide ± rituximab

C. Treat-to-target reference states (the "no-flare" goals against which a flare is judged):

- **Low disease-activity state (LLDAS):** clinical **SLEDAI ≤4**, on HCQ, stable immunosuppressive/biologic, with prednisone **≤5 mg/day**.
- **DORIS remission:** clinical **SLEDAI = 0**, with prednisone **≤5 mg/day** and stable maintenance therapy.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Flare risk-factor wheel:** central hub "SLE FLARE" with labelled spokes — *UV light/sun*, *EBV/infection*, *Pregnancy & postpartum*, *Non-adherence / HCQ withdrawal*, *Rapid steroid taper*, *Smoking*, *Oestrogen (OCP/HRT)*, *Rising anti-dsDNA / falling C3–C4*. Annotate "HCQ + sunscreen + adherence = flare prevention".
- **Severity ladder (3-tier bar):** three ascending blocks labelled **MILD** (SLEDAI ≤6 / BILAG C), **MODERATE** (SLEDAI 7–12 / ≥2 BILAG B), **SEVERE** (SLEDAI >12 / ≥1 BILAG A); side-label the matching platelet count, %BSA rash and first-line drug for each tier; add a baseline line for "LLDAS / DORIS remission".

Clinical / Diagnostic significance

- **Distinguish flare from infection:** in active SLE the **ESR rises but CRP is usually normal** — a high CRP without serositis/arthritis should raise suspicion of **infection** (a major mimic in an immunosuppressed patient).
- **Distinguish flare from damage:** activity is reversible with immunosuppression; damage (e.g., glucocorticoid-induced cataract, avascular necrosis, ESRD) is not — escalating immunosuppression for damage only adds toxicity.
- **Renal flare** is often silent: a UPCr rising above 0.5 and/or falling eGFR with active sediment (haematuria, cellular casts) should prompt renal biopsy; class III/IV (±V) nephritis needs aggressive therapy.

- **Pregnancy planning:** conceive when disease is quiescent for ≥6 months, continue **HCQ**, use AZA/tacrolimus if immunosuppression is needed, and avoid MMF, methotrexate, cyclophosphamide and warfarin.
- **Severity grade determines therapy intensity:** mild → HCQ ± brief low-dose steroid; moderate → add a steroid-sparing agent ± biologic; severe/organ-threatening → pulse methylprednisolone plus MMF/cyclophosphamide ± rituximab, with the steroid tapered to ≤5 mg/day as fast as feasible.

High-yield exam pointers

- SLE is **relapsing–remitting** in ~70%; a flare = increase in activity requiring treatment change, *not* fixed damage.
- **Top modifiable flare triggers:** UV light, infection (EBV), pregnancy/postpartum, **HCQ discontinuation / non-adherence**, smoking, oestrogens, rapid steroid taper.
- **HCQ prevents flares**, improves survival and is recommended for *all* SLE patients (≤5 mg/kg/day; annual retinal screening).
- **Anti-dsDNA ↑ + C3/C4 ↓** predicts a flare, especially **nephritis**.
- Severity is graded by **SLEDAI** (≤6 mild, 7–12 moderate, >12 severe) and **BILAG** (A severe, B moderate, C mild, D inactive, E never involved).
- **SELENA–SLEDAI Flare Index** grades flares as mild/moderate vs severe; **SRI/BICLA** are composite trial endpoints; **SLICC/ACR Damage Index** measures damage, not activity.
- **Severe flare = organ-threatening** (CNS, renal, pulmonary, mesenteric vasculitis, platelets <20 $\times 10^9$/L) → IV methylprednisolone pulse + MMF/cyclophosphamide ± rituximab.
- **Treat-to-target:** aim for **LLDAS** (SLEDAI ≤4, prednisone ≤5 mg/day) or **DORIS remission** (SLEDAI 0).
- **CRP normal in pure lupus flare** — a raised CRP points to infection or serositis.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Systemic Lupus Erythematosus" (risk factors/environmental triggers, anti-dsDNA/complement monitoring, EULAR mild/moderate/severe activity figure, SLEDAI/BILAG/SRI/BICLA, LLDAS/DORIS targets, pregnancy and flare prevention with HCQ); "Antiphospholipid Syndrome" (flare-related triggers of catastrophic APS).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders: Systemic Lupus Erythematosus" (waxing–waning course, severity-matched therapy, CRP-vs-infection pearl, HCQ flare prevention, glucocorticoid dosing for mild vs severe disease).
- **Rook's Textbook of Dermatology, 10e** — "Lupus Erythematosus and Antiphospholipid Syndrome" (relapsing–remitting epidemiology, disease-activity indices SELENA/SLEDAI/SLEDAI-2K/BILAG/CLASI, UV- and smoking-induced flares, anti-dsDNA/complement as predictors).

Coverage note: The corpus names and uses the SLEDAI, BILAG, SELENA, SRI, BICLA, CLASI and SLICC/ACR indices and provides the EULAR categorical mild/moderate/severe activity cut-offs (used as the main severity table here), but it does **not** spell out the numeric thresholds of the *SELENA–SLEDAI Flare Index* (e.g., SLEDAI change >3 for mild/moderate vs >12 for a severe flare, with Physician Global Assessment descriptors) or the full BILAG-2004 organ glossary. The SFI mild/moderate-vs-severe framing and the BILAG A–E category meanings given above are standard, universally accepted rheumatology, included for completeness and flagged here as not detailed verbatim in the available chapters.

◆ ◆ ◆

Disease-modifying antirheumatic drugs

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

Definition / Introduction — Disease-modifying antirheumatic drugs (**DMARDs**) are agents that, unlike pure analgesics or NSAIDs, **slow or arrest the structural (radiographic) progression** of inflammatory arthritis in addition to relieving symptoms. They are the cornerstone of management of **rheumatoid arthritis (RA)** and are also used in other immune-mediated arthritides (psoriatic arthritis, SLE, vasculitis). They are conventionally divided into **conventional synthetic (csDMARDs)**, **biologic (bDMARDs)** and **targeted synthetic (tsDMARDs)** classes. They share a characteristically **delayed onset of action** (≈6–12 weeks for csDMARDs) and require structured laboratory monitoring for toxicity.

Classification of DMARDs

Class	Sub-group	Representative agents
Conventional synthetic (csDMARD)	—	Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine
Biologic (bDMARD)	TNF-α inhibitors	Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab pegol

Class	Sub-group	Representative agents
	IL-6 receptor blockers	Tocilizumab, Sarilumab
	IL-1 receptor antagonist	Anakinra
	T-cell co-stimulation blocker	Abatacept (CTLA-4–Ig)
	Anti-CD20 (B-cell depletion)	Rituximab
Targeted synthetic (tsDMARD)	JAK inhibitors	Tofacitinib, Baricitinib, Upadacitinib

- **Biosimilars** — agents engineered to have the same active properties as a licensed reference biologic, with similar efficacy and toxicity (available for infliximab, etanercept, adalimumab); they reduce cost.
- *Methotrexate* is the **DMARD of first choice** and the "**anchor drug**" for most combination regimens.
- *Hydroxychloroquine*, although DMARD-like, has **not** been shown to delay radiographic progression and so is **not strictly a true DMARD**; it is used for early/mild disease or as an adjunct.

Conventional synthetic DMARDs (csDMARDs)

- **Methotrexate (MTX)** — a **folate antagonist (dihydrofolate reductase inhibitor)**; at the low *weekly* doses used in RA its anti-inflammatory action is mediated chiefly by **promoting adenosine release**. Onset 4–6 weeks; about one-third of patients reach low disease activity on monotherapy. Given **10–25 mg once weekly orally or subcutaneously** (CMDT: start 7.5–15 mg/week, titrate to a maximal oral dose of ~20 mg/week). **Folic acid 1 mg/day** (or weekly leucovorin) is co-prescribed to reduce stomatitis, cytopenias, GI and hepatic toxicity. SQ route is used when oral is poorly tolerated or absorption is limiting.
- **Leflunomide** — inhibits **dihydro-orotate dehydrogenase**, blocking *de novo* pyrimidine synthesis; efficacy similar to MTX as monotherapy or in combination. Dose **10–20 mg/day** orally. Very long half-life with active metabolite detectable for up to ~2 years (cholestyramine washout if rapid elimination needed, e.g., pregnancy planning).
- **Sulfasalazine** — reduces joint inflammation and **retards radiographic progression** (RCT-proven). Start **500 mg twice daily**, maintenance **1000–1500 mg twice daily**. Check **G6PD before starting** (haemolysis risk).
- **Hydroxychloroquine** — antimalarial, **not immunosuppressive**, low toxicity; **200–400 mg/day (≤5 mg/kg)** to limit retinal toxicity. Mainly used within "**oral triple therapy**" (MTX + sulfasalazine + hydroxychloroquine).

Biologic DMARDs (bDMARDs)

Biologics are **protein therapeutics** targeting cytokines or cell-surface molecules; the **TNF inhibitors** (first approved 1999) revolutionised RA care. Most are used **in combination with background methotrexate**, typically after an inadequate response to MTX.

Target / mechanism	Agent	Dosing (representative)
TNF-α — chimeric mAb	Infliximab	3 mg/kg IV at wk 0, 2, 6, then every 8 wk (up to 10 mg/kg q4wk)
TNF-α — soluble TNF-R2–Fc fusion	Etanercept	50 mg SQ weekly
TNF-α — humanized mAb	Adalimumab	40 mg SQ every other week
TNF-α — humanized mAb	Golimumab	50 mg SQ monthly
TNF-α — pegylated Fab′ fragment	Certolizumab pegol	400 mg SQ wk 0, 2, 4 → 200 mg every other week
IL-6 receptor mAb	Tocilizumab / Sarilumab	Tocilizumab 4–8 mg/kg IV monthly *or* 162 mg SQ; Sarilumab 200 mg SQ every other week
IL-1 receptor antagonist	Anakinra	100 mg SQ daily (limited use; lower efficacy)
T-cell co-stimulation (CTLA-4–Ig blocks CD28–CD80/86)	Abatacept	Weight-based IV q4wk *or* 125 mg SQ weekly
CD20 B-cell depletion	Rituximab	1000 mg IV ×2 (days 0 and 14); repeat ~q24 weeks

- **TNF inhibitors** reduce signs/symptoms, **slow radiographic damage**, and improve function/quality of life.
- **Abatacept** blocks the CD28–CD80/86 co-stimulatory signal to T cells.
- **Rituximab** (anti-CD20) is approved for **refractory RA** (TNF-inhibitor failure) with MTX; **more effective in seropositive** disease. Rare risk of **progressive multifocal leukoencephalopathy (PML)** (~1:25,000) and blunting of vaccine response.
- **IL-6R blockers** are effective as monotherapy or with MTX; raise **LDL cholesterol** and carry a risk of **GI perforation** (avoid in diverticulitis/recent peptic ulcer).
- **Biologics should not be combined with one another** (additive infection risk without added benefit).

Targeted synthetic DMARDs — JAK inhibitors

- **Mechanism** — small oral molecules inhibiting **Janus kinases (JAK1, JAK2, JAK3, Tyk2)**, which transduce intracellular signals from cytokine receptors (common γ-chain cytokines IL-2/-4/-7/-9/-15/-21, IFN-γ, IL-6, IL-12/-23) via the **JAK–STAT** pathway.
  - *Tofacitinib* — JAK1/JAK3 inhibitor; **5 mg twice daily** (or 11 mg XR daily).
  - *Baricitinib* — JAK1/JAK2 inhibitor; **2 mg daily**.
  - *Upadacitinib* — selective JAK1 inhibitor; **15 mg daily**.
- Advantage: **oral** route; used as monotherapy or with MTX.
- **Safety signal** — an FDA **black-box warning** (from an RCT vs TNF inhibitors in MTX-treated patients) of increased **serious infection, herpes zoster, thrombosis/VTE, major adverse cardiovascular events (MACE), malignancy and death**, greatest in the **elderly**.

Adverse effects, screening and monitoring

Drug	Serious toxicity	Baseline screen	Monitoring
Methotrexate	Hepatotoxicity, myelosuppression, interstitial pneumonitis; **teratogenic (Pregnancy category X)**	CBC, LFTs, viral hepatitis panel, CXR	CBC, creatinine, LFTs every 2–3 months
Leflunomide	Hepatotoxicity, myelosuppression; **teratogenic**	CBC, LFTs, viral hepatitis panel	LFTs periodically
Sulfasalazine	Granulocytopenia, haemolysis (G6PD deficiency)	**G6PD level**, CBC, LFTs	CBC every 2–4 wk ×3 months, then q3 months
Hydroxychloroquine	**Irreversible retinal damage**, cardiotoxicity	Eye exam (esp. >40 y)	OCT + visual fields every 12 months
TNF inhibitors	Serious bacterial/fungal infection, **reactivation of latent TB**, demyelination, drug-induced lupus	**TB screening (PPD or IGRA)**, hepatitis panel	Monitor for infection/injection or infusion reactions
Rituximab	Infection, **hepatitis B reactivation**, PML, infusion reaction	Viral hepatitis panel, CBC	CBC at intervals
JAK inhibitors	Infection (zoster), thrombosis, MACE, malignancy, transaminitis, dyslipidaemia	TB screening, varicella vaccination	CBC, LFTs, lipids at intervals

- **Latent TB** must be screened (PPD/IGRA) before any biologic or JAK inhibitor; if positive, **treat LTBI for ≥1 month before** starting.
- TNF inhibitors are **contraindicated** in active infection, **chronic hepatitis B**, and **NYHA class III/IV heart failure**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **DMARD molecular-target schematic of the rheumatoid synovium** — draw a synovial joint with infiltrating immune cells and arrows to each drug target. Labels: *TNF-α* (infliximab/etanercept/adalimumab/golimumab/certolizumab), *IL-6 / IL-6R* (tocilizumab/sarilumab), *IL-1 / IL-1Ra* (anakinra), *CD20 B cell* (rituximab), *T-cell co-stimulation CD28–CD80/86* (abatacept/CTLA-4–Ig), *intracellular JAK1/2/3–Tyk2 → STAT* (tofacitinib/baricitinib/upadacitinib).
- **Treat-to-target algorithm** — flow boxes: *Early RA diagnosis → Methotrexate + folic acid (anchor) ± short glucocorticoid bridge → Reassess at 3–6 months (DAS28 / CDAI / SDAI) →* if target not met → *Triple csDMARD therapy* **or** *Add TNF inhibitor ± MTX* **or** *Non-TNF biologic ± MTX → Switch class / JAK inhibitor → Goal: low disease activity or remission*.

Clinical / Diagnostic significance

- **Treat-to-target ("T2T")** — the guiding principle: aim for **low disease activity or clinical remission**, with **frequent reassessment** using composite indices (DAS28, SDAI, CDAI, RAPID3) and rapid step-up of therapy when targets are unmet. *ACR/EULAR provisional remission*: tender joints ≤1, swollen joints ≤1, CRP ≤1 mg/dL, patient global ≤1 — **or** SDAI ≤3.3.

- **Sequencing** — begin with **methotrexate**; if inadequate at 3–6 months, escalate to a combination (**oral triple therapy** = MTX + sulfasalazine + hydroxychloroquine) **or** add a TNF / non-TNF biologic ± MTX. MTX + anti-TNF is superior to MTX alone for symptoms and for retarding structural damage. Triple therapy is **non-inferior to MTX + etanercept** and is economical.
- **Switching** — anti-TNF failure may respond to a **different mechanism** (abatacept, rituximab, IL-6R blocker, JAK inhibitor); evidence suggests switching to abatacept can beat a second anti-TNF.
- **Glucocorticoid bridging** — low–moderate dose prednisone (5–10 mg/day) gives rapid control until DMARDs act; chronic use is minimised (osteoporosis — consider bisphosphonate prophylaxis).
- **Pregnancy** — **methotrexate and leflunomide are contraindicated (teratogenic)**; **hydroxychloroquine and sulfasalazine are the safest**; anti-TNF agents are generally acceptable but usually stopped in the third trimester.
- **Comorbidity/mortality** — RA excess mortality is largely **cardiovascular**; controlling inflammation plus CV risk-factor management improves outcomes. In resource-limited settings, **TB and viral hepatitis reactivation** drive screening practice.

High-yield exam pointers

- DMARD = drug that **slows radiographic progression**, not just symptoms; csDMARDs act in **6–12 weeks**.
- **Methotrexate = anchor/first-choice DMARD**; weekly dosing + **folic acid**; key toxicities = hepatotoxicity, cytopenias, **pneumonitis**, teratogenicity.
- **Hydroxychloroquine is not a true DMARD** (no radiographic benefit); main risk = **retinal toxicity** → annual OCT/visual fields, dose ≤5 mg/kg.
- **Oral triple therapy** = MTX + sulfasalazine + hydroxychloroquine.
- **Five TNF inhibitors**: infliximab, etanercept, adalimumab, golimumab, certolizumab; screen **latent TB** first; avoid in chronic HBV and **class III/IV heart failure**.
- **Abatacept** = CTLA-4–Ig (T-cell co-stimulation block); **Rituximab** = anti-CD20 (better in **seropositive** RA, risk of HBV reactivation/PML); **Tocilizumab/Sarilumab** = IL-6R (raise LDL, GI perforation).
- **JAK inhibitors** (tofacitinib, baricitinib, upadacitinib) are **oral tsDMARDs**; **black-box warning** for thrombosis, MACE, malignancy, infection.
- **Do not combine two biologics**; remission target = **SDAI ≤3.3**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Rheumatoid Arthritis" (Treatment section; Table 370-2 *DMARDs Used for the Treatment of Rheumatoid Arthritis*; Table 370-3 *ACR/EULAR Provisional Definition of Remission*).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders" (Rheumatoid Arthritis — synthetic and biologic DMARD dosing, monitoring, combination/triple therapy).
- Mechanistic notes for methotrexate (dihydrofolate reductase inhibition) and leflunomide (dihydro-orotate dehydrogenase inhibition) and the csDMARD/bDMARD/tsDMARD classification are universally accepted standard internal medicine, consistent with the cited chapters.

◆ ◆ ◆

Drug-induced lupus

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

Definition / Introduction — *Drug-induced lupus (DIL)* is an autoimmune phenomenon in which a positive antinuclear antibody (ANA) and clinical features resembling systemic lupus erythematosus (SLE) arise as a consequence of continuous exposure to a particular drug, and characteristically resolve after the offending agent is withdrawn. It accounts for roughly **6–12% of all lupus cases**. Compared with idiopathic SLE it is generally milder, *rarely involves the kidney or brain*, lacks the strong female predominance, and is serologically dominated by **antihistone antibodies**. Recognising DIL is important because it is largely reversible — the single most effective "treatment" is to stop the culprit drug.

Epidemiology and offending drugs

- DIL was first described with **hydralazine in 1954**; since then **more than 100 drugs** have been implicated as potential triggers.
- The **highest incidence is with the antiarrhythmic procainamide**, where the risk has been reported to be as high as **~30%**. With **hydralazine taken for a year or longer the incidence is ~5–8%**; for most other implicated drugs the risk is considerably **lower than 1%**.
- DIL has a **nearly equal sex ratio** (unlike the strong female predominance of SLE), and typically affects an **older age group**, reflecting the age at which the culprit cardiovascular/anti-infective drugs are prescribed.
- *Drugs with definite associations:* **hydralazine, procainamide, isoniazid, minocycline**, with methyldopa and chlorpromazine less commonly.

Risk / drug class	Representative agents
High risk	Procainamide (~30%), hydralazine (~5–8% if ≥1 yr)
Antiarrhythmics / antihypertensives	Procainamide, quinidine, hydralazine, methyldopa, ACE inhibitors, beta-blockers, hydrochlorothiazide
Anti-infectives	Isoniazid, minocycline, rifampin, nitrofurantoin

Risk / drug class	Representative agents
Anticonvulsants	Phenytoin, carbamazepine
Antithyroid	Propylthiouracil
Psychotropics	Chlorpromazine, lithium
Others	Sulfasalazine, proton-pump inhibitors, NSAIDs, oral contraceptives
Biologics	Anti-TNF-α agents (especially **infliximab, etanercept**), interferon-α

- **Drug-induced subacute cutaneous lupus erythematosus (SCLE)** is a related but distinct entity — *more than one-third* of SCLE is drug-induced; **hydrochlorothiazide** is a classic cause, with terbinafine, PPIs, calcium-channel blockers, ACE inhibitors and TNF inhibitors also implicated.

Pathogenesis

- Drug exposure provokes a **loss of self-tolerance**, generating ANA and SLE-like clinical features; in many cases simple **discontinuation of the drug is sufficient** for symptoms to abate.
- **Pharmacogenetic susceptibility — the slow-acetylator phenotype:** hydralazine, procainamide and isoniazid are metabolised by hepatic **N-acetyltransferase 2 (NAT2)**. *Slow acetylators* accumulate the parent drug and develop DIL **earlier, more frequently and at lower cumulative doses** than fast acetylators (universally accepted internal-medicine teaching).
- Proposed mechanisms include drug-induced **disruption of central tolerance, impaired DNA methylation in T cells, and oxidative/reactive-metabolite modification of self chromatin (the histone–DNA complex)**, exposing cryptic antigens — explaining the dominance of **antihistone antibodies**.
- **Biologic-induced lupus** (anti-TNF, IFN-α) is mechanistically distinct: TNF inhibitors can induce **antibodies to dsDNA but usually not antihistone antibodies**, and clinically produce a lupus-like syndrome in only ~0.5–1%.

Clinical features

- Typically an **abrupt onset weeks to several months after starting the drug**, with constitutional and musculoskeletal/serosal symptoms predominating:
  - **Fever**, **arthralgia and myalgia**, **arthritis**
  - **Serositis** — pleuritis (pleuritic chest pain, effusion) and pericarditis
  - **Cutaneous rash** (including photosensitive eruptions; drug-induced SCLE as a variant)
- **Severe organ involvement is characteristically absent** — *renal* (nephritis) and *CNS/neuropsychiatric* disease are rare, distinguishing DIL from SLE.
- **Cytopenias** may occur but are typically **mild**.
- Symptoms **resolve within several weeks to a few months of stopping** the offending agent.

Feature	Drug-induced lupus	Idiopathic SLE
Sex ratio	Nearly **equal**	Strong **female** predominance

Feature	Drug-induced lupus	Idiopathic SLE
Typical age	Older (drug-exposed)	Younger (15–45 yr)
Renal / CNS disease	**Rare**	Common, prognosis-defining
Severity	Generally **milder**	Variable, can be severe
ANA	Positive (often before symptoms)	Positive (≥95%)
ANA pattern	Usually **homogeneous**	Variable (often speckled/homogeneous)
Antihistone Ab	Positive in **~75–95%**	~70% (not specific)
Anti-dsDNA / anti-Sm	Usually **absent** (dsDNA may occur with anti-TNF)	dsDNA & Sm characteristic
Complement (C3/C4)	Usually **normal**	Often **low** in active disease
Course on drug withdrawal	**Resolves**	Persists (chronic)

Investigations and serology

- **ANA is positive in essentially all symptomatic patients**, characteristically in a **homogeneous** pattern, and the ANA frequently **appears before symptoms**.
- **Antihistone antibodies** are the serologic hallmark — present in **~75% (Harrison) up to ~95% (CMDT)** of DIL. *Important caveat:* antihistone antibodies are **also seen in the majority of idiopathic SLE**, so by themselves they **do not distinguish** DIL from SLE.
- **Antibodies to dsDNA, Sm, RNP, SS-A (Ro) and SS-B (La) are characteristically rare** in DIL — their presence should raise suspicion for true SLE. *Exception:* **TNF inhibitors can induce anti-dsDNA** antibodies.
- **Complement levels are usually normal**; mild cytopenias may be present.
- Many of the same drugs induce a **positive ANA in asymptomatic patients who never develop DIL**, so a positive ANA alone does not mandate stopping the drug — the laboratory tests must be interpreted alongside the clinical picture.
- *Skin biopsy* in DIL may be **indistinguishable from SLE** and is not by itself discriminatory.

Diagnosis and differential diagnosis

- DIL is a **clinical-temporal diagnosis** requiring: (1) **exposure to an implicated drug**, (2) compatible SLE-like features developing **during** that exposure, (3) supportive serology (ANA ± antihistone, absence of SLE-specific antibodies, normal complement), and (4) **resolution of symptoms after discontinuation** — the latter is the strongest confirmatory feature.
- *Differential diagnosis:* idiopathic SLE, rheumatoid arthritis, systemic and ANCA-associated vasculitis, primary antiphospholipid syndrome, viral arthralgia, and acute drug reactions.
- **Related drug-induced autoimmune syndrome — drug-induced ANCA vasculitis: propylthiouracil, hydralazine, minocycline, allopurinol, penicillamine and sulfasalazine** can induce a systemic vasculitis with **high-titre p-ANCA (anti-MPO)** and features of microscopic polyangiitis — a useful contrast point in the exam.

Management

- **Withdraw the offending drug** — this is the definitive intervention; constitutional, articular and serosal symptoms typically remit over weeks to months.
- For symptomatic relief while the syndrome settles: **NSAIDs** for arthralgia/serositis and a **short course of low-dose corticosteroids** for more troublesome serositis or persistent arthritis (standard supportive practice).
- **Hydroxychloroquine** may be used for persistent cutaneous/articular symptoms, particularly in drug-induced SCLE.
- The patient (and treating physicians) should be advised to **avoid re-challenge** with the culprit agent.
- Note that the **ANA may persist for months to years** after clinical recovery and does not require treatment — clinical, not serologic, resolution guides management.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Venn / comparison diagram "DIL vs SLE":** two overlapping circles. *DIL circle labels* — drug exposure, equal sex ratio, antihistone antibody, homogeneous ANA, normal complement, no renal/CNS disease, resolves on stopping drug. *SLE circle labels* — female predominance, anti-dsDNA & anti-Sm, low C3/C4, nephritis & neuropsychiatric disease, chronic course. *Overlap labels* — positive ANA, fever, arthritis, serositis, rash, antihistone positivity.
- **Schematic of pathogenesis:** Drug → (slow acetylator / NAT2) → reactive metabolite modifies **histone–DNA (chromatin)** → loss of self-tolerance → **antihistone antibodies + ANA** → SLE-like illness → *drug withdrawal* → resolution. Labels: Culprit drug, NAT2 / slow acetylator, Histone–DNA complex, Antihistone Ab, Homogeneous ANA, Reversibility.

Clinical / Diagnostic significance

- A new **lupus-like illness in an older patient on procainamide, hydralazine, isoniazid or minocycline** should trigger DIL workup before labelling idiopathic SLE.
- **Antihistone positivity with absent anti-dsDNA/Sm and normal complement** strongly favours DIL; conversely, low complement, anti-dsDNA, nephritis or neuropsychiatric disease points to true SLE.
- An **anti-TNF-treated patient** developing arthralgia, rash and serositis with **anti-dsDNA but negative antihistone** is the classic biologic-induced lupus pattern.
- **Hydrochlorothiazide-associated photosensitive annular/papulosquamous rash** with anti-Ro positivity suggests **drug-induced SCLE**.
- Distinguish DIL (reversible, organ-sparing) from **drug-induced ANCA vasculitis** (PTU/hydralazine/minocycline; p-ANCA, can cause glomerulonephritis), which needs immunosuppression, not just drug withdrawal.

High-yield exam pointers

- DIL = **6–12%** of all lupus; first agent described was **hydralazine (1954)**; **>100 drugs** implicated.
- **Highest risk: procainamide (~30%)**; hydralazine **5–8%** if used ≥1 year; most others **<1%**.

- **Antihistone antibody** is the serologic hallmark (75–95%) but is **NOT specific** (also in SLE); **homogeneous ANA**.
- **Anti-dsDNA, anti-Sm absent and complement normal** in classic DIL — their presence argues for true SLE.
- **Renal and CNS involvement are rare**; **sex ratio is nearly equal**; disease is **milder** than SLE.
- **Slow acetylators (NAT2)** develop hydralazine/procainamide/isoniazid DIL earlier and more often.
- **TNF inhibitors** (infliximab, etanercept) induce **anti-dsDNA but usually not antihistone** — exception to the rule.
- **Treatment = stop the drug**; NSAIDs ± short steroids for symptoms; resolves in **weeks to months**; ANA may persist.
- **Drug-induced SCLE** — think **hydrochlorothiazide**, terbinafine, PPIs, CCBs, ACE inhibitors.
- **Drug-induced ANCA vasculitis** — PTU, hydralazine, minocycline, allopurinol, penicillamine, sulfasalazine (high-titre p-ANCA).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Systemic Lupus Erythematosus"** (Drug-Induced Lupus section; Table 368-2, Autoantibodies in SLE; Drug-Induced Autoimmunity).
- **CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders"** (Drug-Induced Lupus; SLE serology and differential diagnosis; drug-induced SCLE and drug-induced ANCA vasculitis).
- **Bolognia, Dermatology — "Drug Interactions"** (slow-acetylator / pharmacogenetic risk factor) for the acetylator phenotype point.
- *Coverage note:* The corpus covers DIL well within the SLE chapters. The **NAT2 slow-acetylator** mechanism and the specific roles of **NSAIDs/short-course corticosteroids/hydroxychloroquine** for residual symptoms are standard, universally accepted internal-medicine teaching corroborated in the corpus only in part (acetylator phenotype via Bolognia); they are included as established facts, not from a dedicated DIL management trial.

◆ ◆ ◆

Takayasu arteritis

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

Definition / Introduction — Takayasu arteritis (TAK) is an idiopathic, chronic, granulomatous **large-vessel vasculitis** with a strong predilection for the **aorta, its major branches, and the pulmonary arteries**. It produces a *panarteritis* that leads to **stenosis, occlusion, post-stenotic dilatation and aneurysm formation**, the clinical hallmark being **absent or diminished pulses** (hence the eponym *"pulseless disease"* / *aortic arch syndrome*). It is an uncommon disease (annual incidence **1.2–2.6 per million**), most prevalent in **adolescent girls and young women**, and although commoner in Asia it is neither racially nor geographically restricted.

Pathology and Pathogenesis (basis of the clinical picture)

- **Vessels involved:** large elastic arteries — aortic arch and its branches; the pulmonary artery may also be involved. Involvement of the major branches is **much more marked at their origin than distally**, explaining the bruits and pulse loss at vessel ostia.
- **Histology:** a **panarteritis** with inflammatory **mononuclear-cell infiltrates** and occasionally **giant cells**; marked **intimal proliferation and fibrosis**, scarring and vascularisation of the media, and **disruption/degeneration of the elastic lamina**. The **vasa vasorum** are frequently involved.
- **Consequences:** luminal **narrowing with or without thrombosis** → tissue ischaemia; weakening of the wall → **aneurysm**. Organ pathology reflects reduced blood flow through stenoses.
- **Immunopathogenesis** is uncertain; circulating immune complexes have been demonstrated but their significance is unclear.

Clinical Manifestations

TAK is a **systemic disease** with both *generalised (constitutional)* and *vascular (ischaemic)* features, classically evolving through overlapping phases:

- **Systemic / "pre-pulseless" phase:** malaise, **fever**, night sweats, **arthralgias**, anorexia and **weight loss** — may precede overt vessel involvement by months.
- **Vascular / occlusive phase:** symptoms and signs of organ ischaemia as constitutional features merge into vascular compromise.
- **Cardinal physical signs: pulses are commonly absent in involved vessels (especially the subclavian)**, an **inter-arm blood-pressure discrepancy**, **arterial bruits** (carotid, subclavian, abdominal), **carotidynia** (tenderness over the carotid arteries) and **limb claudication**.
- **Hypertension occurs in 32–93%** of patients (frequently from renal-artery stenosis) and is a major driver of **renal, cardiac and cerebral injury**.

Pattern of arterial involvement (Harrison Table 375-7) — frequency of arteriographic abnormality and resulting clinical features:

Artery	Arteriographic involvement	Clinical manifestation
Subclavian	**93%**	Arm claudication, Raynaud's phenomenon
Common carotid	58%	Visual changes, syncope, TIA, stroke

Artery	Arteriographic involvement	Clinical manifestation
Abdominal aorta	47%	Abdominal pain, nausea, vomiting
Renal	38%	**Hypertension**, renal failure
Aortic arch / root	35%	**Aortic insufficiency**, congestive heart failure
Vertebral	35%	Visual changes, dizziness
Coeliac axis	18%	Abdominal pain, nausea, vomiting
Superior mesenteric	18%	Abdominal pain, nausea, vomiting
Iliac	17%	Leg claudication
Pulmonary	10–40%	Atypical chest pain, dyspnoea
Coronary	<10%	Chest pain, myocardial infarction

- **Ophthalmic/CNS:** carotid and vertebral disease → visual changes, dizziness, syncope, TIA, stroke; **retinopathy** may be seen.
- **Cardiac:** aortic-root dilatation → **aortic regurgitation and heart failure**; coronary ostial disease → angina/MI; hypertensive heart disease.
- **Renovascular:** renal-artery stenosis → **renovascular hypertension** and renal failure.

Laboratory Findings

- **Acute-phase reactants:** elevated **ESR and/or CRP** — raised in most active cases and useful for monitoring (but neither sensitive nor specific, and may be normal in "burnt-out" disease).
- **Mild anaemia** and **elevated immunoglobulin levels**.
- **No specific autoantibody** exists; ANCA is characteristically negative — distinguishing TAK from ANCA-associated small-vessel vasculitides.

Diagnosis

- **Clinical suspicion:** the diagnosis should be **strongly suspected in a young woman who develops a decrease or absence of peripheral pulses, a discrepancy in blood pressure between the arms, or arterial bruits.**
- **Confirmatory imaging — angiography is the cornerstone.** Characteristic findings: **irregular vessel walls, stenosis, post-stenotic dilatation, aneurysm formation, occlusion, and increased collateral circulation.**
- **Whole-aorta imaging is mandatory** because lesions are widely distributed: **MR or CT arteriography** of the aorta and its major branches should be obtained to delineate the full distribution and severity. **MRI** also detects **inflammatory mural thickening** (early/active disease); **CT angiography** best shows the stenoses, occlusions and dilatations.
- **^{18}F-FDG-PET** can demonstrate large-vessel wall metabolic activity and help assess disease activity (emerging role).

- **Tissue is rarely available or necessary**; biopsy is obtained only if vascular surgery is performed, because the affected vessels are large.
- **Classification criteria (aids, not for clinical diagnosis):** the **1990 ACR criteria** (≥3 of 6 → classification): age at onset ≤40 y, limb claudication, decreased brachial pulse, **>10 mmHg inter-arm systolic BP difference**, bruit over subclavian arteries/aorta, and arteriographic abnormality. These have been updated by the **2022 ACR/EULAR classification criteria**, which formally incorporate imaging.

Differential Diagnosis

- **Giant cell arteritis (GCA):** the other large-vessel granulomatous arteritis, but affects patients **>50 years** (TAK typically **<40**); shares aortic/branch involvement and raised ESR/CRP.
- **IgG4-related disease (aortitis/periaortitis):** histologically distinguished by a **dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis**.
- **Atherosclerosis, fibromuscular dysplasia, congenital coarctation, syphilitic/infective aortitis, and connective-tissue aortopathies** (e.g., Behçet's, Cogan's) when aortic disease is present.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Aortic tree schematic (front view):** label **ascending aorta, aortic arch, brachiocephalic trunk, right & left common carotid, right & left subclavian (mark "93% — pulseless"), vertebral arteries, descending thoracic aorta, abdominal aorta, coeliac axis, superior mesenteric artery, renal arteries (mark "renovascular HTN"), iliac arteries, pulmonary artery**; shade stenosis, post-stenotic dilatation and an aneurysm to depict the lesion types.
- **Cross-section of an affected artery:** label **intimal proliferation/fibrosis, thickened scarred media with giant cells, disrupted elastic lamina, involved vasa vasorum, narrowed lumen ± thrombus** — illustrating the "panarteritis".

Clinical / Diagnostic significance

- **Four-limb BP and bilateral pulse examination with auscultation for bruits** is the single most important bedside screen; central aortic pressure may be needed when both arms are affected.
- **Whole-aorta MR/CT angiography** both confirms the diagnosis and maps lesions for management; serial imaging plus ESR/CRP guide activity monitoring.
- **Management (for context): glucocorticoids** (prednisone **40–60 mg/d**, or **~1 mg/kg/d**, then taper) are first-line; steroid-sparing/refractory options include **methotrexate (up to 25 mg/week), azathioprine, mycophenolate mofetil and TNF inhibitors** (CMDT lists TNF inhibitors as first-line adjunct); **tocilizumab** and **tofacitinib** have limited data. **Antiplatelet therapy** is advised in active disease or critical cranial/vertebrobasilar involvement.
- **Revascularisation** (surgery/angioplasty) is reserved for established critical stenoses and is best performed when **inflammation is medically controlled**.
- **Prognosis:** chronic, relapsing-remitting; overall survival ≥94% in North-American series though 5-year mortality has ranged 0–35%; death is usually from **heart failure, stroke, MI, aneurysm rupture or renal failure**.

High-yield exam pointers

- TAK = **large-vessel granulomatous vasculitis of aorta + branches**; *"pulseless disease"* of **young Asian women**.
- **Subclavian artery is the most commonly involved (93%)** → arm claudication + absent pulse.
- **Triad to suspect:** absent/diminished pulses, **inter-arm BP discrepancy**, and **arterial bruits** in a young woman.
- **Hypertension (32–93%)** is common and often **renovascular** — always measure BP carefully (may underestimate central pressure if subclavians are stenosed).
- **Raised ESR/CRP, mild anaemia, raised immunoglobulins; ANCA-negative, no specific autoantibody.**
- **Diagnosis is by imaging:** whole-aorta **MR/CT angiography** (stenosis, post-stenotic dilatation, aneurysm, occlusion, collaterals); **biopsy rarely needed**.
- **Differentiate from GCA (>50 y)** and **IgG4-related aortitis** (IgG4+ plasma cells, storiform fibrosis, obliterative phlebitis).
- **1990 ACR criteria:** ≥3 of 6 (age ≤40, claudication, ↓brachial pulse, >10 mmHg inter-arm BP difference, subclavian/aortic bruit, arteriographic abnormality).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"The Vasculitis Syndromes"* (Takayasu Arteritis: definition, epidemiology, pathology/pathogenesis, Table 375-7 frequency of arteriographic abnormalities and clinical manifestations, clinical/laboratory features, diagnosis, IgG4-related disease differential, treatment and prognosis).
- **CMDT 2026** — *"Rheumatologic, Immunologic, & Allergic Disorders"* (Takayasu arteritis: carotidynia and bedside signs, MRI/CT-angiography, 2022 ACR/EULAR classification criteria reference, and current management — corticosteroids, methotrexate/azathioprine/MMF/TNF inhibitors, antiplatelet therapy).
- **Coverage note:** The corpus (Harrison ch. on the Vasculitis Syndromes + CMDT 2026) does not enumerate the individual **1990 ACR criteria items** or the **Numano/Hata angiographic types (I–V)**; these are included as universally-accepted standard internal-medicine teaching, and the 2022 ACR/EULAR criteria are cited by CMDT only as a reference (items not listed in the text). The constitutional → vascular → fibrotic "triphasic course," the *pulseless disease/aortic arch syndrome* eponym, and the GCA age cut-off (>50 y) are standard textbook points reinforcing the sourced material.

◆ ◆ ◆

Primary Sjogren's syndrome — extraglandular manifestations

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

Definition / Introduction — Sjögren's disease (syndrome) is a prototype systemic autoimmune disorder characterised by lymphocytic infiltration of the exocrine glands producing **xerostomia** and **keratoconjunctivitis sicca**, together with profound **B-cell hyperactivity**. It occurs alone (*primary* Sjögren's) or with another rheumatic disease (*secondary* — most often rheumatoid arthritis, SLE, limited scleroderma). It predominantly affects middle-aged women (F:M 9–20:1), has a prevalence of ~0.5–1%, and carries the **highest risk of lymphoma among all autoimmune diseases**. Although the glandular sicca complex dominates, roughly **one-third of patients develop extra-glandular (systemic) manifestations**, which determine prognosis and guide treatment.

Classification of extra-glandular manifestations

Extra-glandular disease is best grouped by its **pathogenic mechanism** into four categories — *nonspecific*, *periepithelial* (lymphocytes surrounding parenchymal epithelium — Moutsopoulos' concept of **autoimmune epithelitis**), *immune-complex–mediated* (vasculitic), and *lymphoma*.

Manifestation	Approx. %	Mechanism / Remark
Fatigability / myalgias	25	Nonspecific; overlaps fibromyalgia
Arthralgias / arthritis	60	Nonspecific; **non-erosive**, may give *Jaccoud's arthropathy*
Raynaud's phenomenon	37	Nonspecific; precedes sicca in one-third
Lung involvement	14	Periepithelial; small-airway disease / lymphocytic interstitial pneumonitis
Kidney involvement	9	Periepithelial; interstitial nephritis, often asymptomatic
Liver involvement	6	Periepithelial; primary biliary cholangitis (stage I)
Small-vessel vasculitis	9	Immune-complex; purpura, urticarial lesions
Peripheral neuropathy	2	Immune-complex; sensory or sensorimotor polyneuropathy
Glomerulonephritis	2	Immune-complex; membranoproliferative
Lymphoma	6	Glandular **MALT** lymphoma most common

Nonspecific & musculoskeletal manifestations

- **Constitutional:** fatigability, low-grade fever, myalgias — frequently with a coexistent **fibromyalgia** phenotype.
- **Arthritis/arthralgia (≈60%):** the commonest systemic feature; characteristically **non-erosive**. Reducible deformities (*Jaccoud's arthropathy*) may occur, but bony erosions are absent in primary disease (their presence suggests overlapping RA).
- **Raynaud's phenomenon (≈37%):** present in a third of patients and may *precede* the sicca symptoms by years; unlike scleroderma it is usually not associated with digital ulceration.

Periepithelial (autoimmune epithelitis) manifestations

Periepithelial lymphocytic accumulation around the epithelium of parenchymal organs explains the visceral disease:

- **Lung (≈14%):** usually a dry cough, rarely dyspnoea. Pathology = peribronchial infiltrates (**bronchitis sicca**), small-airway disease and **interstitial pneumonitis** (including lymphocytic interstitial pneumonitis).
- **Kidney (≈9%): interstitial nephritis** producing hyposthenuria and renal tubular dysfunction, classically **distal (type I) renal tubular acidosis** (in up to ~20% per CMDT). Untreated acidosis can cause **nephrocalcinosis**; chronic interstitial nephritis may impair GFR.
- **Liver (≈6%):** autoimmune cholangitis / **primary biliary cholangitis (stage I)** — suggested by antimitochondrial antibodies.
- **Other exocrine epithelia:** xerotrachea, oesophageal dysmotility, atrophic gastritis, dyspareunia from genital dryness, and dry skin.

Immune-complex–mediated (vasculitic) manifestations

Driven by circulating immune complexes and **cryoglobulins**:

- **Cutaneous small-vessel vasculitis (≈9%): palpable purpura** (most typical), urticarial lesions, and skin ulceration — often with mixed **type II or III cryoglobulinaemia** and **low C4**.
- **Peripheral nervous system:** sensory or sensorimotor **polyneuropathy** and **mononeuritis multiplex**; *anti-calponin-3* antibodies have been linked to peripheral neuropathy.
- **Renal: membranoproliferative glomerulonephritis** associated with cryoglobulinaemia (distinct from the periepithelial interstitial nephritis above).
- **Central nervous system (rare):** occasionally **myelitis with anti–aquaporin-4 antibodies** (neuromyelitis optica spectrum); CMDT also notes dysautonomia.
- **Cardiovascular:** like RA and SLE, an **increased risk of cardiovascular disease**.

Lymphoma — the most feared complication

- Sjögren's carries the **highest lymphoma risk of any autoimmune disease**; lifetime incidence ≈5–10% of the cohort.
- Most are **extranodal, low-grade, marginal-zone B-cell (MALT) lymphomas**, often detected incidentally on labial salivary-gland biopsy; affected nodes are typically peripheral.
- **Risk factors (Fig. 373-2):** *clinical* — persistent **parotid/major salivary gland enlargement**, severe tongue atrophy, **palpable purpura**; *haematologic/serologic* — leukopenia, autoantibodies (RF, anti-Ro/SSA, anti-La/SSB), **low C4**, **monoclonal gammopathy**, **cryoglobulins**; *histopathologic* — **germinal-centre formation** and heavy focal lymphocytic infiltrates in salivary tissue.
- **Worse survival** with B symptoms, nodal mass **>7 cm**, and high/intermediate histologic grade. **FDG-PET/CT** helps exclude transformation when lymphoma is suspected.
- Pathogenically, chronic B-cell stimulation driven by elevated **BAFF (B-cell activating factor)** under type I/II interferon signalling, germinal-centre formation and cryoglobulin-producing clones (carrying mutations seen in B-cell malignancies) underlie the malignant evolution — this rationalises the **anti-BAFF/anti-CD20** therapeutic targets.

Treatment of primary Sjögren's

Management is twofold — **symptomatic relief of sicca** (substitution and stimulation of secretions) and **immunomodulation for systemic disease**.

Target	First-line / agents
Dry eyes	Artificial tears (hydroxypropyl methylcellulose, polyvinyl alcohol, 0.5% methylcellulose); topical **cyclosporine 0.05%** or **lifitegrast 5%**; corneal ulcer → eye patching + boric-acid ointment
Dry mouth	Water (best replacement); sugar-free gum/hard candy; **secretagogues — pilocarpine 5 mg TID** or **cevimeline 30 mg TID**; strict oral hygiene + **fluoride** to prevent caries
Arthralgia / mild arthritis	**Hydroxychloroquine 200–400 mg/day** and/or **methotrexate 0.2–0.3 mg/kg/week**
Distal RTA	Oral **sodium bicarbonate 0.5–2 mmol/kg/day** in 4 divided doses
Systemic / vasculitic disease	**Glucocorticoids** + **rituximab** (anti-CD20) — especially purpura and persistent arthritis
Refractory / emerging	Sequential **belimumab → rituximab**; **ianalumab** (anti-BAFF-R); anti-CD40L/CD40; **nipocalimab** (FcRn blocker, FDA Breakthrough 2024)
Vaginal dryness	Propionic-acid gels / lubricants

- **Avoid** drugs that worsen dryness — diuretics, antihypertensives, **anticholinergics**, antidepressants/decongestants.
- **Lymphoma** is managed per standard lymphoma protocols for the general population; low-grade localised MALT lymphoma may be watched or treated with rituximab-based therapy.
- **General principles:** there is no proven disease-modifying therapy that reverses glandular destruction, so treatment is largely organ-directed — escalate from local/symptomatic measures, to hydroxychloroquine for musculoskeletal disease, to glucocorticoids ± rituximab for organ-threatening vasculitic, neurologic, pulmonary or renal involvement. Patient-reported activity (ESSPRI) and systemic activity (ESSDAI) indices guide intensity.
- Formal management recommendations have been issued by **EULAR** and the **British Society for Rheumatology**.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Mechanism-based classification wheel:** central circle "Extra-glandular Sjögren's" with four spokes labelled **Nonspecific** (fatigue, arthralgia, Raynaud's), **Periepithelial / autoimmune epithelitis** (lung, kidney–RTA, liver–PBC), **Immune-complex / vasculitic** (purpura, cryoglobulinaemia, neuropathy, MPGN), **Lymphoma** (MALT).
- **Lymphoma risk-factor triangle (Fig. 373-2):** three sides labelled *Clinical* (parotid enlargement, tongue atrophy, palpable purpura), *Haematologic/Serologic* (leukopenia, RF/anti-Ro/anti-La, **low C4**, monoclonal gammopathy, cryoglobulins), *Histopathologic* (germinal centres, focal lymphocytic infiltrates) → apex "MALT lymphoma".

Clinical / Diagnostic significance

- Suspect primary Sjögren's when sicca is accompanied by **major salivary-gland enlargement, palpable purpura, Raynaud's, or RTA**.
- **Investigations:** Schirmer's I test (**≤5 mm/5 min**), ocular staining (lissamine green/Rose Bengal; ocular staining score ≥5 or van Bijsterveld ≥4), unstimulated whole-saliva flow **≤0.1 mL/min**, salivary-gland ultrasound, **labial minor salivary-gland biopsy (focus score ≥1)**, anti-Ro/SSA, anti-La/SSB, RF, ANA, C4, cryoglobulins and serum protein electrophoresis. The **2016 ACR–EULAR criteria** weight biopsy focal sialadenitis and anti-Ro most heavily.
- **Exclude mimics:** hepatitis C, HIV (CD8 diffuse infiltration), sarcoidosis (non-caseating granulomas), amyloidosis, **IgG4-related disease**, prior head-and-neck radiation, GVHD.
- **Monitor** persistent parotid swelling, falling C4, new monoclonal band or cryoglobulins, and B symptoms — red flags for lymphoma warranting biopsy/FDG-PET.

High-yield exam pointers

- Extra-glandular disease affects ~**1/3** of patients; classify as **nonspecific, periepithelial, immune-complex, lymphoma**.
- Arthritis is **non-erosive** (→ *Jaccoud's*); erosions imply overlap RA.
- **Distal (type I) RTA** from interstitial nephritis is the classic renal lesion → treat with oral **bicarbonate**; **MPGN** is cryoglobulin-driven.
- **Palpable purpura + low C4 + cryoglobulins** = vasculitic Sjögren's and a **lymphoma risk marker**.
- Highest lymphoma risk of any autoimmune disease; commonest = **extranodal marginal-zone (MALT)** lymphoma of salivary gland.
- Secretagogues = **pilocarpine 5 mg TID / cevimeline 30 mg TID**; both are muscarinic agonists — avoid in uncontrolled asthma/narrow-angle glaucoma.
- Systemic/vasculitic disease → **glucocorticoids + rituximab**; emerging B-cell/BAFF/FcRn agents (belimumab→rituximab, ianalumab, nipocalimab).
- **Anti–aquaporin-4 myelitis** is a rare CNS manifestation.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Sjögren's Disease" (Table 373-1 prevalence of extra-glandular manifestations; Fig. 373-2 lymphoma risk factors; Fig. 373-3 / 2016 ACR–EULAR criteria; treatment section).
- CMDT 2026 — "Sjögren Disease" (Chapter 23, Rheumatologic, Immunologic & Allergic Disorders) for current symptomatic and biologic management (topical cyclosporine 0.05%/lifitegrast 5%, ianalumab, nipocalimab) and distal RTA frequency.

◆ ◆ ◆

Familial Mediterranean fever

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Familial Mediterranean fever (FMF) is the prototype of the hereditary recurrent (periodic) fevers — a group of monogenic **autoinflammatory** diseases driven by dysregulated *innate* immunity (myeloid effector cells and germline pattern-recognition receptors) rather than by high-titre autoantibodies or antigen-specific T cells. It is characterised by recurrent, self-limited episodes of fever accompanied by **serosal (peritoneal/pleural), synovial or cutaneous inflammation**, and, if untreated, the eventual development of systemic **AA amyloidosis**. It is caused by gain-of-function mutations in the *MEFV* gene encoding **pyrin**, and is exquisitely responsive to lifelong oral colchicine.

Epidemiology and Genetics

- **Populations:** First recognised among **Armenians, Arabs, Turks, and non-Ashkenazi (North African, Iraqi) Jews**; with genetic testing now documented in Ashkenazi Jews, Italians and other Mediterranean/Middle-Eastern groups, and occasionally in those without known Mediterranean ancestry.
- **Gene:** *MEFV* on chromosome **16p13.3**; product is a **781-amino-acid, ~95-kDa protein, pyrin** (marenostrin), expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial/peritoneal fibroblasts.
- **Inheritance:** Classically **autosomal recessive**, but clear-cut clinical cases occur with only a *single* demonstrable mutation, and certain rare mutations show **dominant** inheritance. Only ~70% of clinically typical patients have two identifiable mutations *in trans* (gain-of-function with a gene-dosage effect).
- **Carrier frequency** is as high as **1:10** in affected populations — a selective advantage is postulated, with population-genetic evidence implicating **bubonic plague pandemics** in selecting for founder mutations that arose in the Middle East in Biblical times.
- A positive **family history** is elicited in only ~50% of cases (small families).
- **Genotype–phenotype:** Most severe disease-associated mutations lie in **exon 10**. **M694V homozygosity** (especially in non-Ashkenazi Jews) → earlier onset and higher frequency of arthritis, erysipeloid rash and amyloidosis. The **E148Q** variant (exon 2), common in Asian

populations, more often raises overall inflammation than causes overt FMF and may increase penetrance of an exon-10 mutation when present *in cis*.

Pathophysiology — the pyrin inflammasome

- Pyrin's N-terminal 92 amino acids form the **PYRIN domain (PYD)**, a homotypic protein-interaction motif also found in **cryopyrin (NLRP3)**.
- Via an intermediary adaptor (ASC), pyrin nucleates a macromolecular **pyrin inflammasome** that activates **caspase-1** (IL-1β–converting enzyme), driving secretion of **IL-1β and IL-18** and **gasdermin-D–mediated pyroptotic cell death**.
- Physiologically, bacterial toxins that inactivate **RhoA GTPase** (blocking cytoskeletal assembly) trigger pyrin inflammasome activation as host defence; FMF mutations are **gain-of-function**, lowering the activation threshold and producing sterile, IL-1β–driven inflammation.
- *(CMDT additionally notes deficiency of a serosal protease that normally inactivates IL-8 and complement C5a, contributing to the neutrophil-rich serositis.)*

Clinical features — the acute attack

- **Onset:** Often in early infancy; **90% have had their first attack by age 20**. In infants, fever (even febrile seizures/hyperpyrexia) may be the sole manifestation.
- **Duration:** Typical episodes last **24–72 h** (arthritis somewhat longer); frequency varies from every few days to remissions of years. Triggers include physical exertion, emotional stress and menses; **pregnancy is often associated with remission**.

Site	Manifestation
Fever	Nearly always present; abrupt, high-grade
Abdomen (>90%)	Sterile **peritonitis** — pain, guarding, rebound, absent bowel sounds, air–fluid levels; neutrophil-rich exudate at laparotomy; *ascites rare*; mimics surgical acute abdomen → "needless laparotomy"
Pleura	Unilateral, sharp, stabbing chest pain; exudative neutrophilic effusion; pleural thickening after repeated attacks
Joints	Acute **monoarthritis** of knee/ankle/hip; large sterile neutrophil-rich effusion *without* commensurate erythema/warmth; radiographic change rare; chronic hip/knee arthritis (~5% pre-colchicine); **chronic sacroiliitis can occur irrespective of HLA-B27**
Skin	**Erysipelas-like erythema** — raised, tender, on dorsum of foot/ankle/lower leg (most often in M694V homozygotes)
Muscle	Exercise-induced (non-febrile) myalgia common; rare **protracted febrile myalgia** lasting weeks
Other	Acute unilateral **scrotal** inflammation (prepubertal boys); rare pericarditis; aseptic meningitis (controversial)

- **Associations:** Increased frequency of **IgA vasculitis (Henoch-Schönlein purpura)** and **polyarteritis nodosa**; the **M694V** mutation is a risk factor for **Behçet's syndrome** and **ankylosing spondylitis**.
- **Laboratory (during attacks):** Elevated **ESR, CRP**, leukocytosis, thrombocytosis (in children), raised fibrinogen, haptoglobin and immunoglobulins; transient albuminuria/haematuria.

AA (secondary) amyloidosis — the major long-term threat

- Caused by tissue deposition of a fragment of **serum amyloid A (SAA)**, an acute-phase reactant, in **kidneys, adrenals, intestine, spleen, lung and testes**; the kidney is affected first → nephrotic-range proteinuria and progressive renal failure.
- **Suspect when proteinuria persists *between* attacks**; confirm by **renal or rectal biopsy** (Congo-red apple-green birefringence).
- **Risk factors: M694V homozygosity**, positive family history (independent of mutation status), **SAA1 genotype**, male sex, **non-compliance with colchicine/IL-1 inhibitor**, and national origin (amyloid risk parallels infant-mortality rate).
- Now largely *preventable* with adherent colchicine prophylaxis.

The hereditary recurrent fevers — differentiation (exam table)

Feature	FMF	TRAPS	HIDS / MKD	CAPS (FCAS / MWS / NOMID)
Gene / protein	*MEFV* / **pyrin**	*TNFRSF1A* / **p55 TNF receptor**	*MVK* / **mevalonate kinase**	*NLRP3* / **cryopyrin**
Inheritance	Recessive (or dominant)	Dominant	Recessive	Dominant (NOMID often *de novo*/mosaic)
Attack length	**1–3 days**	Often **>7 days**	3–7 days	Minutes–3 days (NOMID continuous)
Distinctive clue	Erysipeloid erythema; serositis	Migratory myalgia + overlying erythema; **periorbital oedema/conjunctivitis**	Cervical adenopathy, oral ulcers, palm/sole rash; **↑urinary mevalonate**	Cold-induced urticarial rash (FCAS); **sensorineural deafness** (MWS); aseptic meningitis (NOMID)
Treatment	**Colchicine**; IL-1 inhibitors if refractory	Glucocorticoids, IL-1 inhibitors, etanercept	IL-1 inhibitors; NSAIDs for fever	IL-1 inhibitors (anakinra/canakinumab/rilonacept)

(TRAPS = TNF-receptor-associated periodic syndrome / familial Hibernian fever; HIDS/MKD = hyperimmunoglobulinaemia D / mevalonate kinase deficiency; CAPS = cryopyrin-associated periodic syndromes.)

Diagnosis

- **Largely clinical** in experienced hands; validated clinical criteria sets perform well where pre-test probability is high. Core features: recurrent short (<72 h) febrile serositis episodes in an at-risk ethnic group, family history, and a **therapeutic response to colchicine**.
- **Genetic testing** (*MEFV* sequencing) is a useful adjunct in ambiguous cases; the expert-curated **Infevers** registry catalogues pathogenic mutations vs benign polymorphisms. Note: a single or no mutation does **not** exclude FMF.
- **Differential diagnosis:** other hereditary recurrent fevers; **PFAPA** (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis — commonest periodic fever of childhood); systemic-onset JIA / adult Still's disease; porphyria; **hereditary angio-oedema**; inflammatory bowel disease; and gynaecological disorders in women.

Treatment

- **Daily oral colchicine is first-line** — it reduces attack frequency/severity **and prevents amyloidosis** in compliant patients; intermittent dosing at attack onset is *inferior* and unproven for amyloid prevention.
- **Adult dose 1.2–1.8 mg/day** (CMDT: 0.6 mg 2–3 times daily): substantial benefit in ~two-thirds, some improvement in **>90%**; children need lower (non-weight-proportional) doses.
- **Side effects:** bloating, cramps, **lactose intolerance, diarrhoea** — minimised by low starting dose, dose-splitting, simethicone and dairy avoidance. In **renal insufficiency/elderly**, watch for **colchicine myoneuropathy** (proximal weakness, raised CK).
- **Cautions: never give IV colchicine to a patient already on oral colchicine** (fatal toxicity); **cyclosporine** blocks hepatic colchicine excretion via the **MDR1** transporter (toxicity post renal transplant). Colchicine is **continued in pregnancy** (FMF-attack miscarriage risk outweighs fetal risk) though it may marginally raise trisomy-21 risk if taken at conception.
- **Colchicine-resistant/intolerant disease → IL-1 inhibitors: canakinumab** (anti-IL-1β monoclonal, monthly SC; FDA-approved for FMF on phase-3 data), **rilonacept** (IL-1 receptor fusion protein, weekly SC), **anakinra** (recombinant IL-1 receptor antagonist, daily SC; may also reduce established amyloid). Bone-marrow transplantation has an unacceptable risk–benefit ratio.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pyrin inflammasome cascade:** *MEFV* mutation → mutant **pyrin (PYD)** + adaptor **ASC** → assembled **pyrin inflammasome** → **caspase-1** activation → **IL-1β / IL-18** secretion + **gasdermin-D** → **pyroptosis** → recurrent sterile serositis/fever. Side-label the trigger: bacterial toxin → **RhoA GTPase inactivation**. Show colchicine and anti-IL-1 agents (anakinra/canakinumab/rilonacept) as the therapeutic blockade points.
- **"Spot map" of FMF organ involvement:** stick-figure with labels — *Serosa* (peritonitis, pleurisy), *Joint* (acute monoarthritis – knee/ankle), *Skin* (erysipeloid erythema – dorsum of foot), *Scrotum* (acute scrotal inflammation), and *Kidney → AA amyloidosis (proteinuria)* as the long-term complication.

Clinical / Diagnostic significance

- Consider FMF in any patient of Mediterranean/Middle-Eastern origin with **recurrent self-limited fever + serositis** and unexplained acute abdomens — early diagnosis prevents repeated **negative laparotomies**.
- **Persistent inter-attack proteinuria mandates work-up for AA amyloidosis** (renal/rectal biopsy); it is the leading cause of morbidity/mortality and is preventable.
- A **colchicine therapeutic trial** can be diagnostically confirmatory when genetics are equivocal.
- Lifelong adherence is the single most important determinant of outcome; counsel that colchicine is continued through pregnancy.

High-yield exam pointers

- *MEFV* gene (16p13.3) → **pyrin** → gain-of-function → over-active **pyrin inflammasome** → **IL-1β**.

- Autosomal **recessive** (mostly); carrier frequency up to **1:10**; **90% present before age 20**.
- Attack = **24–72 h** of fever + **sterile peritonitis/pleuritis**, monoarthritis, **erysipeloid erythema**; resolves spontaneously.
- **M694V homozygote** = severe phenotype → arthritis, rash, **amyloidosis**.
- Main complication = **AA amyloidosis** (SAA deposition, renal-first, nephrotic proteinuria) — preventable by colchicine.
- **Colchicine 1.2–1.8 mg/day** is first-line and *amyloid-protective*; **IL-1 inhibitors** (canakinumab/anakinra/rilonacept) for refractory cases.
- **Never give IV colchicine to a patient on oral colchicine.**
- Differential: TRAPS, HIDS/MKD, CAPS, PFAPA, adult Still's, hereditary angio-oedema.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases" (Kastner); and "Amyloidosis" (AA amyloidosis / SAA, colchicine).
- **CMDT 2026** — "Gastrointestinal Disorders" (Familial Mediterranean fever; ascites differential) and "Amyloidosis" management note.

◆ ◆ ◆

Fibromyalgia

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

Definition / Introduction — Fibromyalgia (FM) is characterised by **chronic widespread musculoskeletal pain and tenderness**. Although defined primarily as a *pain syndrome*, patients also commonly report associated **neuropsychological symptoms** — fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. Available evidence implicates the **central nervous system (CNS)** as key to maintaining the pain and other core symptoms. FM belongs to a group of **chronic primary / chronic overlapping pain conditions** and carries substantial negative consequences for physical and social functioning.

Epidemiology and risk factors

- **Worldwide prevalence ~2%** — approximately **4% in women** and **<1% in men**; data are similar across world regions and socioeconomic classes.
- **Sex ratio:** in clinical settings women >> men at **~8:1**; in population studies the ratio is closer to **3:1** (subjective criteria applied to populations raise prevalence and shift the sex ratio).
- Markedly higher in **rheumatic disease** — up to **30%** of patients with rheumatoid arthritis or SLE have comorbid FM; FM occurs in **~10–30%** of patients with degenerative or inflammatory rheumatic disorders (these act as peripheral pain generators).
- **Additional risk factors:** sleep disturbances, physical inactivity, and overweight or obesity.

Clinical manifestations

- **Pain and tenderness:** patients classically report *"pain all over."* Widespread pain is operationalised as being present **above and below the waist, on both sides of the body, and involving the axial skeleton** (neck, back, or chest). The pain is poorly localised, difficult to ignore, severe, and reduces functional capacity.
- **Duration:** pain present **most of the day on most days for at least 3 months**.
- **Evoked pain sensitivity (hyperalgesia/allodynia):** elevated sensitivity may be detected clinically by pain from a **blood-pressure cuff** or **skin-roll tenderness**. Formal **tender-point examination** uses the thumbnail to exert ~**4 kg/m²** pressure (the amount producing blanching of the thumbnail tip) over defined musculotendinous sites; the older **ACR criteria required 11 of 18 tender points**. Tenderness is a continuous variable, so a strict categorical threshold is not essential.
- **Peripheral pain generators / triggers:** arthritis, bursitis, tendinitis, neuropathies; more subtle ones include **joint hypermobility** and **scoliosis**. Myalgias may be triggered by infectious, metabolic, or psychiatric conditions.
- **Neuropsychological symptoms:** fatigue (highly prevalent), stiffness, **non-restorative sleep** (difficulty falling/staying asleep, early-morning awakening, waking unrefreshed; may include **restless legs syndrome**, sleep-disordered breathing, frank **sleep apnea**), and **cognitive dysfunction** ("fibro-fog" — impaired attention/concentration, word-retrieval difficulty, short-term memory loss with age-appropriate processing speed). **Lifetime prevalence of mood disorders approaches 80%** — screen for depression by querying **depressed mood and anhedonia** (depression is neither necessary nor sufficient for diagnosis).
- **Overlapping syndromes (chronic overlapping pain conditions):** myalgic encephalitis/chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes.
- **Psychosocial:** onset and exacerbation often during **perceived stress**; high prevalence of prior interpersonal violence — consider **PTSD**.

Diagnostic criteria (2016, after Wolfe et al.)

The newer criteria **eliminate tender-point counting** and rely on patient-reported widespread pain and symptom burden, using the **Widespread Pain Index (WPI, 0–19)** and **Symptom Severity Score (SSS, 0–12)**.

Component	Detail
WPI (0–19)	Number of body regions with pain/tenderness over the past week
SSS (0–12)	Fatigue + trouble thinking/remembering + waking unrefreshed (each 0–3); plus abdominal pain/cramps, depression, headache over 6 months (each 0/1)
Threshold	**WPI ≥7 and SSS ≥5** *OR* **WPI 4–6 and SSS ≥9**
Generalised pain	Pain in **≥4 of 5 regions** (jaw, chest, and abdomen not counted)
Chronicity	Symptoms present at a similar level for **≥3 months**

Differential diagnosis and investigations

Because musculoskeletal pain is so common, the differential is broad; inflammatory causes are identifiable by specific history, examination, and laboratory/radiographic tests.

Category	Conditions to exclude
Inflammatory	Polymyalgia rheumatica; inflammatory arthritis (RA, spondyloarthritides); connective tissue disease (SLE, Sjögren's)
Infectious	Hepatitis C, HIV, Lyme disease, parvovirus B19, Epstein-Barr virus
Non-inflammatory	Degenerative joint/spine/disk disease; myofascial pain syndromes; bursitis, tendinitis, repetitive strain injuries
Endocrine	Hypo-/hyperthyroidism, hyperparathyroidism
Neurologic	Multiple sclerosis, neuropathic pain syndromes
Psychiatric	Major depressive disorder
Drugs	Statins, aromatase inhibitors

- **Routine labs and radiographs are normal** in uncomplicated FM; testing aims to identify alternative diagnoses, pain generators, or comorbidities.
- **Routine screen:** ESR or CRP, CBC, TSH.
- **Guided by history/examination:** complete metabolic panel, ANA, anti-SSA/anti-SSB, rheumatoid factor and anti-CCP, CPK, viral (hepatitis C, HIV) and bacterial (Lyme) serologies, spine/joint radiographs.
- Use radiography **very sparingly** (only for suspected inflammatory arthritis); **avoid repeat testing**, and particularly **discourage MRI of the spine** unless there are features of inflammatory spine disease or neurologic symptoms.

Pathophysiology and genetics

- **Polygenic vulnerability** — multiple genes in pathways controlling **pain and stress responses**; notably genes for **metabolism, transport, and receptors of serotonin and other monoamines**, shared with mood disorders and other chronic pain conditions.
- **Central pain amplification:** psychophysical testing shows **altered sensory afferent pain processing** and **impaired descending noxious inhibitory control**, producing **hyperalgesia and allodynia**. Functional MRI demonstrates activation of brain pain regions to stimuli that are innocuous in healthy controls.
- Pain perception is modulated by **emotional and cognitive factors** (catastrophising, perceived loss of control) — the rationale for cognitive-behavioural treatment.
- Some patients have a **small-fibre neuropathy**; early reports suggest a possible **autoimmune** contribution and altered peripheral-blood gene/metabolic signatures (not yet diagnostic).

Treatment

Optimal management requires prompt diagnosis, assessment of pain/function/psychosocial context, patient education, and a goal of **improved function and quality of life rather than elimination of pain**. Illness behaviours (e.g., frequent visits) are discouraged.

Non-pharmacologic (first-line):

- **Physical conditioning / aerobic exercise** — the most consistently helpful strategy; begin at low intensity and advance slowly. Physically inactive patients do best with **supervised or water-based** programs; add **strength training** after aerobic goals are met.
- **FDA-approved devices:** a **laser therapy** device and a **TENS** device — an RCT showed TENS reduces movement-evoked pain and fatigue.
- **Meditative movement therapies** — qigong, yoga, Tai Chi; also consider acupuncture and hydrotherapy.
- **Cognitive-behavioural strategies** to improve sleep hygiene and reduce illness behaviour.

Pharmacologic — target **afferent or descending pain pathways**; use **single agents that cover multiple symptom domains**.

Drug class	Examples	Best symptom target
Muscle relaxant	**Cyclobenzaprine**	Pain + sleep disturbance
Sedating tricyclic antidepressant	**Amitriptyline**	Pain + sleep disturbance
α2-δ ligands	**Gabapentin, Pregabalin**	Pain + sleep disturbance
SNRIs	**Duloxetine, Milnacipran**	Pain + fatigue/anxiety/depression

- **Treat any comorbid triggering condition.** Glucocorticoids and NSAIDs help inflammatory triggers but are **not effective against FM symptoms**.
- **Avoid strong opioids** — no demonstrated efficacy and adverse effects worsen both symptoms and function. **Tramadol** (an opioid with mild serotonin-noradrenaline reuptake inhibitor activity) shows some efficacy but is **generally discouraged** because of opioid-related adverse effects.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Body manikin for the Widespread Pain Index** — front-and-back human outline with the 19 WPI sites labelled: right/left jaw, neck, upper back, lower back, chest, right/left shoulder, right/left upper arm, right/left lower arm, right/left hip (buttock), right/left upper leg, right/left lower leg, plus abdomen — and the **5 generalised-pain regions** (Region 1 upper-left, Region 2 upper-right, Region 3 lower-left, Region 4 lower-right, Region 5 axial). Annotate threshold: **WPI ≥7 + SSS ≥5 OR WPI 4–6 + SSS ≥9; ≥4/5 regions; ≥3 months.**
- **Schematic of central pain amplification** — labels: *peripheral pain generator → increased ascending afferent input → impaired descending noxious inhibitory control → CNS amplification → hyperalgesia & allodynia*, with side-boxes for *genetic/serotonin-monoamine vulnerability* and *stress / catastrophising*.

Clinical / Diagnostic significance

- FM is a **clinical diagnosis of central sensitisation**, not a diagnosis of exclusion requiring extensive imaging — over-investigation reinforces illness behaviour.

- **Recognise FM superimposed on rheumatic disease** (RA, SLE): when pain extends beyond what the inflammatory disease explains, with neuropsychological symptoms and diffuse tenderness, treat **central pain** rather than escalating anti-inflammatory therapy.
- **Screen for and treat mood disorders, non-restorative sleep, and sleep apnea** — they drive disability and respond to dual-action agents.
- A **multimodal plan (education + exercise + a single rationally chosen drug + CBT)** outperforms drug monotherapy and is the examiner-favoured management answer.

High-yield exam pointers

- FM = **chronic widespread pain + tenderness ≥3 months**, with fatigue, unrefreshing sleep, cognitive ("fibro-fog"), anxiety/depression; a **CNS central-sensitisation** disorder.
- Prevalence **~2%** (≈4% women, <1% men); clinical F:M **~8:1**; up to **30%** comorbidity with RA/SLE.
- **2016 criteria** use **WPI (0–19) + SSS (0–12)**; **tender points (11/18, 4 kg/m²) are the OLD ACR criteria**.
- Mechanism: **impaired descending inhibition + augmented afferent processing → hyperalgesia and allodynia**; serotonin/monoamine genes; some have **small-fibre neuropathy**.
- **Routine labs normal**; order ESR/CRP, CBC, TSH; avoid repeat testing and spine MRI.
- First-line is **non-pharmacologic — aerobic exercise is the single most helpful intervention**; TENS and a laser device are FDA-approved.
- Effective drugs: **pregabalin/gabapentin, duloxetine/milnacipran, amitriptyline, cyclobenzaprine.**
- **Avoid strong opioids; tramadol discouraged; glucocorticoids/NSAIDs ineffective for FM pain.**

SOURCE & COVERAGE

Harrison 22e — Ch 385 "Fibromyalgia" (L.J. Crofford). 2016 diagnostic criteria per Fig. 385-1 (Wolfe et al., *Semin Arthritis Rheum* 2016); differential diagnosis from Table 385-1; investigations from Table 385-2; drug classes from Table 385-3.

Coverage note: The plain-text extract reproduces the *names/classes* of effective drugs (Table 385-3) but not their **doses**; specific milligram regimens (e.g., pregabalin 300–450 mg/day, duloxetine 60 mg/day, milnacipran 50 mg BID, low-dose amitriptyline at night) and the statement that **pregabalin, duloxetine and milnacipran are the three FDA-approved agents for FM** are standard, universally accepted internal medicine added for completeness and are not verbatim in the provided chapter text. The WPI/SSS scoring breakdown is drawn from Fig. 385-1.

◆ ◆ ◆

Gout

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

Definition / Introduction — Gout is a hyperuricemic metabolic disorder typically manifesting as **episodic inflammatory arthritis** with disabling pain, most often in middle-aged to elderly men and postmenopausal women. It arises from an **increased body pool of urate** due to chronic hyperuricemia, leading to supersaturation and crystallisation of **monosodium urate (MSU)** within joints and connective tissue, with subsequent inflammatory reactions to the crystals. Although chronic hyperuricemia is a prerequisite, only a minority of hyperuricemic individuals develop gout; additional pathophysiologic factors govern crystallisation and the inflammatory response. Humans are the only mammals to develop gout spontaneously, owing to evolutionary species-wide **loss of uricase** (which converts urate to highly soluble allantoin).

Urate metabolism and pathogenesis

- At physiologic pH, uric acid exists largely as **urate**, its ionised form, reflecting its weak acidity (**pKa 5.8**). Systemic urate reflects a balance of dietary intake, endogenous synthesis, and excretion.
- Supersaturation threshold: serum urate **>~6.85 mg/dL** favours MSU crystallisation, crystal growth, and tissue deposition.
- **Overproduction vs under-excretion** — hyperuricemia arises predominantly from **impaired renal urate excretion (90%)** or, less commonly, **overproduction (10%)**, with many cases involving both.
- **Renal handling**: ~two-thirds of daily urate is eliminated renally, one-third via the GI tract. In the proximal tubule, apical reabsorption is **sodium-dependent** via **URAT1** and **OAT10**; basolateral efflux is via the **GLUT9** transporter (the target of anti-uricosurics like *pyrazinoate (PZA)* and *nicotinate*). Intestinal urate efflux occurs through **ABCG2**, followed by degradation by gut bacteria (**intestinal uricolysis**).
- **Crystal-induced inflammation**: triggered crystal shedding from synovial tophi → phagocytosis of MSU by neutrophils; activation of resident synovial macrophages, mast cells, and the **NLRP3 inflammasome** → generation of **pro-IL-1 / IL-1β**, plus IL-6, IL-8, and TNF-α. Neutrophils mount a **respiratory burst** releasing lysosomal enzymes, superoxide anion, **leukotriene B4**, and IL-1.
- Untreated, gout progresses to **chronic gouty arthritis** with low-grade persistent synovitis, erosive deformities, and **tophi** (MSU deposits surrounded by granulomatous inflammation in proteoglycan-rich joints and tendons).

Etiology / classification of hyperuricemia

Mechanism	Causes (per Harrison)
Under-excretion (~90%)	Idiopathic; CKD/renal insufficiency; diuretics (thiazide, loop); low-dose aspirin; insulin-resistance syndrome
Overproduction (~10%)	Increased cell turnover with purine salvage — hematologic malignancies, psoriasis; chemotherapy; tissue hypoxia

Mechanism	Causes (per Harrison)
Inherited metabolic (subset of overproduction)	**PRPP synthetase superactivity** (X-linked) → ↑PRPP, purine nucleotides, urate; **HPRT deficiency** — *Lesch-Nyhan syndrome* and variants (X-linked)

- *PRPP synthetase overactivity*: accelerated production of PRPP, purine nucleotides, and urate → gout and urate nephrolithiasis.
- *HPRT deficiency*: hypoxanthine cannot be recycled and is converted exclusively to urate; reduced IMP/GMP further drives hyperuricemia via loss of feedback inhibition of de-novo purine synthesis. The HPRT gene is on the **X chromosome** (>250 described mutations); homozygous males are affected, carrier (esp. postmenopausal) females may develop gout/stones. **Hyperuricemia in prepubertal boys** should prompt consideration of these enzyme defects.
- **Modifiable risk factors**: obesity, Western diet, alcohol, fructose-rich foods/beverages, sedentary lifestyle, and diuretics.
- **Comorbidity cluster** (part of the insulin-resistance syndrome): obesity, hypertension, type 2 diabetes, myocardial infarction, stroke, CKD, and urate nephrolithiasis.

Clinical manifestations and stages

- **Acute gout flare**: usually **monoarticular** initially. The **1st metatarsophalangeal joint (podagra)** is involved in **70–90%** of cases, followed by tarsal joints, ankles, and knees; finger/wrist/elbow involvement is later (elderly, advanced disease). Oligo- and polyarticular flares develop over time.
- Flares characteristically begin at **night to early morning** and are among the most painful human conditions: the joint becomes warm, red, tender, and swollen, often mimicking cellulitis (**pseudocellulitis**). Untreated flares subside spontaneously within **1–2 weeks**.
- **Intercritical gout**: symptom-free intervals of varying length between flares.
- **Triggers**: purine-rich food, alcohol, diuretic use, **initiation of urate-lowering therapy (ULT)**, local trauma, and medical illness (congestive heart failure, respiratory/hypoxic conditions).
- **Chronic gouty arthritis** (after years of untreated flares): ongoing synovitis, **subcutaneous tophi**, deformity, and bony destruction; rarely gout manifests only as tophi or only as chronic arthritis.
- **Women** account for only **5–20%** of gout patients — usually postmenopausal/elderly, often with OA, hypertension, mild renal insufficiency, and diuretic use; premenopausal gout is rare.

Diagnosis

- **Definitive** = needle aspiration of joint or tophus with **polarising light microscopy**: MSU crystals are **needle/rod-shaped**, seen both intracellularly and extracellularly during flares, showing **strong negative birefringence** under compensated polarised light.
- **Synovial fluid**: cloudy/inflammatory with leukocytes typically **5000–75,000/µL**; may be thick, pasty, chalky. Always **Gram-stain and culture** to exclude septic arthritis, which can coexist with crystals. MSU crystals are demonstrable in the 1st MTP and clinically quiet knees, so **inter-critical arthrocentesis** is diagnostically useful.
- **Serum urate**: can be normal or low *during* an acute flare (inflammatory cytokines, e.g. IL-6, are uricosuric and lower urate ~2 mg/dL) — so seek **historical or post-flare** values; urate is almost

always elevated at some point. Baseline workup: serum creatinine, LFTs, hemoglobin, WBC, **HbA1c**, and serum lipids (comorbidity screen and treatment monitoring).

- **Imaging**: musculoskeletal ultrasound shows the **double-contour sign** over articular cartilage (MSU deposition); **dual-energy CT** identifies MSU by chemical composition. Plain radiographs in advanced tophaceous gout show **cystic changes, well-defined erosions with sclerotic margins and overhanging bony edges**, and soft-tissue masses (absent in early disease).

Management

A. Acute flare — mainstay is early anti-inflammatory therapy (ice and rest are adjuncts); choice depends on comorbidities, concurrent drugs, and prior response.

Drug	Regimen (per Harrison)	Key caution
Colchicine	Low-dose: **1.2 mg** at first sign, then **0.6 mg in 1 h**, with subsequent-day dosing by response	Eliminated via **P-glycoprotein (MDR1)** and **CYP3A4**; reduce dose in renal disease, hepatorenal impairment, or with inhibitors (*clarithromycin, tacrolimus*)
NSAIDs	Indomethacin 25–50 mg tid; naproxen 500 mg bid; ibuprofen 800 mg tid; celecoxib 800 mg then 400 mg at 12 h, then 400 mg bid	Avoid in significant comorbidity (renal/GI/cardiac)
Glucocorticoids	Prednisone 30–50 mg/d initial, tapered; IM injection; **intra-articular** for one/few joints	Effective even in polyarticular gout
IL-1β blockade	**Anakinra** or **canakinumab**	When other options contraindicated or failed

B. Urate-lowering therapy (ULT) — corrects the central cause (chronic hyperuricemia); usually lifelong. **Target serum urate <5–6 mg/dL (300–360 µmol/L)**, a sub-saturation point, to prevent flares and dissolve tophi.

- **Indications**: ≥2 flares/year, severe/prolonged flares, or patient commitment; *always* if subcutaneous tophi, chronic gouty arthritis, or known uric-acid nephrolithiasis.
- **Allopurinol** (xanthine oxidase inhibitor) — **first-line**; single morning dose starting **100 mg/day or less**, titrating up to **800 mg/day**. In CKD start lower (e.g. **50 mg/day if eGFR <30 mL/min**) and titrate slowly. Risk of **SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis)** — risk factors are CKD, higher initial dose, and **HLA-B*5801 carriage**. Screen for **HLA-B*5801** before starting in Southeast Asian (except Japanese descent), Pacific Islander/Native Hawaiian, and Black patients; if positive, use an alternative agent. Mild cutaneous reactions in ~2%.
- **Febuxostat** (xanthine oxidase inhibitor) — hepatic metabolism (glucuronidation/oxidation), **no dose adjustment in moderate–severe CKD**; usable in HLA-B*5801 carriers.
- **Uricosurics — probenecid** (second-line): 250 mg bid up to 3 g/day; needs good renal function (ineffective if creatinine >2 mg/dL [177 µmol/L]). *Benzbromarone* (not in the US) is more effective in CKD.
- **Pegloticase** — pegylated uricase for refractory/intolerant patients; given with **methotrexate** to reduce immunogenicity (which causes loss of efficacy and infusion reactions).

- **Comorbidity drugs that also lower urate**: losartan, amlodipine, fenofibrate, and **SGLT2 inhibitors** (added cardiometabolic-renal benefit).
- **Flare prophylaxis at ULT initiation**: do not start ULT during an active flare; begin in the resolution phase with **colchicine 0.6 mg once–twice daily or naproxen 250 mg bid**, continued until normouricemic and flare-free for **3–6 months** or tophi resolve. Rapid urate lowering shedding MSU from tophi causes paradoxical flares.

Differential — Pseudogout (CPPD) vs Gout

Feature	Gout (MSU)	Pseudogout / CPPD
Crystal	Needle/rod-shaped, **strongly negatively birefringent**	Rhomboid/rod-shaped, **weakly positively or non-birefringent**
Typical joint	1st MTP (podagra), tarsus, ankle, knee	**Knee** (commonest), then wrist; podagra rarely
Radiograph clue	Erosions with overhanging edges, tophi	**Chondrocalcinosis** (linear/punctate cartilage calcification)
Key associations	Insulin-resistance syndrome, CKD, diuretics	Aging, OA, **hyperparathyroidism, hemochromatosis, hypophosphatasia, hypomagnesemia**; *ANKH* gene

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis-and-targets schematic (Fig. 384-1):** boxes/arrows — *Risk factors* (obesity/insulin resistance, diet/alcohol, genes, diuretics & low-dose aspirin) → **Chronic hyperuricemia / increased urate pool** → *SU >~6.85 mg/dL* → **MSU crystallisation, crystal growth, tissue deposition** → **Recurrent acute crystal-induced flares** → **Chronic gouty arthritis (tophi)**. Annotate two therapeutic targets: **Urate-lowering therapy** (allopurinol, febuxostat, probenecid, uricase; target <5–6 mg/dL) acting on the urate pool, and **Anti-inflammatory therapy** (NSAIDs, colchicine, glucocorticoids) acting on the flare. Labels: *Risk factors, Chronic hyperuricemia, MSU crystallisation/deposition, Acute flare, Chronic tophaceous gout, ULT target <5–6 mg/dL, Anti-inflammatory therapy.*
- **MSU crystal under compensated polarised light:** draw **needle-shaped crystal inside a neutrophil**; label *intracellular MSU crystal, needle-shaped, strongly negative birefringence, leukocyte 5000–75,000/μL.*

Clinical / Diagnostic significance

- Crystal-proven diagnosis (synovial fluid microscopy) is the gold standard and simultaneously **excludes septic arthritis**, which may coexist — never assume crystals exclude infection.
- Serum urate is unreliable *during* a flare; use historical/post-flare values for diagnosis and as the **ULT target (<5–6 mg/dL)**.
- Treat-to-target ULT dissolves tophi and prevents flares but must be paired with **flare prophylaxis** and started outside active flares.

- Gout is a marker of **cardiometabolic-renal disease** — screen for and manage obesity, hypertension, diabetes, dyslipidemia, and CKD; favour agents with dual benefit (losartan, fenofibrate, SGLT2i).
- **HLA-B*5801 pharmacogenomic screening** before allopurinol in high-risk ethnicities prevents life-threatening SCARs.

High-yield exam pointers

- Hyperuricemia = **90% under-excretion, 10% overproduction**; supersaturation threshold **~6.85 mg/dL**; urate pKa **5.8**.
- Renal transporters: reabsorption via **URAT1/OAT10** (apical, Na-dependent), efflux via **GLUT9**; gut efflux via **ABCG2**.
- **NLRP3 inflammasome → IL-1β** drives the acute flare (rationale for anakinra/canakinumab).
- **Podagra (1st MTP)** in **70–90%**; flares nocturnal, self-limited in **1–2 weeks**; intercritical periods between attacks.
- Crystals: **needle-shaped, strongly negatively birefringent**, intra- and extracellular; synovial WBC **5000–75,000/μL**.
- **Allopurinol first-line** (start 100 mg/d, up to 800 mg/d; 50 mg/d if eGFR <30); **febuxostat** safe in CKD and HLA-B*5801 carriers.
- Lesch-Nyhan = **HPRT deficiency** (X-linked); **PRPP synthetase superactivity** = X-linked overproduction.
- ULT prophylaxis: **colchicine 0.6 mg od–bid** continued until urate-normal and flare-free **3–6 months** / tophi resolve.
- **Pseudogout** = CPPD, knee, weakly positive birefringence, chondrocalcinosis; check Ca/PO4/Mg/iron in patients <50 y.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 384 "Gout and Other Crystal-Associated Arthropathies" (Hyon K. Choi). Coverage note: All specifics above (drug doses, transporters, crystal morphology, HLA-B*5801, targets) are taken from this chapter; the gout topic is fully covered. The CPPD/pseudogout differential is drawn from the same chapter as supporting context for the differential diagnosis.

◆ ◆ ◆

Granulomatosis with polyangiitis

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

Definition / Introduction — Granulomatosis with polyangiitis (GPA, formerly *Wegener's granulomatosis*) is a distinct clinicopathologic entity characterised by **necrotising granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis**, with variable disseminated small-vessel vasculitis involving both small arteries and veins. It is one of the three **antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides** (with microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis) and is strongly linked to **cytoplasmic ANCA against proteinase-3 (PR3-ANCA/c-ANCA)**. Untreated generalised disease is almost uniformly fatal within ~1 year.

Epidemiology & nosology

- **Prevalence ~3 per 100,000** (Harrison); estimated incidence ~12 cases per million per year (CMDT). Extremely rare in Black compared with White patients.
- **Male : female = 1:1**; mean age of onset **40–60 years** (4th–5th decade), but ~15% of patients are <19 years; onset before adolescence is rare.
- Belongs to the **ANCA-associated vasculitides (AAV)** — small-vessel vasculitis group. Distinguished from microscopic polyangiitis by **granulomatous inflammation and upper-airway/pulmonary-nodular disease**.
- Classification frameworks: the **1992/2012 Chapel Hill Consensus Conference nomenclature** (renamed Wegener's → GPA) and the **2022 ACR/EULAR classification criteria** (DCVAS) used to classify, not diagnose.

Pathology & pathogenesis

- **Histopathologic triad of hallmarks:** (1) **necrotising vasculitis** of small arteries and veins; (2) **granuloma formation** (intra- or extravascular) — palisading histiocytes and giant cells around *geographic necrosis*; (3) **pauci-immune crescentic glomerulonephritis**.
- **Renal lesion:** earliest is a focal, segmental glomerulitis evolving into **rapidly progressive crescentic GN**; immunofluorescence shows scant immunoglobulin/complement — *pauci-immune* — differentiating it from immune-complex and anti-GBM disease. Granulomas are *rarely* seen on renal biopsy.
- **Lung:** multiple, bilateral, nodular or **cavitary** infiltrates; biopsy reveals necrotising granulomatous vasculitis (highest diagnostic yield, ideally thoracoscopic).
- **Immunopathogenesis:** aberrant **TH1-type** cell-mediated response (↑IFN-γ, ↑TNF-α, ↑IL-12) to an airway antigen; suggested role of **ANCA** — when neutrophils/monocytes are primed by TNF-α/IL-1, PR3 and myeloperoxidase translocate to the cell surface, bind circulating ANCA, and trigger **degranulation, reactive-oxygen-species release, and endothelial injury**. Chronic nasal carriage of *Staphylococcus aureus* is associated with higher relapse rates (causal role unproven).

ANCA serology

Feature	c-ANCA (PR3-ANCA)	p-ANCA (MPO-ANCA)
Antigen	**Proteinase-3** (29-kDa serine proteinase, azurophilic granule)	**Myeloperoxidase**
Immunofluorescence	Diffuse granular **cytoplasmic** staining	**Perinuclear** staining
Association in GPA	**>90% of active GPA**; specificity >90%	~10–25% of classic GPA
Caveats	Sensitivity falls to ~60–70% in inactive disease; up to **20% of GPA are ANCA-negative** ("limited"/sinonasal disease)	Predominant in microscopic polyangiitis & EGPA

- Positive immunofluorescence should be **confirmed by antigen-specific enzyme immunoassay** for anti-PR3 or anti-MPO.
- **ANCA titres correlate poorly with disease activity** — a rising titre alone is *not* a harbinger of relapse (only ~43% relapse within 1 year of an ANCA rise) and should **not** by itself trigger escalation of immunosuppression.

Clinical manifestations (frequencies through disease course)

- **Upper airway (~95%):** paranasal sinus pain/drainage, purulent or bloody nasal discharge, nasal mucosal ulceration → nasal septal perforation → ***saddle-nose deformity***; serous otitis media (eustachian blockage); **subglottic stenosis (~16%)** causing airway obstruction.
- **Lung (85–90%):** cough, haemoptysis, dyspnoea, pleuritic pain; up to 30% asymptomatic; endobronchial disease with atelectasis; **diffuse alveolar haemorrhage** (severe).
- **Renal (~77%):** glomerulitis with proteinuria, haematuria, **red-cell casts** → rapidly progressive renal failure if untreated; dominates prognosis.
- **Eye (~52%):** conjunctivitis, episcleritis, **scleritis**, granulomatous sclerouveitis, **retro-orbital mass** → **proptosis** (orbital pseudotumour).
- **Skin (~46%):** palpable purpura, papules, vesicles, ulcers, subcutaneous nodules.
- **Nervous system (~23%): mononeuritis multiplex**, cranial neuritis; rarely cerebral vasculitis/granuloma.
- **Cardiac (~8%):** pericarditis, coronary vasculitis, rarely cardiomyopathy.
- **Constitutional:** fever, malaise, arthralgia, anorexia, weight loss; **migratory oligoarthritis** of large joints. *Newly acquired hypertension is rare* (unlike PAN). Increased risk of **venous thromboembolism (DVT/PE)**.

Investigations & diagnosis

- **Labs:** elevated **ESR/CRP**, normochromic anaemia, leukocytosis, mild hypergammaglobulinaemia, thrombocytosis (acute-phase); urinalysis with dysmorphic RBCs and **red-cell casts**.
- **ANCA** (PR3/c-ANCA): predictive value ~90% with active glomerulonephritis, but only 30–60% with isolated sinus/lung disease — so biopsy is needed there to exclude infection/malignancy.

- **Imaging:** chest CT (more sensitive than CXR) — bilateral nodules, masses, **cavitation**, infiltrates; extensive sinusitis with bony erosion.
- **Tissue biopsy is the diagnostic gold standard:** necrotising granulomatous vasculitis. **Lung** offers highest yield; **renal** biopsy confirms pauci-immune GN; **nasal** biopsy often shows only inflammation.
- **Differential diagnosis:** microscopic polyangiitis, EGPA, anti-GBM (Goodpasture) disease, SLE, relapsing polychondritis, **cocaine/levamisole-induced midline destruction** (anti-elastase ANCA, granulocytopenia, facial skin erosion), extranodal **NK/T-cell lymphoma (nasal type)**, lymphomatoid granulomatosis, infections (histoplasmosis, endocarditis, rhinoscleroma, mucocutaneous leishmaniasis). *Midline lesions in GPA are never irradiated.*

Treatment (induction → maintenance, severity-stratified)

- **Principle:** two phases — **induction** of remission, then **maintenance**. *Severe* = organ/life-threatening (active GN is *always* severe even with normal creatinine; alveolar haemorrhage); *non-severe* = no immediate organ threat.
- **Glucocorticoids:** historically prednisone **1 mg/kg/day** then taper; reduced-dose regimens are **non-inferior with fewer serious infections**; **IV methylprednisolone 1000 mg/day × 3 days** for fulminant/life-threatening disease.

Setting	Induction	Maintenance
Severe disease	**Rituximab 375 mg/m^2 weekly × 4** *or* **cyclophosphamide** (oral 2 mg/kg/day; or IV 15 mg/kg q2wk × 3, then q3wk) + glucocorticoids ± **avacopan**	Rituximab (e.g. 500 mg × 2 then 500 mg q6mo, or 1000 mg q4mo), **azathioprine 2 mg/kg/day**, **methotrexate 20–25 mg/week**, or mycophenolate mofetil — usually ≥2 years
Non-severe disease	**Methotrexate** (15 → 20–25 mg/week) or mycophenolate mofetil + glucocorticoids; rituximab optional	Same agent continued

- **Avacopan** — oral **C5a-receptor inhibitor**; FDA-approved add-on; achieved higher sustained remission than prednisone and allows rapid steroid withdrawal.
- **Cyclophosphamide** is renally cleared (dose-reduce in renal impairment); stop at **3–6 months** and switch to a maintenance agent; bladder toxicity and infertility risk (rituximab avoids these).
- **Plasma exchange (PLEX):** PEXIVAS showed **no benefit** for the composite of ESRD/death — *not routine*; reserve for **co-existing anti-GBM antibody** (and possibly severe creatinine >5.7 mg/dL or fulminant pulmonary haemorrhage). When used with rituximab, separate by ≥48 h.
- **Infection prophylaxis: trimethoprim-sulfamethoxazole** for *Pneumocystis jirovecii* with cyclophosphamide/rituximab; TMP-SMX may help isolated sinonasal disease but **never as sole therapy** for multiorgan GPA. **Subglottic stenosis** responds to mechanical dilation + intralesional glucocorticoid, not systemic immunosuppression alone.
- **Avoid:** etanercept (no benefit, increased solid tumours), belimumab and abatacept (no benefit on relapse).

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Organ map of GPA"** — head-to-kidney schematic with labels: *Sinusitis*, *Nasal septal perforation*, *Saddle-nose deformity*, *Subglottic stenosis*, *Serous otitis media*, *Scleritis/episcleritis/proptosis*, *Bilateral cavitary lung nodules*, *Diffuse alveolar haemorrhage / pulmonary capillaritis*, *Pauci-immune crescentic glomerulonephritis (RBC casts)*, *Palpable purpura*, *Mononeuritis multiplex*.
- **ANCA immunofluorescence panel** — two neutrophils: left labelled *c-ANCA — diffuse granular cytoplasmic staining = anti-PR3*; right labelled *p-ANCA — perinuclear staining = anti-MPO*. Inset: *necrotising granulomatous vasculitis — geographic necrosis with palisading histiocytes and giant cells*.

Clinical / Diagnostic significance

- GPA is a leading cause of the **pulmonary–renal syndrome** (alongside microscopic polyangiitis, anti-GBM disease, SLE) — recognise haemoptysis + active urinary sediment as an emergency.
- **Renal involvement dominates prognosis**; early induction prevents irreversible crescentic GN and dialysis dependence.
- Treatment transformed survival: cyclophosphamide-based regimens give **>90% marked improvement, ~75% complete remission, >80% 5-year survival**; but **50–70% relapse**, leaving residual damage (renal insufficiency, hearing loss, subglottic stenosis, saddle-nose, chronic sinus disease).
- A positive PR3-ANCA in a patient with sinusitis + lung nodules + microscopic haematuria is highly suggestive, but **tissue biopsy remains confirmatory**, especially in ANCA-negative or atypical cases.
- Successful **renal transplantation** is possible after remission in those who reached ESRD.

High-yield exam pointers

- **Classic triad:** upper airway + lower respiratory tract + glomerulonephritis.
- **PR3-ANCA / c-ANCA** in >90% of active GPA; antigen = **proteinase-3 (29 kDa)**; up to 20% ANCA-negative.
- **Pauci-immune crescentic GN** = renal hallmark; **necrotising granulomatous vasculitis** = histologic hallmark.
- **Saddle-nose deformity, subglottic stenosis (~16%), bilateral cavitary lung nodules** are signature lesions.
- **Lung biopsy = highest diagnostic yield**; ANCA titre does **not** track activity.
- **Induction:** rituximab *or* cyclophosphamide + glucocorticoids ± **avacopan (C5a-receptor inhibitor)**; **PLEX not routine** (PEXIVAS).
- **Maintenance:** rituximab / azathioprine / methotrexate ≥2 years; **TMP-SMX for PCP prophylaxis**.
- *Newly acquired hypertension favours PAN, not GPA*; GPA carries increased **VTE** risk.
- Mimics to exclude: **cocaine/levamisole midline destruction, nasal NK/T-cell lymphoma**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "The Vasculitis Syndromes"** (GPA definition, epidemiology, pathology/pathogenesis, ANCA biology, NIH clinical-manifestation frequencies, diagnosis, and detailed induction/maintenance regimens including avacopan and PEXIVAS).
- **CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders"** (current ACR/Vasculitis Foundation and EULAR 2022 management approach, PR3/MPO-ANCA testing, PCP prophylaxis, saddle-nose and subglottic findings).
- *Coverage note:* the spec lists no dedicated rheumatology subspecialty textbook for this topic, so depth is drawn from Harrison 22e supplemented by CMDT 2026; both are cited above. The **2022 ACR/EULAR classification criteria** are named in CMDT but item-level point weights are not reproduced in the corpus, so they are referenced by name only and not fabricated.

◆ ◆ ◆

IgG4-related disease

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

Definition / Introduction — IgG4-related disease (IgG4-RD) is a chronic, immune-mediated **fibroinflammatory** condition characterised by a tendency to form **tumefactive (mass-like) lesions** that mimic malignancy, lymphoma, or infection. It can affect virtually any organ, shows the **same distinctive histopathology at every site**, and has a particular tropism for blood vessels of any calibre—so it is now regarded as a **variable-vessel vasculitis**. It unifies many conditions formerly considered organ-specific entities (e.g. lymphoplasmacytic sclerosing pancreatitis → type 1 autoimmune pancreatitis; Mikulicz's disease; Riedel's thyroiditis). Diagnosis rests on **careful correlation of clinical, serologic, radiologic and pathologic findings**—pathology alone is never sufficient.

Epidemiology

- Typically a **middle-aged to elderly man** — a sharp contrast to most classic autoimmune diseases, which favour young women.
- **Male predominance ~2:1** (CMDT: ~75% of patients are men, usually >50 years); male predominance is even more striking for internal-organ disease (pancreas, kidney, retroperitoneum), whereas head-and-neck disease (orbits, lacrimal, salivary glands) is closer to **1:1**.
- Male patients are ~5 years older at diagnosis and have **higher serologic activity** (higher IgG4, hypocomplementaemia).
- Presentation is usually **subacute**; fever and high CRP are usually absent. Substantial weight loss can occur (exocrine pancreatic failure → maldigestion; endocrine failure → diabetes mellitus).

Pathology and pathophysiology

The histopathology is **consistent across all organs** and forms the diagnostic backbone:

Hallmark	Description
Dense lymphoplasmacytic infiltrate	B and T lymphocytes; B cells in **germinal centres**, with CD19/CD138/IgG4+ plasma cells radiating outward; CD4+ T cells most abundant and diffuse
Storiform fibrosis	"Woven mat / basket-weave" pattern (Latin *storea* = woven mat)
Obliterative phlebitis	Inflammatory obliteration of **veins** — vascular tropism is a hallmark; obliterative *arteritis* also seen, especially in lung
Mild–moderate tissue eosinophilia	Variable; some biopsies eosinophil-rich

- **Against the diagnosis** (atypical features): intense **neutrophilic** infiltration, leukocytoclasis, **granulomatous inflammation**, **multinucleated giant cells**, and **fibrinoid necrosis**.
- **Immunohistochemistry** is essential: IgG4+ plasma cells predominate; quantify by **IgG4+ cells/high-power field** *and* the **IgG4+/IgG+ plasma-cell ratio**. In late fibrotic (acellular) phases, the ratio and the fibrosis pattern matter more than absolute cell counts.
- **Pathophysiology** — despite the name, the IgG4 molecule is *not* the primary driver:
  - IgG4 undergoes **Fab-arm exchange** (half-molecules swap), binds antigen weakly, and has **low affinity for Fcγ receptors and C1q** → it is essentially **non-inflammatory** (poor complement fixation, ADCC, phagocyte activation). IgG4 may even be a **counter-regulatory** response.
  - A unique **CD4+ cytotoxic T lymphocyte (CD4+ CTL)**, oligoclonally expanded at tissue sites, is the proposed **major disease driver** — it secretes **IFN-γ, TGF-β, IL-1** (driving storiform fibrosis) and **perforin, granzyme A/B, granulysin** (cytotoxicity).
  - **Oligoclonal plasmablast expansions** circulate in blood; continuous **B-cell/plasmablast antigen presentation** sustains the CD4+ CTLs — explaining why **B-cell depletion** is therapeutic.

Organ manifestations (key clinical syndromes)

Organ / region	Characteristic presentation
Pancreas	**Type 1 autoimmune pancreatitis** — obstructive painless jaundice, mass mimicking adenocarcinoma; "**sausage-shaped pancreas**" (diffuse enlargement, loss of lobularity), rim of hypoattenuation, irregular main-duct narrowing; 20–50% with new glucose intolerance
Biliary tree / liver	IgG4-related sclerosing cholangitis — mimics **primary sclerosing cholangitis & cholangiocarcinoma**; obstructive jaundice; can progress to hepatic failure within months
Salivary glands	Bilateral submandibular/parotid enlargement (**Mikulicz's disease**); chronic sclerosing sialadenitis
Orbit / periorbital	Painless lid/periocular swelling, **orbital pseudotumor**, dacryoadenitis, orbital myositis (enlarged extraocular muscles); proptosis
Retroperitoneum	**Retroperitoneal fibrosis** — periaortic inflammation extending to iliac vessels; ureteric entrapment → **hydronephrosis**, post-obstructive uropathy, renal atrophy

Organ / region	Characteristic presentation
Kidney	**Tubulointerstitial nephritis** (multiple/bilateral tumoral lesions; strong link with **hypocomplementaemia**); membranous glomerulonephropathy in a minority
Aorta / vessels	Lymphoplasmacytic **aortitis**, periaortitis, inflammatory aneurysm, **dissection**; coronary arteritis (wall thickening, periarterial encasement, stenosis, aneurysm)
Lung	Inflammatory pseudotumor, paravertebral mass, central-airway disease, interstitial pneumonia, pleural thickening/effusion
Thyroid	**Riedel's thyroiditis**; fibrosing variant of Hashimoto's
Meninges / pituitary	**Hypertrophic pachymeningitis** (dural thickening/enhancement, cranial neuropathies); hypophysitis → anterior hypopituitarism and/or central diabetes insipidus, thickened stalk
Lymph nodes	Generalised or localised lymphadenopathy (1–2 cm, non-tender); may be indolent for years

- Two unifying clinical themes: **allergic phenomena** (atopy, asthma, eczema, nasal polyps, sinusitis, peripheral eosinophilia) and **tumefactive pseudotumors** that mimic cancer.
- Multiorgan disease may be present at diagnosis or evolve over months–years; subclinical involvement of other organs is common.

Serology and diagnosis

- **Serum IgG4 is elevated in the majority** but **~30% have normal levels** despite classic histology (these tend to have fewer organs involved; e.g. retroperitoneal fibrosis often has normal IgG4 because disease is already fibrotic). Elevation can reach **30–40× the upper limit of normal** in multi-organ disease.
- Serum IgG4 alone is **not** a reliable diagnostic or activity marker: levels fall with therapy but often do not normalise; remissions occur with persistently high IgG4, and relapses occur with normal IgG4. **Steadily rising IgG4 after a response** flags impending flare.
- **Prozone effect** — very high IgG4 can give a **falsely low** nephelometry result; correct by **serial dilution** of serum. Missing this is dangerous (these patients are at highest risk of multi-organ injury).
- **Histopathology cut-offs (standard reference values):** consensus generally requires **>40% IgG4+/IgG+ ratio** plus organ-dependent IgG4+ cell counts (e.g. **>10/HPF**) together with storiform fibrosis and obliterative phlebitis.
- **Classification / diagnostic frameworks:**
  - **2019 ACR/EULAR classification criteria** — a 3-step approach: (1) an **entry criterion** (characteristic involvement of a typical organ), (2) **exclusion criteria** (clinical, serologic, radiologic, pathologic red flags for mimics), and (3) **eight weighted inclusion domains** (histology, immunostaining, serum IgG4, bilateral lacrimal/parotid/sublingual/submandibular glands, chest, pancreas/biliary tree, kidney, retroperitoneum); a total **≥20 points** classifies the patient as IgG4-RD.

- **Japanese comprehensive diagnostic criteria** — organ enlargement/mass + serum IgG4 **≥135 mg/dL** + histology (>40% IgG4+/IgG+ ratio, >10 IgG4+/HPF); *definite* = all three, *probable* = organ + histology, *possible* = organ + serology.
- **Type 1 AIP** is diagnosed using the **HISORt criteria** — **H**istology, **I**maging, **S**erology, **O**ther-organ involvement, **R**esponse to corticosteroid **t**herapy.

- **Differential diagnosis:** sarcoidosis, Sjögren's (lacrimal enlargement), pancreatic cancer/cholangiocarcinoma, **lymphoma**, granulomatosis with polyangiitis (proptosis, destructive sinus lesions), chronic infections (HIV, HCV), primary sclerosing cholangitis. **Most patients undergo biopsy** mainly to exclude malignancy.

Treatment

- **Not every manifestation needs immediate therapy** — indolent disease (e.g. asymptomatic lymphadenopathy) may be **watched**, but monitoring is essential because organ-threatening disease can evolve, especially with rising IgG4. **Vital-organ involvement must be treated aggressively** (risk of end-stage liver disease, pancreatic failure, renal atrophy, aortic dissection/aneurysm, destructive sinonasal lesions).
- **Glucocorticoids = first line.** Harrison: **prednisone 40 mg/day**, tapered to discontinuation or to **5 mg/day maintenance over 2–3 months**. CMDT: **prednisone 0.6 mg/kg/day** tapered over weeks–months. Response is usually swift and striking, but **steroid-free remissions are uncommon** and steroid toxicity is high in this older, often diabetic population.
- **B-cell depletion — rituximab** is the key second-line agent (and increasingly used early with steroids) for relapsing or glucocorticoid-resistant disease: **two doses of 1 g IV ~15 days apart**, producing a swift fall in serum IgG4 (by limiting repletion of short-lived IgG4-producing plasma cells) and modulating CD4+ CTL function.
- **Conventional steroid-sparing agents — azathioprine, mycophenolate mofetil** (limited evidence) as alternatives.
- **Emerging / targeted therapy — inebilizumab** (anti-CD19, positive phase-3 MITIGATE trial; CMDT cites Stone et al, *NEJM* 2025) and **obexelimab**; anti-CD19 B-cell strategies may become first-line for high steroid-toxicity risk or organ-threatening disease.
- **Prognosis** — depends on the **degree of established fibrosis** (fibrotic organs respond poorly). Bisphosphonates and infection prophylaxis as standard with immunosuppression.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Histopathology of IgG4-RD (low-/high-power composite):** label — *dense lymphoplasmacytic infiltrate*, *germinal centre/lymphoid follicle*, *storiform ("basket-weave") fibrosis*, *IgG4+ plasma cells (IHC)*, *obliterative phlebitis (vein with obliterated lumen)*, *eosinophils*.
- **Pathophysiology schematic:** *B cell/plasmablast (antigen presentation)* → *CD4+ cytotoxic T cell* → arrows to *IFN-γ, TGF-β, IL-1* (→ **storiform fibrosis**) and *perforin/granzyme/granulysin* (→ **tissue injury**); side box *IgG4 plasma cell* → *IgG4 (Fab-arm exchange, non-inflammatory)*; therapy arrow *rituximab/inebilizumab* → *B-cell depletion*.

Clinical / Diagnostic significance

- **Great mimic of malignancy** — pancreatic mass, cholangiocarcinoma, orbital/lung pseudotumor; recognising IgG4-RD prevents unnecessary major surgery (e.g. Whipple, thyroidectomy).
- A **trial of corticosteroid response** can be diagnostically useful in AIP (the "R" of HISORt), but a non-resolving "mass" still mandates biopsy to exclude cancer.
- **Renal involvement + hypocomplementaemia** and the **prozone effect** are practical traps every physician must know.
- Screen newly diagnosed patients for **occult multi-organ disease** (history, exam, cross-sectional imaging, IgG4) and for **secondary diabetes/exocrine insufficiency**.

High-yield exam pointers

- IgG4-RD = **fibroinflammatory, tumefactive, multi-organ "variable-vessel vasculitis."**
- Pathology triad: **storiform fibrosis + obliterative phlebitis + IgG4+ lymphoplasmacytic infiltrate** (with eosinophils); ratio **IgG4+/IgG+ >40%**.
- Demographics: **older man, ~2:1 male**, subacute, afebrile.
- Classic syndromes: **type 1 AIP ("sausage pancreas"), Mikulicz's disease, Riedel's thyroiditis, retroperitoneal fibrosis, hypertrophic pachymeningitis, orbital pseudotumor.**
- **~30% have normal serum IgG4**; beware the **prozone effect** (falsely low) — dilute the sample.
- IgG4 is **non-inflammatory** (Fab-arm exchange); the **CD4+ cytotoxic T cell** is the proposed driver.
- Classification: **2019 ACR/EULAR criteria (≥20 points)**; AIP → **HISORt**.
- Treatment: **glucocorticoids first-line; rituximab** for relapse/resistance; **inebilizumab/obexelimab** emerging; pathology alone never diagnostic — correlate clinically.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "IgG4-Related Disease" (clinical features, organ table, serology incl. prozone effect, pathology/pathophysiology, glucocorticoid + rituximab regimens, emerging anti-CD19 therapy).
- **CMDT 2026** — "IgG4-Related Disease" (epidemiology, diagnosis, prednisone 0.6 mg/kg/day, rituximab/inebilizumab, azathioprine/mycophenolate) and "Liver, Biliary Tract & Pancreas Disorders" (type 1 autoimmune pancreatitis, imaging, **HISORt** criteria, prednisone 40 mg/day taper).
- *Coverage note:* The Harrison/CMDT corpus describes the pathology, serology and management in depth but does **not enumerate** the exact point weights of the 2019 ACR/EULAR criteria or the numeric histology/serology cut-offs (IgG4+/IgG+ >40%, >10 IgG4+/HPF, serum IgG4 ≥135 mg/dL); these are stated from the universally accepted ACR/EULAR and Japanese consensus criteria and are standard internal-medicine reference values.

◆ ◆ ◆

Hyperuricaemia

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

Definition / Introduction — Hyperuricemia is a sustained elevation of serum urate above the saturation point of monosodium urate (MSU), i.e. **>~6.85 mg/dL**, beyond which crystallization, growth and tissue deposition occur. Humans are uniquely susceptible because evolutionary loss of **uricase** (which converts urate to the highly soluble *allantoin*) raises baseline urate; at physiologic pH uric acid exists largely as urate (weak acid, *pKa 5.8*). Hyperuricemia is the central prerequisite for gout and is tightly linked to the insulin-resistance/cardiometabolic-renal cluster, yet only a minority of hyperuricemic individuals ever develop gout. Management therefore is *not* simply "lower the number" but a graded strategy: correct reversible causes, decide *who* needs lifelong urate-lowering therapy (ULT), drive serum urate to a sub-saturation target, and cover the patient against paradoxical flares.

Pathophysiologic basis that dictates treatment

- Serum urate reflects the **balance of dietary intake, endogenous synthesis and excretion**. Hyperuricemia arises predominantly from **impaired renal urate excretion (~90%)** and, less commonly, **overproduction (~10%)**; many patients have both.
- **Overproduction** drivers: high cell turnover (hematologic malignancy, psoriasis, chemotherapy, tissue hypoxia) and inherited enzyme defects — **PRPP synthetase superactivity** and **HPRT deficiency** (*Lesch-Nyhan syndrome* and variants, X-linked).
- Two-thirds of urate is eliminated renally (proximal-tubule transporters **URAT1, OAT10, GLUT9, ABCG2**) and one-third via the gut (intestinal uricolysis) — these transporters are the targets of *uricosuric* drugs and explain anti-uricosuric effects of pyrazinoate/nicotinate.
- These mechanisms define the two drug strategies: **reduce production** (xanthine oxidase inhibitors), **increase excretion / degrade urate** (uricosurics, recombinant uricase).

Non-pharmacologic measures and reversible causes (first step)

- Pursue *before/alongside* drugs; in most patients hyperuricemia cannot be corrected by these alone, but they reduce drug dose and address comorbidity.
- **Weight control** (obesity/insulin-resistance syndrome), **healthy diet** with reduced purine load, **limitation of alcohol**, and **decreased fructose-rich foods and beverages**.
- **Stop/avoid urate-raising drugs where feasible — thiazide and loop diuretics**, low-dose aspirin.
- Treat the dense comorbidity burden (hypertension, type 2 diabetes, CKD, ischemic heart disease); some agents lower urate as a bonus — **losartan, amlodipine, fenofibrate, and SGLT2 inhibitors** — the last offering combined urate reduction plus cardio-renal benefit.

When to start urate-lowering therapy (ULT)

- **Goal:** correct the chronic hyperuricemia/expanded urate pool (the central cause of gout) — a commitment that is **usually lifelong**.
- Consider ULT when hyperuricemia is *not* correctable by risk-factor modification, judged by:
  - **≥2 gout flares per year**, or flares of marked severity/duration, and patient willingness for long-term therapy.
- **Absolute (always-treat) indications:** any patient with **subcutaneous tophi**, **chronic gouty arthritis**, or **known uric acid nephrolithiasis** — start ULT regardless of flare frequency.

Urate-lowering and acute-flare drugs

Drug	Class / mechanism	Dosing & target	Key cautions
Allopurinol	Xanthine oxidase inhibitor; *first-line* ULT	Single morning dose; start ≤100 mg/d, titrate to max **800 mg/d**; in CKD with eGFR <30 mL/min start **50 mg/d** and titrate slowly	Mild cutaneous reaction ~2%; rare **SCARs (SJS, TEN)** — risk ↑ with CKD, higher start dose, **HLA-B*5801** carriage
Febuxostat	Xanthine oxidase inhibitor	Alternative XO inhibitor; hepatic metabolism (glucuronidation + oxidation) — **no dose adjustment in moderate–severe CKD**	Useful in HLA-B*5801 carriers / allopurinol intolerance
Probenecid	Uricosuric; *second-line*	Start **250 mg BD**, increase up to **3 g/d** to target; alone or with an XO inhibitor	Needs good renal function — **ineffective if serum creatinine >2 mg/dL (177 µmol/L)**
Benzbromarone	Uricosuric	More effective uricosuric in CKD	*Not available in the United States*
Pegloticase	Pegylated recombinant uricase (IV)	For patients who fail/cannot tolerate full doses of other agents	Combine with **methotrexate** to cut immunogenicity (anti-drug antibodies → loss of efficacy, infusion reactions)
Colchicine	Anti-inflammatory (flare Rx / prophylaxis)	Flare: **1.2 mg at first sign, then 0.6 mg in 1 h**, then daily dosing; prophylaxis **0.6 mg OD–BD**	Eliminated via **P-glycoprotein (MDR1)** & **CYP3A4** — reduce dose in renal disease or with clarithromycin/tacrolimus

Drug	Class / mechanism	Dosing & target	Key cautions
NSAIDs	Anti-inflammatory (flare Rx)	Indomethacin 25–50 mg TID; naproxen 500 mg BD; ibuprofen 800 mg TID; celecoxib 800 then 400 mg at 12 h, then 400 mg BD	Avoid with significant comorbidity (renal, GI, cardiac)
Glucocorticoids	Anti-inflammatory (flare Rx)	Prednisone **30–50 mg/d** tapered; or IM; or intra-articular for 1–few joints	Useful when NSAIDs/colchicine contraindicated
Anakinra / canakinumab	IL-1β blockade	Reserved for refractory flares	When standard agents fail/contraindicated

- **Target serum urate:** drive to a sub-saturation point — typically **<5–6 mg/dL (300–360 µmol/L)** — to prevent recurrent flares and dissolve tophi. A lower target (<5 mg/dL) accelerates tophus dissolution.
- **HLA-B*5801 screening:** allele carriage is high among **Southeast Asian (except Japanese descent), Pacific Islander/Native Hawaiian, and black** patients; screen *before* allopurinol in these groups and, if positive, use an **alternative agent** (e.g. febuxostat).

Initiating ULT and flare prophylaxis (the practical pitfall)

- **Do not start ULT during an active flare** — abruptly lowering urate can worsen the ongoing attack.
- ULT may be started **in the resolution phase or after a flare**, always **under anti-inflammatory prophylaxis** — e.g. **colchicine 0.6 mg once–twice daily** or **naproxen 250 mg twice daily**.
- **Start low, titrate slowly:** low starting dose with gradual up-titration reduces both SCAR risk and the **paradoxical mobilization flares** caused by MSU crystals shedding from dissolving synovial tophi during rapid urate reduction.
- **Continue prophylaxis** until the patient is **normouricemic and flare-free for 3–6 months**, or until tophi resolve.

Special situations (standard medicine — see Coverage note)

- **Asymptomatic hyperuricemia:** routine ULT is generally *not* indicated for an incidentally high urate without gout, tophi, or urate stones; manage lifestyle and reversible causes, and treat comorbidities.
- **Tumor lysis syndrome (overproduction state):** prevent/treat with vigorous **IV hydration**, **allopurinol** prophylaxis, and **rasburicase** (recombinant urate oxidase) for high-risk/established cases; rasburicase is **contraindicated in G6PD deficiency** (hemolysis/methemoglobinemia).
- **Secondary/overproduction hyperuricemia** (myeloproliferative disease, inherited enzyme defects): control the underlying disorder; XO inhibition is preferred over uricosurics to avoid stone formation.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis-and-therapeutic-targets flow diagram (after Fig. 384-1):** boxes top-to-bottom — *Risk factors* (obesity/insulin resistance, diet/alcohol, genes, diuretics/low-dose aspirin) → **Chronic hyperuricemia / increased urate pool → SU >6.85 mg/dL → MSU crystallization, crystal growth, tissue deposition → Recurrent gout flares (acute crystal-induced inflammation) → Chronic gouty arthritis / tophi**. Add two side-arrows labelled "**Urate-lowering therapy (target SU <5–6 mg/dL): allopurinol, febuxostat, probenecid, uricase**" pointing at the hyperuricemia box, and "**Anti-inflammatory therapy: NSAIDs, colchicine, glucocorticoids**" pointing at the flare box, plus a "**Dissolution → normal urate level**" return arrow.
- **Treatment algorithm box:** label nodes — *Confirm hyperuricemia/gout → Lifestyle + stop diuretics → Indication for ULT? (≥2 flares/yr, tophi, chronic arthritis, urate stones) → Check HLA-B*5801 in high-risk ethnicity* → *Allopurinol (or febuxostat) start-low titrate-to-target → Add colchicine/NSAID prophylaxis 3–6 months*.

Clinical / Diagnostic significance

- **Confirm before committing to lifelong therapy:** definitive diagnosis of gout rests on **needle-shaped, strongly negatively birefringent MSU crystals** in synovial fluid/tophus under polarized light; always culture fluid as septic arthritis can coexist.
- Serum urate may be **normal or low during an acute flare** (uricosuric effect of IL-6, ~2 mg/dL fall) — do not exclude gout on a single normal value; recheck after the flare and use it as the **therapeutic target**.
- **Baseline workup before/with ULT:** serum creatinine/eGFR, LFTs, hemoglobin, WBC count, HbA1c and lipids — to detect comorbidity, choose drug/dose, and monitor toxicity.
- **Imaging adjuncts:** musculoskeletal **ultrasound double-contour sign** and **dual-energy CT** detect urate deposition early; radiographic punched-out erosions with overhanging edges mark advanced tophaceous disease.
- ULT response is monitored by serial serum urate to the **<5–6 mg/dL** target; persistent failure to reach target should prompt adherence checks, dose escalation, or a switch/add of class.

High-yield exam pointers

- **Allopurinol is first-line ULT;** start ≤100 mg/d (50 mg/d if eGFR <30), titrate up to **800 mg/d**, target serum urate **<5–6 mg/dL**.
- **Screen HLA-B*5801** before allopurinol in Southeast Asian/Pacific Islander/Native Hawaiian/black patients; if positive use **febuxostat**.
- **Febuxostat needs no dose adjustment** in moderate–severe CKD (hepatic metabolism).
- **Probenecid** (uricosuric, 2nd-line) is **ineffective if creatinine >2 mg/dL**; **benzbromarone** works better in CKD but is unavailable in the US.
- **Pegloticase** (pegylated uricase) for refractory/tophaceous gout — give with **methotrexate** to limit immunogenicity.

- **Never start ULT during an acute flare;** begin in resolution phase under **colchicine/NSAID prophylaxis**, continued **3–6 months** until normouricemic and flare-free or tophi resolve.
- **Start low–go slow** to avoid SCARs (SJS/TEN) and paradoxical mobilization flares.
- **Always-treat indications:** tophi, chronic gouty arthritis, uric acid nephrolithiasis.
- **Rasburicase** for tumor-lysis hyperuricemia — **contraindicated in G6PD deficiency**.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 384 "Gout and Other Crystal-Associated Arthropathies" (urate physiology, indications/targets for ULT, allopurinol/febuxostat/probenecid/benzbromarone/pegloticase dosing and cautions, flare prophylaxis, HLA-B*5801 screening, acute-flare agents).

Coverage note: The provided chapter addresses hyperuricemia management within the *gout* framework. It does **not** explicitly cover (a) the threshold/decision for treating purely **asymptomatic hyperuricemia**, or (b) **tumor lysis syndrome** prophylaxis (IV hydration, **rasburicase**, G6PD contraindication). These points are included only as **universally accepted standard internal medicine**, not drawn from Ch 384, and are flagged here accordingly.

◆ ◆ ◆

Microscopic polyangiitis

Asked in: Paper III 09/2025 · Paper III Nov 2019 (2×) — RGUHS MD General Medicine

Definition / Introduction — Microscopic polyangiitis (MPA) is a **pauci-immune, non-granulomatous, necrotizing vasculitis** of small vessels (capillaries, venules, arterioles) — with frequent involvement of small- and medium-sized arteries — that characteristically produces **necrotizing glomerulonephritis** and **pulmonary capillaritis**. The term *microscopic polyarteritis* was coined by **Davson (1948)** to denote the glomerulonephritis seen in some patients with polyarteritis nodosa; the **1992 Chapel Hill Consensus Conference** formalised "microscopic polyangiitis" as a distinct entity defined by small-vessel necrotizing vasculitis with **few or no immune deposits**. It is one of the three **ANCA-associated vasculitides (AAV)**, alongside granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), and is the commonest cause of the **pulmonary–renal syndrome**.

Epidemiology & Nomenclature

- **Incidence ~3–5 per 100,000**; **mean age of onset ~57 years**; **males slightly more often affected** than females.
- Classified under the **Chapel Hill** category of *ANCA-associated small-vessel vasculitis* — grouped with GPA and EGPA because all share ANCA positivity and pauci-immune small-vessel vasculitis, but each retains a **distinct clinical phenotype** and should be regarded as a separate disease.
- The hallmark **distinguishing MPA from GPA is the absence of granulomatous inflammation**; absence of asthma/eosinophilia distinguishes it from EGPA, and the involvement of

venules/capillaries (and glomerulonephritis) distinguishes it from classic polyarteritis nodosa (PAN).

Etiopathogenesis (ANCA biology)

- **Pauci-immune lesion**: immunohistochemistry shows a *paucity of immunoglobulin deposition* in the vessel wall, implying immune-complex formation does **not** drive pathogenesis (contrast with cryoglobulinemic/IgA vasculitis).
- **ANCA** are autoantibodies against neutrophil/monocyte cytoplasmic granule proteins. Two patterns by indirect immunofluorescence:
  - **p-ANCA (perinuclear)** — target **myeloperoxidase (MPO)**; this is the **predominant association in MPA**.
  - **c-ANCA (cytoplasmic)** — target **proteinase-3 (PR3)**, a 29-kDa serine proteinase; predominant in GPA.
- **Pathogenic sequence**: TNF-α / IL-1 (or alternative-complement activation) **primes** neutrophils → MPO/PR3 **translocate to the cell surface** → circulating ANCA bind and activate the neutrophil → **degranulation, reactive-oxygen-species release, and adhesion to/killing of endothelial cells** → release of IL-1, IL-8 and further leukocyte recruitment → **necrotizing small-vessel injury**. Adoptive-transfer experiments in mice support a direct pathogenic role of anti-MPO.
- **Complement** (alternative pathway, generating **C5a**) is now recognised as central — the basis for the C5a-receptor antagonist **avacopan**.
- **Drug-induced MPA / MPO-ANCA vasculitis**: implicated agents include **propylthiouracil, hydralazine, allopurinol, penicillamine, minocycline, and sulfasalazine** — typically high-titre p-ANCA; withdrawal of the drug is the first therapeutic step.

Clinical and Laboratory Manifestations

- **Constitutional onset**: may be gradual (fever, weight loss, myalgia/arthralgia) or **acute**.

Organ system	Manifestation in MPA
Renal	**Necrotizing pauci-immune (crescentic) glomerulonephritis** in **≥79%**; frequently **rapidly progressive (RPGN)** → renal failure; haematuria, RBC casts, sub-nephrotic proteinuria
Pulmonary	**Alveolar haemorrhage** from **pulmonary capillaritis** in **~12%** (haemoptysis may be first symptom); interstitial fibrosis mimicking UIP carries a poor prognosis
Neurological	**Mononeuritis multiplex** (vasculitic neuropathy)
Cutaneous	**Palpable purpura**, splinter haemorrhages, ulcers, vesiculobullous lesions
GI	Mesenteric/visceral vasculitis (abdominal pain, bleeding)
NOT typical	**Upper-airway destructive disease and pulmonary nodules are absent** — their presence suggests **GPA** instead

- **Laboratory**: features of inflammation — raised **ESR/CRP, anaemia, leukocytosis, thrombocytosis**; **ANCA positive in ~75%**, predominantly **anti-MPO (p-ANCA)**, though PR3-ANCA may occur. The renal lesion is a **segmental necrotizing glomerulonephritis**, often with intraglomerular thrombi/localised intravascular coagulation.

Diagnosis

- Based on **histologic evidence of vasculitis or pauci-immune glomerulonephritis** in a patient with a **compatible multisystem clinical picture**.
- **Tissue biopsy** (kidney, skin, nerve/muscle, or lung) remains essential — especially when the clinical picture is atypical — even though MPA is strongly ANCA-associated. Renal biopsy shows **focal segmental necrotizing GN with crescents and absent/scanty immune deposits on immunofluorescence** (pauci-immune).
- Exclude **mimics** (infective endocarditis, anti-GBM disease, SLE, cryoglobulinemia, cholesterol emboli, thrombotic microangiopathy) before committing to immunosuppression.

Differential Diagnosis (key separators)

Feature	MPA	GPA	EGPA	PAN
Vessel size	Small (± medium)	Small–medium	Small–medium	**Medium (muscular arteries)**
Granulomas	**Absent**	**Present** (necrotizing)	Present (eosinophil-rich)	Absent
Dominant ANCA	**MPO / p-ANCA (~75%)**	PR3 / c-ANCA (>90%)	MPO in ~40–48%	**ANCA-negative**
Upper airway / nodules	Absent	**Prominent** (sinusitis, nasal, lung nodules/cavities)	Allergic rhinitis/sinus polyps; asthma	Absent
Glomerulonephritis	**Common (RPGN)**	Common	Less common	**Absent** (arteritis, not GN)
Lung haemorrhage	**Common (capillaritis)**	Common	Uncommon	**Pulmonary arteries spared**
Distinctive clue	Pulmonary–renal syndrome	Saddle-nose, granulomas	**Asthma + eosinophilia >1000/µL**	HBV association, microaneurysms

Treatment

Trials enrol GPA and MPA together; MPA is managed identically to GPA (Harrison).

- **Severe (organ-/life-threatening) disease — Remission INDUCTION**:
  - **Glucocorticoids + either cyclophosphamide OR rituximab**.
  - **Cyclophosphamide** 2 mg/kg/day **oral** (reduce dose in renal impairment); or IV pulse **15 mg/kg** ×3 doses every 2 weeks then every 3 weeks (similar remission, higher relapse than daily oral).
  - **Rituximab** (anti-CD20) **375 mg/m² weekly × 4 weeks** — *non-inferior to cyclophosphamide* (RAVE/RITUXVAS), and superior in relapsing disease; preferred when fertility preservation matters or for relapse.

- **Glucocorticoid regimen**: historically prednisone **1 mg/kg/day** then taper; a **reduced-dose regimen (PEXIVAS)** is **non-inferior with fewer serious infections**. Life-threatening disease → **IV methylprednisolone 1000 mg/day × 3 days**.
- **Avacopan** (oral **C5a-receptor antagonist**) — a glucocorticoid-sparing add-on; in the ADVOCATE trial achieved higher sustained remission at 52 weeks with markedly lower steroid exposure.
- **Plasma exchange (PLEX)**: **no benefit** on the composite of ESRD/death in the large PEXIVAS trial; reserve for **coexisting anti-GBM antibody**, and consider in selected fulminant cases (severe RPGN, creatinine >5.7 mg/dL — improved renal recovery at the cost of infection). Separate PLEX and rituximab by **≥48 h**.

- **Remission MAINTENANCE** (after cyclophosphamide induction, switch at 3–6 months):
  - **Rituximab** (e.g. 500 mg ×2 then 500 mg every 6 months) — **lowest relapse rate**; or **azathioprine** 2 mg/kg/day; or **methotrexate** 15 → 20–25 mg/week; or **mycophenolate mofetil** 1 g BID (higher relapse). Continue **≥2 years**; individualise duration (relapse risk rises after stopping).
- **Non-severe disease**: methotrexate or mycophenolate (± rituximab) with lower-dose glucocorticoids.
- **Prognosis**: **5-year survival ~74%** with treatment; death from alveolar haemorrhage, renal, cardiac or GI disease. **Relapse in ≥34%** (25–50% across AAV). **Early diagnosis is the key prognostic determinant** — late diagnosis means more renal fibrosis and worse outcomes.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pauci-immune crescentic glomerulus**: label *Bowman's capsule, cellular crescent compressing the tuft, segmental fibrinoid necrosis of capillary loops, ruptured GBM, and "negative" immunofluorescence (absent immune deposits)*.
- **ANCA pathogenesis flow diagram**: label *TNF-α/IL-1 priming → MPO/PR3 surface translocation → ANCA binding → neutrophil activation (ROS, degranulation, C5a) → endothelial injury → necrotizing small-vessel vasculitis*, with the *avacopan block at the C5a receptor* and *rituximab block at CD20 B-cell*.

Clinical / Diagnostic significance

- Suspect MPA in any **pulmonary–renal syndrome** (haemoptysis/alveolar haemorrhage + RPGN with active urinary sediment); it is **several-fold commoner than anti-GBM disease** as a cause.
- A **p-ANCA/anti-MPO positive RPGN** with **pauci-immune crescentic GN on biopsy** and **no granulomata/no upper-airway destruction** strongly favours MPA over GPA.
- **Send anti-GBM with ANCA** in every pulmonary–renal presentation — "double-positive" patients (anti-MPO + anti-GBM) require **plasma exchange**.
- **Mononeuritis multiplex** with constitutional symptoms and renal involvement is a high-yield clue; nerve/muscle biopsy can confirm vasculitis.
- Always **exclude drug-induced MPO-ANCA vasculitis** (PTU, hydralazine, minocycline, allopurinol) — withdrawing the drug may suffice in limited disease.

- Monitor for **treatment-related infection** (the major cause of early mortality), hepatitis-B reactivation with rituximab, and cyclophosphamide-related bladder toxicity/infertility/malignancy.

High-yield exam pointers

- MPA = **pauci-immune, non-granulomatous, necrotizing small-vessel vasculitis**; *no granulomas* (vs GPA), *no asthma/eosinophilia* (vs EGPA), *glomerulonephritis present and pulmonary arteries involved* (vs PAN).
- **Davson 1948** coined "microscopic polyarteritis"; **Chapel Hill 1992** defined MPA.
- **ANCA positive in ~75%**, predominantly **anti-MPO / p-ANCA**.
- **Glomerulonephritis ≥79%**, **alveolar haemorrhage ~12%**; **commonest cause of pulmonary–renal syndrome**.
- **Renal biopsy** = focal segmental **necrotizing crescentic GN, pauci-immune** on IF.
- **Induction** = glucocorticoid + (**cyclophosphamide or rituximab 375 mg/m^2 ×4**) ± **avacopan**; **methylprednisolone pulse** for life-threatening disease.
- **PLEX** no longer routine (PEXIVAS) — reserve for **anti-GBM positivity** / selected fulminant cases.
- **Maintenance** with **rituximab** (lowest relapse) / azathioprine / methotrexate for ≥2 years.
- **5-yr survival ~74%; relapse ≥34%**; outcome hinges on **early diagnosis**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "The Vasculitis Syndromes" (Microscopic Polyangiitis; ANCA biology; treatment of ANCA-associated vasculitis) and "Glomerular Diseases" (ANCA small-vessel vasculitis / pauci-immune crescentic glomerulonephritis).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders" (Microscopic Polyangiitis — essentials, drug-induced MPO-ANCA, treatment) and "Kidney Disease" (rapidly progressive GN).

Coverage note: The corpus does not contain the **2022 ACR/EULAR MPA classification-criteria point scores**, so these were deliberately not stated; the answer uses the **Chapel Hill 1992** nomenclature, which is fully sourced. All numbers, drug doses, eponyms and percentages above are taken verbatim from the cited chapters.

◆ ◆ ◆

Mixed connective tissue disease

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

Definition / Introduction — Mixed connective tissue disease (MCTD) is an *overlap syndrome* in which features of **systemic sclerosis (SSc, usually limited cutaneous)**, **systemic lupus erythematosus (SLE)**, **polymyositis/dermatomyositis** and **rheumatoid arthritis** coexist in the same patient, characteristically accompanied by **high titres of autoantibody to U1-ribonucleoprotein (anti-U1-RNP)**. The defining initial presentation is **Raynaud's phenomenon with "puffy" (swollen) fingers and myalgia**. More broadly, an **overlap syndrome** is defined as typical SSc features coexisting with clinical and laboratory evidence of another autoimmune disease — most commonly **polymyositis, Sjögren's syndrome, polyarthritis, autoimmune liver disease, or SLE**. MCTD was first delineated by *Sharp and colleagues (1972)*.

Pathogenesis and immunology

- **Autoantibody-driven autoimmune connective-tissue disease**; the serological hallmark is **anti-U1-RNP**, which produces a **high-titre speckled antinuclear antibody (ANA)** pattern on HEp-2 immunofluorescence.
- Anti-U1-RNP is directed against the **U1 small nuclear ribonucleoprotein**, chiefly the **70-kDa polypeptide (U1-70K) and the A and C proteins** — a *standard-textbook* specificity not detailed in the provided chapter.
- The B-cell hyperactivity, TH2-polarised T-cell response, and endothelial/microvascular injury that underlie SSc are shared mechanisms relevant to MCTD: chronic **B-cell activation** (elevated BAFF/APRIL), profibrotic cytokines (**TGF-β, IL-6, IL-13**), and a vasculopathy driving **Raynaud's phenomenon and pulmonary arterial hypertension (PAH)**.
- Strong association with **HLA class II (notably HLA-DR4)** genotypes (*standard immunology, flagged below*), in contrast to the anti-Sm/anti-dsDNA-linked HLA associations of SLE.

Clinical features (multisystem)

- **Hallmark triad** to recall: **Raynaud's phenomenon + swollen/puffy hands ("sausage" fingers) + high-titre anti-U1-RNP**.
- Over time, **sclerodactyly, soft-tissue calcinosis (calcinosis cutis) and cutaneous telangiectasia** appear (scleroderma-spectrum features).
- **SLE-like features**: malar (butterfly) erythema, photosensitivity, serositis, cytopenias, alopecia.
- **Myositis**: proximal muscle weakness with raised muscle enzymes (polymyositis overlap).
- **Inflammatory arthritis/arthralgia**: may be erosive; some patients are **seropositive (RF/anti-CCP) with a rheumatoid-arthritis overlap**.

Organ system	Characteristic MCTD manifestations
Vascular	Raynaud's phenomenon (early, near-universal); abnormal nailfold capillaroscopy; digital ischaemia
Skin/hands	Puffy fingers, sclerodactyly, calcinosis cutis, telangiectasia, malar rash, photosensitivity

Organ system	Characteristic MCTD manifestations
Musculoskeletal	Inflammatory polyarthritis (± erosive), myositis with proximal weakness
Pulmonary	**PAH** (leading cause of death), interstitial lung disease (ILD), pleuritis
Gastrointestinal	Oesophageal dysmotility, GERD, reduced lower-oesophageal-sphincter tone (*standard SSc-spectrum feature*)
Cardiac	Pericarditis/pericardial effusion, conduction defects, myocardial involvement
Renal	Membranous/mesangial nephropathy; severe diffuse glomerulonephritis and scleroderma renal crisis are **relatively uncommon**
Neurological	Trigeminal (sensory) neuropathy; aseptic meningitis (often NSAID-related) — *standard, flagged*

Autoantibodies and laboratory features

- **Anti-U1-RNP in high titre is required** for the diagnosis; by definition the speckled ANA is strongly positive.
- **Absence of anti-Sm and anti-dsDNA** in high titre helps distinguish MCTD from classic SLE (*standard serology, flagged*); anti-Sm, when strongly positive, points toward SLE rather than MCTD.
- Other **overlap-associated antibodies** recognised in the SSc chapter (useful for the differential of overlap syndromes):

Autoantibody	Pattern	Principal association
U1-RNP	Speckled	**MCTD** — PAH, inflammatory arthritis, myositis overlap
PM/Scl	Nucleolar	Calcinosis cutis, ILD, myositis overlap (SSc–polymyositis)
Ku	Speckled	SLE / myositis overlap
Ro52 / TRIM21	—	Overlap, older-age onset, ILD
Topoisomerase I (Scl-70)	Speckled	Diffuse SSc, ILD (not MCTD)
Centromere (ACA)	Discrete speckled	Limited SSc, isolated PAH (not MCTD)

- Supportive labs: raised acute-phase reactants, anaemia, hypergammaglobulinaemia, raised creatine kinase (if myositis), low complement (variable), abnormal nailfold videocapillaroscopy.
- **Screening for organ involvement**: pulmonary function tests with DLCO, high-resolution CT chest (ILD), **transthoracic echocardiography ± right-heart catheterisation for PAH**, ECG, and CK/EMG for myositis.

Diagnostic criteria and classification of overlap syndromes

- MCTD is listed among the **overlap syndromes** in the scleroderma-spectrum classification (alongside **SSc/polymyositis overlap**).

- Several validated **classification criteria sets** exist (*standard rheumatology — not detailed in the provided Harrison chapter*): **Sharp, Alarcón-Segovia, Kasukawa, and Kahn** criteria. All require **high-titre anti-U1-RNP** plus a defined combination of clinical features.

Criteria set	Core requirement
Alarcón-Segovia (most widely used)	Serologic: anti-U1-RNP ≥1:1600 (haemagglutination) **plus ≥3 of 5** clinical — hand oedema, synovitis, myositis, Raynaud's, acrosclerosis (synovitis or myositis required)
Kasukawa	Raynaud's or swollen fingers/hands + positive anti-RNP + at least one feature from **each** of the SLE-, SSc-, and PM-like categories
Sharp	Major + minor clinical criteria with high-titre anti-RNP and low anti-Sm
Kahn	Anti-U1-RNP + Raynaud's + ≥2 of synovitis, myositis, swollen fingers

Management

- **Manifestation-directed and largely glucocorticoid-responsive** disease; therapy is tailored to the dominant organ involvement (*treatment specifics below are universally-accepted standard medicine; the provided chapter details only musculoskeletal therapy*).
- **Arthralgia/arthritis & musculoskeletal disease**: short courses of **NSAIDs, methotrexate, hydroxychloroquine**, and cautious **low-dose glucocorticoids**; physical/occupational therapy to prevent contractures (grounded in the SSc chapter).
- **Raynaud's phenomenon**: cold avoidance, **dihydropyridine calcium-channel blockers**; PDE5 inhibitors/prostanoids for digital ulcers.
- **Myositis & severe inflammatory disease**: moderate-to-high-dose **glucocorticoids** with steroid-sparing agents (**methotrexate, azathioprine, mycophenolate mofetil**).
- **ILD**: **mycophenolate mofetil or cyclophosphamide**, with **rituximab** in refractory disease.
- **PAH** (the prognosis-determining complication): **endothelin-receptor antagonists, PDE5 inhibitors, and prostacyclin analogues** — early screening and treatment are essential.
- **GERD/oesophageal disease**: proton-pump inhibitors, prokinetics, lifestyle measures.

Prognosis and course

- Generally **more favourable than diffuse SSc or severe SLE**, with many manifestations responding to glucocorticoids.
- **Pulmonary arterial hypertension is the leading cause of mortality** in MCTD; progressive ILD and cardiac disease also drive poor outcomes.
- The disease may **evolve over time** — some patients differentiate into a more clearly defined **SSc or SLE** phenotype, fuelling the ongoing debate over whether MCTD is a truly distinct entity or a transitional/overlap state.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Venn diagram of overlap syndromes**: three overlapping circles labelled **"SLE", "Systemic sclerosis", "Polymyositis"** (with a smaller "RA" overlap), and the **central intersection labelled "MCTD — anti-U1-RNP"**. Annotate central shared features: *Raynaud's, puffy hands, arthritis, myositis*.
- **Pathophysiology flow diagram**: *Genetic susceptibility (HLA-DR4)* → *Anti-U1-RNP autoimmunity / B-cell activation* → *Endothelial injury & vasculopathy* → branches to **"Raynaud's / digital ischaemia"** and **"Pulmonary arterial hypertension (leading cause of death)"**; parallel branch *TH2 cytokines (TGF-β, IL-6, IL-13)* → **"Fibrosis: sclerodactyly, ILD"**.

Clinical / Diagnostic significance

- **Anti-U1-RNP in high titre is the single most important diagnostic test**; a high-titre speckled ANA in a patient with Raynaud's and puffy hands should prompt its measurement.
- Distinguishing MCTD from SLE matters prognostically: MCTD typically **spares the patient from severe diffuse lupus nephritis and severe CNS lupus**, but carries a **high risk of PAH** demanding lifelong echocardiographic surveillance.
- Recognising the **overlap antibody panel** (PM/Scl, Ku, Ro52) helps classify atypical connective-tissue disease and predicts ILD/myositis risk.
- Early detection and aggressive treatment of **PAH and ILD** are the key determinants of survival.

High-yield exam pointers

- MCTD = **SSc + SLE + polymyositis + RA features + high-titre anti-U1-RNP**; first described by **Sharp (1972)**.
- **Speckled ANA**, high-titre **anti-U1-RNP**; classically **anti-Sm/anti-dsDNA negative** (helps separate from SLE).
- Earliest/most consistent clue: **Raynaud's phenomenon + swollen "puffy" hands + myalgia**.
- Later scleroderma features: **sclerodactyly, calcinosis cutis, telangiectasia**.
- **PAH = leading cause of death**; screen with echocardiography ± right-heart catheterisation.
- **Glucocorticoid-responsive** disease — better prognosis than diffuse SSc; severe lupus nephritis and renal crisis are uncommon.
- Most widely used classification criteria: **Alarcón-Segovia**; others — Kasukawa, Sharp, Kahn.
- May **evolve into SSc or SLE**; debated as a distinct entity vs an overlap state.

SOURCE & COVERAGE

Harrison's Principles of Internal Medicine, 22e — Ch 372 "Systemic Sclerosis (Scleroderma) and Related Disorders" (MCTD/overlap-syndrome section, Tables 372-2 and 372-4). **Coverage note:** The provided chapter covers MCTD only briefly within the scleroderma spectrum — it grounds the definition, overlap concept, anti-U1-RNP/speckled-ANA serology and its associations (PAH, inflammatory arthritis, myositis), the early Raynaud's/puffy-hands/myalgia presentation, later sclerodactyly/calcinosis/telangiectasia, SLE-like skin features, the overlap-antibody panel (PM/Scl, Ku, Ro52), and musculoskeletal therapy. Items added as *universally-accepted standard internal medicine* and flagged in-text — Sharp 1972 origin, anti-U1-70K/A/C antigen specificity, HLA-DR4 association, the named classification criteria (Sharp, Alarcón-Segovia, Kasukawa, Kahn) and their thresholds, oesophageal/neurological detail, and the manifestation-directed pharmacotherapy (Raynaud's, myositis, ILD, PAH) — fall outside the verbatim text of the provided chapter.

◆ ◆ ◆

Neuropathic joint diseases

Asked in: Paper III 09/2025 — RGUHS MD General Medicine

Definition / Introduction — Neuropathic joint disease (*Charcot joint*, neuro-osteoarthropathy) is a progressive, destructive arthritis that develops in a joint deprived of normal pain sensation, proprioception, or both. With loss of these protective mechanisms the joint is subjected to repeated, unperceived trauma, leading to severe cartilage and bone damage with a characteristic mismatch between gross radiographic destruction and the relative *absence of pain*. First described by *Jean-Martin Charcot* in the knees of patients with *tabes dorsalis*, it is now seen most frequently in the foot and ankle of patients with diabetes mellitus.

Etiology and characteristic joint distribution

The distribution of joint involvement is determined by the underlying neurological disorder, because the affected joints correspond to the territory of sensory loss.

Underlying disorder	Typical joint(s) affected
Diabetes mellitus (most frequent cause)	Tarsal and **tarsometatarsal** joints; then metatarsophalangeal and talotibial
Tabes dorsalis (tertiary syphilis)	Knees, hips, ankles
Syringomyelia	Glenohumeral (shoulder), elbow, wrist (upper limb)
Leprosy, **yaws**	Feet, hands
Meningomyelocele	Ankle, foot
Congenital indifference / insensitivity to pain	Ankle, foot
Peroneal muscular atrophy (*Charcot–Marie–Tooth disease*)	Foot, ankle

Underlying disorder	Typical joint(s) affected
Amyloidosis	Variable peripheral joints

- Harrison's *Table 386-2* lists diabetes mellitus, amyloidosis, tabes dorsalis, leprosy, meningomyelocele, congenital indifference to pain, syringomyelia and peroneal muscular atrophy as the recognised associations.
- An arthritis resembling neuropathic disease has been reported after **frequent intra-articular glucocorticoid injections**, attributed to the analgesic effect promoting overuse of an already-damaged joint (steroid cartilage damage is more typical of animal models than humans).

Pathophysiology — two complementary mechanisms

- **Neurotraumatic theory ("German" theory):** loss of deep pain, proprioception and protective neuromuscular reflexes allows cumulative *microtrauma* — ligamental tears and bone fractures — to accumulate unchecked, producing progressive joint disorganisation.
- **Neurovascular theory ("French" theory):** an abnormal **autonomic nervous system** drives dysregulated (increased) blood flow to the joint, causing active bone **resorption** and osteopenia; loss of bone, particularly in the diabetic foot, may be the *initial* finding.
- In diabetes, **peripheral neuropathy, autonomic neuropathy and trauma** act together; denervation of intrinsic foot muscles causes clawing of the toes and anterior displacement of the submetatarsal fat pads, altering biomechanics and raising plantar pressures.
- It is not understood why only a minority of patients with neuropathy go on to develop clinically evident neuropathic arthropathy.

Pathology: changes resemble a *severe osteoarthritic joint* — fragmentation and eventual loss of articular cartilage, **eburnation** of underlying bone, marginal osteophytes, and, with advanced disease, surface erosions, fractures, devitalised bone, intra-articular loose bodies and microscopic cartilage/bone fragments.

Clinical features

- Usually **begins in a single joint** and later involves others, depending on the neurological substrate.
- The joint becomes **progressively enlarged** from bony overgrowth and synovial effusion; it is classically *swollen, boggy and relatively painless*.
- May evolve with surprising **rapidity** — a totally disorganised joint with multiple bony fragments can appear within weeks to months.
- **Hallmark:** far *less pain than expected* from the degree of destruction; occasional sudden pain occurs from intra-articular fractures of osteophytes. Free-floating cartilage/bone fragments cause mechanical (locking) symptoms.

Diabetic (Charcot) foot — exam favourite:

- Estimated incidence in diabetes ~**0.5%**, typically in patients ≥**50 years** who have had diabetes for several years.
- Onset often attributed to antecedent trauma (e.g. *twisting* the foot); may follow a foot fracture or dislocation.

- Foot and ankle become swollen; downward collapse of the tarsal bones produces convexity of the sole — the **"rocker-bottom" foot**.
- Large osteophytes protrude dorsally; **calluses** form over the metatarsal heads and may break down into infected **ulcers and osteomyelitis**.
- The destructive change at the tarsometatarsal joints is termed a **Lisfranc fracture-dislocation**; radiographs show resorption and tapering of the distal metatarsals.

Radiographic features, staging and differential diagnosis

- **Early imaging** mimics osteoarthritis: joint-space narrowing, subchondral sclerosis, osteophytes, periarticular fractures, joint subluxation and effusions.
- **Late:** marked destructive *and* hypertrophic changes — striking osteolysis, fragmentation, dislocation and bony sclerosis ("disorganisation").
- A useful descriptive mnemonic for the classic atrophic-hypertrophic picture is the **"6 D's"**: *Distension* (effusion), increased *Density* (sclerosis), *Debris* (loose bodies), *Disorganisation*, *Dislocation/subluxation*, and *Destruction*.
- **Eichenholtz staging** of the Charcot foot (orthopaedic standard): *Stage 0* — acute inflammatory/prodromal (hot, swollen, red foot, near-normal X-ray); *Stage 1* — development/fragmentation; *Stage 2* — coalescence (debris absorption, reduced warmth); *Stage 3* — consolidation/reconstruction (bony remodelling, stable but deformed foot).

Feature	Neuropathic joint	Osteomyelitis
Joint margins on X-ray	**Distinct/well-defined**	**Blurred/ill-defined**
Indium-111–labelled WBC scan	No increased uptake	**Increased uptake**
Technetium bone scan	Increased uptake	Increased uptake (*non-discriminatory*)
Synovial neutrophils	Few (non-inflammatory)	**Increased**

- **Diagnosis** rests on the clinical picture plus characteristic radiographs in a patient with a known **sensory neuropathy**.
- **Differential diagnosis:** osteomyelitis, avascular necrosis, advanced osteoarthritis, stress fractures and **calcium pyrophosphate deposition disease (CPPD)** — more than one may coexist.
- **Synovial fluid** is *non-inflammatory*, often xanthochromic or frankly bloody, and contains fragments of synovium, cartilage and bone; CPPD crystals favour a crystal arthropathy, whereas a high synovial neutrophil count raises concern for superadded osteomyelitis. Tissue culture is often needed to exclude infection.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Labelled lateral radiograph of a diabetic Charcot foot:** label *collapse/loss of the medial longitudinal arch*, *bony fragmentation and dislocation in the midfoot*, *tarsometatarsal (Lisfranc) destruction*, *dorsal osteophytes*, and the resulting *"rocker-bottom" sole convexity*.
- **Pathophysiology flow diagram:** *Sensory + autonomic neuropathy* → two limbs — (1) *Neurotraumatic*: loss of pain/proprioception → repeated microtrauma → ligament tears/fractures; (2) *Neurovascular*: autonomic dysregulation → increased blood flow → bone resorption/osteopenia — both converging on → *progressive joint destruction / disorganisation (Charcot joint)*.

Clinical / Diagnostic significance

- **Screening prevents disease:** patients who cannot feel the **5.07 Semmes-Weinstein monofilament** have lost protective sensation and are at risk of unperceived neuropathic injury; regular foot examination, protective inserts and orthotics are pivotal.
- **Acute Charcot foot is a clinical emergency in disguise** — a hot, swollen, red foot in a neuropathic diabetic is frequently misdiagnosed as cellulitis, gout or DVT; missing it allows progression to fixed rocker-bottom deformity and ulceration.
- Distinguishing neuropathic joint from **osteomyelitis** is the central diagnostic challenge in the diabetic foot and directs whether antibiotics/surgery are needed (use joint-margin definition, indium-111 WBC scan, MRI and tissue culture).
- Established joint damage does **not** reverse with control of the underlying disease, so *early* recognition is everything.

High-yield exam pointers

- *Charcot joint* = destructive arthropathy from loss of **pain + proprioception**; named after **Jean-Martin Charcot** (first described in tabes dorsalis).
- **Diabetes mellitus** is the commonest cause today (incidence ~0.5%); **tabes dorsalis → knee/hip**, **syringomyelia → shoulder/upper limb**, **diabetes → tarsometatarsal foot**.
- Two mechanisms: **neurotraumatic** (microtrauma) + **neurovascular** (autonomic-driven bone resorption).
- Classic paradox: **gross destruction with disproportionately little pain**; joint is enlarged, boggy, unstable.
- Diabetic foot signs: **rocker-bottom deformity**, **Lisfranc fracture-dislocation**, calluses → infected ulcers/osteomyelitis.
- Radiology "**6 D's**"; **Eichenholtz** stages 0–3 for the Charcot foot.
- Neuropathic vs osteomyelitis: **distinct joint margins** and **negative indium-111 WBC scan** favour neuropathic; technetium scan does *not* discriminate.
- Synovial fluid **non-inflammatory**, often **bloody/xanthochromic**.
- Treatment: **non-weight-bearing for ≥8 weeks**, bracing/splinting (with vigilant skin surveillance), and **arthrodesis** for unstable joints (nonunion common); **no proven pharmacotherapy**.

Management

- **Primary aim — stabilise and offload the joint.** Treating the underlying disorder, even successfully, usually does not reverse established joint disease.
- **Acute Charcot foot:** early recognition with **strict non-weight-bearing/immobilisation (total-contact cast) for at least 8 weeks** may prevent severe deformity.
- **Bracing and splinting** assist weight-bearing and limit further trauma, but require close surveillance because the insensate patient cannot perceive pressure from a poorly fitted device.
- **Surgery: arthrodesis (fusion)** of an unstable joint — with or without orthobiologics — can improve function and reduce pain when conservative measures fail; **nonunion is frequent**, especially with inadequate immobilisation.
- Aggressive **foot care, ulcer prevention and glycaemic control**; CMDT notes that **pharmacotherapy has not demonstrated efficacy** for the arthropathy itself.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Arthritis Associated with Systemic Disease, and Other Arthritides" (Neuropathic Joint Disease section: etiology, *Table 386-2*, pathophysiology, clinical features, diagnosis vs osteomyelitis, treatment; *Fig. 386-1* diabetic Charcot foot).
- **CMDT 2026** — "Rheumatologic, Immunologic & Allergic Disorders" (Neurogenic Arthropathy / Charcot Joint; synovial-fluid differential) and "Diabetes Mellitus & Hypoglycemia" (Charcot foot arthropathy, rocker-bottom deformity, 5.07 Semmes-Weinstein monofilament).

Coverage note: The corpus (Harrison + CMDT) covers this topic well for an internal-medicine answer. Two items added for exam completeness are *not* verbatim in the cited corpus but are universally accepted standard teaching: the **Eichenholtz staging** of the Charcot foot and the radiographic **"6 D's"** mnemonic; the *neurotraumatic ("German") / neurovascular ("French")* theory labels are the conventional names for the two mechanisms that Harrison describes in full.

◆ ◆ ◆

Palindromic rheumatism

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

Definition / Introduction — Palindromic rheumatism (PR) is a relapsing-remitting inflammatory arthropathy characterised by **recurrent, abrupt, self-limiting attacks of acute arthritis and peri-arthritis** that resolve completely within hours to a few days, leaving **no residual joint deformity and no radiographic erosions**. The term (Greek *palindromos*, "running back again") was coined by *Hench and Rosenberg in 1944* to describe the "coming-and-going" pattern. It is best regarded not as a static disease but as an **abortive / pre-clinical phase of inflammatory arthritis**, since a substantial proportion of patients evolve into rheumatoid arthritis (RA) — making it an important exam differential for the patient with intermittent, undifferentiated arthritis.

Clinical features of the attack

- **Onset:** sudden, often peaking within a few hours; patient frequently well one moment and incapacitated the next. Attacks may begin at any time, including at night.
- **Joint pattern:** typically **monoarticular or oligoarticular (1–3 joints)** per attack; over time many joints are affected in succession. Commonly involved — **metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrists, knees, shoulders**; can also involve ankles, elbows, hips.
- **Peri-articular involvement:** a hallmark is **para-articular soft-tissue and tendon-sheath inflammation** (peri-arthritis) producing diffuse swelling beyond the joint line; transient subcutaneous nodules may appear during attacks.
- **Local signs:** affected joint becomes warm, red, tender and swollen — clinically mimicking gout or septic arthritis (pseudocellulitis-like appearance).
- **Duration:** attacks are **brief — hours to 2–3 days** (occasionally up to a week), then resolve **spontaneously and completely**.
- **Inter-critical period:** between attacks the patient is **entirely asymptomatic with a normal joint examination** — analogous to the intercritical phase of gout.
- **Frequency:** highly variable — from several attacks per week to only a few per year; the disease may run for years.
- **No systemic damage:** unlike RA, there is **no progressive deformity, no joint-space narrowing and no bony erosion**, which is the single most useful distinguishing feature.

Laboratory and imaging features

- **Acute-phase reactants** (*ESR, CRP*) are typically elevated **during an attack** and normalise in the inter-critical period.
- **Rheumatoid factor (RF):** positive in roughly half of patients; **anti-citrullinated peptide antibodies (ACPA / anti-CCP)** are positive in a significant minority. In RA, anti-CCP carries a diagnostic specificity approaching **95%**, so its presence in a patient with palindromic attacks strongly predicts evolution to RA.
- **Antinuclear antibody (ANA):** may be positive in the subset destined to develop a connective-tissue disease such as SLE.

- **Synovial fluid:** inflammatory (raised WBC, neutrophil-predominant) but **sterile and crystal-negative** — aspiration with **polarised-light microscopy** is essential to exclude crystal arthropathy (negatively birefringent needle-shaped monosodium urate of gout; weakly positively birefringent rhomboid calcium pyrophosphate of CPPD).
- **Radiographs:** characteristically **normal** even after years — absence of erosions distinguishes PR from established RA. (Subclinical synovitis may be seen on ultrasound/MRI in those progressing to RA.)

Natural history and risk of progression

Palindromic rheumatism is prognostically heterogeneous; broadly three outcomes are recognised:

Outcome	Approx. proportion	Comment
Evolution to rheumatoid arthritis	roughly one-third to one-half	Most important outcome; attacks become more frequent then merge into persistent symmetrical synovitis
Evolution to another connective-tissue disease	smaller subset	SLE, Sjögren's, Behçet's, systemic sclerosis-overlap reported
Persistent palindromic course or complete remission	remainder	Some have lifelong intermittent attacks; a minority remit fully

Predictors of progression to RA:

- **Seropositivity** — positive RF and especially positive **anti-CCP/ACPA** (high-titre carries greatest risk).
- **Female sex.**
- **Small-joint (hand/wrist) involvement.**
- **More frequent attacks** and longer disease duration.
- Family history of RA.

Diagnosis and differential diagnosis

- Diagnosis is **clinical and one of exclusion** — no internationally validated criteria exist. Commonly cited **proposed (Guerne–Weisman / Hannonen) criteria** require: recurrent sudden brief attacks of arthritis/peri-arthritis over **≥6 months**, direct **observation of at least one attack by a physician**, involvement of **≥3 different joint areas** across attacks, and **exclusion of other arthropathies**.
- A detailed **attack diary** documenting site, duration and complete resolution is invaluable.

Differential	Discriminating feature
Gout / CPPD (pseudogout)	Crystals on polarised microscopy; podagra, tophi; chondrocalcinosis on X-ray
Early rheumatoid arthritis	Symptoms persistent >6 weeks, symmetrical, erosions develop, high-titre anti-CCP

Differential	Discriminating feature
Reactive / spondyloarthritis	Antecedent infection, enthesitis, sacroiliitis, psoriasis, HLA-B27
SLE / other CTD	Multisystem features, ANA/anti-dsDNA, cytopenias
Familial Mediterranean fever & periodic fever syndromes	Recurrent fever + serositis, ethnic background, *MEFV* mutation
Whipple's disease / Behçet's	GI/oral-genital features; *Tropheryma whipplei*; pathergy
Septic arthritis	Single hot joint, fever, positive Gram stain/culture

Management

- **Acute attack: NSAIDs** are first-line; **colchicine** and short courses of **oral or intra-articular glucocorticoids** are alternatives for severe attacks. Because attacks are brief, the aim is symptom control and shortening the episode.
- **Disease-modifying / prophylactic therapy** (for frequent attacks or seropositive patients at risk of RA):
  - **Hydroxychloroquine** is the most widely used agent — reduces attack frequency and is reported to **delay or prevent progression to RA**.
  - **Sulfasalazine** and **methotrexate** are options in refractory or clearly RA-evolving disease.
  - **Colchicine** prophylaxis benefits some patients (especially where crystal disease cannot be fully excluded).
- **Monitoring:** periodic clinical review with RF/anti-CCP and acute-phase reactants to detect early conversion to persistent RA, at which point full RA-directed DMARD therapy (e.g., methotrexate ± biologic) is instituted.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Timeline of disease activity (preferred):** an X-axis labelled *"Time"* with intermittent vertical spikes labelled *"Acute attack (hours–days)"* separated by flat baselines labelled *"Complete inter-critical remission — normal joints, normal X-ray"*; add an arrow at the right labelled *"Progression to RA (persistent synovitis, erosions)"*. Contrast with a second curve labelled *"Established RA — sustained activity."*
- **Hand outline:** shade the **MCP, PIP, and wrist** joints labelled *"common sites"*, with a dashed halo around a joint labelled *"para-articular / peri-arthritic swelling"* to depict the characteristic soft-tissue involvement.

Clinical / Diagnostic significance

- PR is a **"window of opportunity"** — recognising seropositive PR identifies patients in a **pre-RA state** in whom early hydroxychloroquine/DMARD may modify natural history.
- **Joint aspiration with polarised microscopy** is mandatory at first presentation to exclude gout, pseudogout and sepsis, all of which can present identically.

- Documenting **complete radiographic and clinical resolution between attacks** is the key step that separates PR from early erosive RA and crystal arthropathy.
- Anti-CCP/RF status drives both prognosis and the decision to start prophylactic therapy.

High-yield exam pointers

- **Eponym:** *Hench and Rosenberg, 1944*; *palindromos* = "to run back again."
- **Hallmark triad:** recurrent **brief** attacks + **complete** inter-critical remission + **no erosions/deformity**.
- **1–3 joints** per attack, peaks in hours, lasts **hours to 2–3 days**; MCP/PIP/wrist/knee favoured; **peri-articular** swelling typical.
- **Seropositivity (RF, anti-CCP) predicts progression to RA**; anti-CCP specificity ~95%.
- **One-third to one-half evolve into RA**; smaller subset to SLE/other CTD; rest remit or stay palindromic.
- **Hydroxychloroquine** reduces attack frequency and may prevent RA conversion; NSAIDs/colchicine/steroids abort acute attacks.
- **Always aspirate** to exclude gout, pseudogout and septic arthritis (a diagnosis of exclusion).
- Radiograph is **characteristically normal** — a discriminator from established RA.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Disorders of the Joints and Adjacent Tissues / Gout and Other Crystal-Associated Arthropathies" (palindromic rheumatism listed among mimics of acute crystal arthritis; synovial-fluid analysis, MSU/CPPD birefringence, crystal-exclusion principles) and **"Rheumatoid Arthritis"** (RF/anti-CCP performance and ~95% ACPA specificity, 2010 ACR–EULAR classification framework, differential diagnosis of early inflammatory arthritis, predictors of persistent/erosive disease).
- **CMDT 2026** — "Rheumatologic, Immunologic & Allergic Disorders" (management principles of inflammatory arthritis; hydroxychloroquine/DMARD use).

Coverage note: The Harrison/CMDT corpus does **not** carry a dedicated section on palindromic rheumatism — it appears only as a named differential of crystal arthritis in the gout chapter, with the RA chapter supplying the antibody, prognostic and differential-diagnosis framework. The disease-specific detail (attack characteristics, Hench–Rosenberg eponym, ~one-third-to-one-half RA conversion, Guerne–Weisman proposed criteria, hydroxychloroquine prophylaxis) is therefore drawn from **universally accepted standard rheumatology** and aligned with the corpus where it overlaps; specific conversion percentages are approximate and vary between series.

◆ ◆ ◆

Polyarthritis

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

Definition / Introduction — *Polyarthritis* denotes inflammatory involvement of **four or more joints** (≥5 by some classifications), distinguishing it from *monoarthritis* (one joint) and *oligo-/pauciarticular* disease (two or three joints). It is a syndrome, not a diagnosis, with a broad differential spanning immune-mediated, infective, crystal-induced, reactive and degenerative disorders. The diagnostic art lies in answering four cardinal questions — *Is it articular? Is it inflammatory? Is it acute or chronic? How many and which joints?* — and then refining by pattern (symmetry, distribution, temporal evolution) and extra-articular clues, so that "red flag" conditions are not missed while needless testing is avoided.

The diagnostic framework — four cardinal questions

- **Articular vs non-articular.** Articular disorders show *deep/diffuse pain, swelling (synovial proliferation, effusion or bony enlargement), limited active AND passive movement, crepitus, instability or deformity.* Non-articular/peri-articular lesions (bursitis, tendinitis, fibromyalgia) cause focal/point tenderness, pain on active but not passive motion, and lack true synovial swelling — a frequent masquerader of "polyarthritis."
- **Inflammatory vs non-inflammatory.** Inflammation is suggested by the cardinal signs (erythema, warmth, pain, swelling), **prolonged morning stiffness (often hours, ≥30–45 min) that improves with activity**, systemic features (fever, rash, weight loss), and laboratory evidence — raised **ESR/CRP**, thrombocytosis, anaemia of chronic disease, hypoalbuminaemia. Non-inflammatory (e.g., osteoarthritis) shows brief *gel-phenomenon* stiffness (≤45 min, often <15 min) worsened by activity, and normal inflammatory markers.
- **Acute (≤6 weeks) vs chronic (>6 weeks).** Acute polyarthritis tends to be infective, crystal-induced, reactive or viral; chronic polyarthritis tends to be immune-mediated (RA, SLE) or degenerative.
- **Number and distribution of joints** — polyarticular (≥4), with attention to *which* joints (small vs large; upper vs lower; axial involvement), *symmetry*, and *temporal pattern*.

Causes of polyarthritis (grouped)

Category	Representative diseases
Chronic inflammatory, symmetric small-joint	Rheumatoid arthritis (RA); SLE; mixed connective tissue disease; polyarticular juvenile idiopathic arthritis
Seronegative spondyloarthritis (often asymmetric, lower-limb, axial)	Psoriatic arthritis; reactive arthritis; enteropathic (IBD-associated) arthritis; ankylosing spondylitis
Crystal-induced	Chronic tophaceous gout (may evolve into a polyarticular RA-mimic); CPPD (pseudogout)
Infective / post-infective	Polyarticular septic arthritis; gonococcal arthritis; *acute viral* — Chikungunya, parvovirus B19, hepatitis B, rubella; *chronic* hepatitis C polyarthritis; acute rheumatic fever
Connective-tissue / vasculitic	Systemic sclerosis, inflammatory myositis (polymyositis/dermatomyositis), Still's disease, sarcoid arthropathy, granulomatosis with polyangiitis (GPA)

Category	Representative diseases
Non-inflammatory / degenerative	Generalised (nodal) osteoarthritis
Paraneoplastic	Hypertrophic pulmonary osteoarthropathy (lung/GI carcinoma) — clubbing, periosteal new bone, RF-negative

Pattern recognition — the key to narrowing the differential

- **Temporal evolution:** *chronic/persistent* (OA, RA); *additive* — new joints add while old persist (RA, psoriatic arthritis); *intermittent* — symptom-free intervals (crystal arthritis, Lyme); *migratory* — inflammation moves from joint to joint (acute rheumatic fever, gonococcal and viral arthritis).
- **Symmetry & distribution: RA** is symmetric and additive, affecting **PIP, MCP, intercarpal and carpometacarpal (wrist)** joints with palpable synovial hypertrophy and *swan-neck/boutonnière* deformities, and characteristically **spares the DIP joints**. **Spondyloarthritis, reactive arthritis and gout** are typically *asymmetric and oligoarticular*, favouring the **lower limbs**; spine/sacroiliac involvement points away from RA. **Psoriatic arthritis** may involve DIP joints with **dactylitis** ("sausage digit"), nail pitting/onycholysis and *pencil-in-cup* radiographic change.
- **Extra-articular clues:** fever (Still's disease, infection, vasculitis), rash (SLE, psoriatic), nail changes (psoriatic/reactive), oral/genital ulcers and uveitis (Behçet's, spondyloarthritis), sicca (Sjögren's), Raynaud's (scleroderma/MCTD), proximal weakness (myositis). GPA arthritis prefers **larger joints (hips, ankles, wrists) and spares the small hand joints**, helping separate it from RA.

Pattern	Think of
Symmetric small-joint polyarthritis, DIP-sparing	Rheumatoid arthritis
Asymmetric, lower-limb, axial/sacroiliac	Spondyloarthritis, reactive arthritis
Acute symmetric self-limiting + fever, recent infection	Viral (Chikungunya, parvovirus B19)
Migratory + carditis/erythema marginatum	Acute rheumatic fever
DIP + nail disease + dactylitis	Psoriatic arthritis
Polyarthralgia >50 yr, proximal stiffness, RF-negative	Polymyalgia rheumatica

Clinical evaluation & investigations

- **History:** age/sex/ethnicity (gout & spondyloarthritis — men; RA, SLE, fibromyalgia — women), onset/chronology, evolution pattern, precipitants (trauma, drugs — Table 382-2, antecedent infection, comorbidities), and a full rheumatic review of systems.
- **Examination:** count tender/swollen joints (a *28-joint count* — PIPs, MCPs, wrists, elbows, shoulders, knees — is standard), distinguish true synovitis (boggy, grape-like) from bony hypertrophy (firm) and effusion (fluctuant; "bulge sign"/patellar ballottement at the knee), assess range of motion and deformity, and seek extra-articular signs.
- **Laboratory (targeted, confirmatory — not a screening battery):** FBC; **ESR/CRP**; **uric acid** (men 4.0–8.6 mg/dL; women 3.0–5.9; up to 50% normal during an acute attack); **RF** (positive in ~80%

of RA but also in chronic infection, SLE, Sjögren's) and **anti-CCP/ACPA** (more specific — high-titre or RF/anti-CCP *double positivity* predicts erosive disease); **ANA** with reflex profiling when SLE/CTD suspected; ASO/anti-DNase B (rheumatic fever); viral serology and hepatitis screen. Remember low pre-test probability gives poor predictive value (4–5% of healthy people are RF/ANA positive).

- **Synovial fluid analysis** — *always* indicated when sepsis, crystals or haemarthrosis is suspected, and for a flare in a single joint of a chronic polyarthritis (see table).
- **Imaging:** plain radiographs for chronicity/erosions/chondrocalcinosis; **ultrasound with power Doppler** detects early synovitis/erosions; **MRI** for early erosive change, osteonecrosis and axial disease; **DECT** localises urate deposition.

Synovial fluid	Appearance	WBC/µL	PMN	Examples
Normal	Clear, viscous	<200	<25%	—
Non-inflammatory	Clear, viscous, amber ("string sign")	<2000	mononuclear	OA, trauma
Inflammatory	Turbid, yellow, low viscosity	2000–50,000	PMN predominant	RA, gout, psoriatic, SLE
Septic	Opaque, purulent	>50,000 (often >100,000)	>75%	Septic arthritis
Haemorrhagic	Bloody	—	—	Trauma, coagulopathy, neuropathic

Crystals: monosodium urate — long, **needle-shaped, negatively birefringent** (gout); calcium pyrophosphate — short, **rhomboid, positively birefringent** (pseudogout). Gram stain and culture (plus NAAT for gonococcus, AFB/fungal culture for chronic monoarthritis) whenever infection is possible — crystal and septic arthritis can co-exist.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagnostic algorithm for musculoskeletal/polyarthritis evaluation** (Harrison Fig. 382-1): boxes/branches labelled — *Is it articular? → Acute vs Chronic (>6 wk) → Inflammation present? (morning stiffness, soft-tissue swelling, systemic symptoms, ESR/CRP) → Number of joints (1–3 vs >3) → Symmetric? → PIP/MCP/MTP involved? → Rheumatoid arthritis / SLE / Scleroderma / Psoriatic / Reactive / Enteropathic.*
- **Hand joint-distribution map** (Fig. 382-3) labelled: *1st CMC & DIP/PIP = OA (Heberden's & Bouchard's nodes); PIP/MCP/wrist = RA (DIP-sparing, swan-neck/boutonnière); DIP + dactylitis + nail pitting = psoriatic arthritis; 2nd–3rd MCP = haemochromatosis/CPPD.*

Clinical / Diagnostic significance

- **Red-flag polyarthritis:** new-onset febrile polyarthritis demands exclusion of **polyarticular septic arthritis** (mortality ~30%), disseminated gonococcal infection, endocarditis and crystal disease before labelling it autoimmune.

- **Early RA recognition matters** — disease-modifying therapy (DMARDs) should begin as soon as the diagnosis is certain to prevent erosions and deformity; NSAIDs do not alter progression.
- **Viral polyarthritis** (Chikungunya, parvovirus B19) mimics early RA but is usually febrile, self-limiting within weeks, and serology-confirmed — avoids unnecessary immunosuppression. **Hepatitis C** causes a chronic, *non-erosive*, RF-positive but anti-CCP-negative polyarthritis.
- **Don't miss mimics:** PMR (polyarthralgia >50 yr, RF-negative, proximal girdle stiffness, high ESR), GPA (large joints, small-hand-sparing), and paraneoplastic hypertrophic osteoarthropathy (clubbing, periosteal reaction, RF-negative).

High-yield exam pointers

- Polyarthritis = **≥4 joints** (Harrison); CMDT defines polyarticular as **≥5 joints**, oligoarticular 2–4 — quote both.
- The **four questions**: articular?, inflammatory?, acute/chronic?, how many/which joints — the spine of every answer.
- **Symmetric, DIP-sparing, PIP/MCP/wrist = RA; asymmetric, lower-limb, DIP + dactylitis = psoriatic/spondyloarthritis.**
- Temporal patterns: **migratory** = rheumatic fever, gonococcal, viral; **additive** = RA, psoriatic; **intermittent** = crystal, Lyme.
- **Anti-CCP is more specific than RF**; double positivity predicts erosive RA; up to 50% of active RA/SLE have a normal ESR/CRP.
- **Synovial WBC:** <2000 non-inflammatory, 2000–50,000 inflammatory, >50,000 (PMN >75%) septic. MSU = negatively birefringent needles; CPPD = positively birefringent rhomboids.
- ESR, RF and ANA are **confirmatory, not screening** tests — low yield when pre-test probability is low.
- **Febrile polyarthritis = exclude sepsis first.**

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Approach to Articular and Musculoskeletal Disorders" (J.J. Cush) — diagnostic framework, joint-pattern and temporal classification, synovial fluid analysis (Fig. 382-6), ANA patterns (Table 382-4), drug-induced musculoskeletal conditions, imaging; and "Osteoarthritis" for the degenerative differential.
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders" (Yazdany et al.) — diagnostic value of the joint pattern (Table 23–1), joint-fluid examination (Tables 23–2/23–3), and the differential diagnosis of polyarthritis/RA-mimics (viral, hepatitis C, gout, spondyloarthritis, PMR, GPA, paraneoplastic).

Coverage note: The corpus covers the *approach to* and *differential of* polyarthritis thoroughly within these two chapters; disease-specific classification criteria (e.g., 2010 ACR/EULAR RA criteria, Jones criteria) are detailed in their dedicated chapters and are summarised here only as far as the cited sources support.

◆ ◆ ◆

Psoriatic arthritis

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

Definition / Introduction — Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthritis in the spondyloarthritis spectrum, associated with cutaneous and/or nail psoriasis and usually negative rheumatoid factor. It may involve peripheral joints, sacroiliac joints and spine, entheses, tendon sheaths, and whole digits, producing dactylitis. Untreated disease can cause progressive erosive damage, deformity, disability, reduced quality of life, and increased cardiometabolic morbidity.

Etiopathogenesis and epidemiology

- **Psoriasis is common**: skin psoriasis affects about 2-3% of the population; PsA develops in a substantial minority of patients with psoriasis, with Harrison giving an approximate prevalence of 30% among psoriasis patients and Bolognia reporting 5-30% depending on the series.
- **Temporal relation**: in nearly 80% of PsA patients, psoriasis precedes musculoskeletal disease; in about 10%, arthritis may precede skin disease, and simultaneous onset also occurs. Hence, hidden psoriasis must be actively sought.
- **Age**: PsA most often appears in adult life, classically around 30-50 years, while psoriatic disease also has peaks in early and later adulthood.
- **Genetic and immune basis**: PsA is part of the spondyloarthritis family, with HLA-B27 especially relevant in axial PsA; Harrison reports HLA-B27 in about 20% of all PsA and about 50% of axial PsA.
- **Cytokine axis**: psoriatic disease is driven predominantly by **IL-17** and **IL-23** pathways, with contributions from TNF-alpha, IL-1 beta, and IL-6. This explains the efficacy of TNF, IL-17, IL-12/23, and IL-23 inhibitors.
- **Nail-joint link**: nail disease is a strong predictor of PsA because the nail unit is anatomically linked to the distal interphalangeal (DIP) joint enthesis. Nail involvement is much more frequent in PsA than psoriasis without arthritis.
- **Comorbid disease burden**: depression, obesity, metabolic syndrome, diabetes mellitus, fatty liver disease, hypertension, and cardiovascular disease are common and must be screened for.

Clinical phenotypes

Phenotype	High-yield clinical features
Asymmetric oligoarthritis	Often early PsA; fewer than 4 joints; commonly lower limb or small joints of hands/feet; may later become polyarticular and more symmetric.
Symmetric polyarthritis	Resembles rheumatoid arthritis but usually seronegative, with psoriasis/nail disease, DIP disease, dactylitis, enthesitis, or axial features.
DIP-predominant arthritis	Classic clue; DIP pain, swelling, stiffness, and deformity with nail pitting, onycholysis, subungual hyperkeratosis, or oil-drop change.
Spondylitis / sacroiliitis	Inflammatory back or neck pain, morning stiffness, improvement with activity; sacroiliitis may be unilateral/asymmetric and syndesmophytes are often bulky, asymmetric, and nonmarginal.

Phenotype	High-yield clinical features
Arthritis mutilans	Severe destructive form with osteolysis, telescoping digits, acro-osteolysis, and major deformity; uncommon but exam-important.

- Phenotypes overlap; do not force a patient into only one group. Modern descriptions add **enthesitis**, **dactylitis**, and **tenosynovitis** as core musculoskeletal domains.
- **Dactylitis** is diffuse inflammatory swelling of a whole finger or toe, due to involvement of joints, tendons, bone, and soft tissue; persistent dactylitis predicts structural damage.
- **Enthesitis** commonly affects the Achilles tendon insertion, plantar fascia, quadriceps insertion on the patella, patellar tendon insertion on the tibia, medial/lateral epicondyles, pelvic rim, spinous processes, and intercostal muscle insertions.

Cutaneous, nail and extra-articular disease

- **Skin psoriasis**: sharply demarcated erythematous plaques with silvery micaceous scale, commonly on scalp, elbows, knees, gluteal cleft, palms/soles, and intertriginous sites. Koebner phenomenon, infection, stress, lithium, beta blockers, antimalarials, and systemic glucocorticoid withdrawal may exacerbate psoriasis.
- **Hidden psoriasis**: inspect scalp, umbilicus, gluteal/natal cleft, genitals, inframammary areas, palms/soles, and external auditory canal in all seronegative arthritis.
- **Nail matrix disease**: pitting, leukonychia, crumbling, and red spots in the lunula.
- **Nail bed disease**: onycholysis, subungual hyperkeratosis, oil-drop/salmon patch change, and splinter hemorrhages.
- **Eye disease**: uveitis occurs in about 5% of PsA; acute anterior uveitis is typical, but posterior or bilateral disease may occur.
- **Gut and mucosal disease**: Crohn disease or ulcerative colitis may coexist; painful mouth ulcers and rarely urethritis can occur.
- **Systemic risk**: patients with psoriasis/PsA have increased cardiovascular risk, endothelial dysfunction, subclinical atherosclerosis, depression, and suicidality; obesity worsens disease activity and treatment response.

Diagnosis and classification

- The diagnosis is primarily **clinical**: inflammatory musculoskeletal disease plus psoriasis, nail disease, family history, typical pattern, dactylitis, enthesitis, or characteristic imaging.
- **CASPAR criteria**: inflammatory articular disease involving joint, spine, or enthesis plus >=3 **points**:

CASPAR item	Points
Current psoriasis diagnosed by rheumatologist/dermatologist	2
Personal history of psoriasis	1
Family history of psoriasis in first- or second-degree relative	1
Typical psoriatic nail dystrophy: pitting, onycholysis, hyperkeratosis	1

CASPAR item	Points
Negative rheumatoid factor	1
Current dactylitis or past dactylitis recorded by a rheumatologist	1
Juxta-articular new bone formation on hand/foot radiograph, excluding osteophytes	1

- CASPAR is a classification tool with high specificity and sensitivity, useful in exams and studies; bedside diagnosis still rests on pattern recognition and exclusion of mimics.
- **Laboratory tests are supportive, not diagnostic**: ESR/CRP are elevated in only about 50% despite active disease; high ESR/CRP predicts more severe disease and damage.
- RF is usually negative; low-titer RF or anti-CCP can occur in fewer than 10%, so seropositivity does not completely exclude overlap or coexisting RA.
- If PsA presents as monoarthritis, perform **synovial fluid analysis** to exclude septic arthritis, gout, and CPPD. Inflammatory fluid with WBC >2000/mcL, no crystals, and negative Gram stain/culture supports inflammatory arthritis in the right clinical setting.

Investigations and imaging

- **Baseline assessment**: tender/swollen joint count, dactylitis count, enthesitis examination, nail count, psoriasis body surface area, axial symptoms, function, pain score, ESR/CRP, CBC, renal and liver function, and cardiometabolic risk profile.
- **Disease activity tools**: DAPSA and Minimal Disease Activity are commonly used; skin burden can be estimated by palms, with one patient palm approximating 1% body surface area.
- **Plain radiographs**: obtain hands, feet, pelvis, spine, and symptomatic joints. Early disease may show soft-tissue swelling; periarticular osteopenia is usually absent.
- **Characteristic X-ray signs**: marginal erosions with **fluffy periosteal new bone**, joint-space narrowing, bony ankylosis, **pencil-in-cup deformity**, ray-distribution damage, osteolysis, and **acro-osteolysis** in arthritis mutilans.
- **Axial imaging**: pelvic radiograph may show asymmetric or unilateral sacroiliitis; spine films may show bulky, asymmetric, nonmarginal "chunky" syndesmophytes, often involving cervical and lumbar spine.
- **Ultrasound with Doppler**: useful for synovitis, tenosynovitis, erosions, and differentiating inflammatory enthesitis from mechanical pain or fibromyalgia tender points.
- **MRI**: detects synovitis, erosions, enthesitis, and active axial inflammation with bone marrow edema on STIR before radiographic change. CT is reserved when MRI is unavailable/contraindicated; bone scan is neither sensitive nor specific.

Management

- **Aim**: treat to target, with remission or low disease activity, prevention of structural damage, restored function, social participation, and improved quality of life.
- **Team and domains**: manage with rheumatology plus dermatology; add ophthalmology, gastroenterology, psychiatry, cardiology, endocrinology, dietetics, physiotherapy, and occupational therapy according to domains.

- **NSAIDs**: useful initially for short-term relief of peripheral arthritis, enthesitis, dactylitis, and axial symptoms; rarely sufficient alone and require monitoring for renal, gastrointestinal, hypertensive, and cardiovascular toxicity.
- **Local glucocorticoid injections**: useful for active arthritis, enthesitis, or dactylitis. Avoid injections around weight-bearing lower-limb entheses because of tendon rupture risk.
- **Systemic glucocorticoids**: generally avoid; if unavoidable for acute arthritis flare, use the lowest effective dose for the shortest time because tapering may precipitate pustular psoriasis.
- **Conventional synthetic DMARDs**: methotrexate, sulfasalazine, or leflunomide should be considered early for active peripheral arthritis, enthesitis, or dactylitis. Methotrexate is preferred when clinically relevant psoriasis is present; csDMARDs are not useful for predominant axial disease.
- **Targeted oral agents**: apremilast may be used for active non-axial musculoskeletal disease or skin disease; JAK inhibitors such as tofacitinib or upadacitinib are options, generally after TNF inhibitor failure and with attention to cardiovascular, malignancy, zoster, and thrombotic risk.
- **Biologic DMARDs**: TNF inhibitors include etanercept, adalimumab, infliximab, certolizumab, and golimumab; IL-12/23 inhibition includes ustekinumab; IL-17 inhibition includes secukinumab, ixekizumab, and bimekizumab; IL-23 inhibition includes guselkumab and risankizumab.
- **Domain choice**: for predominant skin disease with musculoskeletal disease, IL-12/23, IL-17, or IL-23 inhibitors are preferred over TNF inhibitors. For axial disease after NSAID failure, use a biologic or JAK inhibitor rather than csDMARD. For active IBD, prefer monoclonal anti-TNF, IL-12/23, IL-23, or JAK inhibitor therapy and avoid IL-17 inhibitors in active IBD. For uveitis, monoclonal anti-TNF therapy is preferred.
- **Precautions**: screen for latent tuberculosis, hepatitis B, and hepatitis C before biologics or JAK inhibitors. Avoid starting immunosuppression during severe infection. TNF inhibitors may worsen congestive heart failure or demyelinating disease; IL-17 inhibitors can cause mucocutaneous Candida and worsen active IBD.
- **Skin/nail therapy**: topical glucocorticoids, vitamin D analogues, topical retinoids, PUVA/UVB, and cyclosporine can help skin and nail disease but have limited musculoskeletal efficacy. Oral glucocorticoids should not be used for psoriasis.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Hand/foot PsA diagram**: label DIP arthritis, PIP involvement, dactylitis/sausage digit, nail pitting, onycholysis, fluffy periosteal new bone, pencil-in-cup deformity, ankylosis, and acro-osteolysis.
- **Domain-based management wheel**: label peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, nail disease, IBD, and uveitis; place NSAIDs, csDMARDs, biologic DMARDs, and targeted synthetic DMARDs around the wheel.

Clinical / Diagnostic significance

- In any **seronegative inflammatory arthritis**, look for psoriasis in hidden sites and examine nails; a single patch in scalp, umbilicus, or gluteal cleft can clinch the diagnosis.

- Distinguish PsA from **RA** by DIP disease, nail dystrophy, dactylitis, enthesitis, asymmetric/ray distribution, absence of nodules/RF, and axial disease.
- Distinguish PsA from **OA** by inflammatory stiffness, soft-tissue swelling, erosions with new bone, nail disease, dactylitis, and absence of pure osteophyte/Heberden-node pattern.
- Distinguish PsA monoarthritis from **gout, CPPD, and septic arthritis** by synovial fluid microscopy, Gram stain, and culture; psoriasis increases uric acid turnover, so gout can coexist.
- Distinguish axial PsA from ankylosing spondylitis by asymmetric sacroiliitis, bulky nonmarginal syndesmophytes, cervical involvement, and prominent peripheral/nail disease.
- Early diagnosis matters because PsA can produce irreversible erosions, joint lysis, ankylosis, deformity, and functional loss within months in aggressive cases.
- Cardiovascular prevention is part of PsA care: screen and treat hypertension, diabetes, dyslipidemia, obesity, smoking, fatty liver disease, depression, and suicidality.

High-yield exam pointers

- PsA = psoriasis/nail disease + seronegative inflammatory arthritis + enthesitis/dactylitis/axial disease.
- Five classical phenotypes: asymmetric oligoarthritis, symmetric polyarthritis, DIP arthritis, spondylitis, arthritis mutilans.
- Dactylitis is a severity marker; enthesitis commonly affects Achilles insertion and plantar fascia.
- Nail findings: pitting, onycholysis, subungual hyperkeratosis, oil-drop change, splinter hemorrhages.
- CASPAR: inflammatory articular disease plus >=3 points; current psoriasis scores 2.
- X-ray triad for exams: erosions plus fluffy new bone, pencil-in-cup deformity, asymmetric sacroiliitis/chunky syndesmophytes.
- ESR/CRP may be normal; RF/anti-CCP are usually negative but low-titer positivity can occur.
- Treatment is domain-based and treat-to-target; csDMARDs help peripheral disease, not axial disease.
- Avoid systemic steroids when possible; tapering can precipitate pustular psoriasis.

SOURCE & COVERAGE

Harrison 22e — "Spondyloarthritis"; Harrison 22e — "Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders"; Bolognia Dermatology — "Psoriasis"; CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders"; Braunwald — "Rheumatic Diseases and the Cardiovascular System".

◆ ◆ ◆

Raynaud's phenomenon

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

Definition / Introduction — *Raynaud phenomenon (RP)* is a syndrome of **episodic, reversible digital ischaemia** caused by an exaggerated vasoconstrictor response of digital arteries and cutaneous arterioles to **cold exposure or emotional stress**. It manifests as a sharply-demarcated, often *triphasic* colour change of the digits — **pallor → cyanosis → rubor**. It is broadly divided into **primary (idiopathic) RP** (no underlying disease) and **secondary RP** (associated with another disorder, most importantly systemic sclerosis). Distinguishing the two is the central clinical task, because secondary RP can progress to ulceration, gangrene and digital loss.

Pathophysiology

- The final common pathway is **inappropriate vasospasm of digital arteries, precapillary arterioles and cutaneous arteriovenous shunts**, triggered by cold or sympathetic (emotional) stimuli.
- Three interacting categories of abnormality are recognised:
  - **Neural** — exaggerated sympathetic / **α-adrenergic (α2) vasoconstrictor** reactivity of digital vessels.
  - **Vascular / endothelial** — endothelial dysfunction with reduced vasodilators (**nitric oxide**, prostacyclin) and excess vasoconstrictors (**endothelin-1**); in secondary RP there is true structural vasculopathy with intimal proliferation.
  - **Intravascular** — platelet activation, raised plasma viscosity and impaired fibrinolysis (relevant in blood dyscrasias).
- In **systemic sclerosis** the digital vessels show a **proliferative obliterative vasculopathy**, so vasospasm is superimposed on fixed structural narrowing — explaining the severity, ischaemic ulcers and autoamputation seen in secondary RP.
- The therapeutic rationale follows the mechanism: **calcium-channel blockers / α-blockers** counter vasoconstriction, **PDE-5 inhibitors and nitrates** augment the NO–cGMP pathway, and **endothelin-receptor antagonists / prostacyclins** correct the vasodilator deficit.

Clinical features — the triphasic colour response

- Classic well-demarcated colour sequence on cold/stress exposure:
  - **Pallor (white)** — *ischaemic phase*; vasospasm of digital arteries.
  - **Cyanosis (blue)** — deoxygenated blood pooling in dilated capillaries and venules; accompanied by cold, numbness or paraesthesia.
  - **Rubor (red)** — on rewarming, *reactive hyperaemia* with throbbing, painful, warm digits.
- The full triphasic response is typical but **not universal** — some patients have only pallor + cyanosis, others only cyanosis.
- **Fingers > toes** (toes affected in ~40%); attacks usually begin in one or two fingertips and extend to involve whole/all fingers; the **thumbs are characteristically spared**.
- Rare sites: **earlobes, tip of nose, tongue, nipple, penis**.

- Frequent association with **migraine** and **variant (Prinzmetal) angina** from coronary vasospasm — suggesting a shared vasospastic predisposition.
- Attacks terminate spontaneously or on rewarming; the patient is typically **asymptomatic between attacks**.

Primary versus secondary RP

Feature	Primary RP (Raynaud disease)	Secondary RP
Frequency	>50% of all RP; 2–6% of adults	Less common
Sex / age	Women ≈5×; onset **15–30 / 20–40 yr**	Either sex; older onset
Pattern	**Symmetric, bilateral**, all fingers	May be **unilateral / 1–2 digits only**
Underlying disease	None (by definition, after exclusion)	Rheumatic/other disease present
Nailfold capillaries	**Normal** (regular hairpin loops)	**Abnormal** — dilated/giant loops, dropout
ANA / serology	Negative	Often positive
Tissue damage	**No** pitting, ulcer or gangrene; <1% lose part of a digit	**Yes** — pitting, ulcers, gangrene, autoamputation
Course	Mild; improves spontaneously in ~15%, progresses in ~30%	Depends on underlying disease

- *LeRoy–Medsger criteria* for **primary RP**: symmetric attacks, **no necrosis/ulceration**, no identifiable secondary cause, **normal nailfold capillaries**, negative ANA and normal ESR.

Causes of secondary RP (Harrison/CMDT classification)

Category	Examples
Connective-tissue / rheumatic	**Systemic sclerosis** (80–90%; presenting symptom in 30%), **SLE** (~20%), dermatomyositis/polymyositis (~30%), rheumatoid arthritis, **MCTD**, Sjögren syndrome
Arterial occlusive	Atherosclerosis (common in **men >50 yr**), **thromboangiitis obliterans/Buerger** (young male smokers), acute arterial occlusion/embolism, **thoracic outlet syndrome**
Pulmonary	Pulmonary (arterial) hypertension
Neurological	Carpal tunnel syndrome, complex regional pain syndrome, intervertebral disc disease, syringomyelia, spinal cord tumour, stroke, poliomyelitis
Blood dyscrasias	**Cold agglutinins, cryoglobulinaemia, cryofibrinogenaemia**, myeloproliferative disorders, lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia)
Trauma / occupational	**Vibration injury** (chain-saw, jackhammer), **hammer-hand syndrome**, electric shock, frostbite, typing, piano playing
Drugs & toxins	**Ergot derivatives, methysergide, β-blockers**, sympathomimetics, serotonin agonists (sumatriptan), cocaine, nicotine/caffeine; chemotherapy — **bleomycin, vinblastine, cisplatin, gemcitabine**; vinyl chloride, epoxy resins

Category	Examples
Endocrine / misc.	Hypothyroidism, phaeochromocytoma, migraine

Diagnostic approach

- **Clinical diagnosis** — based on the characteristic colour changes; the key step is to **screen for a secondary cause**.
- **Bedside examination** is often normal; radial, ulnar and pedal pulses are normal in primary RP (diminished/absent pulses point to occlusive disease/Buerger). Look for **sclerodactyly, digital pitting/ulcers, skin tightening, telangiectasia, calcinosis, rash, synovitis**.
- **Nailfold capillaroscopy** — the single most useful office test. Place a drop of **grade-B immersion oil** at the cuticle and view with a **dermatoscope or ophthalmoscope set to 40 dioptres**. *Dropout of capillaries with dilatation of remaining loops (giant capillaries)* indicates **secondary RP, most often systemic sclerosis**. The finding is **highly specific but of low sensitivity**.
- **Serology** — ANA, anti-centromere (limited SSc/CREST), anti–Scl-70 (topoisomerase I, diffuse SSc), anti–RNA polymerase III, ENA panel; complement, cryoglobulins, cold agglutinins as indicated.
- **Other** — ESR/CRP, FBC (myeloproliferative/hyperviscosity), TFTs; nerve-conduction studies for carpal tunnel; vascular imaging only if fixed occlusive disease is suspected. **Digital angiography is not indicated** for diagnosis of primary RP.

Management

- **General / non-pharmacological (first-line, often sufficient in primary RP):**
  - **Keep the whole body warm** — gloves/mittens *plus* warm clothing for trunk, head and feet to prevent cold-induced reflex vasoconstriction.
  - **Stop smoking**; protect hands from trauma; treat fissures with emollients; **avoid precipitating drugs** (β-blockers, ergot, sympathomimetic decongestants/amphetamines).
- **Pharmacological (reserve for severe symptoms or tissue injury):**
  - **Dihydropyridine calcium-channel blockers = first-line** — slow-release **nifedipine 30–120 mg/day**, **amlodipine 5–20 mg/day** (also felodipine, isradipine, nisoldipine); more effective than verapamil, nicardipine and **diltiazem** (less effective). CCBs work better in **primary** than secondary RP.
  - **α1-adrenergic antagonists** — prazosin (also doxazosin, terazosin).
  - **PDE-5 inhibitors — sildenafil, tadalafil, vardenafil** — useful in **secondary RP (e.g. systemic sclerosis)**, added to or substituted for CCBs.
  - **Topical nitrates** (nitroglycerin); **ARBs**; **SSRIs (fluoxetine)** as add-ons.
  - **Endothelin-receptor antagonist bosentan** — prevents/heals **digital ulcers** in systemic sclerosis.
  - **IV prostacyclin / analogues — epoprostenol, iloprost, treprostinil** — for **critical digital ischaemia / threatened digital loss**.

- **Procedural — digital (peripheral) sympathectomy** for progressive ischaemia refractory to medical therapy. **Botulinum toxin** injection has shown inconsistent/negative results in controlled trials.
- **Admit** patients with **critical digital ischaemia** (severe pain, demarcation) for intensive therapy; refer secondary RP to a rheumatologist.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Triphasic colour change of a digit** — three finger panels in sequence with labels: *Phase 1 — Pallor (white): digital artery vasospasm / ischaemia*; *Phase 2 — Cyanosis (blue): deoxygenated blood in dilated capillaries-venules, numbness*; *Phase 3 — Rubor (red): reactive hyperaemia on rewarming, throbbing pain*. Add trigger arrow "Cold / emotional stress".
- **Nailfold capillaroscopy comparison** — two boxes: *Primary RP — regular, evenly-spaced hairpin capillary loops (normal)* vs *Secondary RP (scleroderma pattern) — dilated/giant loops, haemorrhages and capillary dropout (avascular areas)*.

Clinical / Diagnostic significance

- RP is the **commonest and earliest manifestation of systemic sclerosis** (presenting symptom in 30%, may precede skin disease by years) and is a core feature of the **CREST syndrome** (*Calcinosis, Raynaud, oEsophageal dysmotility, Sclerodactyly, Telangiectasia*) of limited cutaneous SSc.
- The triad of **RP + abnormal nailfold capillaroscopy + a specific autoantibody** (anti-centromere or anti–Scl-70) strongly predicts evolution to a definite connective-tissue disease and warrants surveillance for **interstitial lung disease and pulmonary hypertension**.
- **Red flags for secondary RP**: onset >40 yr or in a male, **asymmetric/unilateral** attacks, digital pitting/ulcers/gangrene, abnormal nailfolds, positive ANA, systemic features.
- Recognising RP as a marker of **vasospasm** also flags associations with **migraine** and **coronary (variant) angina**.

High-yield exam pointers

- **Triphasic colour change = white → blue → red** (pallor–cyanosis–rubor); thumbs typically **spared**.
- **Primary RP**: >50% of cases, young women, **bilateral/symmetric, normal nailfolds, negative ANA, no tissue loss** (<1% lose a digit).
- **Secondary RP**: **systemic sclerosis (80–90%)** is the prototype; also SLE (~20%), DM/PM (~30%), RA, MCTD.
- **Nailfold capillaroscopy** (immersion oil + ophthalmoscope at 40 D): **dilated loops + dropout = secondary RP**; highly specific, low sensitivity.
- **First-line drug = dihydropyridine CCB** (nifedipine/amlodipine); CCBs work better in primary RP.
- **PDE-5 inhibitors, bosentan and IV prostacyclins (iloprost)** are reserved for **secondary RP with digital ulcers / critical ischaemia**.

- *LeRoy–Medsger criteria* define primary RP (symmetric, no necrosis, normal capillaries, ANA negative, normal ESR).
- **Buerger disease and acrocyanosis** are key differentials — Buerger: male smokers, absent pulses, 1–2 digits; acrocyanosis: **persistent (not episodic)**, diffuse cyanosis, no pallor phase.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — *"Arterial Diseases of the Extremities"* (Raynaud phenomenon: classification, primary vs secondary, clinical features, treatment) and *"Systemic Sclerosis (Scleroderma) and Related Disorders"* (secondary RP, scleroderma vasculopathy, nailfold/acro-osteolysis).
- **CMDT 2026** — *"Raynaud Phenomenon"* and *"Systemic Sclerosis"* (Rheumatologic, Immunologic & Allergic Disorders) — essentials of diagnosis, Table 23–9 causes of secondary RP, nailfold capillaroscopy technique, drug regimens and doses.
- *Coverage note:* The named **LeRoy–Medsger criteria** for primary RP and the explicit **neural/vascular/intravascular** mechanistic triad are universally-accepted standard internal medicine but are not stated verbatim in the cited corpus; all disease associations, percentages, drugs and doses given here are taken directly from Harrison 22e and CMDT 2026.

◆ ◆ ◆

Reactive arthritis

Asked in: Paper III 09/2025 · Paper III Jul 2021 · Paper III Nov 2019 (3×) — RGUHS MD General Medicine

Definition / Introduction

Reactive arthritis (ReA) is a sterile, immune-mediated inflammatory arthritis that develops *after* a urogenital or gastrointestinal infection with well-defined triggering microorganisms that are **not cultivable from the affected joints**. It belongs to the **peripheral spondyloarthritis (pSpA)** family, is strongly linked to **HLA-B27**, and classically presents as an asymmetric lower-limb oligoarthritis accompanied by extra-articular (ocular, mucocutaneous, genitourinary) features. The historical triad of arthritis, conjunctivitis and urethritis was formerly termed *Reiter syndrome*, an eponym now largely abandoned.

Place within spondyloarthritis & classification

- **Spondyloarthritis (SpA)** is a family of immune-mediated arthritides sharing axial/peripheral joint disease, enthesitis, dactylitis, uveitis, psoriasis, IBD, absence of rheumatoid factor/nodules, familial clustering and **HLA-B27** association (Moll & Wright, 1974).
- The **2009 ASAS** classification splits SpA into **axial SpA** (radiographic = ankylosing spondylitis, and non-radiographic) and **peripheral SpA**.
- **ReA is a peripheral SpA**, alongside **psoriatic arthritis, IBD-associated arthritis and undifferentiated pSpA**. Its hallmark features per the SpA spectrum table are: *urethritis, history of preceding Salmonella/Shigella/Yersinia/Campylobacter/Chlamydia infection, mucosal ulcers, conjunctivitis and keratoderma blennorrhagica*.

- **Nomenclature discipline (Harrison):** the term ReA is *restricted* to acute SpA triggered by a genitourinary or GI infection and related to HLA-B27. Arthritides following acute rheumatic fever, meningococcus, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Chlamydia pneumoniae*, beta-haemolytic streptococci, some live vaccines and COVID do **not** fit the SpA construct and are termed "**post-infectious arthritides**", not ReA.

Aetiopathogenesis

Component	Detail
GI (dysenteric) triggers	*Salmonella, Shigella, Yersinia enterocolitica, Campylobacter* — develops 1–4 weeks after enteritis
Urogenital (venereal) trigger	*Chlamydia trachomatis* (± *Ureaplasma urealyticum*)
Genetic	**HLA-B27** present in **50–80%** of patients (Harrison); CMDT: ~80% in White, 50–60% in Black patients
Latent interval	**1 day to 4 weeks** between infecting episode and arthritis
Joint fluid	**Culture-negative** (sterile) — distinguishes from septic arthritis

- **Mechanism:** an antecedent mucosal infection at the gut or urogenital tract, in a genetically predisposed (HLA-B27$^+$) host, drives a **barrier-integrity loss** allowing translocation of bacteria/microbial peptides that incite immune activation at joints and entheses. Proposed HLA-B27 mechanisms include the "**arthritogenic peptide**" theory (HLA-B27 presents microbial peptides to CD8$^+$ T cells → molecular mimicry), **HLA-B27 homodimer** interaction with KIR3DL2 driving IL-17, and unfolded-protein-response–linked IL-23 release. The downstream effector axis is **TNF-α and the IL-23/IL-17 pathway**.
- **HLA-B27 may promote intracellular survival/persistence** of the triggering organism (e.g., *Chlamydia*) in macrophages, providing a route to chronicity.
- **Epidemiology:** young adults, male predominance for venereal-triggered disease; overall incidence ≈ **3.4 cases per 100,000 person-years**; about **2.6%** of patients develop ReA after an enteric infection (Campylobacter/Salmonella/Shigella/Yersinia). Prevalence parallels the **North–South gradient of HLA-B27** (classic Scandinavian post-dysentery outbreaks, now declining with improved hygiene).

Clinical features

- **Inflammatory musculoskeletal disease is essential for diagnosis.** Typical pattern: **asymmetric, oligoarticular** (≤4 joints) inflammatory arthritis of **large weight-bearing lower-limb joints** (knee, ankle).
- **Enthesitis** (Achilles tendinitis, plantar fasciitis — heel pain), **tendonitis, bursitis, dactylitis** ("sausage digit"), **inflammatory back pain** and **sacroiliitis**.

System	Manifestation
Joints	Asymmetric LL oligoarthritis; enthesitis; dactylitis; sacroiliitis/spondylitis (≥20%, esp. after recurrences)

System	Manifestation
Ocular	**Conjunctivitis** (mild, early); **acute anterior uveitis** (later, more significant, HLA-B27$^+$)
Genitourinary	**Urethritis** (sterile); **circinate balanitis**
Mucocutaneous	**Keratoderma blennorrhagica** (palms/soles, indistinguishable from pustular psoriasis); painless **oral ulcers/stomatitis**; nail changes mimicking psoriasis; *erythema nodosum*
Cardiac	**Carditis and aortic regurgitation** (uncommon)
Systemic	Fever, weight loss common at onset

- **Classic triad** ("can't see, can't pee, can't bend the knee"): **arthritis + conjunctivitis + urethritis** — the full triad is present in a minority.

Investigations / Diagnosis

- **Clinical diagnosis** — recognition of the pattern plus identification of an **antecedent infection**, and **exclusion** of other causes (notably septic/gonococcal arthritis and other post-infectious arthritides).
- **Identify the trigger: stool cultures** (Salmonella, Shigella, Campylobacter, Yersinia) — often negative by the time arthritis appears, as GI symptoms have resolved; **molecular testing / NAAT for *Chlamydia trachomatis*** — *all patients should be offered Chlamydia screening.*
- **HLA-B27** — supports diagnosis and predicts chronicity/uveitis; not diagnostic alone.
- **Inflammatory markers:** ESR/CRP raised (non-specific). **RF and anti-CCP negative** (seronegative).
- **Synovial fluid:** inflammatory but **sterile (culture-negative)** — crucial to exclude septic arthritis.
- **Imaging:** plain films may show enthesophytes, "fluffy" periostitis, sacroiliitis in chronic/recurrent disease; MRI for early sacroiliitis/enthesitis.
- Serology for enteric pathogens is used mainly in **epidemiological studies** (low yield in routine practice).

Differential diagnosis

Mimic	Discriminating feature
Gonococcal (disseminated GC) arthritis	Marked improvement within 24–48 h of antibiotics; positive cultures/NAAT; tenosynovitis, pustular skin lesions
Septic (non-gonococcal) arthritis	Monoarticular, synovial WBC often >50,000/µL, positive Gram stain/culture
Psoriatic arthritis	Pre-existing psoriasis; keratoderma is histologically identical to pustular psoriasis
Ankylosing spondylitis / axSpA	Predominant axial disease, no antecedent infection
Rheumatoid arthritis	Symmetric small-joint polyarthritis, RF/anti-CCP positive

Mimic	Discriminating feature
Behçet disease	**Painful** oral/genital ulcers (ReA ulcers are **painless**), ocular & joint overlap
Acute rheumatic fever / crystal arthritis	Migratory; ASO/streptococcal evidence; crystals on polarised microscopy

Management / Treatment

- **No formal ReA treatment guidelines exist**; management mirrors that of **peripheral SpA**.
- **Acute arthritis (first line): NSAIDs** at the highest tolerable dose are the mainstay. **Intra-articular glucocorticoids** for mono-/oligoarthritis; **short-term low-dose systemic glucocorticoids** for polyarticular involvement.
- **Antibiotics: not used routinely.** Treating an active non-gonococcal STI reduces the chance of ReA developing. For **chronic *Chlamydia*-induced ReA**, one RCT showed a **6-month course of rifampin (300 mg BD) plus either doxycycline (100 mg BD) or azithromycin** outperformed placebo — *not replicated*, so long-term antibiotics are **not** recommended generally.
- **Chronic ReA (>6 months / NSAID-refractory): conventional DMARDs — sulfasalazine (1 g BD, up to 3 g/day) or methotrexate (up to 25 mg/week)**; if refractory, **TNF inhibitors** (or anti–IL-17 biologics), as used across the other spondyloarthropathies.
- **Course/prognosis:** often **self-limiting**, resolving over weeks to months; recurrences are common. **HLA-B27 positivity predicts evolution to chronicity**, recurrent disease and sacroiliitis/AS, sometimes with permanent articular destruction.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **"Clinical features of reactive arthritis" – stick-figure schematic** with labels: *Acute anterior uveitis / conjunctivitis* (eye), *painless oral ulcers* (mouth), *urethritis + circinate balanitis* (genitalia), *keratoderma blennorrhagica* (soles), *asymmetric oligoarthritis of knee & ankle* (lower limbs), *dactylitis ("sausage digit")*, *enthesitis – Achilles/plantar fascia (heel)*, *sacroiliitis* (pelvis).
- **Pathogenesis flow diagram:** *Triggering infection (GI: Salmonella/Shigella/Yersinia/Campylobacter OR GU: Chlamydia) → Barrier-integrity loss / antigen translocation → HLA-B27⁺ host (arthritogenic peptide → CD8⁺ T cell; TNF-α & IL-23/IL-17 axis) → Sterile reactive synovitis + enthesitis (1 day–4 weeks later).*

Clinical / Diagnostic significance

- **Always exclude septic and gonococcal arthritis first** by synovial fluid analysis and culture — the single most important practical step in any acute mono-/oligoarthritis.
- A **sterile arthritis + recent diarrhoea or urethritis** in a young adult should trigger HLA-B27 testing and *Chlamydia* screening of the patient (and partner).
- **Anterior uveitis** in an HLA-B27⁺ patient is an ophthalmic emergency requiring urgent slit-lamp review; it may recur and threaten vision.

- ReA can be the **presenting illness of underlying HIV** and may run a more severe, treatment-resistant course in that setting — screen when clinically appropriate.

High-yield exam pointers

- **Triggers:** GI — *Salmonella, Shigella, Yersinia, Campylobacter*; GU — *Chlamydia trachomatis*. **Latent interval 1 day–4 weeks.**
- **HLA-B27 positive in 50–80%**; predicts chronicity, sacroiliitis and uveitis.
- **Joint fluid is STERILE (culture-negative)** — defining feature vs septic arthritis.
- **Classic triad** = arthritis + conjunctivitis + urethritis ("can't see, can't pee, can't bend the knee"); old eponym *Reiter syndrome*.
- Skin/mucosa: **keratoderma blennorrhagica** (≈ pustular psoriasis), **circinate balanitis**, **painless** oral ulcers.
- **RF/anti-CCP negative** (seronegative spondyloarthritis); part of **peripheral SpA**.
- **Treatment:** NSAIDs first → intra-articular/short systemic steroids → **sulfasalazine/methotrexate** → **TNFi**; antibiotics *not* routine.
- **≥20% develop sacroiliitis/AS** with recurrence; mostly self-limiting but may become chronic.
- **DDx pearl:** gonococcal arthritis improves dramatically within 24–48 h of antibiotics; Behçet ulcers are **painful** whereas ReA ulcers are **painless**.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e — "Spondyloarthritis"** (Reactive Arthritis section: clinical features, triggers, HLA-B27 association/pathogenesis, diagnosis and treatment; SpA spectrum/ASAS classification).
- **CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders"** (Reactive Arthritis: Essentials of Diagnosis, clinical findings, differential diagnosis, current treatment including the rifampin-plus-doxycycline/azithromycin regimen and biologics).

Coverage note: The corpus does not use the eponym *Reiter syndrome* or the "can't see, can't pee, can't bend the knee" mnemonic — these are included as universally accepted standard internal-medicine teaching for completeness; all organism lists, doses, percentages and criteria above are taken verbatim from Harrison 22e and CMDT 2026.

◆ ◆ ◆

Seronegative spondyloarthritis

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — *Seronegative spondylarthritis (spondyloarthritis, SpA)* is a family of immune-mediated inflammatory arthritides that share overlapping clinical, genetic and pathological features and are united by the **absence of rheumatoid factor (RF) and anti-CCP antibodies** ("seronegative") and by a striking association with **HLA-B27**. First delineated by *Moll and Wright (1974)* as distinct from rheumatoid arthritis (RA), the group is characterised by **sacroiliitis/inflammatory spinal lesions, asymmetric large-joint lower-limb oligoarthritis, enthesitis, dactylitis ("sausage digit")**, and extra-articular features (acute anterior uveitis, psoriasis, inflammatory bowel disease [IBD]) with a familial tendency. Cumulative prevalence is ~2–3% — commoner than RA.

Concept of "seronegative" and the SpA spectrum

- **"Seronegative"** historically distinguished these arthritides from "seropositive" RA: RF and anti-CCP are *negative*, and rheumatoid nodules are absent.
- The 2009 **ASAS** (Assessment of SpondyloArthritis international Society) framework divides SpA by *dominant* clinical pattern into **axial SpA (axSpA)** and **peripheral SpA (pSpA)** — "axial" involvement is implied by the name but is *not* mandatory.
- Distinguishing musculoskeletal signature: **asymmetric, mono-/oligoarticular (≤4 joints) inflammatory arthritis of large lower-limb joints (esp. knee) with enthesitis, tendonitis and dactylitis** — contrasting with the symmetric polyarticular MCP/PIP involvement of RA.

Spondyloarthritis (SpA)	Conditions included
Axial SpA (axSpA)	Radiographic axSpA = **Ankylosing spondylitis (AS)**; Non-radiographic axSpA (nr-axSpA)
Peripheral SpA (pSpA)	**Psoriatic arthritis (PsA)**; **Reactive arthritis (ReA)**; **IBD-associated arthritis**; **Undifferentiated pSpA**
Sometimes included under pSpA	SAPHO syndrome; acne-associated arthritis; hidradenitis suppurativa–associated arthritis

Causes — aetiology and pathogenesis

SpA is a prototypic immune-mediated disease that uniquely **couples inflammation to structural damage** — inflammatory bone loss coexists with *pathological new bone formation* (syndesmophytes, ankylosis → "bamboo spine").

- **Genetic susceptibility (strongest):**
  - **HLA-B27** — an MHC class I allele, *the* major genetic risk factor; present in 85–90% of AS but only ~5–8% of healthy Caucasians. Risk of axSpA is ~5% in B27-positive subjects, rising to ~20% in B27-positive first-degree relatives of patients.
  - Pathogenic allotypes (e.g. **HLA-B*2704, B2705**) confer risk, whereas **HLA-B*2706 and B2709** do not — implicating specific peptide presentation.
  - Non-MHC genes: **ERAP1** (peptide-trimming enzyme; epistasis with HLA-B27), **IL-23R** polymorphisms (shared across SpA), and **HLA-Cw6** in PsA.

- **Proposed HLA-B27 mechanisms:** (1) *arthritogenic peptide* theory — B27 presents microbial peptides to CD8+ T cells with molecular mimicry; (2) **HLA-B27 homodimer** formation engaging **KIR3DL2** on T/NK cells → IL-17; (3) misfolding → **unfolded protein response / autophagy** → IL-23.
- **Environmental / triggering factors in genetically predisposed hosts:**
  - **Gut barrier loss and intestinal dysbiosis** — germ-free HLA-B27 transgenic rats fail to develop disease; subclinical gut inflammation is seen in up to 50% of new-onset SpA.
  - **Antecedent infection (ReA):** enteric *Salmonella, Shigella, Yersinia, Campylobacter* or urogenital *Chlamydia trachomatis*.
  - **Mechanical stress** at entheses → microdamage, immune activation and aberrant repair (new bone formation).
- **Effector cytokine hubs: TNF-α** (common to all domains) and the **IL-23/IL-17** axis (γδ T cells, Tc17/Th17, ILC3 at entheses) drive osteoproliferation via prostaglandin E2, IL-17A/F, IL-22, BMP and Wnt pathways — the rationale for biologic therapy.

Tabulated differences between the types

Feature	Ankylosing spondylitis (r-axSpA)	Psoriatic arthritis (PsA)	Reactive arthritis (ReA)	IBD-associated arthritis
Peak onset / sex	2nd–3rd decade, <45 y; **M:F 2:1**	Any age; ≈ M = F	Young men predominate	Any age
HLA-B27	**85–90%**	~20% overall (≈50% if axial/spondylitic)	**50–80%**	~50% *when sacroiliitis present* (B27 not a risk factor for IBD itself)
Trigger / association	None; familial, B27	Cutaneous & nail **psoriasis**	**GI** (*Salmonella/Shigella/Yersinia/Campylobacter*) or **GU** (*Chlamydia*) infection, 1 day–4 weeks earlier	Crohn's disease / ulcerative colitis
Sacroiliitis	**Bilateral, symmetric**	Often **asymmetric / unilateral**, may have spondylitis without sacroiliitis	Asymmetric / unilateral	Bilateral, symmetric (indistinguishable from AS)
Syndesmophytes	Thin, **marginal, vertical**, symmetric	**Chunky, non-marginal**, asymmetric	Coarse, non-marginal, asymmetric	As in AS
Peripheral arthritis	~30–40%; asymmetric oligoarthritis, lower limb; **hips** (root joint)	Oligoarticular→polyarticular; **DIP** disease; arthritis mutilans	Asymmetric **oligoarthritis, lower limbs**	Asymmetric oligoarthritis of large joints; may parallel or run independent of bowel activity

Feature	Ankylosing spondylitis (r-axSpA)	Psoriatic arthritis (PsA)	Reactive arthritis (ReA)	IBD-associated arthritis
Enthesitis / dactylitis	Enthesitis common; **dactylitis rare**	Both common; dactylitis a *severity marker*	Both common	Variable
Skin / mucosa	Psoriasis in ~10%	Psoriasis (definitional); **nail disease ~90%**	**Keratoderma blennorrhagica, circinate balanitis, oral ulcers**	Mucosal/IBD activity (± erythema nodosum)
Eye	**Acute anterior uveitis** ~40% (unilateral, episodic)	Uveitis ~5% (may be posterior/bilateral)	**Conjunctivitis** (early) + anterior uveitis	Anterior uveitis
Hallmark / eponym	"Bamboo spine"; Romanus (shiny-corner) & Andersson lesions	"Pencil-in-cup" deformity; "fluffy" periosteal new bone	*Reiter triad* = arthritis + urethritis + conjunctivitis	Gut–joint axis; arthritis may pre-date IBD

Classification criteria worth knowing

- **Modified New York criteria for AS** — *definite AS* = ≥1 clinical + 1 radiographic criterion:

Clinical criteria	Radiographic criterion
Low back pain >3 months, improved by exercise, not by rest	Bilateral grade ≥2 **sacroiliitis**, OR
Limited lumbar motion (frontal & lateral planes)	Unilateral/bilateral grade 3–4 sacroiliitis
Reduced chest expansion	*(Sacroiliitis graded 0–4: 0 normal → 4 total ankylosis)*

- **CASPAR criteria (PsA):** inflammatory articular disease *plus* ≥3 points from — current psoriasis (2) / personal/family history (1); psoriatic nail dystrophy; RF negative; dactylitis; juxta-articular new bone on radiograph (each 1). Specificity 98.7%, sensitivity 91.4%.
- **ASAS criteria for peripheral SpA:** arthritis or enthesitis or dactylitis **plus** ≥1 of (psoriasis, IBD, preceding infection, HLA-B27, uveitis, sacroiliitis on imaging) **or** ≥2 of the remaining SpA features.
- **Inflammatory back pain** (vs mechanical): insidious onset <45 y, >3 months, morning stiffness >30 min, night pain (second half), improves with exercise/not rest, good NSAID response.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Spectrum of SpA tree** — *Root box*: "Seronegative Spondyloarthritis (RF/anti-CCP negative, HLA-B27 linked)". *Branch 1* — **Axial SpA**: radiographic axSpA (= Ankylosing spondylitis) and non-radiographic axSpA. *Branch 2* — **Peripheral SpA**: Psoriatic arthritis, Reactive arthritis, IBD-associated arthritis, Undifferentiated pSpA. Side note: "sometimes included — SAPHO, acne-associated, hidradenitis suppurativa".
- **Pelvic/spine radiograph schematic** — label: **bilateral symmetric sacroiliitis**, **squaring of vertebral bodies**, **shiny corner (Romanus) sign**, **marginal vertical syndesmophytes**, **"bamboo spine"**, and (for PsA) **"pencil-in-cup" deformity** with **fluffy periosteal new bone**.

Clinical / Diagnostic significance

- **Investigations:** RF and anti-CCP *negative*; ESR/CRP raised in only ~30–50% (neither sensitive nor specific). **HLA-B27** supports diagnosis but is not confirmatory (occurs in healthy people). **X-ray pelvis (AP/Ferguson view)** for sacroiliitis; **MRI sacroiliac joints (STIR)** detects early osteitis/bone-marrow oedema before radiographic change; low-dose CT is an emerging alternative.
- **Differential diagnosis of "sacroiliitis":** DISH (flowing right-sided thoracic osteophytes, normal SI joints), osteitis condensans ilii (multiparous women), septic sacroiliitis (TB, brucellosis), insufficiency fracture.
- **Management (treat-to-target → low disease activity/remission):** NSAIDs at full dose first-line for axial disease + physiotherapy and smoking cessation; **csDMARDs (sulfasalazine, methotrexate)** help *peripheral* disease only (ineffective for axial). Escalate to **TNF inhibitors** (etanercept, adalimumab, infliximab, golimumab, certolizumab) or **IL-17 inhibitors** (secukinumab, ixekizumab; bimekizumab), then **JAK inhibitors** (tofacitinib, upadacitinib). Screen for **latent TB, HBV, HCV** before biologics. PsA adds IL-12/23 (ustekinumab), IL-23 (guselkumab, risankizumab), PDE-4 (apremilast), TYK2 (deucravacitinib). **Systemic steroids are ineffective/avoided in axSpA.**
- **Domain-/comorbidity-tailored choice:** TNF *monoclonal antibodies* preferred for coexistent uveitis or IBD; **IL-17 inhibitors are contraindicated in active IBD**; JAKi reserved post-TNF failure (CV/malignancy black-box warning).

High-yield exam pointers

- "Seronegative" = **RF and anti-CCP negative, no nodules**; unifying link is **HLA-B27** (strongest in AS, 85–90%).
- **Moll & Wright (1974)** separated SpA from RA and described **5 PsA patterns**: asymmetric oligoarticular, symmetric polyarticular, DIP-predominant, spondylitis, arthritis mutilans.
- **Modified New York criteria** define AS; sacroiliitis graded **0–4**; **CASPAR** for PsA; **ASAS** criteria for axial & peripheral SpA.
- **ReA** = *sterile* arthritis 1–4 weeks after enteric/urogenital infection; **Reiter triad** = arthritis + urethritis + conjunctivitis ("can't see, can't pee, can't climb a tree"); keratoderma blennorrhagica + circinate balanitis.

- **AS sacroiliitis = bilateral/symmetric** with **marginal vertical syndesmophytes**; **PsA = asymmetric** with **chunky non-marginal syndesmophytes** and "pencil-in-cup".
- **Acute anterior uveitis** (unilateral, episodic) is the commonest extra-articular feature of axSpA (~40%).
- Late complications of AS: vertebral fracture (lower cervical), cauda equina syndrome, aortic regurgitation, AV block, apical pulmonary fibrosis, **IgA nephropathy / AA amyloidosis**.
- **IL-17 inhibitors are contraindicated in active IBD**; TNF monoclonals preferred when uveitis/IBD coexist.

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Spondyloarthritis" (Deodhar & Elewaut): definition, SpA spectrum, HLA-B27/pathogenesis, modified New York & sacroiliitis grading, CASPAR & ASAS criteria, and individual disease descriptions (AS, PsA, ReA, IBD-associated, undifferentiated pSpA).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders" (Axial spondyloarthritis, Psoriatic arthritis, Reactive arthritis, IBD-associated spondyloarthritis): current diagnostic essentials and treatment (NSAIDs, TNFi, IL-17i, JAKi; domain-based PsA therapy).

◆ ◆ ◆

Sjögren's syndrome

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

Definition / Introduction — Sjögren's syndrome (Sjögren's disease) is a prototype systemic autoimmune disorder characterised by **lymphocytic infiltration of the exocrine glands** (chiefly lacrimal and salivary) producing **keratoconjunctivitis sicca** (dry eyes) and **xerostomia** (dry mouth), together with profound **B-cell hyperactivity**. It exists as a *primary* disorder or *secondary* to another rheumatic disease (most often rheumatoid arthritis, SLE, limited scleroderma, primary biliary cholangitis, Hashimoto thyroiditis). It is the autoimmune disease with the **highest risk of lymphoma**, making it an ideal model of both autoimmunity and lymphoid malignancy.

Epidemiology and Pathogenesis

- **Demographics:** middle-aged women predominate — female-to-male ratio **10–20:1** (CMDT quotes ~9:1); peak onset 40–60 years but any age including childhood. Prevalence ~**0.5–1%**; 5–20% of patients with other autoimmune diseases express sicca features. *Earlier-onset* disease is more aggressive (more systemic features and autoantibodies).
- **Core lesion:** activated **T lymphocytes** dominate early periductal infiltrates; in heavy lesions **B-cell populations** prevail with formation of **ectopic germinal centres**. Follicular, myeloid and plasmacytoid dendritic cells and macrophages are also present; inflammasome activation correlates with lymphoma risk.
- **Autoimmune epithelitis** (term coined by *Moutsopoulos*): ductal/acinar epithelial cells are active participants — they (1) express costimulatory molecules and surface **Ro/La autoantigens**, (2)

secrete proinflammatory cytokines and lymphocyte-attracting chemokines, (3) express **Toll-like receptors (TLR) 3, 7, 9** linking innate immunity to autoreactivity, and (4) display ICAM/CD40. Epithelial cells show *increased apoptosis*, whereas infiltrating lymphocytes resist it.

- **BAFF axis:** epithelial **B-cell–activating factor (BAFF)**, induced by type I/II interferons, is elevated in serum (especially with hypergammaglobulinaemia/autoantibodies) and exerts an antiapoptotic effect on B cells — the central driver of B-cell hyperactivity.
- **Genetics: HLA-DQA1*0501**; interferon/BAFF-axis genes (**IRF5, STAT4, BAFF**); B-cell genes (**EBF1, BLK**); and combined deficiencies of the classical complement pathway. Triggers include viruses, hormonal factors and stressful life events on a genetically primed background.

Clinical Manifestations

Glandular (sicca) features

- **Xerostomia:** difficulty swallowing dry food, burning mouth, increased **dental caries** (caries at the gum line strongly suggests Sjögren's), dry erythematous sticky mucosa, atrophic filiform papillae and a **deeply fissured tongue**; saliva is scanty or cloudy.
- **Keratoconjunctivitis sicca:** gritty/sandy foreign-body sensation, burning, redness, photophobia (photophobia may herald corneal ulceration); due to destruction of corneal and bulbar conjunctival epithelium.
- **Parotid/major salivary gland enlargement** (intermittent or persistent) in about two-thirds; other glands → dry nose/throat/**xerotrachea**, oesophageal dysmotility, atrophic gastritis, vaginal dryness with dyspareunia, dry skin.

Extraglandular (systemic) manifestations — in ~one-third; classified as nonspecific, periepithelial, immune-complex–mediated, and lymphoma (Harrison Table 373-1):

Manifestation	~Prevalence	Remarks
Fatigue / myalgias	25%	Overlapping fibromyalgia
Arthralgias / arthritis	60%	**Nonerosive**; may give *Jaccoud's arthropathy*
Raynaud's phenomenon	37%	Precedes sicca in one-third
Lung involvement	14%	Small-airway disease, lymphocytic interstitial pneumonitis (bronchitis sicca)
Kidney involvement	9%	Interstitial nephritis → distal (type I) RTA, hyposthenuria; nephrocalcinosis if untreated; *distal RTA in ~20%* (CMDT)
Liver involvement	6%	Primary biliary cholangitis (autoimmune cholangitis)
Small-vessel vasculitis	9%	Palpable **purpura**, urticaria, ulcers (immune-complex, cryoglobulin-associated)
Peripheral neuropathy	2%	Sensory/sensorimotor; mononeuritis multiplex
Glomerulonephritis	2%	Membranoproliferative with type II/III cryoglobulinaemia
Lymphoma	6%	Glandular **MALT** (marginal-zone) lymphoma most common

- **Neurological:** broad spectrum — peripheral neuropathy, dysautonomia, rarely CNS disease; *myelitis with anti-aquaporin-4 antibodies (NMO-spectrum)* is described.
- **Cardiovascular:** increased risk, as in RA and SLE.

Investigations and Autoantibody Profile

- **Ocular tests: Schirmer's I test** (≤5 mm wetting in 5 min is abnormal); tear break-up time / tear lysozyme; slit-lamp staining with **Rose Bengal or lissamine green** → punctate corneal/conjunctival erosions and filaments; **ocular staining score ≥5** (or *van Bijsterveld score ≥4*).
- **Salivary tests: sialometry** — unstimulated whole salivary flow **≤0.1 mL/min**; **salivary gland ultrasound** (hyperechoic bands, hypoechoic foci) of diagnostic and prognostic value; MRI/sialography.
- **Labial minor salivary gland biopsy:** the histopathologic standard — **focal lymphocytic sialadenitis with focus score ≥1** (≥1 focus of ≥50 lymphocytes per 4 mm^2).
- **Serology:** elevated ESR, polyclonal **hypergammaglobulinaemia**, ANA (~95%), **rheumatoid factor** (~70%), and antibodies to **Ro52/Ro60 (SS-A)** and **La (SS-B)**; leukopenia common. Low **C4**, **cryoglobulins**, and **monoclonal gammopathy** flag higher risk of vasculitis/lymphoma. Anti-Ro52 may associate with interstitial lung disease.
- **Niche antibodies:** anticentromere (limited-scleroderma picture), antimitochondrial (autoimmune cholangitis/PBC), anti–21-hydroxylase (blunted adrenal response), anti-CCP (erosive arthritis subset), anti–calponin-3 (peripheral neuropathy), anti-AQP4 (myelitis).

Classification Criteria and Differential Diagnosis

- **2016 ACR/EULAR classification criteria** (applied to patients with at least one symptom of ocular/oral dryness or suspicion from systemic disease, after exclusions) — weighted score, **classify if total ≥4**:

Item	Weight
Labial salivary gland with focal lymphocytic sialadenitis, **focus score ≥1**	3
Anti-SSA/Ro positive	3
Ocular staining score **≥5** (or van Bijsterveld ≥4) in ≥1 eye	1
Schirmer's ≤5 mm/5 min in ≥1 eye	1
Unstimulated whole salivary flow **≤0.1 mL/min**	1

- **Mandatory exclusions:** prior head-and-neck radiation, active **hepatitis C**, **AIDS**, **sarcoidosis**, **amyloidosis**, graft-versus-host disease, **IgG4-related disease**.
- **Differential of sicca / bilateral parotid enlargement:** drugs (anticholinergic, antihypertensive, antidepressant), viral infection (HCV, HIV, mumps, EBV, CMV), sarcoidosis, **IgG4-related disease**, diabetes, amyloidosis, lymphoma. Key discriminators: HIV sicca = young males, parotid **CD8** infiltrate, anti-Ro/La negative, HIV serology positive; sarcoidosis = noncaseating granulomas; HCV = lymphocytic infiltrate but milder, anti-SS-A/B negative.

Lymphoma Risk (high-yield)

- Highest lymphoma risk of any autoimmune disease (~5–10% lifetime); usually **extranodal, low-grade marginal-zone (MALT) B-cell lymphoma**, often found incidentally on labial biopsy.
- **Predictive risk factors** (Harrison Fig 373-2): persistent **parotid enlargement**, severe tongue atrophy, **palpable purpura**, **low C4**, **monoclonal gammopathy**, **cryoglobulins**, leukopenia, RF and anti-Ro/La positivity, and on histology **germinal-centre formation** with heavy focal lymphocytic infiltrates. CMDT adds splenomegaly, vasculitis, peripheral neuropathy and anaemia.
- **Worse survival** with B-symptoms, nodal mass >7 cm, and intermediate/high histological grade. **FDG-PET/CT** helps exclude lymphoma when suspected.

Treatment

- **Symptomatic/local (cornerstone):** artificial tears (hydroxypropyl methylcellulose, polyvinyl alcohol, 0.5% methylcellulose), **topical ciclosporin 0.05%** or **lifitegrast 5%** eye drops; boric-acid ointment/eye-patching for corneal ulcers. Frequent sips of water, sugar-free gum/candies; meticulous oral hygiene with **fluoride** to preserve dentition. **Avoid** drugs that worsen dryness (diuretics, antihypertensives, anticholinergics, antidepressants, decongestants).
- **Secretagogues:** muscarinic agonists **pilocarpine 5 mg** (TID–QID) and **cevimeline 30 mg TID**.
- **Musculoskeletal disease: hydroxychloroquine 200–400 mg/day** and/or **methotrexate 0.2–0.3 mg/kg/week** for arthralgia/mild arthritis.
- **Distal RTA:** oral **sodium bicarbonate 0.5–2 mmol/kg/day** in four divided doses.
- **Systemic/severe disease (vasculitis, purpura, persistent arthritis):** glucocorticoids and **rituximab (anti-CD20)**. Emerging B-cell–directed strategies: sequential **belimumab → rituximab**, **ianalumab** (anti-BAFF-receptor), CD40L/CD40-targeting agents; **nipocalimab** (FcRn blocker; FDA Breakthrough Therapy designation 2024). Lymphoma is treated per standard oncological guidelines.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Pathogenesis of autoimmune epithelitis (flow diagram):** Genetic background (HLA-DQA1*0501, IRF5, STAT4, BLK) + triggers (viruses, hormones, stress) → activated glandular **epithelial cell** (surface Ro/La, TLR 3/7/9, BAFF, chemokines) → recruitment of **T cells** then **B cells** → **ectopic germinal centre** → hypergammaglobulinaemia, anti-Ro/La, cryoglobulins → glandular destruction (sicca) and **risk of MALT lymphoma**. Labels: *epithelial cell, T cell, B cell, BAFF, germinal centre, anti-Ro/anti-La, lymphoma*.
- **Sicca complex face/eye schematic:** dry fissured tongue, dental caries at gum line, parotid enlargement; eye with Schirmer's strip (≤5 mm/5 min) and Rose Bengal-stained punctate keratitis. Labels: *xerostomia, parotid enlargement, keratoconjunctivitis sicca, Schirmer's test, Rose Bengal staining*.

Clinical / Diagnostic significance

- Suspect Sjögren's in any patient with persistent dry eyes/mouth, **bilateral parotid swelling**, Raynaud's, palpable purpura, or features of **distal RTA**; always take a drug history and exclude HCV/HIV, sarcoidosis and IgG4-related disease.
- The triad of **anti-Ro/La + focus score ≥1 labial biopsy + objective sicca tests** secures classification; biopsy and ultrasound carry prognostic weight.
- New or persistent parotid enlargement, purpura, low C4 or cryoglobulins mandates **active lymphoma surveillance**.
- *Checkpoint inhibitors (anti–PD-1/PD-L1)* can trigger de-novo Sjögren's — relevant in oncology patients.
- Anti-Ro/La are transplacental → risk of **neonatal lupus and congenital heart block** in offspring.

High-yield exam pointers

- **Autoimmune epithelitis** — the unifying concept; periepithelial lymphocytic infiltration of lung/kidney/liver.
- F:M **10–20:1**; prevalence ~0.5–1%; primary vs secondary (RA > SLE > scleroderma > PBC).
- **Anti-SSA/Ro and anti-SSB/La** are the hallmark antibodies; RF positive in ~70%, ANA ~95%.
- **Schirmer's ≤5 mm/5 min**; **focus score ≥1** on labial biopsy; unstimulated salivary flow **≤0.1 mL/min**.
- **2016 ACR/EULAR** weighted criteria — anti-Ro and biopsy weighted **3** each; classify at **≥4**.
- **Distal (type I) RTA** in ~20%; interstitial nephritis, hyposthenuria, nephrocalcinosis.
- **Highest lymphoma risk** of all autoimmune diseases → **extranodal marginal-zone (MALT) lymphoma**.
- First-line therapy is **substitutive/secretagogue** (artificial tears, pilocarpine/cevimeline); **rituximab/HCQ/MTX** for systemic disease.
- **Jaccoud's arthropathy** (reversible nonerosive deformity) and **NMO/anti-AQP4 myelitis** are classic associations.

SOURCE & COVERAGE

- Harrison's Principles of Internal Medicine, 22e — "Sjögren's Disease" (pathogenesis, autoimmune epithelitis, extraglandular-manifestation table, lymphoma risk factors, 2016 ACR/EULAR diagnostic algorithm, treatment).
- CMDT 2026 — "Rheumatologic, Immunologic, & Allergic Disorders: Sjögren Disease" (essentials, clinical findings, distal RTA frequency, ocular/oral therapy, lifitegrast, belimumab→rituximab, ianalumab, nipocalimab, prognosis/lymphoma predictors).
- Coverage note: The dedicated 2016 ACR/EULAR criterion **weights** (3/3/1/1/1, threshold ≥4) are universally accepted rheumatology; Harrison lists the same component items and exclusions in its diagnostic algorithm but does not tabulate the numeric weights.

◆ ◆ ◆

Rheumatoid arthritis — extra-articular manifestations and diagnosis

Asked in: Paper III 15 Apr 2026 — RGUHS MD General Medicine

Definition / Introduction — Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated inflammatory disease characterised by a symmetric, erosive polyarthritis of the small joints. Although predominantly articular, RA is fundamentally a **systemic disease**, and clinically significant *extra-articular manifestations (EAMs)* develop during its course in **up to 40% of patients**, sometimes even before the onset of arthritis. EAMs cluster in patients with a history of cigarette smoking, early significant disability, and seropositivity for **rheumatoid factor (RF)** or **anti-citrullinated protein antibodies (ACPA)**; their presence signifies severe disease and shortens survival. Their management rests on **aggressive control of the underlying RA** plus organ-specific therapy.

Determinants and overview of extra-articular disease

- **Risk factors for EAMs:** long-standing disease, high disease activity, smoking, high-titre RF/ACPA seropositivity, the HLA-DRB1 *shared epitope*, and hypocomplementemia (for vasculitis).
- EAMs contribute disproportionately to **morbidity and mortality** — patients with systemic involvement have shortened survival (overall RA mortality ~2× general population; median life expectancy reduced ~7 years in men, ~3 years in women).
- The incidence/severity of some EAMs (notably **Felty's syndrome** and **vasculitis**) has **declined** in the era of early, aggressive DMARD therapy.
- Most frequent EAMs: subcutaneous nodules, secondary Sjögren's, interstitial lung disease, pulmonary nodules, and anaemia.

Systemic and organ-specific extra-articular manifestations

System	Manifestations (key points)
Constitutional	Fatigue, malaise, low-grade fever, weight loss, depression, cachexia; reflect inflammatory burden, may precede arthritis. Fever **>38.3°C (101°F)** should raise suspicion of **vasculitis or infection**.
Cutaneous / Nodules	*Rheumatoid nodules* in **20–40%** — firm, non-tender, adherent to periosteum/tendon/bursa over pressure points (forearm, olecranon, sacrum, Achilles tendon); correlate with seropositivity. Also purpura, **pyoderma gangrenosum**, digital infarcts. *Accelerated nodulosis* in up to 10% on long-term methotrexate.
Ocular	**Keratoconjunctivitis sicca** (secondary Sjögren's, ~10%), **episcleritis**, **scleritis**, **scleromalacia perforans** (from scleral nodules), peripheral ulcerative keratitis.
Oral	Xerostomia, periodontitis.
Pulmonary	**Pleuritis** is the commonest pulmonary feature — exudative effusion (monocytes/neutrophils, characteristically **low glucose, low pH**). **Interstitial lung disease (ILD)** in ~10–12% — patterns are **UIP** (honeycombing) and **NSIP** (ground-glass + reticulation); restrictive PFTs with reduced **DLCO**; diagnosed on **HRCT**. **Pulmonary nodules**; *Caplan's syndrome* = rheumatoid pneumoconiosis (nodules + silica/coal exposure). Also organising pneumonia, bronchiolitis, bronchiectasis, pulmonary vasculitis.
Cardiac	**Pericardium** is the commonest cardiac site — clinical pericarditis <10% but detectable on echo/autopsy in ~50%; asymptomatic effusions up to 20%. Also myocarditis (necrotizing/granulomatous), cardiomyopathy, arrhythmia, mitral regurgitation; accelerated **ischaemic heart disease**.
Vasculitis	*Rheumatoid vasculitis* (now <1%) — long-standing, RF/ACPA-positive, hypocomplementemic disease. Nail-fold/digital pulp infarcts, petechiae, purpura, livedo reticularis, gangrene, painful leg ulcers; **mononeuritis multiplex** / sensorimotor polyneuropathy.
Haematologic	**Normochromic normocytic anaemia of chronic disease** (commonest; tracks CRP/ESR); reactive thrombocytosis. **Felty's syndrome** = triad of **neutropenia + splenomegaly + nodular RA** (<1%, late severe disease). **T-cell large granular lymphocyte (T-LGL) leukaemia** mimics Felty's. **Lymphoma** risk increased 2–4× (commonest = **diffuse large B-cell lymphoma**).
Neurologic	**Cervical (atlantoaxial C1–C2) subluxation** → compressive myelopathy (<10%); peripheral entrapment (carpal tunnel/median nerve); vasculitic neuropathy.
Renal	Membranous nephropathy; secondary (**AA**) **amyloidosis** from chronic inflammation.
Skeletal / Endocrine	Generalised **osteoporosis** (~2× risk; ~⅓ of postmenopausal women with RA) and fragility/hip fractures; hypoandrogenism.

Associated systemic comorbidities (high-yield)

- **Cardiovascular disease is the single most common cause of death in RA** — coronary and carotid atherosclerosis and heart failure are increased ~2-fold, *independent* of traditional risk factors, driven by systemic inflammation. Aggressive control of hypertension, diabetes, obesity, smoking, and RA inflammation improves outcomes.
- **Osteoporosis** — promoted by the inflammatory milieu (osteoclast activation via RANKL), chronic glucocorticoids, and immobility.

- **Infection** — both disease- and immunosuppression-related; a single joint inflamed out of proportion must be aspirated to exclude **septic arthritis**.

General principles of management

- **Treat-to-target (T2T):** early, aggressive therapy started *as soon as the diagnosis is certain*, with frequent escalation/modification of DMARDs to reach **low disease activity or remission** (monitored by **DAS-28, CDAI, SDAI**); ACR/EULAR provisional remission = tender joints ≤1, swollen joints ≤1, CRP ≤1 mg/dL, patient global ≤1, **or** SDAI ≤3.3.
- **Minimise long-term glucocorticoids**; individualise to maximise efficacy and minimise toxicity.
- Multidisciplinary care: smoking cessation, exercise (~150 min/week moderate-vigorous), physiotherapy, foot orthotics/wrist splints, cardiovascular risk reduction, osteoporosis screening/prophylaxis, and vaccination.

Pharmacological management (drug classes)

Class	Agents & key dosing	Major cautions
NSAIDs	Non-selective COX-1/COX-2 inhibition	**Adjunctive/symptomatic only** — do *not* prevent erosions; never monotherapy. Gastritis, PUD, renal injury.
Glucocorticoids	Low-dose prednisone **5–10 mg/d** (bridging/flares); intra-articular **triamcinolone 10–40 mg** (≤4×/yr); high-dose for serious EAMs	Osteoporosis (give bisphosphonate prophylaxis), infection, hyperglycaemia; use shortest duration (<3 months).
Conventional synthetic DMARDs (csDMARDs)	**Methotrexate** = anchor drug, **7.5–25 mg weekly** PO/SC + **folic acid 1 mg/d**; **Sulfasalazine** 500 mg BD→up to 3 g/d; **Leflunomide** 20 mg/d; **Hydroxychloroquine** 200–400 mg/d (**≤5 mg/kg**)	MTX: hepatotoxicity, myelosuppression, pneumonitis, **teratogenic (avoid in pregnancy/significant renal impairment)**. SSZ: check **G6PD**, cytopenias. LEF: teratogenic, long half-life. HCQ: **retinal toxicity** — baseline + annual eye exam.
Biologic DMARDs (bDMARDs)	**TNF inhibitors** (etanercept, infliximab, adalimumab, golimumab, certolizumab); **Abatacept** (CTLA-4 Ig, blocks T-cell co-stimulation); **Rituximab** (anti-CD20 B-cell depletion); **IL-6R inhibitors** (tocilizumab, sarilumab); **Anakinra** (IL-1RA)	All ↑ infection. TNFi: **screen/treat latent TB** before starting; avoid in chronic HBV and **NYHA class III/IV heart failure**; rare demyelination/drug-induced lupus. Rituximab: **HBV reactivation**, rare PML (~1:25,000). IL-6R: dyslipidaemia, neutropenia, **GI perforation**.
Targeted synthetic DMARDs (tsDMARDs)	**JAK inhibitors** — tofacitinib 5 mg BD, baricitinib 2 mg OD, upadacitinib 15 mg OD (oral)	**FDA black-box warning**: ↑ serious infection (herpes zoster), **thrombosis/VTE, MACE, malignancy, death**; screen for TB.

- **Stepwise (treat-to-target) approach:** start **methotrexate** monotherapy; if inadequate response at 3–6 months, escalate to **oral triple therapy (MTX + sulfasalazine + hydroxychloroquine)** *or* add an **anti-TNF / non-TNF biologic ± MTX**. Switching to an agent with a *different mechanism* (e.g., abatacept, rituximab, IL-6R or JAK inhibitor) is appropriate after biologic failure; **biologic DMARDs are not combined** with each other.

Specific management of extra-articular disease

- **General rule:** effective control of underlying RA favourably modifies most EAMs, and early aggressive treatment may *prevent* their occurrence.
- **RA-ILD:** challenging because MTX and leflunomide are themselves pulmonary toxins — treat with **high-dose corticosteroids plus azathioprine, mycophenolate mofetil, or rituximab**.
- **Severe EAMs** (necrotizing scleritis, pericarditis, vasculitis): **high-dose glucocorticoids** ± cytotoxic/immunosuppressive therapy; vasculitic ulcers may need immunosuppression and skin grafting.
- **Felty's syndrome:** treat with DMARDs (methotrexate); distinguish from T-LGL leukaemia.
- **Cervical myelopathy from atlantoaxial subluxation:** neurosurgical stabilisation when neurologic compromise occurs.

DIAGRAMS TO DRAW — IMAGE SUGGESTIONS

- **Diagram 1 — "Extra-articular manifestations of RA" body chart (a labelled human figure):** label organ pointers — *Ocular:* keratoconjunctivitis sicca, episcleritis, scleritis; *Oral:* xerostomia, periodontitis; *Pulmonary:* pleural effusion, pulmonary nodules, interstitial lung disease, organising pneumonia; *Cardiac:* pericarditis, myocarditis, ischaemic heart disease; *Haematologic:* anaemia of chronic disease, neutropenia, splenomegaly, **Felty's syndrome**, lymphoma; *Neurologic:* cervical myelopathy; *Renal:* membranous nephropathy, secondary amyloidosis; *Skin:* rheumatoid nodules, purpura, pyoderma gangrenosum; *Skeletal:* osteoporosis.
- **Diagram 2 — Treat-to-target escalation ladder:** boxes from bottom to top — *MTX monotherapy → MTX + triple therapy OR add anti-TNF/non-TNF biologic ± MTX → switch mechanism (abatacept / rituximab / IL-6R / JAK inhibitor)*; side arrow labelled "**Target = low disease activity / remission (DAS-28, CDAI, SDAI)**"; bracket labelled "glucocorticoid bridge, NSAID adjunct".

Clinical / Diagnostic significance

- Presence of EAMs marks **severe, seropositive disease** and mandates aggressive systemic therapy and vigilant monitoring.
- **Workup pearls:** HRCT + PFTs (DLCO) for suspected ILD; echocardiography for pericardial disease; nerve conduction studies for mononeuritis multiplex; CBC + splenic imaging and peripheral-blood flow cytometry (to exclude T-LGL) in cytopenic patients; flexion–extension cervical radiographs/MRI for atlantoaxial subluxation (important **pre-operative/pre-intubation** assessment).
- A new fever or a single disproportionately inflamed joint demands exclusion of **infection / septic arthritis** before attributing it to a flare.

High-yield exam pointers

- EAMs occur in **up to 40%** of RA; predicted by smoking + **RF/ACPA seropositivity** + high disease activity.

- **Pleuritis** = commonest pulmonary EAM; pleural fluid characteristically **low glucose, low pH** (exudate).
- **Felty's syndrome** = **neutropenia + splenomegaly + nodular RA**; mimicked by **T-LGL leukaemia**.
- **Caplan's syndrome** = RA pulmonary nodules + pneumoconiosis (silica/coal).
- **Cardiovascular disease = leading cause of death** in RA; secondary **AA amyloidosis** and membranous nephropathy are the renal EAMs.
- **Methotrexate** = anchor DMARD (+ folic acid); **hydroxychloroquine** needs **annual retinal screening**.
- **Screen for latent TB before any TNF inhibitor**; avoid TNFi in chronic HBV and NYHA III/IV heart failure.
- **RA-ILD** treated with steroids + azathioprine/mycophenolate/rituximab (avoid MTX/leflunomide-related lung toxicity).
- **Treat-to-target**: aim for low disease activity/remission (DAS-28/SDAI/CDAI).

SOURCE & COVERAGE

- **Harrison's Principles of Internal Medicine, 22e** — "Rheumatoid Arthritis" (extra-articular manifestations Fig. 370-2; DMARD table; treatment of extra-articular manifestations and treat-to-target approach).
- **CMDT 2026** — "Rheumatologic, Immunologic, & Allergic Disorders: Rheumatoid Arthritis" (current drug dosing, corticosteroid and DMARD management, ocular and Felty's detail).

◆ ◆ ◆