

NEURO NOTES

RASHAD ALGHURABI



2026

Neuro Notes



FIRST EDITION



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Dr. Rashad Omar Salem Alghurabi



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Dedication



To my parents,
whose sacrifices made every achievement possible.



To my wife and my three beloved children,
*for their patience, encouragement, and
unconditional love throughout this journey.*



To every neurology trainee and physician
*striving to improve patient care
through lifelong learning.*

This book is dedicated to you.





Preface



Medicine is a field of continuous discovery, and neurology remains one of its most intellectually demanding specialties. This handbook was developed to provide a practical, evidence-based, and clinically focused resource for neurology residents, fellows, and practicing physicians.



The chapters integrate fundamental neuroscience with modern diagnostic approaches, current international guidelines, and practical management strategies. Emphasis has been placed on clinical reasoning, localization, differential diagnosis, and decision-making to support physicians in both training and daily practice.



It is my hope that this handbook serves as a reliable companion for clinicians seeking concise yet comprehensive guidance in the care of patients with neurological disorders.



Dr. Rashad Omar Salem Alghurabi

2026

Acknowledgments



I would like to express my sincere gratitude to my teachers, mentors, colleagues, and patients, whose knowledge, guidance, and experiences have shaped my journey in neurology.



I am especially grateful to my family for their unwavering support, patience, and encouragement throughout the preparation of this work.



Finally, I acknowledge the countless researchers, educators, and professional neurological societies whose contributions to science and clinical practice have made this handbook possible.





About the Author



Dr. Rashad Omar Salem Alghurabi, is a neurologist from Yemen and a graduate of the Faculty of Medicine, Cairo University. He completed his postgraduate neurology training through the Egyptian Fellowship of Neurology.



His clinical and academic interests include cerebrovascular diseases, epilepsy, headache medicine, movement disorders, neurocritical care, and medical education. He is committed to advancing neurological education through evidence-based resources, clinical teaching, and research, with a particular interest in improving neurological care in low-resource settings.



This handbook reflects his dedication to creating a comprehensive, practical reference for neurology trainees and practicing clinicians.





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NEURO-OPHTHALMOLOGY

CHAPTER 1

Clinical Examination of the Afferent Visual System, Optic Disc Phenotypes, and Ischemic Optic Neuropathies

The assessment of the afferent visual system follows a hierarchical structure that localizes lesions along the pathway from the eye to the visual cortex. A systematic approach — visual acuity, color vision, visual fields, and pupillary function — allows the clinician to localize disease before neuroimaging is even obtained.

I. Clinical Examination of the Afferent Visual System

1. Quantitative Visual Acuity (VA)

- **Distance testing:** Standardized at 20 feet using a well-illuminated chart.
- **Near testing:** Performed at 14 inches using a near-card.
- **Refractive neutralization:** The pinhole apparatus differentiates neurologic vision loss from refractive error. If VA improves with a pinhole, the deficit is typically refractive (e.g., cataract or incorrect glasses).
- **Correction:** Patients over 50 years require corrective reading lenses (typically +2.00 to +3.00 diopters) for near testing due to presbyopia.



CLINICAL PEARL

Improvement of visual acuity with a pinhole essentially excludes an optic neuropathy as the cause of reduced acuity — it confirms a refractive etiology.

2. Color Vision & Contrast Sensitivity

- **Tools:** Pseudoisochromatic color plates (e.g., Ishihara or Hardy–Rand–Rittler).
- **Red desaturation:** Compare a bright red object's saturation between the two eyes (optic neuropathy) or across the vertical meridian within one eye (chiasmal/retrochiasmal lesions).



HIGH YIELD

Dyschromatopsia is typically **out of proportion** to the loss of visual acuity in optic neuropathies — a key discriminator from purely retinal or refractive causes.

3. Visual Field (VF) Topography

Meridian Respected	Localization	Typical Defect Pattern
Vertical meridian	Intracranial (chiasm or retrochiasmal pathways)	Bitemporal or homonymous field cuts
Horizontal meridian	Pre-chiasmal / optic nerve	Arcuate or altitudinal defects

Approximately **90%** of visual neurologic pathways subserve the central 30°, making central automated perimetry the standard for most clinical programs.



MEMORY TIP / MNEMONIC

"Vertical = brain, Horizontal = nerve." A defect obeying the vertical meridian points intracranially (chiasm/retrochiasm); a defect obeying the horizontal meridian points to the optic nerve.

4. The Relative Afferent Pupillary Defect (RAPD)

- **Mechanics:** Detected via the swinging flashlight test, identifying a relative difference in light impulse transmission to the Edinger–Westphal nuclei.
- **Quantification:** Neutral density filters are used to balance the light stimulus until the pupillary response is equalized, measuring the log-unit severity of the defect.

Localizing Value of RAPD

Site	Findings
Anterior to chiasm	Present in unilateral/asymmetric optic neuropathy or extensive retinal lesions (e.g., CRAO, large retinal detachment)
Chiasm	Present when visual field loss is markedly asymmetric between the two eyes
Optic tract	A small contralateral RAPD occurs in complete tract lesions, because more crossing nasal fibers exist than temporal fibers

II. Optic Disc Phenotypes & Evaluation

Distinguishing true disc edema from optic disc anomalies (e.g., optic disc drusen) is critical to avoid unnecessary invasive testing.

True Papilledema vs. Pseudopapilledema

Feature	True Papilledema (Raised ICP)	Pseudopapilledema (e.g., ODD / Crowded Disc)
Borders	Blurry disc margins; elevation extends into peripapillary retina	Elevated but often sharp margins; anomalous branching of vessels
Cup	Loss of optic cup (higher grades); spontaneous venous pulsations (SVP) often absent	Small or absent cup ("disc at risk"); SVP may be present
Vessels	Veins dilated/tortuous; obscuration of vessels as they cross the disc	Vessels remain visible; no obscuration of the vascular tree by edema
Ancillary signs	Peripapillary hemorrhages, cotton wool spots, Paton lines	Circumpapillary telangiectasia (in LHON), or no ancillary findings
OCT metrics	RNFL: global/sectoral thickening. GCIPL: spared early.	EDI-OCT: hyporeflective cores with hyperreflective bands (drusen)

Advanced OCT Markers

Marker	What It Measures	Clinical Utility
RNFL (Retinal Nerve Fiber Layer)	Unmyelinated axons	Acutely thickened in papilledema or NAION; thins in atrophy (takes 6–12 months to reach nadir)
mGCIPL (Macular Ganglion Cell–Inner Plexiform Layer)	Ganglion cell bodies	Thins within 2–4 weeks of injury — a sensitive marker of early neuroaxonal loss even while RNFL is still swollen
PHOMS (Peripapillary Hyperreflective Ovoid Masslike Structures)	Ovoid structures herniating over Bruch membrane	Seen in both papilledema and pseudopapilledema, reflecting axoplasmic stasis
 CLINICAL PEARL Because mGCIPL thins within 2–4 weeks — well before RNFL — it is the preferred OCT metric for detecting early neuroaxonal loss in a swollen disc		

III. Ischemic Optic Neuropathies

1. Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)

- **Pathophysiology:** Segmental infarction of the optic disc due to occlusion in the circle of Zinn–Haller.

Risk Factors

Category	Risk Factors
Anatomic	“Disc at risk” — small or absent cup-to-disc ratio in the fellow eye
Medications	Phosphodiesterase-5 inhibitors (e.g., sildenafil), sympathomimetics, and potentially semaglutide
Systemic	Hypertension, diabetes mellitus, obstructive sleep apnea (OSA)

- **Presentation:** Sudden, painless, unilateral vision loss, typically noted upon awakening. Visual field shows altitudinal defects respecting the horizontal meridian.
- **Management:** No restorative treatment exists. Focus is on preventing fellow-eye involvement by managing hypertension, lipids, and OSA.

PITFALL

Do not assume every case of sudden painless monocular vision loss with disc edema in a patient over 50 is NAION — giant cell arteritis (arteritic AION) must always be excluded first, as it is vision- and life-threatening.

2. Giant Cell Arteritis (GCA) & Arteritic AION

EMERGENCY

GCA is a medical emergency requiring swift clinical action to prevent irreversible bilateral blindness and stroke.

Diagnostic Thresholds & Criteria

Category	Finding
Age	Over 50 years; incidence increases with each decade

Category	Finding
Symptoms	Headache, jaw claudication, scalp tenderness, fatigue, malaise
ESR	Often > 50 mm/hr (may be markedly higher)
CRP	Elevated in > 80% of cases
Platelets	Thrombocytosis, reflecting systemic inflammation
Ultrasound	“Halo sign” in temporal arteries (vessel wall edema)
Retinal angiography	Zones of absent or delayed choroidal filling
Biopsy	Temporal artery biopsy remains the diagnostic standard (> 1 cm length)

GCA Emergency Treatment Protocol

Phase	Dosing & Route	Indication / Context
Initial pulse	IV methylprednisolone 1 g daily (or 250 mg every 6 hours) for 3 days	Acute vision loss or threatened vision (e.g., transient obscurations)
Transition	Oral prednisone 1 mg/kg/day (max 60–80 mg)	Following IV pulse; initiate before biopsy results if suspicion is high
Steroid-sparing	Tocilizumab, weekly or monthly SC/IV	Recommended by ACR for newly diagnosed GCA to allow faster steroid weaning
Adjuvant	Aspirin 81 mg daily	Reduces risk of concomitant cerebrovascular/cardiovascular events

WARNING

Tocilizumab blocks IL-6; therefore ESR and CRP **will normalize** and cannot be used to monitor disease activity while the patient is on this drug.

3. Posterior Ischemic Optic Neuropathy (PION)

- **Localization:** Infarction of the retrobulbar optic nerve; the optic disc appears normal acutely.

Perioperative Risk Factors

- Prone positioning (e.g., spinal surgery)
- Long duration of surgery and large volumes of colloid fluid
- Severe systemic hypotension or profound anemia



IMPORTANT NOTE

GCA must be ruled out in all non-surgical patients over 50 years presenting with a normal disc and acute vision loss.

CHAPTER 2

Inflammatory, Infectious, Infiltrative, Metabolic, and Hereditary Optic Neuropathies

This chapter distills clinical diagnostic tiers, biomarkers, genetic data, and precise treatment protocols for inflammatory, infectious, infiltrative, metabolic, and hereditary optic neuropathies.

I. Inflammatory & Demyelinating Optic Neuropathies

Management of demyelinating optic neuritis has transitioned into an “antibody-assisted” era, where identifying specific serologic biomarkers is critical for prognosis and therapy selection.

1. Phenotypic Comparison: MS vs. NMOSD vs. MOGAD

Feature	Multiple Sclerosis (MS)	NMOSD (AQP4-IgG+)	MOGAD (MOG-IgG+)
Sex ratio (F:M)	2.5 : 1	9 : 1	1 : 1
Laterality	Usually unilateral	20–30% bilateral	50% bilateral
Optic disc	2/3 retrobulbar (normal)	< 30% edema	85% edema
Acuity at nadir	30% < 20/200	80% < 20/200	Most < 20/200
Visual prognosis	Excellent (95% > 20/40)	Poor (60% < 20/200 if untreated)	Good (5% < 20/200 chronic)
MRI length	Short-segment (< 50% of nerve)	Longitudinally extensive	Longitudinally extensive

Feature	Multiple Sclerosis (MS)	NMOSD (AQP4-IgG+)	MOGAD (MOG-IgG+)
CSF oligoclonal bands	85% positive	15% positive	10% positive

MEMORY TIP / MNEMONIC

MS, NMOSD, MOGAD — think “mild, severe, swollen.” MS is usually mild and unilateral with a normal disc; NMOSD is severe with poor prognosis; MOGAD nearly always shows disc edema but has a good long-term visual outcome.

2. Demyelinating Treatment Protocols

Disease State	Protocol & Dosing	Clinical Rationale / Contraindications
Acute MS-associated optic neuritis	IV methylprednisolone 1 g/day for 3–5 days	Low-dose oral prednisone (1 mg/kg) is strictly contraindicated: the ONTT showed it increases recurrence risk with no benefit
Acute MS-ON (oral alternative)	High-dose oral methylprednisolone: 1 g powder mixed in a beverage	Used when IV access is difficult; bioequivalent to IV dosing at high enough oral dose
NMOSD (acute)	IV methylprednisolone + plasma exchange: 1 g/day for ≥ 5 days; early PLEX (5–7 cycles)	Early aggressive treatment is mandatory to prevent irreversible blindness
MOGAD (acute)	IV methylprednisolone 1 g/day for 3–5 days, then oral prednisone 1 mg/kg/day	Mandatory 6–8 week taper: MOGAD is exquisitely steroid-sensitive but highly relapse-prone if steroids are stopped quickly
MOGAD (chronic/relapsing)	Maintenance IVIg: 400 mg/kg/day for 5 days, then 400–2000 mg/kg every 4 weeks	Reserved for relapsing cases; rituximab is less effective in MOGAD than in NMOSD

WARNING

Never treat an isolated demyelinating optic neuritis with low-dose oral prednisone alone — this increases the risk of recurrence without accelerating visual recovery.

II. Infectious, Infiltrative, and Metabolic Neuropathies

1. Infectious Diagnostic Features & Treatments

Condition	Clinical Hallmarks	Diagnostic Tier / Treatment
Neuroretinitis (Bartonella)	Macular star exudates; disc edema (often precedes the star)	Tier: Bartonella IgG/IgM titers. Rx: oral doxycycline + rifampin or azithromycin
Syphilis	Uveitis, chorioretinitis, or retrobulbar optic neuritis	Tier: RPR/VDRL + FTA-ABS. Rx: IV penicillin G continuous infusion for 2 weeks
Tuberculosis	Keratitis with uveitis; contiguous optic nerve involvement	Tier: interferon-gamma release assay (IGRA). Rx: multi-agent (isoniazid, rifampin, pyrazinamide, ethambutol)
Fungal (rhino-orbital)	Proptosis, ophthalmoplegia, rapid visual loss in diabetes/immunocompromise	Tier: urgent CT for bony destruction; sinus biopsy. Rx: emergency surgical debridement + systemic antifungals

2. Nutritional & Toxic Optic Neuropathies

Agent / Deficiency	Diagnostic Biomarker / Metric	Clinical Presentation
Vitamin B12	Low serum B12; elevated methylmalonic acid (MMA) and homocysteine	Subacute symmetric vision loss; temporal disc pallor
Ethambutol toxicity	Dose threshold > 15 mg/kg/day	Progressive vision loss, dyschromatopsia; suppressed multifocal ERG
Methanol	Serum level > 20 mg/dL; high anion gap metabolic acidosis	Acute severe vision loss with marked disc edema
Thiamine (B1)	Whole blood thiamine level < 70 nmol/L	Often associated with vertical nystagmus and ophthalmoparesis

EXAM TIP

Bilateral, symmetric, painless, progressive optic neuropathy in a patient with poor nutrition, alcohol use disorder, or bariatric surgery history should always trigger screening for B12, folate, copper, and thiamine deficiency, as well as toxic exposures (ethambutol, amiodarone, methanol).

III. Hereditary Optic Neuropathies

1. Leber Hereditary Optic Neuropathy (LHON)

- **Pathophysiology:** Mitochondrial DNA variants affecting Complex I of the electron transport chain.
- **Demographic:** Males are 3–5 times more likely to be affected; peak onset in the teenage years to early adulthood.

LHON Mutation Genotype–Phenotype Correlations

Mutation	Prevalence / Characteristics	Prognosis
m.11778G>A (MT-ND4)	69% global prevalence	Poor; < 20% show meaningful recovery
m.14484T>C (MT-ND6)	17% global prevalence; most common in Canada	Best prognosis; most likely to show spontaneous improvement
m.3460G>A (MT-ND1)	13% global prevalence	Intermediate prognosis

LHON Management Protocol

- **Idebenone:** 900 mg daily. Mechanism: antioxidant that bypasses Complex I to restore mitochondrial function.
- **Risk mitigation:** Patients must avoid tobacco and limit alcohol to prevent precipitating visual decline in genetic carriers.



CLINICAL PEARL

Suspect LHON in a young man with sequential, painless, severe central vision loss in both eyes over weeks to months, especially with a maternal family history and a trigger such as smoking or heavy alcohol use.

2. Autosomal Dominant Optic Atrophy (ADOA)

- **Gene:** OPA1 (chromosome 3q28–q29).
- **Mechanism:** Abnormal mitochondrial metabolism leading to retinal ganglion cell death.
- **Presentation:** Insidious onset in the first to second decade of life; bilateral, symmetric central vision loss (usually better than 20/200) with excavated (cupped) disc pallor.
- **Treatment:** No current FDA-approved treatment; trials of niacinamide and gene therapy are underway.

**IMPORTANT NOTE**

ADOA and LHON both affect mitochondrial function but differ in mode of inheritance (autosomal dominant vs. maternal/mitochondrial), onset (childhood vs. teens/young adulthood), and disc appearance (diffuse cupped pallor vs. temporal pallor with peripapillary telangiectasia in the acute LHON phase).

CHAPTER 3

Intracranial Pressure Disorders, Chiasmal Syndromes, and Retrochiasmal Visual Pathway Lesions

I. Idiopathic Intracranial Hypertension (IIH)

IIH is a disorder characterized by elevated intracranial pressure (ICP) of unknown etiology, primarily affecting young, overweight women. Diagnosis requires systematic exclusion of secondary causes, most importantly cerebral venous sinus thrombosis (CVST).

1. Revised Diagnostic Criteria (Modified Dandy Criteria)

Category	Required Diagnostic Criteria
Clinical	Papilledema (usually bilateral, can be asymmetric)
Neurologic	Normal examination except for cranial nerve abnormalities (e.g., VI nerve palsy)
Neuroimaging	Normal brain parenchyma; no hydrocephalus, mass, or structural lesion. MRI with MRV is mandatory to exclude CVST
CSF composition	Normal protein, glucose, and cell counts
Opening pressure — Definite	≥ 250 mm H ₂ O (adults); ≥ 280 mm H ₂ O (children)
Opening pressure — Probable	Meets all above criteria, but OP is lower than expected (often due to snapshot variability)

2. Neuroimaging Hallmarks of Raised ICP

These features, while nonspecific in isolation, collectively support a diagnosis of raised ICP.

Anatomic Site	Radiological Finding
Orbit	Flattening of the posterior globe/sclera; optic nerve sheath distension; increased vertical tortuosity of the optic nerve
Sella	Partially empty or empty sella turcica; decreased pituitary height
Venous system	Transverse venous sinus stenosis (bilateral or dominant-side)
Skull base	Expansion of Meckel cave; skull base erosion; encephaloceles

3. Medical Management

Management prioritizes preservation of vision and treatment of headache morbidity.

Medication	Dosing & Titration (IIHTT Data)	Maximal Cap / Clinical Notes
Acetazolamide	Start 250–500 mg BID; increase by 250 mg every 2 days	Max often 2–4 g/day. Side effects: dysgeusia (carbonated drinks taste flat), paresthesia, fatigue
Topiramate	Typically titrated to 50–100 mg BID	Useful adjunct: provides both weak carbonic-anhydrase-mediated ICP reduction and migraine prophylaxis
Furosemide	Off-label	Inhibits Na-K-2Cl cotransporter in the choroid plexus; used when acetazolamide is not tolerated
GLP-1 agonists (e.g., exenatide)	Phase 2 data	Shows acute/chronic ICP reduction; useful for weight-driven remission; not yet standard of care but emerging

4. Surgical Intervention Thresholds

Procedure	Primary Indication
Optic Nerve Sheath Fenestration (ONSF)	Preferred for asymmetric disc swelling and severe vision loss but minimal headache

Procedure	Primary Indication
CSF Shunting (VP/LP)	Indicated for medically refractory headache and impending visual decline
Venous Sinus Stenting (VSS)	Considered when a significant pressure gradient exists across a transverse sinus stenosis

**EXAM TIP**

IIH treatment decisions hinge on which symptom dominates: vision loss favors ONSF or shunting, while refractory headache favors CSF shunting; a dominant venous sinus stenosis with a pressure gradient favors venous stenting.

II. Intracranial Hypotension

Intracranial hypotension (low pressure) can result from a spontaneous CSF leak (SIH) or iatrogenic causes (post-lumbar puncture).

- **Ophthalmic manifestations:** Diplopia (due to VI nerve palsy from brainstem “sagging”) and, rarely, chorioretinal folds.
- **Pachymeningeal enhancement:** Chronic low pressure leads to diffuse dural enhancement on MRI, which can masquerade as pachymeningitis.
- **Cranial nerve palsies:** The VI nerve is most vulnerable due to its long intracranial course; III and IV nerves can also be affected by brainstem traction.

**MEMORY TIP / MNEMONIC**

Both markedly raised ICP and markedly low ICP can cause a sixth nerve palsy — it is a “false-localizing sign” in both directions because of the nerve's long, vulnerable intracranial course.

III. Chiasmal Syndromes

The vertical meridian is the hallmark landmark for localizing lesions to the optic chiasm.

1. Etiology and Features

- **Most common causes:** Pituitary adenoma, craniopharyngioma, meningioma (e.g., tuberculum sellae), and aneurysms.
- **Visual field defect:** Classic bitemporal hemianopia respecting the vertical meridian.

- **Junctional scotoma:** A lesion at the junction of the optic nerve and chiasm causes a central scotoma in the ipsilateral eye and a superior temporal defect in the contralateral eye — traditionally attributed to fibers looping through Wilbrand's knee.

2. Pituitary Apoplexy Emergency



EMERGENCY

Pituitary apoplexy is an acute hemorrhage or infarction within a pituitary adenoma, presenting with sudden severe headache, acute vision loss, and potentially ophthalmoplegia if the cavernous sinus is invaded. Protocol: urgent MRI followed by immediate endocrinology and neurosurgical evaluation for potential decompression.

IV. Retrochiasmal Visual Pathways & Higher Cortical Disorders

Retrochiasmal lesions cause visual field defects on the same side in both eyes (homonymous).

Visual Field Defect	Localization of Lesion	Congruity / Pattern
Homonymous hemianopia	Contralateral optic tract, LGN, radiations, or occipital lobe	Optic tract lesions: incongruous; associated with a small contralateral RAPD
Quadrantanopia	Temporal lobe (Meyer's loop): "pie in the sky" (superior). Parietal lobe: "pie on the floor" (inferior)	The more congruent (identical) the defect, the more posterior the lesion
Macular sparing	Occipital lobe: sparing of central 5–10° due to dual blood supply from PCA and MCA to the occipital tip	Common in PCA territory infarctions



MEMORY TIP / MNEMONIC

"Pie in the SKY hits the TEMPORAL lobe (sky is up); pie on the FLOOR hits the PARIETAL lobe." The more posterior (occipital) the lesion, the more congruent the two eyes' visual field defects.

Higher Cortical Visual Disorders

Syndrome	Clinical Hallmarks	Localization
Anton syndrome	Cortical blindness with visual anosognosia (denial) and confabulation	Bilateral striate cortex (area V1)
Bálint syndrome	Triad: simultanagnosia (cannot see the “forest” for the “trees”), optic ataxia (misreaching), and ocular apraxia (impaired voluntary saccades)	Bilateral occipitoparietal regions (dorsal/action stream)
Pure alexia	Alexia without agraphia — can write but cannot read their own writing	Left occipital lobe + splenium of the corpus callosum
Gerstmann syndrome	Agraphia, acalculia, finger agnosia, and left-right confusion	Dominant (usually left) angular gyrus / parietal lobe
Akinetopsia	Motion blindness; objects appear to move in “stroboscopic” jumps	Bilateral occipitotemporoparietal junction (area V5/MT)

MEMORY TIP / MNEMONIC

Gerstmann syndrome — “A-A-F-L”: Agraphia, Acalculia, Finger agnosia, Left-right confusion — dominant angular gyrus.

IMPORTANT NOTE

Cerebral Visual Impairment (CVI): A broad term for higher-processing visual disorders (e.g., agnosias, spatial neglect) that cannot be explained by ocular disease. CVI is associated with a 47% higher risk of dementia in older populations.

CHAPTER 4

Efferent Ocular Motor Pathologies

This chapter emphasizes clinical localization patterns, diagnostic maneuvers, and specialized management protocols for the ocular cranial nerves, neuromuscular junction disorders, thyroid eye disease, and nystagmus.

I. Ocular Cranial Nerve Palsies

1. Third Nerve (Oculomotor) Palsy

- **Anatomy:** Superior division (levator palpebrae superioris and superior rectus) and inferior division (medial rectus, inferior rectus, inferior oblique, and pupillary fibers).

The “Rule of the Pupil”

Mechanism	Pupillary Fiber Involvement	Typical Pupil Finding
Compressive (e.g., posterior communicating artery aneurysm)	Parasympathetic pupillary fibers travel on the outer edge of the nerve and are compressed early	Dilated, poorly reactive pupil
Microvascular (ischemic)	Ischemia typically involves the central portion of the nerve, sparing peripheral pupillary fibers	Pupil-sparing



EMERGENCY

A third nerve palsy with a dilated, poorly reactive pupil (“pupil-involving”) is a posterior communicating artery aneurysm until proven otherwise — urgent CTA/MRA is mandatory.

- **Aberrant regeneration:** Misdirection of fibers (e.g., medial rectus fibers reaching the iris sphincter) causes pupillary constriction during adduction or near effort rather than light (pseudo-light-near dissociation). Occurs in chronic compression (tumors/aneurysms) but never in microvascular ischemia.



PITFALL

Aberrant regeneration developing acutely (rather than after chronic compression) should raise suspicion for a meningioma or other slow-growing compressive lesion rather than an aneurysm or microvascular event.

2. Fourth Nerve (Trochlear) Palsy

- **Nuclear/fascicular:** A lesion near the nucleus in the dorsal brainstem can cause the rare combination of Horner syndrome and a contralateral fourth nerve palsy, due to decussation of trochlear fibers.
- **Peripheral:** The longest intracranial course of any cranial nerve makes it highly susceptible to trauma, even without loss of consciousness.

**MEMORY TIP / MNEMONIC**

“GOTS worse”: Gaze Opposite, Tilt Same — vertical diplopia from a fourth nerve palsy worsens in contralateral gaze and with ipsilateral head tilt.

- **Congenital vs. acquired:** Congenital palsies often show a long-standing head tilt in old photographs and an abnormally increased vertical fusional amplitude (e.g., 15 prism diopters vs. the normal 2–3 PD).

3. Sixth Nerve (Abducens) Palsy

- **Nucleus:** Damage causes an obligate ipsilateral gaze palsy (not merely an abduction deficit) and frequently includes an ipsilateral peripheral facial nerve palsy, due to the proximity of the facial colliculus.
- **Subarachnoid space:** Susceptible to elevated intracranial pressure; the nerve is stretched over the petrous ridge, making it a classic “false-localizing sign.”
- **Management pattern:** Although microvascular causes are common in patients over 50 years with vascular risk factors, MRI with contrast is generally recommended, because 61% of nonmicrovascular palsies occur in patients with those same risk factors.

**WARNING**

Do not assume a sixth nerve palsy in a vasculopathic patient is automatically microvascular — the majority of nonmicrovascular (compressive, neoplastic) sixth nerve palsies also occur in patients with vascular risk factors. MRI with contrast should be obtained.

II. Neuromuscular Junction Disorders & Myopathies

1. Ocular Myasthenia Gravis (OMG)

- **Presentation:** Fluctuating ptosis and diplopia that does not follow a single nerve pattern; often involves the medial rectus more than the lateral rectus, producing an exodeviation.
- **Pseudo-internuclear ophthalmoplegia:** OMG can mimic an INO (adduction deficit), but unlike true INO, the adducting saccade has a relatively normal velocity until the end of the movement, with symmetric peak saccadic velocities.

Diagnostic Maneuvers

- **Ice pack test:** 2 minutes of ice on the eyelid improves ptosis.

- **Cogan eyelid twitch:** A brief upward twitch of the eyelid when returning to primary position from downgaze.

Antibodies & Electromyography

Test	Finding / Notes
AChR binding antibody	Most sensitive; specificity approximately 99%
MuSK antibody	Associated with diplopia in 95% of cases
Seronegativity	Occurs in 35–50% of OMG cases; single-fiber EMG of the frontalis or orbicularis oculi is used for confirmation

Medications in Ocular Myasthenia Gravis

Medication	Clinical Use	Notes
Pyridostigmine	Symptomatic treatment	Standard first-line therapy
Prednisone	Immunosuppression	Cautious use; prolonged courses often yield better improvement in ocular alignment

III. Thyroid Eye Disease (TED)

- **Pathophysiology:** Autoimmune hyperthyroidism (Graves disease) leads to enlarged extraocular muscles and expanded orbital fat.
- **Biomarkers:** TSH receptor antibodies — specifically thyroid-stimulating immunoglobulin (TSI) — are the best markers of disease activity.
- **Imaging features:** Orbital MRI/CT shows muscle enlargement that spares the tendons.

MEMORY TIP / MNEMONIC

Muscle involvement frequency — “IMSLO”: Inferior rectus > Medial rectus > Superior rectus > Lateral rectus > Obliques.

Management

- **Medical:** Glucocorticoids, teprotumumab (immunomodulatory), or orbital radiation.

- **Surgical:** Orbital decompression is reserved for severe, vision-threatening disease with optic nerve compression.

IV. Nystagmus & Ocular Oscillations

1. Localization of Acquired Nystagmus

Nystagmus Type	Primary Anatomic Localization	Common Etiologies
Downbeat	Cerebellar flocculus/paraflocculus	Neurodegeneration (SCA6, SCA27B), Chiari malformation, lithium toxicity
Upbeat	Midline brainstem (medulla/pons)	Wernicke encephalopathy, stroke, demyelination
Periodic alternating	Cerebellar nodulus/ventral uvula	Stroke, Chiari malformation, neurodegeneration
Seesaw (pendular)	Sellar region (chiasm)	Large chiasmal compressive lesions
Oculopalatal tremor	Guillain-Mollaret triangle	Months after dorsal pontine hemorrhage

2. Saccadic Intrusions

Feature	Square-Wave Jerks	Opsoclonus
Amplitude/pattern	Small horizontal saccades	Rapid, chaotic saccades in all planes
Intersaccadic interval	Present (approximately 200 ms)	Absent
Associations	Parkinson disease, progressive supranuclear palsy	Neuroblastoma (infants), paraneoplastic syndromes (lung/breast cancer in adults), anti-NMDA receptor encephalitis

★ HIGH YIELD

Opsoclonus in a child should immediately prompt a workup for occult neuroblastoma; in an adult, it should prompt a paraneoplastic and autoimmune encephalitis evaluation (including anti-NMDA receptor antibodies).

3. Pharmacological Management of Nystagmus

Medication	Indication	Dosing Context
Dalfampridine (4-aminopyridine)	Downbeat nystagmus	Particularly effective in SCA27B
Baclofen	Periodic alternating nystagmus	Almost always effective for this specific pattern
Gabapentin / memantine	Acquired pendular / oculopalatal nystagmus	May modestly decrease slow-phase velocity; often refractory
IV thiamine	Upbeat nystagmus	Mandatory if Wernicke encephalopathy is suspected



EMERGENCY

Any patient with upbeat nystagmus and a compatible history should receive empiric IV thiamine immediately, before glucose administration, to avoid precipitating or worsening Wernicke encephalopathy.

CHAPTER 5

Pupillary Disorders, Systemic & Neurodegenerative Manifestations, and Advanced Diagnostics

I. Pupillary Anomalies & Autonomic Pathways

The pupils are regulated by a dynamic balance between the parasympathetic (constrictor) and sympathetic (dilator) systems. Dysfunction in these pathways manifests as anisocoria or abnormal pupillary motility.

1. The Anisocoria Approach

The primary clinical branching point is determining which pupil is abnormal, based on asymmetry under different lighting conditions.

Lighting Condition	Abnormal Pupil	Likely Etiology
Worse in bright light	The larger pupil is abnormal	Parasympathetic defect or iris damage
Worse in dim light	The smaller pupil is abnormal	Sympathetic defect (Horner syndrome) or physiologic anisocoria

2. Horner Syndrome (Oculosympathetic Paresis)

- **Clinical triad:** Miosis, mild ptosis (1–2 mm), and anhidrosis.

Three-Neuron Sympathetic Pathway

Neuron Order	Course
1st order (central)	Hypothalamus to the ciliospinal center of Budge-Waller (C8–T2)
2nd order (preganglionic)	Exits the spinal cord, travels over the lung apex, synapses at the superior cervical ganglion
3rd order (postganglionic)	Follows the internal carotid artery plexus to the orbit

Pharmacological Diagnostic Testing for Horner Syndrome

Drug	Dosage / Protocol	Interpretation
Cocaine (4% or 10%)	1 drop in each eye; re-evaluate at 45–60 minutes	Positive: normal pupil dilates, Horner pupil does not — anisocoria increases
Apraclonidine (0.5% or 1%)	1 drop in each eye; re-evaluate at 45–60 minutes	Positive: Horner pupil dilates (reversal of anisocoria) due to α_1 -adrenergic denervation supersensitivity
Hydroxyamphetamine (1%)	No longer commercially available	Traditionally used for localization (1st/2nd order vs. 3rd order lesion)

**EMERGENCY**

A painful Horner syndrome (ipsilateral headache or neck pain) is an internal carotid artery dissection until proven otherwise; urgent MRA/CTA of the head and neck is mandatory.

3. Adie Tonic Pupil

- **Pathophysiology:** Damage to the ciliary ganglion or short ciliary nerves (postganglionic denervation).
- **Acute features:** A large, poorly reactive pupil with sectoral palsy of the iris sphincter (“vermiform” / purse-string movement).
- **Chronic features:** Light-near dissociation (from aberrant reinnervation) and a smaller resting pupil size (“little old Adie’s”).
- **Testing:** Dilute pilocarpine 0.125% constricts the tonic pupil due to denervation supersensitivity, while the normal pupil remains unchanged.

4. Argyll Robertson Pupil

- **Mechanism:** Associated with neurosyphilis; believed to involve gliosis near the aqueduct or ciliary ganglion.
- **Presentation:** Small, irregular pupils that fail to react to light but show a vigorous, brisk reaction to a near stimulus.

**MEMORY TIP / MNEMONIC**

“Argyll Robertson pupils accommodate but do not react” — light-near dissociation with a small, irregular pupil should prompt syphilis serology.

Comparative Summary: Causes of Light-Near Dissociation

Condition	Pupil Size	Key Distinguishing Feature
Argyll Robertson pupil	Small, irregular	Neurosyphilis; bilateral
Adie tonic pupil (chronic)	Initially large, becomes smaller over time	Sectoral palsy, denervation supersensitivity to dilute pilocarpine
Dorsal midbrain (Parinaud) syndrome	Mid-dilated	Associated upgaze palsy and convergence-retraction nystagmus

II. Systemic & Neurodegenerative Manifestations

Neurodegenerative syndromes often present with distinctive “ocular tripwires” that aid early differential diagnosis.

Neurodegenerative Ocular Tracking Markers

Syndrome	Key Eye Movement & Eyelid Markers	Diagnostic Pearl
Parkinson disease (PD)	Convergence insufficiency (40% in patients > 70 years), hypometric saccades, square-wave jerks	Dry eye syndrome occurs in 70% of PD patients
Progressive supranuclear palsy (PSP)	Supranuclear vertical gaze palsy (downward > upward), slowed vertical saccades, frequent square-wave jerks	“Hummingbird sign” on sagittal MRI (disproportionate midbrain atrophy)
Multiple system atrophy (MSA) / CANVAS	Spontaneous downbeat nystagmus, bilateral vestibular loss (HINTS: catch-up saccades), “walking oscillopsia”	CANVAS triad: cerebellar ataxia, neuropathy, and vestibular areflexia
Whipple disease	Oculomasticatory myorhythmia: convergent-divergent nystagmus with low-frequency facial/jaw movements	Pathognomonic for CNS Whipple involvement



MEMORY TIP / MNEMONIC

“Hummingbird sign” = PSP (midbrain atrophy on sagittal MRI). “CANVAS” = Cerebellar ataxia + Neuropathy + Vestibular Areflexia Syndrome.

Systemic & Inflammatory Manifestations

- **Neurosarcoidosis:** Can cause granulomatous optic neuropathy, uveitis, and raised ICP/papilledema due to meningeal involvement.
- **Systemic lupus erythematosus (SLE):** Associated with secondary pseudotumor cerebri syndrome and drug-induced intracranial hypertension.
- **Susac syndrome:** Defined by the triad of encephalopathy, hearing loss, and branch retinal artery occlusions (BRAO); fluorescein angiography is diagnostic.



MEMORY TIP / MNEMONIC

Susac syndrome triad — “EHB”: Encephalopathy, Hearing loss, BRAO.

III. Advanced Specialized Diagnostics & Telemedicine

Modern neuro-ophthalmic diagnostics have transitioned toward high-resolution, noninvasive quantification and automated analysis.

1. Non-Mydriatic Fundus Photography

- **Clinical utility:** Allows detection of optic nerve or retinal abnormalities without pupillary dilation.
- **Impact:** In emergency settings, these cameras identify relevant findings in 8.5% of headache patients, outperforming direct ophthalmoscopy performed by non-specialists.

2. Artificial Intelligence in Optic Disc Classification

- **BONSAI study:** A validated deep-learning system that detects papilledema with 96% sensitivity and 85% specificity.
- **Differential diagnosis:** AI algorithms can now distinguish between optic neuritis and NAION in the acute phase based on fundus images alone.

3. Specialized Vascular Profiling (OCT Angiography)

- **OCTA:** Visualizes retinal microvasculature by detecting light reflectance from moving erythrocytes.

Applications

- **Neurovascular coupling:** Detects decreased vessel density in regions of RNFL loss (e.g., glaucoma, NAION).
- **Disc swelling:** Potential to distinguish papilledema from pseudopapilledema by mapping the superficial capillary plexus.

4. Telemedicine & Remote Consultation

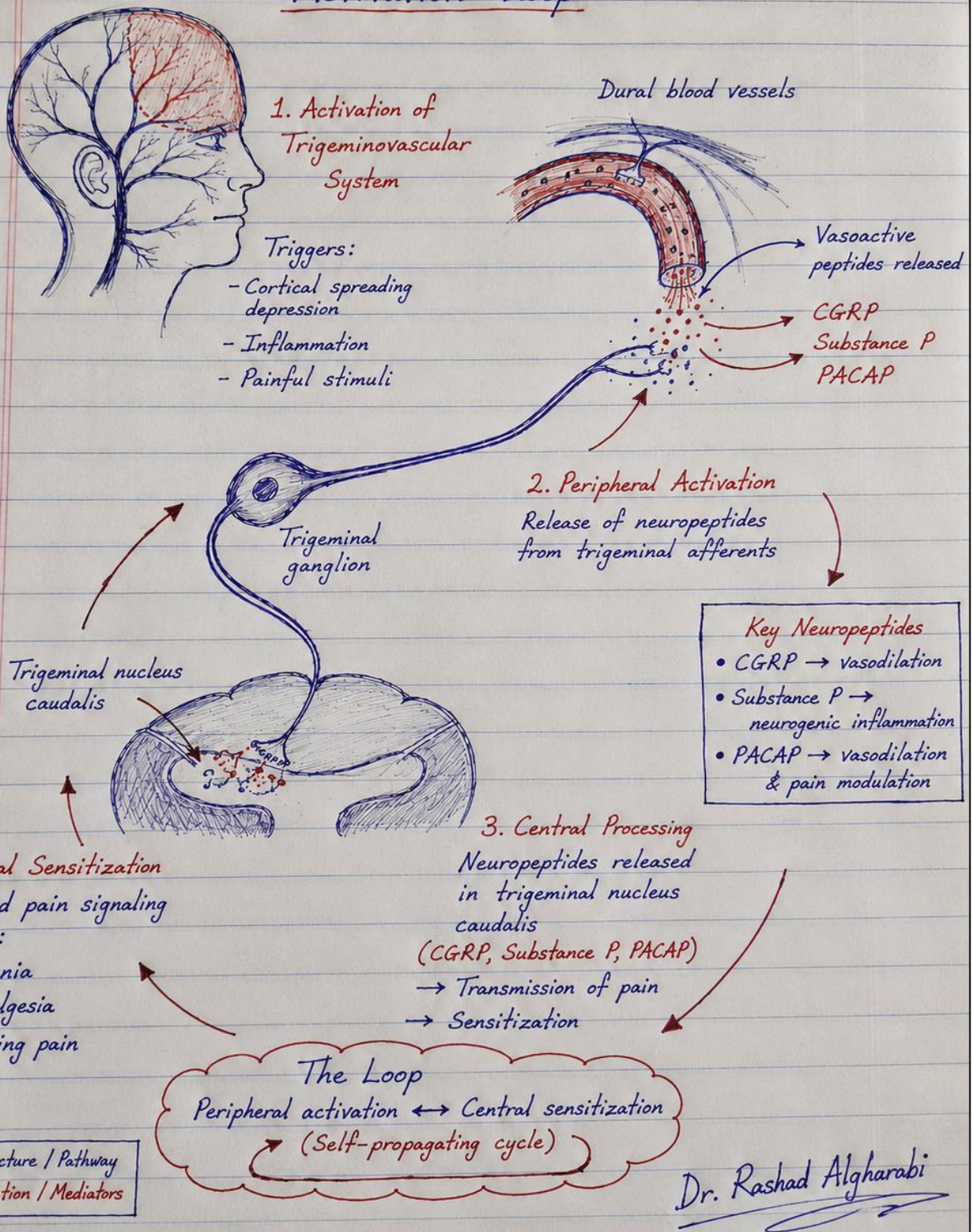
Deployment of non-mydriatic cameras in emergency departments allows for remote interpretation by neuro-ophthalmologists, facilitating the diagnosis of acute central retinal artery occlusion (CRAO) or fulminant papilledema within hours.

★ HIGH YIELD

AI-assisted fundus image analysis (e.g., the BONSAI algorithm) is rapidly becoming a point-of-care triage tool for distinguishing papilledema from pseudopapilledema and for flagging emergent optic disc pathology in non-ophthalmology settings such as the emergency department.

HEADACHE MEDICINE

The Trigeminovascular System Activation Loop



Chapter 1 — Clinical Approach to Headache: History, Examination, and Red Flags

I. Clinical History and Examination

Foundational History Elements

Centrality of history: Headache medicine relies more heavily on the patient's history than perhaps any other field in neurology. Imaging and laboratory testing primarily assist in diagnosing secondary disorders, while all primary headache types are diagnosed largely by history.

Primary vs. secondary: A systematic approach is essential to differentiate the overwhelming majority of outpatient cases (primary disorders such as migraine) from worrisome secondary etiologies.

The opening line: The evaluation should begin with the patient's own words. This immediately signals the patient's goals — whether they are seeking an etiology, a prognosis, or more effective treatment.

Course and Tempo

- **Onset at the beginning:** Elicit the history from the very first headache, often starting in childhood, to determine whether the current pattern represents a change or an intensification of a lifelong disorder.
- **"Volume turned up":** Distinguish whether worsening represents the same headache phenotype with increased intensity, or a completely different, de novo headache.
- **Tempo to peak:** The time from pain onset to peak intensity is highly diagnostic — migraine builds gradually over hours, whereas cluster headache and thunderclap headaches peak within minutes or seconds.

Phenotypic Specifics

- **Location:** Although migraine unilaterality is common, 40% of adults and most children have bilateral head pain. Strictly unilateral, "side-locked" pain is a hallmark of trigeminal autonomic cephalalgias but may also signal secondary causes such as structural lesions or CSF pressure disorders.
- **Character:** Pain is often described as throbbing/pounding (migraine), pressure-like/squeezing (tension-type), or stabbing/ice-pick (cluster).
- **Triggers vs. prodrome:** Many presumed "triggers" (e.g., food cravings, neck pain, photophobia) are actually premonitory symptoms of the attack itself, not true precipitants.

Impact and Interictal Burden

- **Disability:** Assessing the personal impact on work, school, and social life is integral to preventing migraine-related disability and driving preventive treatment decisions.
- **Headache-free days:** It is mandatory to ask how many days per month the patient is completely "clear-headed." Failure to identify a baseline of constant low-level pain (as in hemicrania continua) can delay accurate diagnosis.

CLINICAL PEARL

Always ask: "How many days a month are you completely headache-free?" A patient who says "never" may have a chronic daily headache disorder such as hemicrania continua or chronic migraine masking the true baseline.

Physical and Fundoscopic Examination Requirements

Exam Component	Key Elements	Clinical Significance
Vital signs	Blood pressure, temperature, height, weight, heart rate	Screens for systemic/secondary causes
General neurologic exam	Full examination for focal deficits	Excludes structural or vascular pathology
Fundoscopy (mandatory)	Every new patient	Detects papilledema — a critical red flag for raised intracranial pressure
Peripheral nerve palpation	Greater/lesser occipital, auriculotemporal, supraorbital, supratrochlear, zygomaticotemporal nerves	Tenderness or pain reproduction suggests neuralgic source
Temporal artery palpation	Mandatory in patients > 50 years	Screens for Giant Cell Arteritis
Musculoskeletal exam	Nuchal ROM, cervical paraspinal tenderness, TMJ (jaw opening, crepitus)	Identifies cervicogenic or TMJ contributors
Trendelenburg test	5–10° head-down tilt for 10 minutes	Improvement suggests spontaneous intracranial hypotension (CSF leak)

Table 1.1 — Mandatory components of the headache physical examination.

WARNING

Fundoscopy is not optional. Papilledema may be the only objective sign of a life-threatening secondary cause of headache in an otherwise well-appearing patient.

II. The Red Flags Framework (SNNOOP10)

The following mnemonic details the red flags that mandate further investigation to rule out secondary headache disorders.

MEMORY TIP / MNEMONIC

SNNOOP10 — each letter cues a category of red flag prompting investigation for secondary headache. The "10" reflects the ten P-items that follow N, N, and O, O.

Letter	Red Flag	Clinical Correlation
S	Systemic symptoms (fever, weight loss, constitutional signs)	Infection, nonvascular intracranial disorders, pheochromocytoma, carcinoid
N	Neoplasm in history	Intracranial metastases or primary brain tumors
N	Neurologic deficit or dysfunction (focal deficits, cranial nerve palsy, decreased consciousness)	Vascular/nonvascular intracranial disorders, brain abscess
O	Onset sudden or abrupt (thunderclap)	Subarachnoid hemorrhage, RCVS, meningitis
O	Older age (new headache onset > 50 years)	Giant Cell Arteritis and other cranial/cervical vascular disorders
P	Pattern change or recent onset ("first or worst" headache)	Neoplasm or vascular/pressure disorder
P	Positional / orthostatic headache	Intracranial hypotension or hypertension
P	Precipitated by Valsalva (cough, sneeze, laugh, exercise)	Posterior fossa malformation or Chiari malformation
P	Papilledema on fundoscopy	Increased intracranial pressure from intracranial hypertension or neoplasm
P	Progressive headache with atypical features	Nonvascular intracranial disorder, neoplasm

Letter	Red Flag	Clinical Correlation
P	Pregnancy or puerperium	Preeclampsia, cerebral venous sinus thrombosis, postdural puncture headache
P	Painful eye with autonomic features (ptosis, miosis, tearing)	Posterior fossa, pituitary, or cavernous sinus pathology
P	Posttraumatic onset (within 7 days of injury)	Acute/chronic posttraumatic headache, subdural hematoma
P	Pathology of the immune system (e.g., HIV)	High risk of opportunistic intracranial infection
P	Painkiller overuse or new drug use at headache onset	Medication-overuse headache or drug incompatibility

Table 1.2 — SNNOOP10 red-flag framework for identifying secondary headache.

EXAM TIP

Board questions frequently test SNNOOP10 by embedding a single red flag in a clinical vignette (e.g., "new headache in a 55-year-old with jaw pain while chewing") — recognize the pattern rather than expecting the mnemonic to be named.

III. High-Yield Secondary Headaches

Giant Cell Arteritis (GCA)

Pathophysiology: An inflammatory vasculitis of the cranial and cervical arteries.

Diagnostic Criteria & Screening

- **Age:** Primarily affects adults 50 years or older.
- **Jaw claudication:** Pain or weakness in the jaw while chewing is a highly sensitive clinical screening feature for GCA.
- **Laboratory tests:** ESR and CRP measurement is mandatory for all patients in the at-risk age group.
- **Examination:** Palpation of the temporal arteries is a required directed maneuver.

EMERGENCY / RED FLAG

GCA is a neuro-ophthalmologic emergency. Untreated disease risks irreversible vision loss from anterior ischemic optic neuropathy. Any suspicion in a patient over 50 warrants urgent ESR/CRP and

prompt specialist referral for consideration of high-dose corticosteroid therapy and temporal artery biopsy.

📌 IMPORTANT NOTE

Specific high-dose steroid dosing protocols and confirmatory biopsy timing are specialist-level management decisions and were not detailed in the source material for this chapter; standard practice is urgent corticosteroid initiation on clinical suspicion, without awaiting biopsy confirmation.

Idiopathic Intracranial Hypertension (IIH)

Pathophysiology: Intracranial hypertension without ventriculomegaly or a mass lesion.

Diagnostic Criteria

- **Imaging stigmata:** MRI and MR venography (MRV) may show signs of chronic intracranial hypertension (e.g., empty sella, optic nerve sheath distension, transverse sinus stenosis).
- **Lumbar puncture:** Required to measure opening pressure; diagnosis rests on elevated pressure in the absence of secondary causes.
- **Symptoms:** Transient visual obscurations (TVOs) lasting seconds, pulsatile tinnitus, and headache that may be worse in the morning after prolonged recumbence.
- **Risk factors:** Primarily affects females of childbearing age with obesity. Clinicians must query use of tetracyclines, retinoids (vitamin A), and lithium.

Management: Includes neuro-ophthalmologic assessment for optic disc edema.

📌 IMPORTANT NOTE

Specific acetazolamide dosing and the Modified Dandy diagnostic criteria thresholds were not explicitly detailed in the source chapter text; these are recommended areas for supplementary board review.

Spontaneous Intracranial Hypotension (SIH / CSF Leak)

Pathophysiology: Low CSF pressure typically arising from a spinal CSF leak, often following trivial trauma or lifting.

Diagnostic Criteria

- **Postural aggravation:** The hallmark is orthostatic headache, classically worse upright and relieved by recumbency.
- **Red flags:** Sudden/abrupt onset, positional trigger, and worsening with Valsalva maneuvers.

- **Associated symptoms:** "Coat hanger" headache (occipital/neck/shoulder pain), tinnitus, hearing changes, and "brain fog."
- **MRI findings:** Contrast-enhanced MRI may show pachymeningeal enhancement; however, 19% of patients with a confirmed leak have a normal brain MRI. Specialized myelography (CT, MR, or digital subtraction) may be required for elusive cases such as CSF-venous fistulas.

Management

- **Bedside screening:** Symptomatic improvement during the Trendelenburg test (5–10° head-down) is highly suggestive of the diagnosis.
- **Intervention:** Targeted or nontargeted epidural blood patches are the treatment of choice when a leak is suspected.

CLINICAL PEARL

A normal brain MRI does NOT exclude a CSF leak — nearly 1 in 5 confirmed cases have unremarkable imaging. Base the diagnosis on the orthostatic history and consider spinal imaging when suspicion remains high.

Chapter 2 — Migraine: Pathophysiology and Diagnostic Criteria

I. Migraine Pathophysiology: A Neurally Driven Brain Disorder

Migraine is fundamentally recognized as a complex, heterogeneous neural disorder involving widespread brain dysfunction rather than a purely vascular event.

Trigeminovascular System Activation

- **Neuroanatomy:** Pain-sensitive intracranial vascular structures and meninges are trigeminally innervated. Peripheral sensory afferents (unmyelinated C fibers and myelinated A δ fibers) project from the trigeminal ganglion to the trigeminocervical complex (TCC) in the brainstem.
- **Pain processing:** Projections ascend from the TCC through the thalamus to the somatosensory, limbic, and prefrontal cortices, modulating the sensory and emotional components of pain.
- **Attack initiation:** Functional imaging demonstrates that central areas — specifically the hypothalamus — activate up to 48 hours before pain onset, suggesting the attack initiates centrally before trigeminovascular activation.

Cortical Spreading Depression (CSD)

- CSD is the proposed mechanism for migraine aura.
- CSD is hypothesized to activate peripheral nociceptors through neurotransmitter release, thereby initiating the headache phase.

Neurogenic Inflammation

- Activation of dural nociceptors leads to release of vasoactive neuropeptides, causing vasodilation of dural and pial blood vessels and plasma protein leakage.
- While historically significant, the role of inflammation is now viewed as secondary, because non-vasoconstricting anti-inflammatory inhibitors have failed to show acute treatment efficacy.

Central Neuropeptides: CGRP and PACAP

Neuropeptide	Source	Mechanism / Clinical Relevance
Calcitonin Gene-Related Peptide (CGRP)	Perivascular trigeminal afferents and trigeminal ganglion	IV infusion triggers migraine-like attacks in susceptible individuals; mediates vasodilation and activation/sensitization of peripheral meningeal nociceptors. Central target of gepants and CGRP monoclonal antibodies.
Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)	Sphenopalatine and trigeminal ganglia	Levels increase during attacks and decrease with triptan treatment; may trigger attacks via PAC1 receptor binding, mediating mast cell degranulation and dural C-fiber activation.

Table 2.1 — Key neuropeptides in migraine pathophysiology.

MEMORY TIP / MNEMONIC

Migraine attack sequence: Hypothalamus (premonitory) → Cortical Spreading Depression (aura) → Trigemino-vascular activation & CGRP/PACAP release (headache) → Postdrome. Remember: the brain starts the attack — the vasculature just responds.

II. ICHD-3 Diagnostic Criteria

The diagnosis of migraine is primarily based on the patient's history, requiring specific timelines and symptom clusters as defined by the International Classification of Headache Disorders, 3rd edition (ICHD-3).

Migraine Without Aura (ICHD-3 1.1)

Criterion	Requirement
Episodes	At least 5 lifetime attacks fulfilling the criteria below
Duration	4–72 hours (untreated or unsuccessfully treated); 2–72 hours in children/adolescents
Pain characteristics(≥ 2 of 4 required)	Unilateral location (though 40% of adults and most children have bilateral pain) • Pulsating/throbbing quality • Moderate or severe intensity • Aggravated by or causing avoidance of routine physical activity
Associated symptoms(≥ 1 of 2 required)	Nausea and/or vomiting • Photophobia AND phonophobia

Table 2.2 — ICHD-3 diagnostic criteria for migraine without aura.

Migraine With Aura (ICHD-3 1.2)

- **Aura definition:** Transient positive (shimmering lights, zigzag lines) or negative (scotoma, vision loss) neurologic symptoms arising from the brain.
- **Progression:** Symptoms develop gradually over ≥ 5 minutes.
- **Duration:** Each individual aura symptom lasts 5–60 minutes.
- **Timing:** Aura typically precedes the headache but may occur during or after the pain phase, or even as an isolated event without headache.

EXAM TIP

The "≥ 5 minutes to develop, 5–60 minutes duration" rule for aura is a classic board discriminator against TIA (abrupt onset) and seizure (rapid spread, usually < 2 minutes).

III. Clinical Variants and Specific Syndromes

Chronic Migraine

Defined as headache on ≥ 15 days per month for at least 3 months, where at least 8 of those days meet full migraine criteria (with or without aura) or respond to migraine-specific treatment.

Hemiplegic Migraine

- A rare variant where aura includes motor weakness.
- High genetic load, with mutations identified in CACNA1A, ATP1A2, and SCN1A.

Migraine With Brainstem Aura

- Aura symptoms clearly originate from the brainstem but involve no motor weakness.
- **Manifestations:** Diplopia, ataxia (unsteady gait), vertigo, dysarthria, and decreased level of consciousness.

Vestibular Migraine

Characterized by migraine-associated vertigo; often responds to preventive treatments such as SNRIs.

Retinal Migraine

Involves repeated attacks of monocular visual disturbances (scintillations, blindness).

IMPORTANT NOTE

The source material emphasizes classification overlap of retinal migraine with other conditions rather than detailed diagnostic mechanics; monocular visual loss always warrants ophthalmologic and vascular work-up to exclude retinal or optic nerve pathology before attributing symptoms to retinal migraine.

Pediatric Periodic Syndromes (Episodic Syndromes Associated With Migraine)

Syndrome	Key Features
Abdominal Migraine	≥ 5 attacks of midline/periumbilical pain (dull/sore), lasting 2–72 hours, with pallor, nausea, vomiting, or anorexia. Confers the strongest risk of developing typical migraine later in life.
Cyclical Vomiting Syndrome	≥ 5 attacks of intense nausea and vomiting (≥ 4 times/hour) with predictable periodicity, lasting 1 hour to 10 days.
Benign Paroxysmal Torticollis	Recurrent head tilt associated with pallor, ataxia, or irritability.
Benign Paroxysmal Vertigo	Brief, spontaneous attacks of vertigo in otherwise healthy children.

Table 2.3 — Pediatric periodic syndromes associated with migraine.

IV. Critical Diagnostic Timelines & "Hidden" Attack Phases

Phase	Timing	Key Features
Premonitory (Prodrome)	Up to 48 hours before headache	Uncontrollable yawning, mood changes, cognitive dysfunction ("brain fog"), food cravings (e.g., chocolate), neck stiffness

Phase	Timing	Key Features
Aura	Immediately precedes / accompanies pain	See ICHD-3 criteria above
Headache	4–72 hours (adult)	See ICHD-3 criteria above
Postdrome ("migraine hangover")	Up to 24 hours after pain resolution	Fatigue, cognitive changes, vertigo, sensory sensitivity

Table 2.4 — The four phases of a migraine attack.

Cutaneous Allodynia

Occurs in approximately 60% of patients and signals the presence of central sensitization. Its development makes acute treatments less effective, requiring patients to "treat early."

CLINICAL PEARL

Ask patients whether their scalp hurts to touch, or if wearing glasses or a ponytail becomes painful during an attack — this is cutaneous allodynia, a marker of central sensitization that predicts poorer response to late-administered acute therapy.

Chapter 3 — Migraine Pharmacotherapy

I. Acute (Abortive) Medications

Acute treatments aim for complete pain relief at 2 hours and prompt return to function.

1. Triptans (5-HT_{1B}/1D Receptor Agonists)

Mechanism: Agonists at 5-HT_{1B} and 1D receptors, exerting both vascular (vasoconstrictive) and neural effects within the trigeminocervical complex.

Dosing and Administration

Triptan	Formulations / Doses	Maximum per 24h
Sumatriptan	Oral: 25, 50, 100 mg Nasal: 5, 10, 20 mg spray or 22 mg powder SC: 3, 4, 6 mg	Oral: 200 mg Nasal spray: 40 mg / powder: 44 mg SC: 12 mg
Rizatriptan	5, 10 mg oral / ODT	30 mg (15 mg if taking propranolol)
Eletriptan	20, 40 mg oral	80 mg

Triptan	Formulations / Doses	Maximum per 24h
Zolmitriptan	2.5, 5 mg oral / ODT / nasal	10 mg
Naratriptan	1, 2.5 mg oral	5 mg
Frovatriptan	2.5 mg oral	7.5 mg

Table 3.1 — Triptan dosing summary.

⚠ WARNING

Absolute contraindications: History of coronary heart disease, coronary vasospasm, ischemic stroke, or poorly controlled hypertension.

Caution: Multiple cardiac risk factors warrant careful risk-benefit assessment.

Interactions: Boxed warning for concurrent SSRI/SNRI use (serotonin syndrome risk), though recent evidence suggests this is very rare. Do not use within 24 hours of ergot derivatives.

2. Ditans (Lasmiditan)

Mechanism: Selective 5-HT_{1F} receptor agonist; provides antinociception without significant vasoconstriction — a key advantage in patients with cardiovascular disease.

Dosing: 50, 100, or 200 mg oral; limit to one dose per 24 hours.

⚠ WARNING

Strict 8-hour rule: Patients must not drive or perform activities requiring alertness for at least 8 hours post-dose, due to impaired performance and sedation.

Side effects: High burden of dizziness (13–18%), somnolence, and paresthesia.

3. Gepants (CGRP Receptor Antagonists)

Mechanism: Small-molecule oral antagonists of the CGRP receptor.

Gepant	Dosing	Notes
Ubrogepant	50 or 100 mg; may repeat once after 2 hours. Max 200 mg/24h	Limit to 50 mg if taking verapamil
Rimegepant	75 mg ODT; do not repeat within 24 hours. Max 75 mg/24h	—

Table 3.2 — Gepant dosing summary.

Safety: Generally well tolerated, with no association with vasoconstriction or medication-overuse headache. Avoid in patients taking strong CYP3A4 inhibitors.

MEMORY TIP / MNEMONIC

Triptans and ditans constrict/modulate; gepants and monoclonal antibodies simply block CGRP without vascular effect — this is why gepants are safer in cardiovascular disease and do not carry the same overuse-headache risk as triptans.

II. Preventive Medications: Traditional Options

Traditional prevention is indicated when headache frequency or disability thresholds are exceeded (e.g., ≥ 6 days/month). Titration follows the "start low, go slow" principle.

Drug Class	Agent(s)	Dosing	Key Precautions
Beta-blockers	Propranolol, Metoprolol	Propranolol ~160 mg/day; pediatric start 0.5 mg/kg/day, max 120 mg/day	May worsen asthma and depression; may cause bradycardia
Antiepileptics	Topiramate	Start 25–50 mg; target ~100 mg/day (divided BID); max 200 mg/day	Word-finding difficulties, kidney stones, glaucoma; teratogenic — cleft lip/palate
Antiepileptics	Valproate	15 mg/kg/day up to 30 mg/kg/day; max 1000 mg/day (children)	Highly teratogenic — counsel on contraception and daily folic acid
Antidepressants (TCA)	Amitriptyline	Start 10 mg; effective/max target ~100 mg/day	QT prolongation, sedation, dry mouth, constipation
Antidepressants (SNRI)	Venlafaxine	Often used off-label, e.g., 75 mg daily	—

Table 3.3 — Traditional migraine preventive medications.

EMERGENCY / RED FLAG

Teratogenicity alert: Topiramate and valproate are both highly teratogenic (cleft lip/palate, developmental disorders). Reproductive-age patients require counseling on effective contraception and daily folic acid supplementation before initiation.

III. Preventive Medications: Modern CGRP-Targeted Therapy

These agents are often initiated at an optimal dose, bypassing the gradual titration required by traditional preventives.

Monoclonal Antibodies (mAbs)

Mechanism: Targeted against the CGRP ligand (eptinezumab, fremanezumab, galcanezumab) or its receptor (erenumab).

Agent	Target	Dosing / Schedule
Erenumab	CGRP receptor	70 or 140 mg SC every 4 weeks
Galcanezumab	CGRP ligand	Loading dose 240 mg (two 120-mg injections), then 120 mg SC monthly
Fremanezumab	CGRP ligand	225 mg SC monthly OR 675 mg SC (three 225-mg injections) every 12 weeks
Eptinezumab	CGRP ligand	100 or 300 mg IV infusion every 12 weeks

Table 3.4 — CGRP monoclonal antibody dosing.

- **Erenumab safety:** Associated with constipation and a risk of new-onset or worsening hypertension.
- **Washout:** mAbs have a half-life of approximately 1 month; 95% elimination takes 5 months — critical information for pregnancy planning.

IV. Procedural Therapies

OnabotulinumtoxinA (PREEMPT Protocol)

Indication: Exclusively for chronic migraine (≥ 15 headache days/month).

Standard Dosing

- **Total dose:** 155 units (up to 195 units if following a "follow-the-pain" strategy).
- **Technique:** 31 fixed-site intramuscular injections of 5 units each, across seven muscle groups (trigeminal, occipital, and cervical sensory nerve distributions).
- **Schedule:** Every 12 weeks to maintain therapeutic benefit.

Clinical effectiveness: Effective in patients with comorbid medication-overuse headache (MOH).

EXAM TIP

Remember the PREEMPT numbers: 155 units, 31 sites, 7 muscle groups, every 12 weeks, chronic migraine ONLY (not episodic). These figures are classic board fodder.

Chapter 4 — Tension-Type Headache and Trigeminal Autonomic Cephalalgias

I. Tension-Type Headache (TTH)

Tension-type headache is characterized by lower-severity attacks that are typically featureless compared to migraine.

Diagnostic Criteria (ICHD-3 2.1 & 2.3)

Feature	Description
Location	Bilateral
Quality	Pressing or tightening (non-pulsating); often described as a tight hat or headband
Intensity	Mild or moderate
Physical activity	NOT aggravated by routine physical activity (walking, climbing stairs)
Associated symptoms	No nausea or vomiting; no more than one of photophobia or phonophobia
Duration	30 minutes to 7 days

Table 4.1 — ICHD-3 diagnostic criteria for tension-type headache.

Temporal Subtypes

Subtype	Frequency
Infrequent episodic	≥ 10 episodes, < 1 day/month (< 12 days/year)
Frequent episodic	1–14 days/month for > 3 months
Chronic	≥ 15 days/month for at least 3 months

Table 4.2 — TTH temporal subtypes.

Treatment

- **Acute:** Simple analgesics — acetaminophen and NSAIDs (aspirin, ibuprofen, naproxen) — are first-line.

- **Preventive:** Indicated for high-frequency episodic or chronic TTH; amitriptyline is a common choice.

II. Trigeminal Autonomic Cephalalgias (TACs)

TACs share features of severe, strictly unilateral pain and ipsilateral cranial autonomic symptoms.

1. Cluster Headache (CH)

Cluster headache is defined by its circadian rhythmicity, restlessness, and sensitivity to oxygen.

ICHD-3 Criteria

- **Pain:** Severe or very severe, strictly unilateral orbital, supraorbital, and/or temporal pain.
- **Duration:** 15–180 minutes.
- **Frequency:** From one every other day up to eight per day.
- **Associated features (ipsilateral):** Conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead/facial sweating, miosis, or ptosis.
- **Behavior:** A sense of restlessness or agitation (pacing, rocking) is present in 90% of patients.

MEMORY TIP / MNEMONIC

Cluster headache patients pace and rock ("restless"), unlike migraine patients who seek a dark, still room. This behavioral contrast is a classic bedside discriminator.

Acute Treatment

Treatment	Protocol
Oxygen	100% high-flow oxygen via nonrebreather mask, 12–15 L/min for 15 minutes
Triptan (preferred)	Subcutaneous sumatriptan 6 mg — most effective triptan route
Triptan (alternative)	Nasal zolmitriptan 5–10 mg

Table 4.3 — Cluster headache acute treatment.

Bridge (Transitional) Therapy

- **Prednisone protocol:** 100 mg daily for 5 days, followed by a taper decreasing by 20 mg every 3 days.
- **Nerve blocks:** Greater occipital nerve injections with corticosteroids provide rapid bridge relief.

Preventive Therapy

- **Verapamil (first-line):** Typical investigated dose 360 mg daily (divided TID).
- **Other preventives:** Galcanezumab 300 mg monthly (episodic CH only); lithium 900 mg daily; melatonin 10 mg.

⚠️ WARNING

Mandatory ECG monitoring for verapamil: ECGs (measuring the PR interval) are mandatory before starting, 10–14 days after each dose increase, and every 6 months thereafter, due to the risk of heart block.

2. Paroxysmal Hemicrania (PH)

ICHD-3 Criteria

- **Duration:** 2–30 minutes.
- **Frequency:** > 5 attacks per day (median of nine).
- **Response:** Absolute diagnostic response to therapeutic doses of indomethacin.

Indomethacin Dosing & Safety

Step	Dose	Duration
Trial start	25 mg TID	5–7 days
Step up	50 mg TID	5–7 days
Step up (if needed)	75 mg TID	2 weeks
Target dose	Usually 150–225 mg/day (maintenance)	Ongoing

Table 4.4 — Indomethacin trial protocol for indomethacin-responsive headaches.

⚠️ WARNING

Mandatory gastrointestinal protection with a proton pump inhibitor (PPI) is recommended alongside indomethacin therapy.

Differential: Paroxysmal hemicrania is distinguished from cluster headache by its shorter, more frequent attacks and its absolute response to indomethacin.

3. SUNCT and SUNA

- **Criteria:** Short-lasting unilateral neuralgiform headache attacks lasting 1–600 seconds.

- **Frequency:** One to hundreds of attacks per day.

Subtype	Required Ipsilateral Features
SUNCT	BOTH conjunctival injection AND lacrimation (tearing)
SUNA	Only one, OR neither, of these features present

Table 4.5 — SUNCT vs. SUNA differentiation.

- **Triggers:** Unique for having cutaneous triggers (e.g., touching the face, wind) without a refractory period.

Targeted Management

- **First-line preventive:** Lamotrigine.
- **Other sodium-channel blockers:** Carbamazepine or oxcarbazepine.
- **Bridge:** IV lidocaine (1–3.5 mg/kg/hr) during a 1-week inpatient admission.

4. Hemicrania Continua (HC)

ICHD-3 Criteria

- **Pattern:** Continuous, strictly unilateral headache for > 3 months.
- **Exacerbations:** Periods of moderate or severe intensity associated with autonomic features.
- **Response:** Responds absolutely to therapeutic doses of indomethacin.

CLINICAL PEARL

Hemicrania continua is often misdiagnosed as chronic migraine. Always ask specifically about a constant, low-level background pain between exacerbations — its presence, plus an absolute indomethacin response, secures the diagnosis.

III. Summary Comparison: The Trigeminal Autonomic Cephalalgias

Feature	Cluster Headache	Paroxysmal Hemicrania	SUNCT / SUNA	Hemicrania Continua
Duration	15–180 min	2–30 min	1–600 sec	Constant
Frequency	1 every other day – 8/day	> 5/day	1 to hundreds/day	Constant
Restlessness	90% (common)	80%	65%	70%

Feature	Cluster Headache	Paroxysmal Hemicrania	SUNCT / SUNA	Hemicrania Continua
1st-line prevention	Verapamil	Indomethacin	Lamotrigine	Indomethacin
Imaging focus	MRI (pituitary focus)	MRI (pituitary focus)	MRI (brainstem/pituitary)	MRI (pituitary focus)

Table 4.6 — Comparison chart of the trigeminal autonomic cephalalgias (TACs).

🔑 MEMORY TIP / MNEMONIC

"CPSH" duration ladder: Cluster (15–180 min) > Paroxysmal Hemicrania (2–30 min) > SUNCT/SUNA (1–600 sec, i.e. seconds) — durations shorten as you move down the TAC spectrum, while indomethacin responsiveness becomes the key discriminator for PH and Hemicrania Continua.

Chapter 5 — Medication-Overuse Headache and Other Primary Headache Disorders

I. Medication-Overuse Headache (MOH)

MOH is a secondary headache disorder in which frequent use of acute medications drives the progression of a pre-existing primary headache (typically migraine) into a chronic, daily pattern.

1. ICHD-3 Diagnostic Criteria

Criterion	Description
A	Headache occurring on ≥ 15 days/month in a patient with a pre-existing headache disorder
B	Regular overuse for > 3 months of one or more drugs taken for acute or symptomatic treatment
C	Not better accounted for by another ICHD-3 diagnosis

Table 5.1 — ICHD-3 diagnostic criteria for medication-overuse headache.

Timeline for resolution: The headache is expected to resolve, or return to its underlying pattern, within 2 months after withdrawal of the overused medication.

2. Overuse Thresholds by Drug Class

The risk is driven by the frequency of use, not the dosage.

Drug Class	Overuse Threshold
Triptans, ergots, opioids, combination analgesics	≥ 10 days/month
Simple analgesics (NSAIDs, acetaminophen)	≥ 15 days/month
Mixed overuse (combination of different classes)	≥ 10 days/month total

Table 5.2 — Medication-overuse thresholds by drug class.

⚠ IMPORTANT NOTE

Some sources also cite a ≥15-day threshold for combination analgesics specifically, but clinical practice generally applies the more conservative ≥10-day threshold to minimize risk.

3. Withdrawal and Bridge Therapy Protocols

- **Discontinuation strategy:** No significant difference has been shown between abrupt vs. slow taper, though abrupt withdrawal is often recommended unless safety concerns (e.g., high-dose opioids or barbiturates) require a slow taper.
- **Withdrawal phase:** Patients should expect symptoms such as nausea, dizziness, and sleep disturbances lasting up to 10 days.

Bridge Therapy Options

Category	Regimen
NSAIDs	Naproxen 550 mg twice daily for 2–4 weeks
Steroids	Short prednisone taper starting at 60 mg
Parenteral (inpatient/infusion)	IV dihydroergotamine (DHE), IV sodium valproate, or IV prochlorperazine
Supportive care	Hydration, neuroleptics, tranquilizers, antiemetics

Table 5.3 — Bridge therapy options during medication withdrawal.

💡 CLINICAL PEARL

Initiating a preventive agent — topiramate, onabotulinumtoxinA, or a CGRP monoclonal antibody — during the withdrawal process itself is now considered a pragmatic and effective approach, rather than waiting until the overused medication is fully discontinued.

II. Other Primary Headaches

These syndromes have distinct triggers and specific management profiles that differentiate them from migraine or tension-type headache.

1. New Daily Persistent Headache (NDPH)

- **Core feature:** A daily headache with a distinct, clearly remembered onset.
- **ICHD-3 criteria:** Pain becomes continuous and unremitting within 24 hours (patients often memorize the exact date or event) and has been present for > 3 months.
- **Triggers:** Frequently follows a viral infection (including COVID-19) or a stressful life event.
- **Management:** Highly refractory; treatment is typically extrapolated from chronic migraine protocols (triptans, topiramate, onabotulinumtoxinA, CGRP antibodies).

2. Primary Thunderclap Headache

- **Definition:** Pain that starts instantly at peak intensity.
- **Gold standard:** A diagnosis of exclusion.

EMERGENCY / RED FLAG

Mandatory rule-outs: Clinicians must first exclude subarachnoid hemorrhage (SAH) and reversible cerebral vasoconstriction syndrome (RCVS), as well as meningitis and spontaneous intracranial hypotension, before this diagnosis can be made.

3. Primary Cough, Exercise, and Sexual Headaches

Syndrome	Trigger	Key Notes
Primary cough headache	Valsalva maneuvers (coughing, sneezing, straining, laughing)	Rule out Chiari I malformation or posterior fossa lesion first
Primary exercise/exertion headache	Physical exertion	—
Primary headache associated with sexual activity	Sexual activity (pre-orgasmic or at orgasm)	Pre-emptive treatment with indomethacin often effective

Table 5.4 — Valsalva- and exertion-related primary headaches.

4. Hypnic Headache ("Alarm-Clock Headache")

- **Clinical profile:** Typically affects the elderly.

- **Pattern:** Nocturnal awakening at a consistent time each night.
- **Key differentiator:** Unlike cluster headache, it lacks autonomic features and restlessness.
- **Unique management:** Frequently responsive to bedtime caffeine (a cup of strong coffee) or lithium.

🔍 MEMORY TIP / MNEMONIC

Hypnic headache = the "anti-cluster": both wake patients at night, but hypnic headache has NO autonomic features and NO restlessness, and it responds paradoxically to caffeine at bedtime.

III. Critical Diagnostic Red Flags Applied to This Chapter

When a patient presents with a continuous or abrupt-onset headache, clinicians must screen for the following SNNOOP10 elements:

- **Positional triggers:** Suggestive of CSF pressure disorders (IIH or CSF leak).
- **Older age (> 50):** Raises suspicion for Giant Cell Arteritis.
- **Systemic symptoms:** Fever or weight loss.

Chapter 6 — Trigeminal Neuralgia and Other Cranial Neuralgias

I. Trigeminal Neuralgia (TN): Complete Clinical Profile

Trigeminal neuralgia is a disorder characterized by recurrent, unilateral, brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, and triggered by innocuous stimuli.

1. ICHD-3 Classification & Etiology

Subtype	Etiology
Classical TN	Neurovascular compression (conflict) of the trigeminal nerve root, typically visible on high-resolution MRI (heavily T2-weighted sequences)

Subtype	Etiology
Secondary TN	Underlying disease other than neurovascular compression — commonly Multiple Sclerosis (plaque at the trigeminal nerve root entry zone) or space-occupying lesions
Idiopathic TN	No identifiable cause on imaging or electrophysiological testing

Table 6.1 — ICHD-3 classification of trigeminal neuralgia.

Subclassification: Both classical and idiopathic forms are further divided into "purely paroxysmal" and "with concomitant continuous pain."

2. ICHD-3 Diagnostic Criteria

Feature	Description
Duration	A fraction of a second to 2 minutes
Intensity	Severe
Quality	Electric shock-like, shooting, stabbing, or sharp
Triggering	Precipitated by innocuous stimuli (light touch, cold wind, washing the face, brushing teeth) within the affected distribution

Table 6.2 — ICHD-3 diagnostic criteria for trigeminal neuralgia.

Neurophysiologic mechanism: Pain is thought to result from demyelination, leading to ephaptic transmission of amplified pain signals and pathologic spontaneous firing within the trigeminal ganglion.

3. Formal Nerve Branch Identifiers

Division	Notes
V1 (Ophthalmic)	Restricted pain here may involve mild autonomic features (e.g., slight eye watering)
V2 (Maxillary) and V3 (Mandibular)	The most common locations for TN pain

Table 6.3 — Trigeminal nerve divisions in TN.

🔔 IMPORTANT NOTE

If autonomic features are prominent (rather than mild), consider SUNCT or SUNA as an alternative or overlapping diagnosis.

II. Pharmacological & Surgical TN Management

1. First-Line Pharmacotherapy

Agent	Starting Dose	Target/Maintenance Dose	Monitoring
Carbamazepine(only FDA-approved agent for TN)	10–25% of target dose, e.g., 100 mg BID, titrated relatively rapidly	300–800 mg/day	Baseline and periodic serum sodium (hyponatremia); CBC (blood dyscrasias/leukopenia)
Oxcarbazepine(close relative, often better tolerated)	—	600–1200 mg/day	Similar profile, generally better tolerated

Table 6.4 — First-line pharmacotherapy for trigeminal neuralgia.

2. Refractory & Procedural Management

When medical therapy fails or is intolerable, interventional options must be discussed.

Procedure	Description
Microvascular Decompression (MVD / Janetta procedure)	Indicated for classical TN where nerve compression is identified; often the most effective long-term surgical option
Stereotactic radiosurgery (Gamma Knife)	High-energy radiation aimed at the nerve root to interrupt pain signaling
Percutaneous rhizotomy	Thermal (radiofrequency), chemical (glycerol), or mechanical (balloon compression) ablation of the nerve
OnabotulinumtoxinA	Emerging off-label option; 5–75 units spread across the painful distribution every 12 weeks

Table 6.5 — Refractory and procedural management options for TN.

III. Other Cranial Neuralgias & Persistent Pain Syndromes

1. Glossopharyngeal Neuralgia

Feature	Description
Distribution	Posterior tongue, tonsillar fossa, pharynx, angle of the lower jaw, and/or the ear
Triggers	Swallowing, coughing, talking, or yawning

Feature	Description
Vagal association	Due to proximity and interconnectedness with the vagus nerve, attacks may be associated with bradycardia and syncope

Table 6.6 — Glossopharyngeal neuralgia.

🚨 EMERGENCY / RED FLAG

Cardiac syncope associated with glossopharyngeal neuralgia can be dramatic and dangerous — consider cardiac monitoring during diagnostic work-up, especially before procedural intervention.

2. Occipital Neuralgia

Nerve	Origin
Greater occipital nerve	C2 dorsal ramus
Lesser occipital nerve	C2 ventral ramus
Third occipital nerve	C3 dorsal ramus

Table 6.7 — Occipital nerve anatomy.

- **Diagnostic nerve block:** Diagnosis is confirmed if pain is temporarily eased by a local anesthetic block.
- **Block parameters:** 1–2 cc of 0.25–0.5% bupivacaine, or 1–2% lidocaine, per injection site.

3. Nervus Intermedius Neuralgia

- **Location:** Pain is felt deep within the auditory canal.
- **Secondary cause:** Most commonly herpes zoster (part of the Ramsay Hunt spectrum).

4. Painful Trigeminal Neuropathy (Atypical / Persistent Facial Pain)

- **Description:** Known in ICHD-3 as painful trigeminal neuropathy (and in ICOP as "other trigeminal neuropathic pain disorders").
- **Phenotype:** Continuous or nearly continuous burning, squeezing, or aching pain, often associated with sensory deficits or allodynia.
- **Etiology:** May follow trauma, infection (postherpetic), or be idiopathic.

IV. Expert Clinical Pearls: Neuro-Rheumatology & Comorbidities

- **Inflammatory markers:** Systemic conditions like Giant Cell Arteritis must be ruled out in patients over 50 with new-onset persistent facial or head pain (screen with ESR/CRP).
- **Neurodegeneration risk:** Chronic neuropathic pain from TN is associated with an increased risk of Alzheimer disease and central neurodegeneration, potentially linked to chronic neuroinflammation and hippocampal volume reduction.

CLINICAL PEARL

Any new facial/head pain in a patient over 50 deserves ESR/CRP screening, regardless of how classic the neuralgic phenotype appears — GCA can mimic or coexist with cranial neuralgias.

Chapter 7 — Headache in Special Populations

I. Pregnancy and Lactation Management

Management of headache during pregnancy requires balancing the health of the pregnant individual with potential fetal risks. Migraine often improves during gestation, particularly after the first trimester.

1. Acute (Abortive) Medications

Tier	Agent	Notes
First-line (safest)	Acetaminophen	Considered the first-line analgesic; some observational studies suggest associations with neurodevelopmental issues, but it remains the standard initial choice
First-line (safest)	Metoclopramide	Safely treats both migraine pain and associated nausea
First-line for rescue	Triptans	Now supported by a large body of evidence for safety during pregnancy; eletriptan preferred during lactation due to low excretion in breast milk
Second-line / restricted	NSAIDs (ibuprofen, naproxen)	Must be AVOIDED in the third trimester — risk of premature closure of the ductus arteriosus
Second-line rescue	Prednisone	May be used as second-line rescue

Table 7.1 — Acute migraine treatment in pregnancy.

🚨 EMERGENCY / RED FLAG

Absolute contraindications in pregnancy: Ergot derivatives and DHE (potent vasoconstrictors, strictly prohibited); gepants (rimegepant, ubrogepant) and lasmiditan (currently avoided due to lack of human safety data).

2. Preventive Medications in Pregnancy

⚠️ WARNING

Avoid: Valproate and topiramate are highly teratogenic. Valproate is associated with major congenital malformations and neurodevelopmental deficits; topiramate increases the risk of cleft lip and palate.

Safe alternatives: Non-pharmacologic options such as neuromodulation devices are often preferred. Pharmacologic options include magnesium and low-dose beta-blockers (e.g., propranolol).

II. Pediatric Headache Syndromes

Migraine is the leading cause of neurologic disability in youth, affecting approximately 10% of children and adolescents.

1. Clinical Presentation Variations

Feature	Pediatric Pattern
Location	Frequently bilateral (frontotemporal) in younger children, unlike the unilateral pattern typical of adults
Duration	Shorter attacks, lasting 2–72 hours
Associated symptoms	Cranial autonomic symptoms (eye watering, nasal congestion) occur in 55–70% of pediatric migraineurs

Table 7.2 — Pediatric vs. adult migraine presentation.

2. Pediatric Periodic Syndromes

Syndrome	Key Features
Abdominal migraine	Recurrent midline/periumbilical pain lasting 2–72 hours, with pallor, nausea, or vomiting. Confers the strongest risk of future typical migraine.
Cyclical vomiting syndrome	Intense nausea and vomiting (≥ 4 times/hour) lasting 1 hour to 10 days.
Benign paroxysmal torticollis	Recurrent head tilt in infants.

Table 7.3 — Pediatric periodic syndromes (review).

3. Specialized Pediatric Treatment

Acute Treatment

Line	Agent(s)	Notes
First-line	Ibuprofen 10 mg/kg	—
Triptans	Rizatriptan ODT (≥ 6 years); zolmitriptan nasal, almotriptan, sumatriptan/naproxen (≥ 12 years)	Age-specific FDA approval

Table 7.4 — Pediatric acute migraine treatment.

⚠️WARNING

Medication overuse limits in children: Restrict ibuprofen/acetaminophen to < 14 days/month and triptans to < 9 days/month.

Prevention: Cognitive Behavioral Therapy (CBT) combined with amitriptyline is a high-evidence approach. Topiramate (starting at 2–3 mg/kg/day) and propranolol are also used.

III. Geriatric Onset Headache

In older adults, the diagnostic focus shifts significantly toward identifying secondary etiologies.

Secondary Causes to Rule Out

Etiology	Key Screening Points
Giant Cell Arteritis (GCA)	Critical screen for any new headache > 50 years; check ESR/CRP; query jaw claudication
Mass lesions / neoplasms	New-onset headache in the elderly is a primary red flag for brain tumor or metastasis

Etiology	Key Screening Points
Subdural hematoma	High suspicion required following even minor falls or head trauma in this age group

Table 7.5 — Secondary causes of new-onset headache in older adults.

Hypnic Headache ("Alarm-Clock Headache") — Revisited

- A rare primary disorder typically affecting the elderly.
- Characterized by nocturnal awakening at a consistent time.
- **Management:** Unique responsiveness to bedtime caffeine (a cup of strong coffee) or lithium.

EXAM TIP

Any "new headache after 50" vignette should trigger an automatic mental checklist: GCA (ESR/CRP, jaw claudication) → mass lesion (imaging) → subdural hematoma (history of falls/anticoagulation) → then consider primary causes like hypnic headache only after secondary causes are excluded.

Chapter 8 — Vascular Causes of Headache

I. Reversible Cerebral Vasoconstriction Syndrome (RCVS)

RCVS is a clinical-radiologic syndrome characterized by severe "thunderclap" headaches and diffuse segmental constriction of cerebral arteries.

Clinical Presentation

- **Thunderclap onset:** Pain starts instantly at peak intensity.
- **Temporal pattern:** While typically an acute event, a continuous daily headache can emerge after an initial pattern of single or multiple thunderclap headaches; patients typically experience recurrent thunderclap attacks over 1–2 weeks.

Triggers

Category	Examples
Vasoactive substances	Adrenergic agents (decongestants, cocaine), serotonergic drugs (SSRIs, SNRIs), herbal supplements
Physiological states	Postpartum period; physical exertion / Valsalva maneuvers

Table 8.1 — RCVS triggers.

Diagnostic Workup

🔍 EMERGENCY / RED FLAG

Gold standard: Primary thunderclap headache is a diagnosis of exclusion — clinicians must first rule out subarachnoid hemorrhage (SAH) and RCVS via brain and cerebrovascular imaging.

- **Vascular imaging:** CTA or MRA is required to identify the characteristic "string of beads" pattern of diffuse segmental vasoconstriction.
- **CSF analysis:** Typically normal or near-normal — this helps distinguish RCVS from primary CNS vasculitis.

Complications

Complication	Notes
Convexity subarachnoid hemorrhage (cSAH)	Often the first radiological sign
Ischemic stroke	Particularly in watershed distributions
Posterior Reversible Encephalopathy Syndrome (PRES)	May co-occur

Table 8.2 — Complications of RCVS.

Management Protocols

- **Elimination of triggers:** Immediate discontinuation of all adrenergic or serotonergic agents.
- **Calcium channel blockers:** Nimodipine is the first-line choice for preventing further vasoconstriction.
- **Dosing:** Standard oral dosing is 60 mg every 4 hours. In severe or refractory cases, IV nimodipine infusions may be utilized in an intensive care setting.

🔍 MEMORY TIP / MNEMONIC

RCVS vs. SAH: Both cause thunderclap headache, but RCVS classically presents with RECURRENT thunderclap attacks over 1–2 weeks ("string of beads" on angiography, normal CSF), while SAH is typically a single catastrophic event with xanthochromic CSF.

II. Cervical Artery Dissections (Carotid and Vertebral)

Dissections are a leading cause of stroke in young and middle-aged adults and frequently present with headache as the sentinel symptom.

Clinical Syndromes

Dissection Type	Presentation
Carotid dissection	Strictly unilateral pain with associated miosis and ptosis (partial Horner syndrome)
Vertebral dissection	Typically presents with posterior neck pain and occipital headache

Table 8.3 — Carotid vs. vertebral artery dissection.

Progression: Pain is often followed by ischemic stroke or transient ischemic attack (TIA).

Diagnostic Evaluation

- **Imaging:** Brain and vascular imaging (CTA, MRA, or carotid ultrasound) is mandatory for patients presenting with posttraumatic headache or side-locked pain with autonomic features, to investigate for dissection.
- **Gold standard:** Digital Subtraction Angiography (DSA) remains the historical gold standard, though high-resolution MRI with fat-saturated sequences is now the clinical standard.

Therapeutic Choices

- **Antithrombotic therapy:** Options include antiplatelet therapy (e.g., aspirin) or anticoagulation (e.g., heparin/warfarin).
- **Clinical consensus:** Randomized trials (e.g., CADISS) suggest no significant difference in stroke prevention between antiplatelets and anticoagulants for most patients.

🚨 EMERGENCY / RED FLAG

New unilateral head/neck pain with a partial Horner syndrome (miosis + ptosis, without anhidrosis) in a young patient is carotid dissection until proven otherwise — obtain urgent vascular imaging.

III. Cerebral Amyloid Angiopathy (CAA) and Headache

CAA is an important consideration in the differential of transient neurological symptoms in older populations.

"Amyloid Spells"

- **Phenotype:** Transient neurological symptoms that can present as migrainous aura mimics (e.g., spreading paresthesias or visual disturbances).

- **Mechanism:** Thought to be caused by focal subarachnoid hemorrhage or spreading cortical depression triggered by blood products.

Imaging Hallmarks

Finding	MRI Sequence	Significance
Cortical superficial siderosis (cSS)	T2*-weighted or susceptibility-weighted (SWI)	Linear blood products along the cortical sulci
Microhemorrhages	T2*/SWI	Multiple lobar microhemorrhages characteristic of CAA

Table 8.4 — Imaging hallmarks of cerebral amyloid angiopathy.

CLINICAL PEARL

In an older adult presenting with recurrent "migraine aura-like" spreading sensory or visual symptoms without a personal migraine history, consider amyloid spells and request SWI/GRE sequences to look for cortical superficial siderosis.

IV. Critical Vascular Screening (SNNOOP10, Vascular Focus)

Vascular etiologies must be screened for when any of the following red flags are present:

Red Flag	Vascular Concern
Sudden/abrupt onset	SAH or RCVS
Pregnancy/puerperium	RCVS, cerebral venous thrombosis (CVT), arterial dissection
Older age (> 50)	Giant Cell Arteritis — requires immediate ESR/CRP and monitoring for jaw claudication

Table 8.5 — Vascular red flags in headache presentation.

Chapter 9 — Comorbidities, Behavioral Management, and Neuromodulation

I. Psychiatric Comorbidities and Screening

Headache disorders, particularly migraine, share a bidirectional relationship with several psychiatric conditions, where each condition increases the risk and severity of the other.

Comorbidity Profile

- **Major Depressive Disorder (MDD) and Anxiety (GAD):** The most frequently encountered psychiatric comorbidities. Depression is a significant risk factor for the chronification of migraine (progression from episodic to chronic).
- **PTSD:** Highly prevalent in specific populations, such as transgender individuals and veterans, and is associated with increased migraine frequency and severity.
- **Interictal burden:** Anxiety often manifests as a "fear of the next attack," leading to lifestyle restrictions and social stigma even when the patient is pain-free.

Clinic-Based Screening Tools

Tool	Items	Purpose
PHQ-9 (Patient Health Questionnaire)	9 questions	Screens for and grades the severity of depression
GAD-7 (General Anxiety Disorder-7)	7 questions	Screens for anxiety
PCL-C (PTSD Checklist for DSM-5)	17 questions	Assesses Posttraumatic Stress Disorder
ASC-12 (Allodynia Symptom Checklist)	12 questions	Identifies cutaneous allodynia — a marker of central sensitization and risk factor for treatment resistance

Table 9.1 — Psychiatric and central-sensitization screening tools used in headache clinics.

EXAM TIP

Know the item counts: PHQ-9 (9), GAD-7 (7), PCL-C (17), ASC-12 (12) — the number in each tool's name is itself the item count for PHQ-9 and GAD-7, a handy anchor.

II. Behavioral and Non-Pharmacological Interventions

Biobehavioral management is a cornerstone of interdisciplinary care, particularly for patients with high disability or medication overuse.

Cognitive Behavioral Therapy (CBT)

- **Indication:** Strongly recommended for both adults and children, especially when combined with pharmacotherapy.

- **Clinical goal:** Focuses on pain-coping strategies, identifying "disproof" of triggers, and managing comorbid mood distress.

Biofeedback and Relaxation Training

- **Protocols:** Techniques include mindfulness training, acceptance and commitment therapy, and motivational interviewing.
- **Indications:** For patients who prefer non-drug options, those with contraindications to medications (e.g., pregnancy), or as an adjunct to reduce the dose of preventive drugs.

Patient Education

High-intensity "headache literacy" programs have been shown to reduce monthly headache days, disability, and clinic calls.

III. Neuromodulation Devices in Headache Medicine

Neuromodulation offers a non-invasive, non-pharmacologic alternative for both acute and preventive management.

Device	Acute Protocol	Preventive Protocol
Non-invasive Vagus Nerve Stimulation(nVNS — gammaCore)	Bilateral 120-second stimulations to right and left neck within 20 min of onset; may repeat once after 15 min if pain persists	Pediatric/adolescent: two 2-minute treatments, 3 times per day. Also used for cluster headache and is "indomethacin-sparing" in hemicrania continua
Supraorbital Transcutaneous Neurostimulation(tNS — Cefaly)	60-minute stimulation session as needed during an attack	20-minute daily session
Single-Pulse Transcranial Magnetic Stimulation(sTMS)	Two magnetic pulses delivered to the occiput at onset of aura or headache	Adolescent: two pulses over 2 min, repeated 15 min later (total 4 pulses), twice daily
Remote Electrical Neuromodulation(REN — Nerivio)	45-minute stimulation of the upper arm, initiated within 1 hour of attack onset	One 45-minute session every other day

Table 9.2 — Neuromodulation devices: acute and preventive protocols.

CLINICAL PEARL

Neuromodulation devices are particularly valuable in pregnancy, medication-intolerant patients, and those wishing to avoid systemic drug exposure altogether.

IV. Quality of Life (QoL) and Disability Indexes

Validated metrics are essential for identifying candidates for prevention and tracking interdisciplinary treatment success.

Instrument	Structure	Disability Cut-off
MIDAS (Migraine Disability Assessment)	5-item questionnaire (plus 2 supplementary questions); calculates days of functional impairment over 3 months	Score ≥ 11 → moderate-to-severe disability; preventive therapy should be offered
HIT-6 (Headache Impact Test-6)	6 items assessing impact of headache on daily functioning	Score ≥ 50 → threshold for offering/considering preventive treatment
PedMIDAS	Pediatric adaptation of MIDAS	Score ≥ 30 → recommended threshold for considering off-label anti-CGRP monoclonal antibodies in adolescents
MTOQ (Migraine Treatment Optimization Questionnaire)	Assesses acute treatment adequacy at follow-up	Used to confirm pain freedom at 2 hours, reliability, and functional restoration for $\geq 50\%$ of attacks

Table 9.3 — Quality of life and disability assessment instruments.

📌 MEMORY TIP / MNEMONIC

Cut-off recall: MIDAS ≥ 11 , HIT-6 ≥ 50 , PedMIDAS ≥ 30 — each threshold signals it is time to offer preventive therapy.

Chapter 10 — Master Differential Diagnosis & High-Yield Exam Summary

I. Primary Headache Differential at a Glance

Headache Type	Location	Duration	Key Distinguishing Feature
Migraine (no aura)	Unilateral (bilateral in 40% adults / children)	4–72 h	Pulsating, moderate–severe, nausea/photophobia/phonophobia, aggravated by activity
Tension-type	Bilateral	30 min – 7 days	Pressing/tightening, mild–moderate, NOT aggravated by activity
Cluster	Strictly unilateral orbital/temporal	15–180 min	Ipsilateral autonomic features, restlessness (90%), circadian pattern
Paroxysmal hemicrania	Strictly unilateral	2–30 min	> 5 attacks/day; absolute indomethacin response
SUNCT/SUNA	Strictly unilateral	1–600 sec	Cutaneous triggers, no refractory period
Hemicrania continua	Strictly unilateral	Continuous > 3 mo	Constant background pain + exacerbations; absolute indomethacin response
Trigeminal neuralgia	Unilateral, V2/V3 > V1	Fraction of second – 2 min	Electric shock-like, triggered by innocuous stimuli
Thunderclap (2° or primary)	Variable	Instant peak	Must exclude SAH/RCVS first

Table 10.1 — Primary headache differential diagnosis summary.

II. "Cannot-Miss" Secondary Headache Red Flags — Master Table

Presentation	Must Exclude	First Test
Thunderclap onset	SAH, RCVS, CVT, pituitary apoplexy	Noncontrast CT + LP (if CT negative) / CTA-MRA
Age > 50, jaw claudication	Giant Cell Arteritis	ESR, CRP ± temporal artery biopsy
Positional (worse upright)	Spontaneous intracranial hypotension	MRI brain with contrast ± spine imaging

Presentation	Must Exclude	First Test
Positional (worse recumbent), papilledema, TVOs	Idiopathic intracranial hypertension	MRI/MRV + LP opening pressure
Progressive, worse in morning, Valsalva-aggravated	Mass lesion / Chiari malformation	MRI brain
Post-traumatic, anticoagulated, elderly	Subdural hematoma	CT head
New headache in pregnancy/puerperium	Preeclampsia, CVT, RCVS	BP/urine protein, MRV/MRA
Painful eye + Horner syndrome	Carotid dissection	CTA/MRA neck
Fever, immunosuppression	Meningitis, opportunistic CNS infection	LP, blood cultures, MRI

Table 10.2 — High-yield secondary headache 'cannot-miss' presentations.

🚨 EMERGENCY / RED FLAG

These nine presentations account for the overwhelming majority of secondary-headache board vignettes. Pattern-match the presentation to the red-flag category before considering the specific diagnosis.

III. Indomethacin-Responsive Headaches — High-Yield Mnemonic

📌 MEMORY TIP / MNEMONIC

"**ICH**OSE" indomethacin-responsive headaches:

- **H**emicrania continua
- **C**hronic / episodic Paroxysmal hemicrania
- **H**eadache — primary cough, exercise, and sexual headache (often responsive)
- **O**rgasmic/exertional headache

An absolute, dramatic response to therapeutic-dose indomethacin is itself a diagnostic criterion for paroxysmal hemicrania and hemicrania continua — response (or lack thereof) can be used clinically as a diagnostic test, often termed the "indomethacin test."

IV. Drug Classes Contraindicated or Cautioned Across Headache Medicine

Drug / Class	Contraindication / Caution	Reason
Triptans	CAD, prior stroke, uncontrolled HTN, coronary vasospasm	Vasoconstrictive effect
Ergots / DHE	Pregnancy; within 24h of triptans	Potent vasoconstriction
Valproate / Topiramate	Pregnancy / reproductive age without contraception	Teratogenicity (NTDs, cleft lip/palate)
Lasmiditan	Driving/operating machinery for 8h post-dose	Sedation, dizziness
Gepants	Strong CYP3A4 inhibitors	Altered drug clearance
Carbamazepine	Unmonitored use	Hyponatremia, blood dyscrasias
Verapamil (for CH)	No baseline/serial ECG	Risk of heart block (PR prolongation)
NSAIDs	Third trimester of pregnancy	Premature ductus arteriosus closure

Table 10.3 — Contraindications and cautions across major headache drug classes.

V. Final High-Yield Board Review Checklist

EXAM TIP

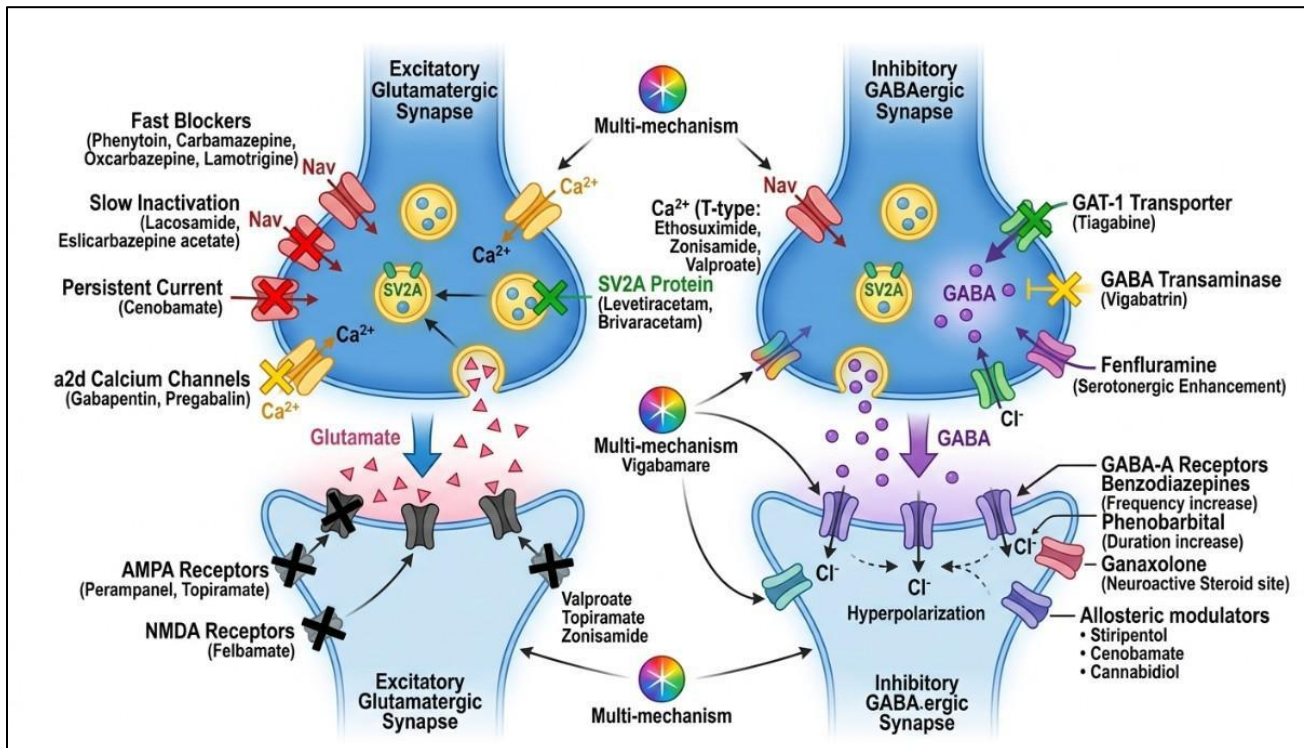
1. Always start with the patient's own words — the "opening line" reveals the true clinical goal.
2. Apply SNNOOP10 to every new or changed headache pattern.
3. Fundoscopy and temporal artery palpation are mandatory examination components, not optional extras.
4. Know exact ICHD-3 timelines: migraine (4–72h), TTH (30min–7d), cluster (15–180min), PH (2–30min), SUNCT/SUNA (1–600sec), TN (fraction of a second – 2min).
5. Distinguish MOH overuse thresholds: triptans/opioids/ergots ≥ 10 days/month vs. simple analgesics ≥ 15 days/month.
6. Remember PREEMPT protocol numbers for chronic migraine: 155 units, 31 sites, 7 muscle groups, every 12 weeks.

7. CGRP mAb washout is 5 months (95% elimination) — essential for pregnancy planning.
8. Verapamil for cluster headache requires baseline and serial ECGs due to heart block risk.
9. Indomethacin-absolute-response headaches: paroxysmal hemicrania and hemicrania continua.
10. Thunderclap headache is always a diagnosis of exclusion — rule out SAH and RCVS first.

CLINICAL PEARL

When in doubt on a board vignette, ask three questions in sequence: (1) Is there a red flag (SNNOOP10)? (2) Does the timeline/duration match a specific primary headache syndrome? (3) Is there an absolute treatment response (indomethacin, oxygen) that clinches the diagnosis? This three-step approach resolves the majority of headache board questions.

EPILEPSY



CHAPTER I

Definitions, Pathophysiology, and Electro-Clinical Semiology

Foundations of Epilepsy: Core Definitions, ILAE Classification, and Localization

I. Definitions & Pathophysiology

A. Core Definitions

Term	Definition
Seizure	A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Epilepsy (2014 ILAE Practical Definition)	- At least two unprovoked (or reflex) seizures occurring >24 hours apart, OR - One unprovoked (or reflex) seizure with a recurrence probability similar to the general recurrence risk after two unprovoked seizures (at least 60%) over the next 10 years, OR - Diagnosis of an epilepsy syndrome
Status Epilepticus (SE)	A condition resulting from failure of the mechanisms responsible for seizure termination, or from initiation of mechanisms leading to abnormally prolonged seizures (time point t_1). Carries a risk of long-term consequences, including neuronal death and injury, after time point t_2 .
Convulsive SE (Tonic-Clonic)	t_1 = 5 minutes; t_2 = 30 minutes
Established SE	SE lasting >5 minutes
Refractory SE	Persistent seizures despite two adequately dosed antiseizure medications (ASMs) of different classes (e.g., a benzodiazepine and fosphenytoin)
Super-Refractory SE	Persistent seizures despite ≥ 24 hours of treatment with anesthetizing ASMs

★ EXAM TIP / HIGH YIELD

Board Pearl: The seizure/epilepsy distinction hinges on the **recurrence risk**, not simply seizure count. A single unprovoked seizure with a structural lesion, epileptiform EEG, or remote symptomatic etiology can meet the **>60% recurrence threshold** and justify a diagnosis of epilepsy after only one seizure.

B. Cellular Pathophysiology and Mechanisms

- Physiology of EEG:** Scalp waveforms represent the summation of excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) from pyramidal neurons. At least 10 cm² of synchronized cortical activation is required for scalp detection.
- Paroxysmal Depolarization Shift (PDS):** The cellular correlate of interictal epileptiform discharges; cellular excitability is governed by the balance of GABAergic inhibition and glutamatergic excitation.

- **Excitation–Inhibition Imbalance:** Often driven by loss-of-function variants in inhibitory interneurons (e.g., *SCN1A*/Nav1.1 haploinsufficiency in Dravet syndrome) or gain-of-function variants in excitatory neurons (e.g., *SCN8A*/Nav1.6).
- **Channelopathies:** Many epilepsies arise from variants in genes encoding voltage-gated ion channels (sodium, potassium, calcium) or synaptic vesicle proteins (e.g., *SV2A*, *PRRT2*).
- **Epileptogenesis:** The process transforming a normal brain into one capable of generating spontaneous seizures. May involve post-infectious cerebral inflammation (as in NORSE/FIRES) or progressive structural reorganization following injury.

II. ILAE Classification System (2017)

A. Tier 1 — Seizure Type by Onset

Onset Category	Subtype	Key Features
Focal Onset	Focal Aware	Awareness fully preserved; originates within a network limited to one hemisphere
	Focal Impaired Awareness	Awareness impaired at any point during the event
	Motor Onset	Automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, or tonic
	Nonmotor Onset	Autonomic, behavioral arrest, cognitive, emotional, or sensory
	Focal to Bilateral Tonic-Clonic	Progression from focal onset (formerly “secondarily generalized”)
Generalized Onset	Motor	Tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic-atonic, atonic, epileptic spasms
	Nonmotor (Absence)	Typical, atypical, myoclonic, eyelid myoclonia
Unknown Onset	Motor	Tonic-clonic, epileptic spasms
	Nonmotor	Behavioral arrest

Note: “Generalized Onset” seizures originate at some point within, and rapidly engage, bilaterally distributed networks; “Unknown Onset” reflects insufficient information to classify the true onset.

B. Tier 2 — Epilepsy Type

Epilepsy Type	Defining Features
Focal Epilepsy	Includes unifocal and multifocal disorders and hemispheric seizures
Generalized Epilepsy	Characterized by generalized spike-wave discharges on EEG and generalized seizure types
Combined Generalized and Focal Epilepsy	Patients exhibit both focal and generalized seizure types (e.g., Dravet syndrome, Lennox-Gastaut syndrome)
Unknown Epilepsy	Insufficient evidence to characterize as focal or generalized

C. Tier 3 — Epilepsy Syndrome

Clusters of features (age of onset, seizure types, EEG, imaging) that often carry specific etiologic and prognostic implications. Representative syndromes:

Syndrome	Age / EEG Signature
Childhood Absence Epilepsy	4–10 years; 3-Hz generalized spike-wave
Juvenile Myoclonic Epilepsy	10–24 years; myoclonic jerks on awakening; 3.5–6 Hz polyspike-wave
Lennox-Gastaut Syndrome	Multiple seizure types (must include tonic); slow spike-wave (<2.5 Hz); generalized paroxysmal fast activity in sleep

i IMPORTANT NOTE

Full syndrome-specific detail (onset, EEG hallmarks, first-line therapy) for all major pediatric, juvenile, adult, and rare epilepsy syndromes is presented in Chapters II and III.

III. Clinical Semiology & Localization

A. Lobe-Based Mapping of Focal Seizures

Lobe	Semiology
Temporal (Mesial)	- Epigastric aura (rising sensation) is the classic onset - Oroalimentary automatisms (lip-smacking) and manual automatisms (fumbling/picking)
Temporal (Psychic/Cognitive)	- Déjà vu, jamais vu, dreamy states, or ictal fear (amygdala involvement) - Ictal aphasia suggests onset in the dominant temporal hemisphere
Frontal	- Hypermotor/hyperkinetic: complex movements — bicycling, thrashing, rocking - Strong nocturnal predominance (frequently arises from sleep) - Fencing posture (asymmetric tonic posturing): arm abduction/elevation with head version, classic for supplementary motor area (SMA) seizures
Parietal	Somatosensory aura — tingling, numbness, or pain
Occipital	Elementary visual hallucinations (multicolored circles), illusions, or amaurosis (transient blindness)

B. Lateralizing Signs

- Unilateral Clonic Activity:** High lateralizing value — localizes to the **contralateral** hemisphere.
- Asymmetric Tonic Limb Posturing (“Sign of Four”):** Extension of one arm with flexion at the elbow of the other, resembling the numeral ‘4’. The extended arm is **contralateral** to the seizure focus.

YD MEMORY TRICK

Localizing Auras — quick recall:

Temporal = rising epigastric + déjà vu → “gut feeling of familiarity”

Frontal = nocturnal + hypermotor → “night-time acrobat”

Parietal = sensory (tingling/pain)

Occipital = visual (colored circles, amaurosis)

IV. Diagnostic Workup & Prognosis

A. EEG Protocols

Study	Duration	Yield / Indication
Routine EEG	20–40 min	Only 29%–55% sensitive for interictal epileptiform discharges (IEDs) on a single study
Extended EEG	>40 min	Increases yield by 19% over routine EEG
Ambulatory EEG	1–4 days	Preferred for events provoked by daily activities, or when inpatient admission is not feasible
Inpatient Video-EEG Monitoring (VEM)	Days (as needed)	Essential in drug-resistant epilepsy to characterize spells, distinguish from nonepileptic events, and localize for surgery

IFCN Criteria for Interictal Epileptiform Discharges (IEDs)

A wave must satisfy at least 4 of the following 6 criteria to be classified as epileptiform:

- Sharp/spiky morphology
- Duration distinct from the background
- Asymmetry (e.g., steeper rising phase)
- Followed by an after-going slow wave
- Disruption of background activity
- Distribution suggestive of a cerebral source

B. Neuroimaging

Modality	Application
Structural MRI (Epilepsy Protocol / HARNESS)	Mandatory sequences: 3D high-resolution T1, 3D FLAIR, and high-resolution coronal T2 perpendicular to the hippocampal axis
Mesial Temporal Sclerosis (MTS)	Hippocampal volume loss, loss of internal architecture, increased T2/FLAIR signal
FDG-PET	Identifies interictal hypometabolism; particularly useful in nonlesional focal epilepsy
Ictal SPECT	Measures cerebral hyperperfusion during a seizure
fMRI	Noninvasive mapping of eloquent cortex (language, motor)

C. Prognosis After a First Unprovoked Seizure

General recurrence risk: 36% at 2 years; 46% at 5 years.

Factors that more than double the recurrence risk (to >60%):

- Interictal epileptiform discharges (IEDs) on EEG
- Significant brain imaging abnormality
- Nocturnal seizure (occurring from sleep)
- Prior brain insult (e.g., stroke, trauma)

◆ CLINICAL PEARL

Clinical Pearl: Any of the above four risk factors after a first unprovoked seizure raises recurrence risk above the 60%/10-year threshold — satisfying the ILAE 2014 definition and justifying a diagnosis of epilepsy (and often ASM initiation) after only one seizure.

CHAPTER II

Neonatal, Infantile, and Childhood Epilepsy Syndromes

Onset from Birth Through 12 Years

I. Neonatal & Infantile Syndromes (Onset < 2 Years)

A. Self-Limiting Neonatal Epilepsy

Feature	Detail
Age of Onset	2–7 days of life
Clinical Features	Occurs in otherwise healthy, typically developing infants after uncomplicated gestation and delivery. Seizures are usually focal and remit within weeks.
EEG Hallmark	“Theta pointu alternant” pattern (runs of 4–7 Hz theta with intermixed sharp waves that may alternate sides). Burst suppression or persistent slowing must be absent.
Genetic Hallmark	Often associated with KCNQ2 variants (haploinsufficiency)
Treatment	Most cases are self-limited; when treatment is necessary, ion channel-targeting agents are preferred

B. West Syndrome (Infantile Epileptic Spasms Syndrome)

Age of Onset: Peak between 3–12 months.

Diagnostic Triad

- **Epileptic Spasms:** Brief tonic truncal stiffening, occurring in clusters

- **Hypsarrhythmia:** Highly disorganized pattern of high voltage (>200 μ V) with multifocal epileptiform discharges, most apparent during non-REM sleep
- **Developmental Regression:** Loss of previously acquired milestones

Treatment Protocols

Scenario	Regimen
First-line (general)	ACTH 150 U/m ² IM daily for 2 weeks in children <2 years
Tuberous Sclerosis Complex (TSC)	Vigabatrin is preferred first-line; start 50 mg/kg/d, titrate to 100–150 mg/kg/d

⚠ WARNING

Prognostic Warning: Persistence of hypsarrhythmia for >3 weeks despite treatment is associated with poor cognitive outcomes.

C. Dravet Syndrome

Feature	Detail
Age of Onset	First year of life (typically 3–9 months)
Clinical Features	Prolonged hemiclonic or generalized clonic seizures, frequently triggered by fever or heat. Myoclonic and focal seizures typically arise later in the disease course.
Genetic Hallmark	>80% of patients have a pathogenic SCN1A variant, causing Nav1.1 haploinsufficiency in inhibitory interneurons
EEG Hallmark	Background slowing and multifocal/generalized discharges typically emerge after age 2 years

Drug choices: Fenfluramine, Cannabidiol, and Stiripentol (used with clobazam and valproate) are indicated for Dravet-associated seizures.

⚠ WARNING

CONTRAINDICATED IN DRAVET SYNDROME: Sodium channel blockers — Carbamazepine, Phenytoin, Oxcarbazepine, and Lamotrigine — are strictly contraindicated, as they often exacerbate seizures in these patients.

II. Childhood-Onset Syndromes (Onset 2–12 Years)

A. Lennox-Gastaut Syndrome (LGS)

Age of Onset: 18 months to 8 years.

Diagnostic Criteria

- **Multiple seizure types:** Must include tonic seizures (especially in sleep); also atonic, atypical absence, and myoclonic
- **Cognitive impairment:** Present at onset or develops over time

EEG Hallmarks

- Generalized slow spike-and-wave complexes (<2.5 Hz)
- Generalized paroxysmal fast activity (GPFA), especially during sleep

Drug choices: Rufinamide is specifically indicated for LGS. Clobazam, Cannabidiol, Fenfluramine, Felbamate, and Topiramate are also FDA-indicated adjunctive treatments.

B. Childhood Absence Epilepsy (CAE)

Feature	Detail
Age of Onset	4–10 years
Clinical Features	Abrupt interruption of activity with a blank stare, lasting seconds, with rapid recovery to baseline. Classic trigger: hyperventilation.
EEG — Interictal	Regular 2.5–4 Hz generalized spike waves
EEG — Ictal	Classic 3-Hz generalized spike-wave discharges

Drug Choices

Agent	Comment
Ethosuximide (first-line)	Superior balance of efficacy and lack of cognitive side effects
Valproate	Equally effective but associated with more cognitive adverse effects
Lamotrigine	Less effective than ethosuximide or valproate for absence seizures

C. Self-Limiting Epilepsy with Centrotemporal Spikes (SeLECTS)

Feature	Detail
Age of Onset	4–10 years
Clinical Features	Nocturnal focal motor seizures involving the mouth (dysarthria, sialorrhea, facial twitching), or focal-to-bilateral tonic-clonic seizures occurring exclusively from sleep. Remission expected by adolescence.
EEG Hallmark	High-amplitude centrotemporal biphasic epileptiform discharges, significantly activated by sleep

III. Rare & Genetic Syndromes

A. Ohtahara Syndrome and Early Myoclonic Encephalopathy (EME)

Feature	Detail
Classification	Grouped under Early Infantile Developmental and Epileptic Encephalopathy
Age of Onset	0–3 months
Clinical Features	Tonic seizures (Ohtahara) or myoclonic jerks (EME)
EEG Hallmark	Burst suppression pattern, multifocal discharges, diffuse background slowing

Feature	Detail
Prognosis	Severely drug-resistant with a high risk of profound neurologic disability

B. Landau-Kleffner Syndrome (LKS)

Feature	Detail
Classification	Part of the spectrum of Developmental/Epileptic Encephalopathy with Spike-and-Wave Activation in Sleep
Clinical Feature	Acquired epileptic aphasia — a child with previously normal development loses language comprehension and expression
EEG Hallmark	Continuous (or near-continuous) spike-and-wave discharges during slow-wave sleep
Treatment	Often requires high-dose steroids or aggressive ASM management to resolve the “electrical status” and improve language outcomes

★ EXAM TIP / HIGH YIELD

High-Yield Age-of-Onset Ladder (memorize this sequence):

0–3 months — Ohtahara / EME

2–7 days — Self-limiting neonatal epilepsy

3–9 months — Dravet syndrome

3–12 months (peak) — West syndrome

18 months–8 years — Lennox-Gastaut syndrome

4–10 years — CAE and SeLECTS

10–24 years — JME (Chapter III)

CHAPTER III

Juvenile, Adult, and Elderly Epilepsy Syndromes

Onset from Adolescence Through Late Life

I. Juvenile-Onset Syndromes

A. Juvenile Myoclonic Epilepsy (JME)

Usual Age of Onset: 10–24 years.

Clinical Features: Myoclonic jerks (main seizure type, occurring predominantly upon awakening), generalized tonic-clonic seizures (GTCS), and typical absence seizures. Sleep deprivation and stress are frequent triggers.

EEG Hallmarks

- **Interictal:** Irregular, generalized 3–5.5 Hz spike-wave and polyspike-wave discharges

- **Ictal:** Generalized polyspike wave with myoclonic jerks
- **Activation:** Photoparoxysmal response seen in 30%–90% of cases

Long-Term Management

Population	First-Line Agent	Rationale
Males	Valproate	Remains the most effective agent for controlling all seizure types
Females (childbearing potential)	Levetiracetam	Preferred over lamotrigine — better efficacy against myoclonic jerks and lower teratogenic risk than valproate

⚠ WARNING

Contraindicated in JME: Sodium channel blockers (e.g., carbamazepine, phenytoin) and narrow-spectrum agents (gabapentin, tiagabine) may exacerbate myoclonic and absence seizures.

◆ CLINICAL PEARL

JME requires lifelong therapy — it is not a self-limiting syndrome, and ASM withdrawal carries a high relapse rate even after years of seizure freedom.

B. Juvenile Absence Epilepsy (JAE)

Feature	Detail
Usual Age of Onset	9–13 years
Clinical Features	Typical absence seizures, GTCS, and rare myoclonic jerks. Compared with CAE, absences are often less frequent but GTCS are more common.
EEG Hallmarks	Interictal and ictal regular 3–5.5 Hz generalized spike-wave discharges
Prognosis	Unlike CAE, JAE is generally not self-limited, and remission is less likely

II. Adult-Onset Epilepsy

A. Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS)

Etiology: Often associated with a history of complex febrile seizures in early childhood (age <2 years).

Clinical Semiology

- **Aura:** Most commonly a rising epigastric (“abdominal”) sensation, psychic symptoms (déjà vu, jamais vu), or ictal fear
- **Ictal phase:** Progression to focal impaired awareness seizures with oroalimentary automatisms (lip-smacking) and manual/distal automatisms (fumbling, picking)

Diagnostic Imaging Signature

Modality	Finding
Structural MRI (Epilepsy Protocol)	Hippocampal volume loss (atrophy), loss of internal architecture, increased T2/FLAIR hyperintensity

Modality	Finding
FDG-PET	Regional interictal hypometabolism in the anteromesial temporal lobe

EEG: Interictal anterior temporal spikes/sharp waves; ictal rhythmic temporal theta (5–7 Hz) or alpha patterns.

⚠ WARNING

Management: MTLE-HS is highly associated with drug-resistant epilepsy. Seizure freedom with ASM alone is only ~10% — early referral for surgery (anterior temporal lobectomy or laser interstitial thermal therapy, LITT) is indicated.

B. Adult Neocortical Epilepsy

Etiology: Typically arises from structural lesions — focal cortical dysplasia (FCD), low-grade tumors (gangliogliomas, DNETs), vascular malformations (cavernous hemangiomas), or remote traumatic brain injury.

Imaging Signatures

Lesion	Imaging Appearance
FCD Type II	Blurring of the gray-white matter junction; subcortical radial “transmantle” bands
Cavernoma	“Popcorn-ball” appearance — mixed signal on T1/T2 with blooming artifact on SWI

Management: Lesionectomy is often effective, though the true size of the epileptogenic zone may be underestimated on standard MRI.

III. Late-Onset Epilepsy (Elderly)

A. Etiology and Pathophysiology

- **Leading causes:** Cerebrovascular disease (stroke) is the most frequent cause, followed by neurodegenerative disorders (Alzheimer disease), brain tumors, and traumatic injury.
- **Vascular precursor epilepsy:** New-onset epilepsy in the elderly may predict future major cerebrovascular events, indicating occult small vessel disease.

B. Clinical Presentation Challenges

- **Semiology:** Often subtler than in younger adults — transient epileptic amnesia, focal confusion, or altered awareness without prominent motor signs.
- **Postictal state:** Significantly prolonged compared to younger cohorts.

⚠ WARNING

Diagnostic Pitfall: Frequently misdiagnosed as dementia or toxic-metabolic encephalopathy. Nonconvulsive status epilepticus (NCSE) is common in this population, carries high mortality, and is frequently missed due to low clinical suspicion.

C. ASM Drug Selection and Tolerability in the Elderly

Selection must account for age-related pharmacokinetic changes, high comorbidity burden, and potential for polypharmacy.

Agent	Recommendation
Lamotrigine	Highly preferred — superior balance of efficacy and tolerability. ECG monitoring advised before initiation in patients with structural heart disease (potential PR-interval effects).
Levetiracetam	Favored — no hepatic metabolism, minimal drug-drug interactions
Lacosamide	Suitable for rapid titration; monitor for PR-interval prolongation
Enzyme Inducers (Phenytoin, Carbamazepine, Phenobarbital)	AVOID — increase risk of dyslipidemia, metabolic syndrome, and cardiovascular disease; reduce efficacy of other medications (e.g., anticoagulants such as apixaban)
Valproate	AVOID — higher risk of weight gain, thrombocytopenia, and reversible parkinsonism/dementia in seniors

★ EXAM TIP / HIGH YIELD

High-Yield Summary — Elderly ASM Selection:

PREFER: Lamotrigine, Levetiracetam ($\pm$ ECG monitoring for Lamotrigine/Lacosamide)

AVOID: Enzyme inducers (CBZ, PHT, PB) and Valproate

CHAPTER IV

Clinical Pharmacology of Antiseizure Medications (ASMs)

Mechanisms, Kinetics, Monitoring, and Board-Relevant Precautions

This chapter organizes ASMs by mechanistic class. A consolidated therapeutic drug monitoring summary is provided in the table below, followed by drug-by-drug detail.

Quick-Reference: Therapeutic Drug Monitoring Ranges

Drug	Therapeutic Range	Key Monitoring
Carbamazepine	4–12 $\mu\text{g/mL}$	CBC, LFTs
Phenytoin	Total 10–20 $\mu\text{g/mL}$; Free 1–2 $\mu\text{g/mL}$	Albumin (protein binding)
Oxcarbazepine (MHD)	15–35 $\mu\text{g/mL}$	Sodium
Valproate	50–100 $\mu\text{g/mL}$	LFTs, platelets
Lamotrigine	2–20 $\mu\text{g/mL}$	Rash surveillance
Zonisamide	10–40 $\mu\text{g/mL}$	—

Drug	Therapeutic Range	Key Monitoring
Levetiracetam	20–50 µg/mL	—
Ethosuximide	40–100 µg/mL	—
Lacosamide	4–12 µg/mL	ECG (PR interval)

I. Traditional Sodium Channel Blockers

1. Carbamazepine (CBZ)

Mechanism: Blocks voltage-gated sodium channels (Na_v) in a voltage- and use-dependent fashion, inhibiting high-frequency repetitive firing.

Kinetics: Strong hepatic enzyme inducer (CYP3A4); undergoes autoinduction (induces its own metabolism), requiring gradual titration. Metabolized to the active carbamazepine-10,11-epoxide.

Board Tips & Precautions

- **HLA-B*1502 screening** mandated in patients of Asian descent to predict SJS/TEN risk
- **Hyponatremia** is a common side effect
- **Contraindication:** may exacerbate generalized absence and myoclonic seizures
- **Hematologic:** benign leukopenia is common; rare risk of aplastic anemia

2. Phenytoin (PHT)

Mechanism: Prolongs the fast-inactivated state of the sodium channel.

Kinetics: Nonlinear (saturable) kinetics — small dose increases can cause disproportionate, toxic serum concentration jumps. Highly protein-bound (~90%). Potent enzyme inducer.

Board Tips & Precautions

- **Cosmetic:** gingival hyperplasia, hirsutism, acne
- **Chronic:** cerebellar atrophy, peripheral neuropathy, decreased bone density
- **IV loading:** fosphenytoin preferred; IV phenytoin carries risk of Purple Glove Syndrome

3. Oxcarbazepine (OXC) & Eslicarbazepine Acetate (ESL)

Mechanism: Sodium channel blockade; ESL may specifically enhance slow inactivation.

Kinetics: OXC is a prodrug rapidly converted to its active monohydroxy derivative (MHD). ESL has a long CSF half-life, justifying once-daily dosing. Both are weak CYP3A4 inducers.

Board Tips: Hyponatremia is more frequent and severe with OXC than CBZ, especially in the elderly. ESL is generally better tolerated than OXC.

II. Broad-Spectrum Agents (Multiple Mechanisms)

4. Valproate (VPA)

Mechanism: Multiple — GABA potentiation, T-type calcium channel blockade, sodium channel blockade.

Kinetics: Potent enzyme inhibitor (raises levels of lamotrigine, phenobarbital, and rufinamide). Highly protein-bound.

⚠ WARNING

Black Box Warnings: Idiosyncratic hepatotoxicity and pancreatitis.

Teratogenicity: Highest risk of major malformations (>10%), reduced verbal IQ, and autism — avoid in females of childbearing potential.

Other: Significant weight gain, risk of PCOS. Monitor LFTs and platelets (thrombocytopenia risk).

5. Lamotrigine (LTG)

Mechanism: Blocks sodium channels; also likely has mechanisms effective against absence seizures.

Kinetics: Metabolized via glucuronidation. Half-life is doubled by valproate and halved by enzyme inducers or estrogen/pregnancy.

Board Tips & Precautions

- **SJS/TEN:** risk minimized by very slow titration
- **Pregnancy:** one of the lowest teratogenicity rates — drug of choice for many women
- **Cardiac:** new FDA warning regarding potential rhythm/conduction abnormalities

6. Topiramate (TPM) & Zonisamide (ZNS)

Mechanism: Multiple — sodium channel blockade, GABA augmentation, and AMPA/kainate glutamate receptor antagonism (TPM); T-type calcium channel blockade (ZNS). Both are weak carbonic anhydrase inhibitors.

Kinetics: TPM is primarily renally eliminated (70%). ZNS has an exceptionally long half-life (~60 hours).

Board Tips & Precautions

- **Cognitive (“Dopamax” effect):** word-finding difficulty and cognitive slowing, especially with TPM
- **Somatic:** kidney stones, weight loss, oligohidrosis/hyperthermia
- **TPM teratogenicity:** increased risk of oral clefts and low birth weight

III. SV2A-Binding Agents

7. Levetiracetam (LEV) & Brivaracetam (BRV)

Mechanism: Binding to the synaptic vesicle protein SV2A, reducing neurotransmitter release. BRV has 20-fold higher affinity and greater selectivity.

Kinetics: LEV has no hepatic metabolism and minimal drug interactions. BRV metabolism is via hydrolysis and CYP2C19.

⚠ WARNING

Psychiatric (“Keppra-rage”): LEV is notorious for irritability, hostility, and agitation. BRV may have significantly fewer behavioral side effects than LEV.

IV. GABA-Targeted & Novel Agents

8. Ethosuximide (ESX)

Mechanism: Blocks T-type calcium channels in thalamic neurons.

Board Tip: First-line for typical absence seizures; not effective for focal or tonic-clonic seizures.

9. Lacosamide (LCM)

Mechanism: Enhances slow inactivation of sodium channels.

Board Tips: May cause dose-dependent PR-interval prolongation. Generally weight-neutral and well-tolerated.

10. Perampanel (PER)

Mechanism: Selective, noncompetitive AMPA glutamate receptor antagonist.

Kinetics: Long half-life (~105 hours) allows once-daily dosing.

⚠ WARNING

Black Box Warning: Serious psychiatric events, including aggression, hostility, and homicidal ideation.

11. Cenobamate (CNB)

Mechanism: Dual — preferentially blocks the persistent sodium current and acts as a positive allosteric modulator of the GABA

Board Tips: Exceptional efficacy in drug-resistant focal epilepsy. Requires slow titration to prevent DRESS syndrome.

12. Vigabatrin (VGB)

Mechanism: Irreversible inhibitor of GABA transaminase.

⚠ WARNING

Vision Risk: Primary risk is permanent, bilateral concentric visual field constriction (30–40% of patients). Used first-line for infantile spasms.

13. Cannabidiol (CBD)

Mechanism: Exact mechanism unknown; modulation of GABA and intracellular calcium.

Interactions: Increases levels of N-desmethyclobazam (clobazam's active metabolite), causing sedation. Monitor LFTs (especially with concurrent VPA).

14. Clobazam (CLB)

Mechanism: 1,5-benzodiazepine; binds the GABA_A α_2 subunit (less sedative than traditional benzodiazepines).

Monitoring: Levels of the active metabolite N-desmethyclobazam are critical during drug interactions.

★ EXAM TIP / HIGH YIELD

High-Yield ASM Contraindication Map:

Absence/Myoclonic (JME, CAE): AVOID sodium channel blockers (CBZ, PHT, OXC, gabapentin, tiagabine) — may exacerbate

Dravet syndrome: AVOID sodium channel blockers (CBZ, PHT, OXC, LTG)

Pregnancy: AVOID Valproate (highest teratogenicity); prefer Lamotrigine/Levetiracetam

CHAPTER V

Emergency Neurocritical Care: Status Epilepticus (SE)

Definitions, Timelines, and Acute Management Algorithms

✗ EMERGENCY

Status epilepticus is a neurological emergency. Under-dosing of first-line benzodiazepines is the most common preventable error and leads to respiratory failure and treatment resistance.

I. Timelines & Operational Definitions

SE is defined by failure of the mechanisms responsible for seizure termination, or by initiation of mechanisms leading to abnormally prolonged seizures.

SE Type	t ₁ (Treat by)	t ₂ (Injury risk)	Notes
Convulsive SE (CSE)	5 minutes	30 minutes	Overt tonic-clonic convulsions
Non-Convulsive SE (NCSE)	10 minutes or longer	Not well defined	Continuous absence, focal sensory, or focal impaired awareness seizures

SE Type	t ₁ (Treat by)	t ₂ (Injury risk)	Notes
Focal SE	Not well defined	Not well defined	Includes focal motor SE (formerly epilepsy partialis continua) and focal sensory SE

Term	Definition
Refractory SE (RSE)	SE persistent after failure of two adequately dosed ASMs of different classes (typically a benzodiazepine and a non-sedating IV ASM)
Super-Refractory SE (SRSE)	SE persisting ≥24 hours after initiation of anesthetizing continuous IV infusions

II. Step-by-Step Acute Pharmacotherapy Algorithm

Phase 1 — Emergent Therapy (0–10 minutes)

Goal: immediate termination of seizure activity using full-dose benzodiazepines.

Agent	Dose	Notes
IV Lorazepam	0.1 mg/kg/dose (Adult Max: 4 mg)	May repeat once
IM Midazolam	10 mg if >40 kg; 5 mg if 13–40 kg	Single dose
IV Diazepam	0.15–0.2 mg/kg/dose (Adult Max: 10 mg)	May repeat once
Rectal Diazepam	0.2–0.5 mg/kg (Max: 20 mg)	Single dose if IV/IM access delayed

Phase 2 — Urgent Therapy (10–30 minutes)

If SE persists, administer a non-sedating IV ASM. No agent below has demonstrated clear superiority over the others; efficacy ranges 45%–47%.

Agent	Loading Dose	Notes
IV Fosphenytoin	20 mg PE/kg (Max 1500 mg PE)	Max infusion rate 150 mg/min
IV Levetiracetam	60 mg/kg (Max 4500 mg)	Typically infused over 15 min
IV Valproate	40 mg/kg (Max 3000 mg)	Max infusion rate 20 mg/kg/min
IV Lacosamide	5–10 mg/kg (FDA adult load: 200 mg)	Infuse over 15–30 min; monitor PR interval
IV Phenobarbital	15 mg/kg	Reserve for when others unavailable

Phase 3 — Refractory SE (30–60 minutes)

Persistent seizures require continuous IV anesthetic infusions (CIVIs) titrated to seizure cessation or burst suppression (5–15 second interburst interval) on continuous EEG (cEEG). Intubation and mechanical ventilation are mandatory.

Agent	Loading Dose	Maintenance
Midazolam CIVI	0.2–0.5 mg/kg	0.1–2.0 mg/kg/h
Propofol CIVI	1–2 mg/kg bolus q3–5 min (up to 10 mg/kg)	1–15 mg/kg/h initially, titrate to max 5 mg/kg/h (avoid PRIS)
Ketamine CIVI	1–2.5 mg/kg	3–10 mg/kg/h (combine with a benzodiazepine)
Pentobarbital CIVI	5–15 mg/kg (max rate 50 mg/min)	0.5–5 mg/kg/h

⚠ WARNING

Propofol Infusion Syndrome (PRIS): titrate to a maximum of 5 mg/kg/h maintenance to avoid this potentially fatal complication.

Phase 4 — Super-Refractory SE (>24 hours)

Evidence is limited; management should be personalized and multimodal.

- **Immunomodulation:** indicated if NORSE (New-Onset Refractory Status Epilepticus) is suspected

Agent	Dose
Methylprednisolone	20–30 mg/kg/d (Max 1 g/d) for 3–5 days
IVIG	0.4–2 g/kg/d for 3–5 days
Rituximab	Consider if pathogenic antibodies identified or highly suspected

- **Ketogenic diet:** should be considered within 7 days of onset in cryptogenic NORSE cases
- **Other options:** inhalational anesthesia (volatile anesthetics), therapeutic hypothermia (possibly effective in adults), surgical resection, and neuromodulation (VNS, RNS, DBS)

III. Non-Convulsive Status Epilepticus (NCSE)

A. Clinical Presentation and Management Traps

- **Presentation:** Subtle — confusion, aphasia, blank staring, or depressed level of consciousness/coma

⚠ WARNING

Diagnostic Pitfall: Frequently misdiagnosed as toxic-metabolic encephalopathy in the elderly, causing significant treatment delay (median 150 min vs. 30 min for CSE).

Management Trap: Avoid over-aggressive anesthetic treatment in patients with metabolic encephalopathies (e.g., triphasic waves) unless Salzburg criteria are strictly met. Aggressive CIVIs in elderly/frail patients carry a 4-fold increase in infection risk and 9-fold increase in mortality.

B. Salzburg EEG Diagnostic Criteria for NCSE

The whole EEG recording must be abnormal, and the following must be continuously present for ≥10 seconds:

Pattern	Interpretation
Epileptiform discharges (ED) > 2.5 Hz	Definitive NCSE
ED $\leq$ 2.5 Hz OR continuous rhythmic delta-theta (>0.5 Hz) PLUS one of: typical spatiotemporal evolution, subtle clinical ictal phenomena time-locked to EEG, or clinical AND EEG improvement with IV ASM	Definitive NCSE
EEG improves without clinical improvement	"Possible NCSE" only

C. Biomarkers

Peri-ictal MRI: DWI/FLAIR hyperintensity occurs in 26% of SE patients — commonly cerebral cortex, thalamus (pulvinar), and hippocampus. These findings predict increased mortality and RSE progression.

★ EXAM TIP / HIGH YIELD

SE Algorithm at a Glance:

0–10 min → Full-dose benzodiazepine (do not under-dose)

10–30 min → Non-sedating IV ASM (fosphenytoin / levetiracetam / valproate / lacosamide)

30–60 min → Anesthetic CIVI + intubation + cEEG to burst suppression

>24 h → Immunotherapy ± ketogenic diet if NORSE suspected

CHAPTER VI

Advanced Neurodiagnostics: EEG Interpretation and Epilepsy Imaging

Board-Style Study Guide

I. Normal vs. Abnormal EEG Backgrounds

A. EEG Physiology and Recording Standards

Physiological basis: EEG signals are the summation of excitatory (EPSP) and inhibitory postsynaptic potentials (IPSP) from the dendritic arbors of pyramidal neurons. Scalp detection requires at least 10 cm² of synchronized cortical activation.

The 10-20 and 10-10 systems: Electrodes are identified by region (Fp, F, T, P, O, C) and number (odd = left, even = right, z = midline). Adding six subtemporal electrodes from the 10-10 system (F9/10, T9/10, P9/10) increases sensitivity for interictal discharges from 27% to 53%.

B. Normal Awake and Sleep Variants

State	Defining Feature
Adult awake background	Posterior-dominant rhythm (PDR) of alpha frequency (8–12 Hz); reactive to eye opening; anterior-posterior gradient
Drowsiness (N1)	Loss of the PDR; appearance of slow roving eye movements
Normal sleep (N2)	Sleep spindles (11–16 Hz) and K-complexes
Pediatric maturation	PDR begins at ~3 Hz at ~3 months of age, increasing to 8 Hz by 8 years

i IMPORTANT NOTE

Dysmaturity: In neonates, a background ≥ 2 weeks behind expected postmenstrual age can predict poor neurologic outcomes.

C. Defining Epileptiform Discharges (IEDs)

The International Federation of Clinical Neurophysiology (IFCN) requires ≥ 4 of the following 6 criteria for a wave to be classified as epileptiform:

#	Criterion
1	Sharp or spiky morphology (duration 20–200 ms)
2	Duration distinct from the surrounding background
3	Asymmetry of the standing wave (e.g., steeper rising phase)
4	Followed by an after-going slow wave
5	Disruption of background activity (e.g., local attenuation or flattening)
6	Distribution suggestive of a cerebral source (physiologic field)

Terminology: Spikes = < 70 ms; Sharp waves = 70–200 ms. Polyspikes = multiple spike components in sequence, often seen in JME.

II. EEG Localization & Paradigms

A. Slowing Paradigms

Pattern	Meaning
Generalized (diffuse) slowing	Global encephalopathic state or diffuse cerebral dysfunction (metabolic, toxic, degenerative)
Focal slowing	Underlying structural or functional lesion in that region. Effacement of fast frequencies suggests neocortical pathology; undulating delta suggests subcortical dysfunction.
TIRDA (Temporal Intermittent Rhythmic Delta Activity)	Highly specific for temporal lobe epilepsy, particularly mesial temporal structures

Pattern	Meaning
OIRDA (Occipital Intermittent Rhythmic Delta)	Primarily seen in children; classically associated with Childhood Absence Epilepsy, but may contain admixed spikes and also occurs in focal seizures
FIRDA (Frontal Intermittent Rhythmic Delta)	Common in metabolic/toxic encephalopathy; if unilateral or asymmetric, may indicate a structural lesion

B. Periodic Discharges and the Ictal-Interictal Continuum

- **Triphasic waves:** Generalized periodic discharges with a blunt morphology and anterior-posterior time lag; traditionally associated with metabolic encephalopathy
- **Ictal-interictal continuum:** Patterns (e.g., periodic discharges at 1.0–2.5 Hz) that do not meet formal seizure criteria but carry a risk of neuronal injury and correlate with increased metabolic demand

Salzburg EEG criteria for NCSE: see Chapter V, Section III — definitive NCSE requires epileptiform discharges >2.5 Hz for ≥10 seconds, OR ≤2.5 Hz/rhythmic delta-theta plus evolution, clinical ictal signs, or clinical/EEG improvement with IV ASM.

III. Structural & Functional Imaging Protocols

A. The HARNESS MRI Epilepsy Protocol (Standardized 3T/1.5T)

The Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNES) protocol is mandatory for detecting subtle lesions such as FCD and MTS:

Sequence	Purpose
3D High-Resolution T1 (MPRAGE)	Best for evaluating brain anatomy, morphology, and blurring of the gray-white junction
3D High-Resolution FLAIR	Ideal for assessment of gliosis and hyperintense cortical lesions
High-Resolution 2D Coronal T2 (Turbo Spin Echo)	Must be acquired perpendicular to the long axis of the hippocampus (coronal-oblique) to visualize internal hippocampal architecture for sclerosis
Optional: SWI	Cavernomas / hemosiderin detection
Optional: Gadolinium-enhanced T1	Tumors / infections

B. Functional and Advanced Modalities

Modality	Application
FDG-PET	Identifies interictal hypometabolism; crucial for lesion-negative (MRI-normal) focal epilepsy. Concordant hypometabolism predicts good surgical outcome.
Ictal SPECT & SISCOM	Measures cerebral hyperperfusion during seizure onset. SISCOM (Subtraction Ictal SPECT Coregistered on MRI) improves localization by subtracting interictal from ictal signals.
Functional MRI (fMRI)	Noninvasively maps eloquent cortex (language, motor, memory) using the BOLD effect
Wada Test (Intracarotid Amobarbital Procedure)	Invasive test for language lateralization and memory support

Modality	Application
MEG (Magnetoencephalography)	Records magnetic fields to identify dipole clusters for source localization

C. Imaging Fingerprints — Quick Reference

Lesion	Signature
MTS	Atrophy, loss of internal architecture, T2/FLAIR hyperintensity in the hippocampus
Cavernoma	“Popcorn-ball” appearance (mixed T1/T2 signal) with blooming artifact on SWI
FCD Type II	Blurring of the gray-white junction; subcortical radial “transmantle” bands

★ EXAM TIP / HIGH YIELD

EEG Rhythm Recall:

TIRDA → Temporal lobe epilepsy

OIRDA → Childhood Absence Epilepsy (children)

FIRDA → Metabolic/toxic encephalopathy

Triphasic waves → Metabolic encephalopathy (anterior-posterior lag)

CHAPTER VII

Drug-Resistant Epilepsy (DRE) and Neuromodulation Surgery

Board-Style Study Guide

I. Drug-Resistant Epilepsy (DRE) Definition

Official ILAE Operational Definition: Failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules (as monotherapies or in combination) to achieve sustained seizure freedom.

◆ CLINICAL PEARL

Clinical Significance: Approximately one-third of patients continue to have seizures despite the availability of more than 20 new ASMs since 1993. Failure of the first two ASMs indicates a low likelihood of success with subsequent medical trials — mandating referral to a comprehensive epilepsy center for surgical evaluation.

II. Presurgical Evaluation & Resection

A. Phase I — Non-Invasive Evaluation

Mandatory Testing

- **High-quality volumetric MRI:** to detect structural lesions (e.g., MTS, focal cortical dysplasia)
- **Interictal and ictal EEG:** to establish electro-clinical concordance with the putative seizure focus
- **Neuropsychological testing:** to establish a cognitive baseline and assess functional integrity of the surgical target

Tailored additions: FDG-PET (interictal hypometabolism), ictal SPECT/SISCOM (ictal hyperperfusion), fMRI/DTI (mapping eloquent cortex/tracts), MEG/ESI (source localization), and the Wada test (IAP) for language and memory lateralization.

B. Phase II — Invasive Evaluation

Indications: Required in 30%–40% of surgical candidates, typically when non-invasive data are discordant or the focus is near eloquent cortex.

Modality	Notes
Stereoelectroencephalography (sEEG)	Robotically assisted depth electrodes; fewer complications (1%–4% hemorrhage/infection) and less pain than grids
Subdural Grids/Strips	Placed via craniotomy; used for surface mapping and functional stimulation

C. Resective Surgeries & Neuropsychological Outcomes

Anterior Temporal Lobectomy (ATL)

Outcome Domain	Statistic
Seizure freedom at 1 year	70% (ATL) vs. 7% with medical therapy alone
Verbal memory decline	Up to 44% of left (dominant) temporal resections; 20% of right temporal resections
Naming decline	34% reduction following dominant-side resections
Visual deficit	Superior quadrantanopia (“pie in the sky”) in 18% of all temporal resections, due to Meyer’s loop disruption

Selective Amygdalohippocampectomy: targeted resection of mesial structures to spare lateral neocortex.

Laser Interstitial Thermal Therapy (LITT): minimally invasive MRI-guided thermal ablation. Preferred for MTLE with high memory risk, hypothalamic hamartomas, and deep periventricular nodules.

III. Palliative & Disconnection Surgeries

A. Corpus Callosotomy

Indication: Reduces frequency of tonic and atonic “drop attacks” in generalized or multifocal epilepsy.

Outcomes: Eliminates drop seizures in 55% of patients; 19% achieve total seizure freedom.

⚠ WARNING

Disconnection Syndrome: Lasting attention difficulty and deficits in naming, writing, reading, and bimanual coordination.

B. Functional Hemispherotomy

Indications: Severe epilepsy restricted to one hemisphere (e.g., perinatal stroke, Rasmussen encephalitis, Sturge-Weber syndrome).

Surgical goal: Preservation of the cortex while disconnecting the underlying white matter.

Outcomes: 73% seizure-free rate in pediatric populations.

⚠ WARNING

Risks: Permanent hemiparesis, hemianopsia, and side-dependent language dysfunction.

IV. Neuromodulation Devices

Device	Target	Seizure Reduction	Key Adverse Effects
Vagus Nerve Stimulation (VNS)	Left vagus nerve (open-loop or heart-rate-triggered closed-loop)	36% at 3 mo; 51% at 1 yr; sustained seizure freedom rare (0–8%)	Voice changes (62%), cough, may worsen OSA
Thalamic DBS	Anterior nucleus of the thalamus (ANT)	40% at 3 mo; 56% at 2 yr; sustained freedom only 3%	Infection (9%), paresthesia (18%), worsening depression (15%), memory symptoms (13%)
Responsive Neurostimulation (RNS)	1–2 leads at up to 2 seizure foci (e.g., bilateral hippocampi)	44% at 1 yr; 53% at 2 yr; 66% at 6 yr (progressive improvement)	28% achieve ≥3 months seizure freedom long-term

RNS mechanism: A closed-loop system that continuously senses intracranial electrocorticography (ECoG) and delivers stimulation in response to detected ictal onset patterns — uniquely also provides objective ECoG data to guide future resections.

★ EXAM TIP / HIGH YIELD

Surgical Outcome Cheat-Sheet:

ATL for MTLE-HS: 70% seizure-free at 1 year (best evidence-based epilepsy surgery outcome)

Corpus callosotomy: for drop attacks (tonic/atonic), NOT a cure — palliative

Hemispherotomy: unilateral catastrophic epilepsy, 73% seizure-free

RNS uniquely improves over time (44% → 66% by year 6)

CHAPTER VIII

Epilepsy in Special Populations I

Women's Health, Catamenial Epilepsy, and Pregnancy

I. Catamenial Epilepsy: Pathophysiology and Cyclic Treatment

Definition: A pattern where seizure frequency exacerbations correlate with specific phases of the menstrual cycle, affecting approximately 40% of women with epilepsy. Diagnosis requires a ≥ 2 -fold increase in seizure frequency during a specific phase in at least two of three consecutive cycles.

Pathophysiology of Seizure Patterns

- **Estrogen (pro-convulsant):** Preovulatory surges contribute to seizure clusters
- **Progesterone (anti-convulsant):** Reduction or withdrawal is implicated in perimenstrual and luteal-phase patterns

Pattern	Timing	Mechanism
C1 — Perimenstrual	Around onset of menses (Day 1)	Progesterone withdrawal
C2 — Periovulatory	Ovulation (Day -14)	Estrogen surge
C3 — Luteal/Anovulatory	Luteal phase, often anovulatory cycles	Relative progesterone deficiency

Cyclic Treatment Strategies

- **Non-hormonal pulsing:** For regular menses, pulsing Acetazolamide or Clobazam before and during menses
- **Hormonal therapy:** Progesterone supplements are superior to placebo for robust perimenstrual exacerbations. Synthetic options include medroxyprogesterone or GnRH analogs for irregular menses.

II. Contraception and ASM Interactions

Enzyme-inducing ASMs (EIAEDs): Carbamazepine, Oxcarbazepine, Phenytoin, Phenobarbital, Primidone, and Topiramate (≥ 200 mg/d) induce CYP3A4, decreasing OCP efficacy by accelerating estrogen/progestin metabolism.

Reciprocal Interactions

- **OCP effect on Lamotrigine:** Estrogen-containing OCPs accelerate glucuronidation, significantly dropping Lamotrigine levels and increasing breakthrough seizure risk
- **Progestin-only effects:** Perampanel (≥ 8 mg/d) specifically decreases progestin levels without necessarily affecting estrogen

⚠ WARNING

Contraceptive Failure Rates in Women with Epilepsy: 15.2% for hormonal contraception vs. only 3.1% for IUDs. IUDs are the preferred highly effective reversible method, as they lack drug interactions with ASMs.

III. Pregnancy Management

A. Pre-Conception: Folate and ASM Selection

Folate dosing: Minimum 0.4 mg daily for all women of childbearing potential; many centers advocate 1–4 mg daily periconceptually and throughout pregnancy. Associated with decreased risk of miscarriage, preterm birth, and improved neurodevelopmental outcomes.

Teratogenic Profiles — Major Malformation Rates

Agent	Malformation Rate	Notes
Valproate	10.3%	Risk exceeds 20% at doses >1500 mg/d. STRICTLY AVOID — neural tube defects, lower IQ, autism spectrum disorder
Phenobarbital	6.5%	High risk
Phenytoin	6.4%	Intermediate risk
Carbamazepine	5.5%	Intermediate risk
Topiramate	3.9%	Associated with oral clefts and highest rate of small-for-gestational-age (18.5%)
Lamotrigine, Ocarbazepine	Levetiracetam, ≤3%	Lowest-risk options

B. Gestational Phase: Pharmacokinetics and Monitoring

Pregnancy induces an increased volume of distribution, enhanced renal clearance, and induced hepatic metabolism.

- **ASM level drops:** Significant gestational decreases occur for Lamotrigine, Levetiracetam, Lacosamide, Ocarbazepine, Topiramate, and Zonisamide. Lamotrigine clearance increases specifically via estrogen-driven glucuronidation.
- **Stable ASMs:** Carbamazepine and Valproic acid levels remain relatively stable throughout gestation.

◆ CLINICAL PEARL

Monitoring protocol: Monthly (or more frequent) therapeutic drug monitoring of free levels is recommended to adjust doses and prevent convulsive seizures, which pose risks of fetal hypoxemia and trauma.

C. Postpartum and Lactation

Dose normalization: Following delivery, ASM doses (particularly Lamotrigine) must be tapered back toward pre-pregnancy levels; rate depends on individual drug PK and clinical seizure control.

Lactation Safety

- **Extensive transfer into breast milk:** Phenobarbital, Lamotrigine, and Zonisamide
- **Overall safety:** Most ASMs transfer in amounts significantly lower than via the placenta; breastfeeding is generally encouraged
- **Monitoring:** Watch infants for excessive sedation, as infant drug elimination mechanisms are not fully developed

i IMPORTANT NOTE

Postpartum Safety Precautions: To manage risks from sleep deprivation and breakthrough seizures, parents should change and dress the baby on the floor (using a pad), sponge-bathe on the floor instead of in a tub, and use padded carrycots rather than baby carriers.

★ EXAM TIP / HIGH YIELD

Pregnancy ASM Ranking (highest → lowest teratogenic risk):

Valproate (10.3%) > Phenobarbital (6.5%) > Phenytoin (6.4%) > Carbamazepine (5.5%) > Topiramate (3.9%) > Lamotrigine/Levetiracetam/Oxcarbazepine (≤3%)

CHAPTER IX

Epilepsy in Special Populations II

Autoimmune, Psychogenic, and Geriatric Epilepsy

I. Autoimmune Epilepsy and Encephalitis

A. Clinical Markers and Presentation

- **Onset and frequency:** Acute or subacute onset of seizures, often with very high seizure frequency, or as New-Onset Refractory Status Epilepticus (NORSE)
- **Specific clinical sign:** Faciobrachial dystonic seizures (FBDS) are pathognomonic — brief, frequent unilateral contractions of the face and arm
- **Etiological context:** Immune-mediated attack on the CNS, which may be paraneoplastic (associated with underlying malignancy) or non-paraneoplastic

B. Neural Autoantibodies and Diagnostic Profiles

Antibody	Clinical Signature
Anti-NMDA receptor	Psychiatric prodrome (anxiety, psychosis, mood changes) → movement disorders (orofacial dyskinesias) → autonomic instability → seizures. Strong link to ovarian teratomas — mandatory cancer screening on diagnosis.
Anti-LGI1	Frequently presents with hyponatremia and faciobrachial dystonic seizures (FBDS)
Anti-CASPR2	Often associated with Morvan syndrome, peripheral nerve hyperexcitability, and limbic encephalitis
Anti-GAD	Linked to chronic focal epilepsy
ANNA-1 (anti-Hu)	Can present as NORSE; requires rigorous malignancy screening

C. Treatment Paradigms

Line	Agent(s)
First-line	High-dose Methylprednisolone (20–30 mg/kg/d, max 1 g/d, for 3–5 days) or IVIg (0.4–2 g/kg/d for 3–5 days)
Second-line	Rituximab or Cyclophosphamide — if inadequate response to first-line agents, or if a pathogenic antibody is identified
Maintenance	Long-term immunomodulation (e.g., mycophenolate or rituximab) for at least 3 months if acute treatment was effective

◆ CLINICAL PEARL

Board Pearl: Early initiation of immunotherapy is critical — delayed treatment worsens outcomes in autoimmune encephalitis, and any suspicion of NORSE should trigger prompt autoimmune/paraneoplastic workup alongside standard SE management.

II. Psychogenic Non-Epileptic Seizures (PNES / Functional Seizures)

A. Clinical Features and Differentiating Factors

Feature	PNES Characteristics
Duration/Course	Long duration (frequently >2 minutes); waxing and waning (fluctuating) intensity
Motor signature	Pelvic thrusting, side-to-side head movements, arching of the back (arc de cercle), asynchronous limb movements
Physical signs	Ictal eye closure (with resistance to manual opening) is highly specific for PNES. Ictal weeping, vocalization (stuttering/whispering), and lack of postictal stertorous breathing/snoring are also common.
Recovery	Rapid recovery to baseline, without prolonged postictal confusion or acidosis

B. Diagnostic Gold Standard

Video-EEG Monitoring: The definitive diagnostic standard is capture of a typical clinical event on video-EEG that lacks an electrographic ictal correlate (i.e., no evolving rhythmic discharges, spikes, or sharp waves) in a presentation where such activity would be expected.

Supportive tool: Outpatient smartphone videos of events, reviewed by experts, can have high specificity (93.3%) when video-EEG is not immediately feasible.

★ EXAM TIP / HIGH YIELD

Epileptic Seizure vs. PNES — Key Discriminators

Feature	Epileptic Seizure	PNES
Duration	Typically <2 min	Often >2 min
Course	Stereotyped, evolves predictably	Waxing and waning
Eye closure	Eyes typically open	Ictal eye closure, resists opening
Movements	Synchronous, stereotyped	Asynchronous, pelvic thrusting, arc de cercle
Postictal state	Confusion, stertorous breathing common	Rapid recovery, no acidosis

III. Geriatric Epilepsy and Systemic Disease

A. Post-Stroke Epilepsy (PSE)

- **Etiology:** Cerebrovascular disease (stroke) is the most common cause of new-onset epilepsy in adults over 60
- **Vascular precursor epilepsy:** New-onset epilepsy in the elderly can be a precursor to a future major stroke, often indicating occult or juxtacortical small vessel disease

B. Antiseizure Medication Drug-Drug Interactions

The elderly often take multiple medications for comorbidities, increasing interaction risk.

Interaction	Clinical Consequence
Enzyme inducers (CBZ, PHT, PB) + anticoagulants	Reduced efficacy of apixaban, rivaroxaban, warfarin, and many cardiac drugs
Amiodarone + Phenytoin	Amiodarone inhibits phenytoin metabolism → toxic accumulation

C. ASM Preferences and Bone Health

Recommendation	Agent(s)
First-line	Lamotrigine (superior efficacy/tolerability balance). Levetiracetam also favored — no hepatic metabolism, minimal interactions.
Precaution	ECG monitoring recommended with Lamotrigine or Lacosamide in seniors with structural heart disease (PR-interval prolongation risk)
Avoid — bone health	Enzyme-inducing ASMs (Phenytoin, Carbamazepine, Phenobarbital) and Valproate are associated with decreased bone density and increased fracture risk. Prefer non-enzyme-inducing agents (Levetiracetam, Lamotrigine).

⚠ WARNING

Fall-Risk Alert: In an already fall-prone elderly population, enzyme-inducing ASMs and Valproate compound fracture risk via decreased bone density — favor Lamotrigine or Levetiracetam whenever appropriate.

CHAPTER X

Complications, Safety, SUDEP, and Transitional Care Systems

Board-Style Reference Guide

I. Sudden Unexpected Death in Epilepsy (SUDEP)

A. Definition and Incidence

Definition: SUDEP is the sudden, unexpected, non-traumatic, non-drowning death in an individual with epilepsy, where postmortem examination does not reveal a structural or toxicological cause of death.

Incidence: Only 3% of total deaths in a general epilepsy practice study were directly epilepsy-related, but SUDEP is a leading cause of premature mortality and years of life lost, particularly in younger cohorts and those with drug-resistant epilepsy.

B. Pathophysiological Mechanisms

- **Postictal Generalized EEG Suppression (PGES):** A period of profound brain inactivity following a convulsive seizure, often correlated with the terminal event
- **Cardiorespiratory failure:** Central apnea, airway obstruction, and cardiac arrhythmias leading to cardiopulmonary arrest
- **Latency:** EMU observations indicate a latency of up to 13 minutes between the terminal seizure and total arrest

C. Definitive Risk Factors

Risk Factor	Detail
Uncontrolled GTCS	Single most significant risk driver for SUDEP
Nocturnal seizures	Seizures from sleep are associated with higher mortality
Unsupervised status	Being unattended at night significantly increases probability of a fatal outcome (lack of peri-ictal stimulation/aid)
Polytherapy and comorbidities	High ASM drug load, plus psychiatric/cardiovascular comorbidities, contribute to overall mortality risk

D. SUDEP Prevention Strategies

- **Optimizing seizure control:** Achieving seizure freedom is the most effective means of reducing SUDEP risk
- **Nocturnal monitoring and surveillance:** A caregiver who can provide aid or postictal stimulation may be protective
- **Wearable detection devices:** Accelerometry, electrodermal activity (sympathetic arousal marker), and heart rate monitoring can alert caregivers to motor seizures, facilitating timely intervention

✗ EMERGENCY

SUDEP Counseling Mandate: All patients with epilepsy — particularly those with uncontrolled GTCS — and their families should be counseled about SUDEP risk and prevention strategies. This is a required element of comprehensive epilepsy care, not an optional discussion.

II. Psychopathology, Screening, & Safety Counseling

A. Psychiatric Comorbidities

Prevalence: Anxiety occurs in approximately 40% of people with epilepsy (PWE); depression in 25%. Both are even more prevalent among those with nonepileptic events (NEEs) or drug-resistant epilepsy.

Bidirectionality: Evidence supports bidirectional associations between epilepsy and comorbidities such as cerebrovascular disease and depression; psychiatric distress can lower the seizure threshold and potentially facilitate epileptogenesis.

B. Screening Tools & Acronyms

Tool	Full Name	Items	Positive Screen
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy	6	Score >13 (Major Depressive Disorder / suicidality)
brEASI	Brief Epilepsy Anxiety Survey Instrument	8	Score ≥7 (derived from 18-item EASI)
GAD-7	Generalized Anxiety Disorder 7-Item Scale	7	Score >6
PHQ-9	Patient Health Questionnaire-9	9	Score ≥10

C. Safety Counseling Mandates

Domain	Counseling Points
Bathing/Swimming	Showers preferred over baths; no unsupervised swimming
General precautions	Avoid heights without harnesses; wear helmets while biking; avoid using front burners on a stovetop
Driving restrictions	Must follow local regulations; typically requires a mandatory seizure-free window for events involving altered awareness or decreased responsiveness
Parenting safety	Change and dress the baby on the floor; sponge-bathe the infant on the floor; use padded carrycots

i IMPORTANT NOTE

Driving-restriction specifics vary by jurisdiction — counsel patients according to local regulatory requirements rather than a single fixed rule.

III. Transitional Care Systems

A. Transition Protocols

- **Transition Plan of Care:** A formal quality measure (AAN Child Neurology Quality Measurement Set) requiring a documented plan for moving adolescents from pediatric to adult neurology systems
- **Atypical cognitive profiles:** Transition systems must address specific cognitive dimensions of adolescents, such as frontal lobe function deficits common in benign epilepsies like JME

B. System Structures and Challenges

- **Insurance transitions:** Disruptions in coverage during transition to adulthood are associated with increased ED visits and hospitalizations for children with drug-resistant epilepsy
- **Disability support:** Systems must address long-term impacts of Developmental and Epileptic Encephalopathies (DEE), where cognitive deficits are a direct consequence of early-life seizures, requiring coordinated vocational and psychological support
- **Multidisciplinary inclusivity:** Transition teams should include social workers and neuropsychologists to mitigate social determinants of health and address higher rates of trauma and learning disorders in this population

★ EXAM TIP / HIGH YIELD

SUDEP High-Yield Recall:

#1 modifiable risk factor → uncontrolled GTCS

#1 prevention strategy → achieving seizure freedom

Mechanism triad → PGES + cardiorespiratory failure + lack of nocturnal supervision

CEREBROVASCULAR DISEASE

CHAPTER 1

Acute Ischemic Stroke Management

I. Formal Definitions and Classifications

Acute Ischemic Stroke (AIS) is clinically defined as an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction. Historically, the differentiation between AIS and **Transient Ischemic Attack (TIA)** relied on a time-based definition, where symptoms resolving within 24 hours were classified as TIA. However, modern standards have shifted toward a tissue-based definition: a TIA is now defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia **without acute infarction** on neuroimaging. Conversely, AIS is confirmed by the presence of objective evidence of permanent tissue injury (infarction) on imaging, regardless of the duration of clinical symptoms.

Feature	TIA (Tissue-Based)	AIS
Definition basis	No acute infarction on neuroimaging	Objective evidence of permanent tissue injury (infarction)
Old definition	Symptoms resolving within 24 hours	Symptoms persisting beyond 24 hours
Current standard	Tissue-based (imaging-defined)	Tissue-based (imaging-defined)

Table 1.1 — Evolution from time-based to tissue-based definitions of TIA vs. AIS.

⚠ WARNING

Up to 20% of suspected AIS cases are eventually diagnosed as non-vascular “stroke mimics.” This underscores the necessity of combining clinical assessment with rapid neuroimaging before committing to reperfusion therapy.

II. Pathophysiology of Cerebral Ischemia

The progression of an ischemic event is characterized by the dynamic relationship between the ischemic core and the penumbra.

Ischemic Core vs. Penumbra

- **Ischemic Core:** Area of severe oligemia where blood flow has fallen below the threshold required for cellular viability, leading to irreversible tissue injury and necrosis. On noncontrast CT, this is approximated using the Alberta Stroke Program Early CT Score (ASPECTS), which deducts points from 10 for early ischemic changes in specific MCA-territory regions.
- **Ischemic Penumbra:** The “at-risk” but salvageable tissue surrounding the core that suffers from moderate ischemia. Penumbral tissue maintains structural integrity but ceases functional electrical activity; it can be salvaged if reperfusion is achieved within the therapeutic window.

Cerebral Edema Cascade

Ischemia triggers a cascade beginning with cytotoxic edema, resulting from the failure of ATP-dependent ion pumps and subsequent intracellular water accumulation. This may progress to vasogenic edema (disruption of the blood-brain barrier) and, in severe cases, hemorrhagic transformation, which occurs in 2% to 7% of patients following reperfusion therapy.

★ MEMORY TIP / MNEMONIC

“CORE dies, PENUMBRA can be saved” — the entire goal of hyperacute stroke therapy (thrombolysis/thrombectomy) is to rescue the penumbra before it becomes core.

III. Clinical Presentation and Stroke Mimics

Hallmark Presentations

Standard presentations often follow the BE-FAST framework.

Letter	Feature	Meaning
B	Balance	Sudden loss of balance or coordination
E	Eyes	Sudden vision loss or double vision
F	Face	Facial droop
A	Arm	Arm weakness/drift
S	Speech	Slurred speech or aphasia
T	Time	Time of onset — call emergency services immediately

Table 1.2 — BE-FAST hyperacute stroke recognition mnemonic.

Typical deficits include contralateral hemiparesis, hemisensory loss, aphasia (dominant hemisphere), and hemineglect (non-dominant hemisphere).

Atypical and Sex-Specific Deficits

Women are significantly more likely than men to present with nonfocal symptoms, which often lead to diagnostic delays. These atypical presentations include:

- **Generalized nonspecific weakness:** 49% in women vs. 36% in men.
- **Mental status changes and confusion:** 37% in women.
- **Headache and lightheadedness.**
- **Incontinence or atypical sensory changes.**

⚠ WARNING

Nonfocal presentations in women are a well-documented source of diagnostic delay. Maintain a high index of suspicion for AIS in women presenting with isolated confusion, generalized weakness, or headache — do not anchor on the absence of “classic” focal deficits.

Acute Stroke Mimics

Clinicians must rapidly differentiate AIS from conditions that simulate focal deficits.

Mimic	Distinguishing Features
Migraine with aura	Often associated with “positive” neurologic symptoms (scintillations, tingling) or a slower, marching progression of deficits
Seizure (Todd's paralysis)	Postictal focal weakness that can exactly simulate AIS
Metabolic dysfunction	Hypoglycemia (must be checked prior to thrombolysis) or electrolyte imbalances
Infections	Systemic infections (sepsis) or encephalopathy in patients with old strokes (recrudescence)
Psychiatric disorder / conversion	Often presents with distress and non-anatomic patterns of weakness

Table 1.3 — Common acute stroke mimics and key distinguishing features.

EXAM TIP

Always check point-of-care glucose before administering thrombolysis. Hypoglycemia is a fully reversible and common stroke mimic.

IV. Thrombolysis Protocols and Agents

Standard Agents and Administration

Agent	Window	Dosing	Infusion	Notes
Alteplase (rtPA)	0–4.5 h from last known well	0.9 mg/kg (max 90 mg)	10% bolus over 1 min; 90% infused over 60 min	Historic standard of care
Tenecteplase (TNK)	FDA-approved 2025 for AIS	0.25 mg/kg (max 25 mg)	Single IV bolus	Simpler administration; increasingly preferred
Reteplase	Investigational / emerging use	Per trial protocol	—	Better 90-day outcomes than alteplase within 4.5 h in recent studies, but increased hemorrhage risk

Table 1.4 — Standard thrombolytic agents in acute ischemic stroke.

Extended Window Protocols (>4.5 Hours)

Protocol / Trial	Window	Key Selection Criteria
DWI-FLAIR Mismatch (WAKE-UP)	Unknown onset	DWI hyperintensity without corresponding FLAIR hyperintensity identifies patients likely within 4.5 h of onset with high specificity
Perfusion Selection (EXTEND)	4.5–9.0 h (or wake-up)	Perfusion/core mismatch ratio >1.2; absolute difference >10 mL; ischemic core <70 mL
Posterior Circulation (EXPECTS)	4.5–24 h	No thrombectomy planned; no early hypodensity on CT
Extended Tenecteplase (TRACE III)	4.5–24 h	Perfusion-imaging selected; not a thrombectomy candidate

Table 1.5 — Extended-window thrombolysis trial paradigms.

Special Populations

- **Pregnancy / Postpartum:** IV rtPA is reasonable for disabling symptoms. Alteplase and tenecteplase are large molecules (59,000 Da) and do not cross the placenta.
- **Pediatrics (ages 2–18):** Dosing is identical to adults — 0.9 mg/kg (10% bolus, 90% infusion over 60 min).
- **Central Retinal Artery Occlusion (CRAO):** Thrombolysis is not proven beneficial; trials failed to show visual improvement and noted increased hemorrhage risk.

V. Comprehensive Eligibility for IV Thrombolysis

Inclusion Criteria

- Diagnosis of ischemic stroke with a disabling neurologic deficit, regardless of severity.
- Symptom onset within 4.5 hours (Guideline) or 3 hours (FDA label).

Blood Pressure and Glucose Requirements

- **Glucose:** Must be measured before initiation.
- **Blood pressure:** Must be maintained <185/110 mm Hg for initiation.

Absolute and Relative Contraindications

Category	Absolute Contraindications	Relative Contraindications / Warnings
Imaging	CT showing extensive hypodensity or any intracranial hemorrhage	—

Category	Absolute Contraindications	Relative Contraindications / Warnings
Trauma / Surgery	Moderate–severe TBI <14 days; intracranial or spine surgery <14 days; acute spinal cord injury <3 months	Major non-CNS trauma (14 days–3 months); major non-CNS surgery <10 days
Neurologic history	—	Ischemic stroke <3 months; prior intracranial hemorrhage
Bleeding risk	—	GI or GU bleeding <21 days
Medical / Neoplastic	Intra-axial neoplasm; infective endocarditis; aortic arch dissection; amyloid-related imaging abnormalities (ARIA)	—
Coagulopathy / Labs	Platelets <100,000/mm ³ ; INR >1.7; aPTT >40 sec; PT >15 sec	—
Procedures	Dural puncture <7 days; arterial puncture at a noncompressible site <7 days	—
Cardiac	Recent STEMI <3 months; acute pericarditis; left atrial or ventricular thrombus	—
Other	Systemic active malignancy; pregnancy/postpartum period; preexisting severe disability	—

Table 1.6 — IV thrombolysis contraindications, absolute vs. relative.

✗ EMERGENCY

Blood pressure must be lowered to <185/110 mm Hg BEFORE thrombolytic administration, and maintained <180/105 mm Hg for at least the first 24 hours after treatment to reduce hemorrhagic transformation risk.

VI. Mechanical Thrombectomy (EVT) Infrastructure

Standard Anterior Circulation (0–6 Hours)

- **Inclusion:** Proximal large artery occlusion (ICA or M1 segment of MCA).

ASPECTS Grading

A 10-point scale that deducts 1 point for hypodensity in each of the following specific regions:

Level	Regions Scored
Basal ganglionic level	Caudate (C), Insular ribbon (I), Internal Capsule (IC), Lentiform nucleus (L), M1 (anterior cortex), M2 (lateral cortex), M3 (posterior cortex)
Supraganglionic level	M4 (anterior rostral), M5 (lateral rostral), M6 (posterior rostral)

Table 1.7 — ASPECTS scoring regions (Figure 4-2).

Extended Window (6–24 Hours)

Trial	Window	Selection Criteria
DEFUSE 3	6–16 h	Core <70 mL; penumbra/core ratio ≥ 1.8 ; absolute penumbra ≥ 15 mL
DAWN	6–24 h	Clinical-to-core mismatch (NIHSS vs. imaging volume); excludes cores >50 mL

Table 1.8 — Extended-window thrombectomy selection criteria.

Large Core, Posterior, and Distal Scenarios

- **Large core infarctions:** ASPECTS 3–5 (and select patients with ASPECTS 0–2 if <80 years old and <6 hours from onset) should be considered if NIHSS ≥ 6 and pre-stroke mRS 0–1.
- **Basilar artery occlusion:** Indicated for moderate-to-severe symptoms (NIHSS ≥ 10) up to 24 hours from onset.
- **MeVO / DVO (medium/distal vessel occlusion):** Currently limited evidence for routine use, but may be considered for moderate-to-severe deficits.

VII. Early Antithrombotic and Adjunct Therapies

Aspirin Protocol

- **Timing:** Initiate within 48 hours.
- **Dosing:** Initial dose of 160–325 mg.

Short-Term Dual Antiplatelet Therapy (DAPT)

Regimen	Indication	Loading Dose	Maintenance
Clopidogrel + Aspirin	Minor stroke (NIHSS ≤ 3) or high-risk TIA (ABCD ² ≥ 4) within 72 h	Clopidogrel 300–600 mg	Clopidogrel 75 mg daily $\times$ 21 days; Aspirin 50–325 mg daily
Ticagrelor + Aspirin	Minor stroke (NIHSS ≤ 5) or high-risk TIA (ABCD ² ≥ 6) within 24 h	Ticagrelor 180 mg	Ticagrelor 90 mg BID $\times$ 30 days; Aspirin 300–325

Regimen	Indication	Loading Dose	Maintenance
			mg Day 1, then 75–100 mg daily

Table 1.9 — Short-term DAPT regimens for minor stroke / high-risk TIA.

Severe Symptomatic Intracranial Stenosis

DAPT (Aspirin + Clopidogrel) for up to 90 days in conjunction with intensive risk factor management.

Salvage and Adjunct Therapies

- **Argatroban (direct thrombin inhibitor):** Improves outcomes in patients with early neurologic deterioration (NIHSS decline ≥ 2) occurring within 48 hours.
- **Tirofiban (GP IIb/IIIa inhibitor):** Reduces early neurologic deterioration compared to aspirin.

✗ PITFALL

Argatroban and eptifibatide are NOT recommended as adjuncts to IV thrombolysis due to increased death risk. Do not combine GP IIb/IIIa inhibitors or direct thrombin inhibitors with thrombolytics outside of trial protocols.

✦ CLINICAL PEARL

In suspected AIS, always sequence your workup as: (1) fingerstick glucose, (2) noncontrast CT to exclude hemorrhage, (3) determine last known well, (4) assess thrombolysis and thrombectomy eligibility in parallel — time lost is brain lost (“time is brain”).

CHAPTER 2

Clinical Neuroanatomy: Cerebral Arteries, Thalamus, and Brainstem Syndromes

I. Middle Cerebral Artery (MCA) Syndromes

The MCA territory is divided into deep (lenticulostriate) and superficial (cortical) segments. Symptoms vary significantly based on segment level and hemispheric dominance.

M1 Segment (Stem) Occlusion

- **Localization:** Occludes the origin of the lenticulostriate arteries (supplying the basal ganglia and internal capsule) and the distal cortical branches.
- **Presentation:** A “global” MCA syndrome characterized by dense contralateral hemiplegia and hemisensory loss affecting the face, arm, and leg equally.

- **Hallmarks:** Ipsilateral conjugate gaze deviation (toward the lesion) and profound global aphasia (dominant) or severe hemineglect (non-dominant).

M2 Segment (Division) Occlusions

Division	Territory	Dominant Hemisphere	Motor/Sensory/Visual
Superior division	Frontal and superior parietal lobes	Broca aphasia (expressive)	Face and arm >> leg deficits
Inferior division	Temporal and inferior parietal lobes	Wernicke aphasia (receptive)	Contralateral homonymous hemianopia or superior quadrantanopsia ("pie in the sky") from Meyer's loop involvement

Table 2.1 — MCA M2 superior vs. inferior division syndromes.

Lenticulostriate Artery Infarcts

- **Localization:** Small-vessel (lacunar) infarcts in the basal ganglia or internal capsule.
- **Presentation:** Classic pure motor hemiparesis or dysarthria–clumsy hand syndrome.

Hemisphere	Characteristic Features
Dominant (left)	Aphasia (global, Broca, or Wernicke) and apraxia (inability to perform learned motor tasks)
Non-dominant (right)	Hemineglect, anosognosia (denial of deficit), and impaired prosody

Table 2.2 — Hemispheric specificity of cortical MCA syndromes.

★ MEMORY TIP / MNEMONIC

"Broca is broken speech, Wernicke is word salad" — Broca's (superior division/frontal) = non-fluent, effortful; Wernicke's (inferior division/temporal) = fluent but nonsensical.

II. Anterior Cerebral Artery (ACA) Syndromes

- **Localization:** Supplies the medial frontal cortex, the medial parietal lobe, and the anterior two-thirds of the corpus callosum.

Clinical Presentation

- **Motor/Sensory:** Contralateral leg-dominant weakness and sensory loss; the face and arm are often spared or only mildly affected.

- **Cognitive/Behavioral:** Abulia (lack of initiative / “slowness” of thought or speech) and profound apathy.
- **Hallmarks:** Urinary incontinence (frontal micturition center damage) and the alien hand sign (autonomous, non-purposeful hand movement due to callosal involvement).
- **Physical exam:** Presence of frontal release signs (e.g., grasp, snout, or suck reflexes).

★ MEMORY TIP / MNEMONIC

ACA = “LEG artery.” Leg-dominant weakness distinguishes ACA strokes from MCA strokes, which are face/arm-dominant.

III. Posterior Cerebral Artery (PCA) Syndromes

- **Localization:** Supplies the occipital lobe, the medial temporal lobe, the thalamus, and the midbrain.

Clinical Presentation

- **Visual:** Contralateral homonymous hemianopsia, typically with macular sparing (due to collateral supply to the occipital pole from the MCA).
- **Disconnection:** Alexia without agraphia (patient can write but cannot read what they have written) occurs when the lesion involves the dominant occipital lobe and the splenium of the corpus callosum.
- **Anton syndrome:** Cortical blindness with denial of the deficit, seen in bilateral PCA territory infarcts.

Thalamic Branch Syndromes of the PCA

- **Thalamoperforating (midbrain):** Weber syndrome — ipsilateral CN III palsy and contralateral hemiparesis.
- **Thalamogeniculate:** Dejerine-Roussy syndrome (central poststroke pain) — localizes to the posterolateral thalamus, presenting with hemisensory loss followed by severe, chronic, burning pain.

IV. Anterior Choroidal Artery (AChA) Syndromes

- **Localization:** Arises from the distal internal carotid artery (C7 segment). Supplies the posterior limb of the internal capsule, the lateral geniculate body, and parts of the optic radiations.

The Classic Triad

Deficit	Mechanism
Contralateral hemiparesis	Involvement of the posterior limb of the internal capsule
Contralateral hemianesthesia	Involvement of the thalamic sensory projections
Contralateral homonymous hemianopsia	Involvement of the lateral geniculate body or proximal optic radiations

Table 2.3 — Anterior choroidal artery classic triad.

V. Vascular Brainstem Syndromes

Medullary Syndromes

Syndrome	Responsible Artery	Structures Damaged	Clinical Presentation
Lateral Medullary (Wallenberg)	PICA or Vertebral Artery (V4 segment)	Nucleus ambiguus (CN IX, X); vestibular nuclei; inferior cerebellar peduncle; spinothalamic tract; spinal trigeminal nucleus; descending sympathetics	Dysphagia, hoarseness, loss of gag reflex; vertigo/nystagmus; ipsilateral limb ataxia; crossed sensory loss (ipsilateral face, contralateral body); ipsilateral Horner syndrome
Medial Medullary (Dejerine)	Anterior spinal artery (ASA) or paramedian vertebral branches	Corticospinal tract (CST); medial lemniscus; hypoglossal nucleus (CN XII)	Contralateral hemiparesis (face spared); contralateral loss of vibration/proprioception; ipsilateral tongue deviation toward the lesion
Reinhold–Jaeger (Hemimedullary)	Vertebral artery (proximal to PICA)	Combined lateral and medial medullary structures	Ipsilateral CN XII palsy and tongue atrophy combined with the full constellation of Wallenberg syndrome symptoms

Table 2.4 — Medullary vascular syndromes.

Pontine Syndromes

Syndrome	Responsible Artery	Structures Damaged	Clinical Presentation
Lateral Pontine (Marie-Foix)	AICA or long circumferential basilar branches	Middle/inferior cerebellar peduncles; CST; spinothalamic tract	Ipsilateral limb ataxia; contralateral hemiparesis; contralateral body pain/temperature loss. Often spares cranial nerves
Medial Pontine (Foville)	Basilar artery (paramedian branches)	Abducens nucleus (CN VI); PPRF; CST; medial lemniscus	Ipsilateral lateral rectus palsy (VI); ipsilateral conjugate gaze palsy (PPRF); contralateral hemiparesis
Locked-in Syndrome	Basilar artery (bilateral occlusion)	Bilateral ventral pons (CST and corticobulbar tracts); tegmentum spared	Complete quadriplegia and lower cranial nerve paralysis (aphonia/dysphagia); preserved consciousness and vertical eye movements

Syndrome	Responsible Artery	Structures Damaged	Clinical Presentation
Millard-Gubler	Basilar perforators (ventral pons)	CST; CN VI fibers; CN VII fibers	Contralateral hemiparesis; ipsilateral CN VI palsy (diplopia); ipsilateral CN VII palsy (complete facial droop including forehead)
Raymond-Cestan	Basilar long circumferential branches	Medial lemniscus; spinothalamic tract; superior cerebellar peduncle	Ataxia (SCP) and contralateral loss of all sensory modalities (ML + STT). Spares motor tracts and cranial nerves

Table 2.5 — Pontine vascular syndromes.

Midbrain Syndromes

Syndrome	Responsible Artery	Structures Damaged	Clinical Presentation
Weber	PCA (paramedian mesencephalic) or distal basilar	CST (cerebral peduncle); CN III fibers	Ipsilateral CN III palsy (ptosis, “down and out” eye, fixed dilated pupil); contralateral hemiparesis (including lower face)
Claude	PCA branches (tegmentum)	CN III fibers; superior cerebellar peduncle (SCP)	Ipsilateral CN III palsy; contralateral limb ataxia and tremor (SCP/red nucleus involvement)
Benedikt	PCA branches	CN III fibers; red nucleus; SCP; medial lemniscus	Ipsilateral CN III palsy; contralateral choreoathetosis and “rubral” tremor; contralateral loss of vibration/proprioception
Nothnagel	PCA branches (quadrigeminal)	CN III fibers; cerebellar fibers (decussation of SCP)	Bilateral or unilateral CN III palsy; profound gait and limb ataxia
Parinaud (dorsal midbrain)	Distal basilar or posterior PCA (or pineal mass)	Superior colliculus; pretectal area; posterior commissure	Paralysis of upward gaze; convergence-retraction nystagmus; light-near dissociation (pupils accommodate but do not react to light)

Table 2.6 — Midbrain vascular syndromes.

Rare / Cross-Brainstem Syndromes

Syndrome	Anatomical Mechanism	Key Clinical Distinctions
Babinski-Nageotte	Multiple medullary segments	Combination of Wallenberg syndrome (lateral) and medial medullary syndrome (contralateral hemiparesis)
Cestan-Chenais	Lateral medulla + medial medullary fibers	Wallenberg symptoms plus contralateral loss of vibration/proprioception (medial lemniscus)
Tapia	Medullary exit zones	Ipsilateral paralysis of the tongue (XII) and ipsilateral vocal cord paralysis (X/ambiguus). Spares long tracts (CST/STT)

Table 2.7 — Rare cross-brainstem syndromes.

EXAM TIP

Brainstem localization strategy: crossed findings (ipsilateral cranial nerve + contralateral body) always localize to the brainstem — determine the level (medulla/pons/midbrain) by which cranial nerve is involved (IX/X = medulla, VI/VII = pons, III = midbrain).

VI. Thalamic Vascular Anatomy and Clinical Syndromes

Vascular Territories and Arterial Supply

The thalamus is divided into four primary vascular territories, largely supplied by branches of the Posterior Cerebral Artery (PCA) and the Posterior Communicating Artery (PCoA).

Territory	Supplying Artery	Origin
Anterior	Tuberothalamic (Polar) artery	Typically arises from the PCoA
Paramedian	Paramedian (thalamoperforating) arteries	Arise from the P1 segment of the PCA
Inferolateral	Thalamogeniculate arteries	Arise from the P2 segment of the PCA
Posterior	Posterior choroidal arteries (medial and lateral)	Arise from the P2 segment of the PCA

Table 2.8 — Thalamic vascular territories.

i NOTE

Artery of Percheron: a rare anatomic variant where a single arterial trunk arises from one P1 segment to provide bilateral supply to the paramedian thalamus and rostral midbrain. Occlusion produces a distinctive bilateral thalamic infarction pattern.

Nuclear Mapping and Functional Connectivity

Territory	Key Nuclei	Functional Connectivity
Anterior	Anterior nucleus (AN); parts of ventral anterior (VA)	Papez circuit (limbic system) — receives input from mammillary bodies, projects to cingulate gyrus
Paramedian	Mediodorsal (MD) nucleus; intralaminar nuclei	Reticular activating system and prefrontal cortex circuits — arousal, memory, executive function
Inferolateral	VPL, VPM, ventral lateral (VL)	Primary sensory relay (VPL/VPM) for body and face; major motor relay (VL) for cerebellar/basal ganglia input
Posterior	Pulvinar; lateral geniculate (LGN); medial geniculate (MGN)	Visual relay (LGN), auditory relay (MGN), complex visual integration/attention (pulvinar)

Table 2.9 — Thalamic nuclear mapping and connectivity.

Clinical Infarction Syndromes

1. Paramedian Thalamic Infarction and Artery of Percheron Triad

Infarcts in this territory are characterized by profound neuro-cognitive and arousal deficits due to disruption of the MD nucleus and reticular activating system.

- **Altered mental status:** Ranging from somnolence to “thalamic coma.”
- **Vertical gaze palsy:** Due to extension into the rostral midbrain (interstitial nucleus of Cajal).
- **Memory impairment:** Acute thalamic amnesia and abulia (loss of drive).

i NOTE

Paramedian infarcts are associated with a “stuttering” or fluctuating clinical course.

2. Inferolateral Infarction and Dejerine-Roussy Syndrome

This territory is the most common site for lacunar-type “pure sensory” strokes.

- **Classic presentation:** Pure hemisensory loss involving all modalities (pain, temperature, vibration, and proprioception) on the contralateral body and face (VPL/VPM involvement).
- **Dejerine-Roussy (central poststroke pain):** Delayed onset of agonizing, burning, or “electric” pain in the anesthetic territory. Often refractory to standard analgesics.

3. Anterior (Tuberothalamic) Infarction

Disruption of the polar artery primarily affects the limbic relay.

- “Thalamic amnesia” (anterograde memory loss) and prominent personality changes. Patients may exhibit apathy, disorientation, and, if the dominant side is involved, a unique “thalamic aphasia” (fluent but with paraphasias and preserved repetition).

4. Posterior (Posterior Choroidal) Infarction

These infarcts present with unique visual and pupillary findings.

- **LGN involvement:** Contralateral homonymous sectoranopia (a wedge-shaped visual field defect).
- **Pulvinar/midbrain extension:** May present with vertical gaze abnormalities or small, sluggish pupils.

Differentiation

- **Deep vs. lobar prognosis:** Deep infarctions (including thalamic/basal ganglia sites) are associated with higher risks of recurrent ischemic events compared to lobar sites.
- **Thalamocapsular patterns:** Infarcts in the transition zone between the lateral thalamus and the internal capsule (thalamocapsular) present with combined sensory and motor deficits (hemiparesis plus hemisensory loss).

◆ CLINICAL PEARL

When a patient presents with fluctuating consciousness, vertical gaze palsy, and memory impairment, think Artery of Percheron occlusion — this bilateral paramedian thalamic infarct is easily missed on initial noncontrast CT and requires MRI with diffusion-weighted imaging for confirmation.

CHAPTER 3

Neuro-Pharmacology: Antiplatelets and Anticoagulants

I. Antiplatelet Agents

1. Aspirin

- **Mechanism of action:** Irreversibly inhibits cyclooxygenase-1 (COX-1), thereby blocking the production of thromboxane A₂, a potent activator of platelet aggregation.

Clinical Trial Evidence

- **IST (International Stroke Trial):** Aspirin 300 mg daily initiated immediately after AIS reduced recurrent strokes within 2 weeks without a significant increase in hemorrhagic risk.
- **Antiplatelet Trialists Collaboration:** Meta-analysis of primary prevention trials showed a 12% relative reduction in serious vascular events, primarily driven by myocardial infarction (MI) reduction rather than stroke prevention.

High-Yield Board Tips and Precautions

- **Dosing:** Standard AIS dosing is 160–325 mg initiated within 48 hours (delaying 24 hours if IV thrombolytics were administered).

- **Primary prevention:** The US Preventive Services Task Force recommends against initiating low-dose aspirin for primary prevention in individuals ≥ 60 years old due to increased bleeding risks.
- **Sex differences:** Primary prevention using aspirin offers stroke prevention in women but primarily MI prevention in men.

2. Clopidogrel

- **Mechanism of action:** A prodrug requiring hepatic bioactivation to an active metabolite that acts as a P2Y₁₂ receptor antagonist, inhibiting ADP-induced platelet aggregation.

Clinical Trial Evidence

- **POINT and CHANCE trials:** Demonstrated that short-term early DAPT with aspirin and clopidogrel (300/600 mg load, 75 mg daily) for 21 days is superior to monotherapy for minor stroke (NIHSS ≤ 3) or high-risk TIA (ABCD² ≥ 4).

High-Yield Board Tips and Precautions

- **Genetic testing:** Clopidogrel requires bioactivation by the CYP2C19 enzyme. Loss-of-function alleles are common and can result in reduced antiplatelet efficacy.
- **Indication:** Mandated for 90 days as part of DAPT for severe symptomatic intracranial stenosis (70–99%).

3. Ticagrelor

- **Mechanism of action:** A direct-acting, reversible P2Y₁₂ inhibitor that does not require metabolic bioactivation.

Clinical Trial Evidence

- **THALES trial:** Ticagrelor plus aspirin for 30 days reduced the risk of stroke or death in patients with NIHSS ≤ 5 or ABCD² ≥ 6 , but with a significantly increased risk of major hemorrhage.
- **CHANCE-2:** Demonstrated that ticagrelor is superior to clopidogrel in stroke reduction for patients who are CYP2C19 loss-of-function carriers.

High-Yield Board Tips and Precautions

- **Dosing:** Loading dose of 180 mg, followed by 90 mg BID.

i NOTE

Ticagrelor is commonly associated with dyspnea and, less frequently, ventricular pauses in general cardiology practice. Confirm current prescribing information, as these specific non-bleeding adverse effects should be independently verified for board preparation.

4. Cilostazol

- **Mechanism of action:** Phosphodiesterase-3 (PDE3) inhibitor that increases cyclic AMP levels, leading to reversible inhibition of platelet aggregation and vasodilation.

Clinical Trial Evidence

- **Korean registry data:** A study of over 25,000 patients found that cilostazol monotherapy reduced mortality in patients with Moyamoya disease.
- **LACI-2 trial:** Cilostazol combined with isosorbide mononitrate reduced cognitive impairment in survivors of small vessel (lacunar) strokes.

i NOTE

Cilostazol is classically contraindicated in heart failure due to its PDE3-inhibitor class effect (a mechanism shared with other inotropic agents shown to increase mortality in heart failure). Verify current labeling independently.

Antiplatelet Agent Summary

Agent	Mechanism	Key Indication	Key Caution
Aspirin	Irreversible COX-1 inhibition → ↓thromboxane A2	Immediate post-AIS; secondary prevention	GI bleeding; avoid new primary prevention ≥60y
Clopidogrel	Prodrug; P2Y12 antagonist	DAPT for minor stroke/TIA; intracranial stenosis (90 d)	CYP2C19 loss-of-function → reduced efficacy
Ticagrelor	Direct, reversible P2Y12 inhibitor	DAPT alternative, esp. CYP2C19 LOF carriers	↑Major hemorrhage risk
Cilostazol	PDE3 inhibitor → ↑cAMP	Moyamoya disease; lacunar stroke cognitive protection	Avoid in heart failure (verify locally)

Table 3.1 — Antiplatelet agent comparison.

II. Anticoagulant Agents

1. Unfractionated Heparin

- **Mechanism of action:** Binds to antithrombin III, greatly accelerating its ability to inactivate thrombin (Factor IIa) and Factor Xa.
- **Clinical use:** Used hyperacutely for Cerebral Venous Thrombosis (CVT) management (e.g., IV bolus followed by drip), even in the presence of intracranial hemorrhage.

i NOTE

Monitor for heparin-induced thrombocytopenia (HIT) during prolonged unfractionated heparin therapy; verify institutional monitoring protocol.

2. Low-Molecular-Weight Heparin (LMWH / Enoxaparin)

- **Mechanism of action:** Primarily inactivates Factor Xa with less effect on thrombin (Factor IIa).
- **Pregnancy:** LMWH is the anticoagulant of choice during pregnancy and lactation for CVT or high-risk thrombophilia, as it is safe and has predictable effects.
- **Monitoring:** Anti-Xa activity levels may be checked if needle placement for regional anesthesia is required within 12 hours of a dose (target ≤ 0.1 IU/mL).

3. Warfarin

- **Mechanism of action:** Vitamin K antagonist that inhibits the synthesis of Factors II, VII, IX, and X by inhibiting the VKORC1 enzyme.

Clinical Trial Evidence

- **WASID trial:** Demonstrated that warfarin is not superior to aspirin for preventing recurrence in symptomatic intracranial stenosis and carries a higher risk of major hemorrhage.

High-Yield Board Tips and Precautions

- **Pregnancy:** Contraindicated in the first trimester due to teratogenicity; it is safe during lactation.
- **Indications:** Remains the indicated agent for patients with mechanical heart valves.
- **ICH risk:** Associated with a higher risk of intracerebral hemorrhage compared to direct oral anticoagulants (DOACs).

4. Direct Oral Anticoagulants (DOACs / NOACs)

Agent	Mechanism
Dabigatran	Direct thrombin (Factor IIa) inhibitor
Apixaban, Rivaroxaban, Edoxaban	Direct Factor Xa inhibitors

Table 3.2 — DOAC mechanisms of action.

Clinical Evidence

- **Atrial fibrillation (AF):** DOACs are generally recommended over warfarin for AF due to a 50% lower risk of ICH and a 20% relative reduction in total stroke risk.
- **ESUS:** Trials (NAVIGATE ESUS, RE-SPECT ESUS) failed to show a benefit of DOACs (rivaroxaban, dabigatran) over aspirin for embolic stroke of undetermined source.
- **COMPASS:** Low-dose rivaroxaban (2.5 mg BID) plus aspirin showed benefit in broader vascular risk reduction populations.
- **PRESTIGE-AF:** In ICH survivors with AF, DOAC therapy reduced ischemic stroke but was associated with a significant increase in recurrent ICH (RR 11.2).

High-Yield Board Tips and Precautions

- **Renal/weight considerations:** Dosing adjustments are required for renal impairment; a “renally impaired subgroup” analysis was reported in RE-SPECT ESUS.
- **Contraindications:** Generally avoided in Cerebral Amyloid Angiopathy (CAA) or patients with imaging markers of CAA (e.g., cortical superficial siderosis) due to unacceptably high recurrent ICH risks.

⚠ WARNING

Specific DOAC reversal agents (e.g., idarucizumab for dabigatran, andexanet alfa for Factor Xa inhibitors) should be verified against current institutional protocols and are not detailed further here.

Anticoagulant Agent Summary

Agent	Mechanism	Key Indication	Key Caution
Unfractionated heparin	Potentiates antithrombin III (IIa and Xa)	Hyperacute CVT (even with ICH)	HIT risk; requires monitoring
LMWH (enoxaparin)	Primarily Factor Xa inhibition	Pregnancy/lactation CVT and thrombophilia	Renal dose adjustment
Warfarin	Vitamin K antagonist (VKORC1)	Mechanical heart valves	Teratogenic in 1st trimester; higher ICH risk than DOACs
DOACs	Direct thrombin (dabigatran) or Factor Xa inhibition	AF stroke prevention (preferred over warfarin)	Avoid in CAA; not superior to aspirin in ESUS

Table 3.3 — Anticoagulant agent comparison.

✦ CLINICAL PEARL

Warfarin remains preferred over DOACs specifically for mechanical heart valves and, per WASID trial data, is not superior to aspirin for intracranial atherosclerotic disease — DOACs and warfarin are not interchangeable across all stroke etiologies.

CHAPTER 4

Management of Large Artery Atherosclerosis

I. Definition and Epidemiology

Large Artery Atherosclerosis (LAA) is a common driver of ischemic cerebrovascular disease, accounting for approximately 15% of all ischemic strokes in the United States. Clinically, symptomatic LAA is defined as an ischemic event — such as amaurosis fugax, a TIA, or an ischemic stroke — occurring in the vascular territory of a blood vessel with **at least 50% stenosis or occlusion** attributed to atherosclerotic disease. Despite modern therapeutic advances, LAA remains a high-risk condition; the 1-year risk of stroke recurrence is estimated at 18% for extracranial disease and as high as 20% for intracranial atherosclerosis.

II. Pathophysiology: From Shear Stress to Infarction

The progression of LAA is driven by a complex interplay of systemic risk factors — including hypertension, hyperlipidemia, and tobacco use — and focal mechanical forces.

- **Endothelial dysfunction and plaque formation:** Chronic mechanical shear stress at arterial bifurcations (such as the carotid bulb) triggers endothelial dysfunction, promoting the accumulation of lipids and inflammatory cells within the vessel wall.
- **Artery-to-artery embolization:** The most frequent mechanism of LAA-related infarction, occurring when an unstable or ruptured plaque releases thrombotic material that travels distally to occlude smaller intracranial branches.
- **Hemodynamic low-flow states:** Severe stenosis can lead to hemodynamic hypoperfusion, where blood flow is insufficient to meet the metabolic demands of the distal territory, particularly during transient dips in systemic blood pressure.
- **Perforator disease:** In intracranial LAA, plaque can grow directly over the origin of smaller perforator vessels branching from the parent artery, leading to lacunar-type infarctions.

III. Classic Clinical Syndromes

Territory	Typical Presentation
Carotid territory occlusion/stenosis	Contralateral motor or sensory deficits, aphasia (dominant hemisphere), or hemineglect (non-dominant hemisphere). Amaurosis fugax (transient monocular vision loss) is a hallmark warning sign of ipsilateral carotid disease
Vertebrobasilar territory occlusion/stenosis	Ataxia, dysarthria, vertigo, and bilateral or alternating sensory and motor deficits

Table 4.1 — Anterior vs. posterior circulation LAA syndromes.

⚠ WARNING

Patients with hemodynamic vertebrobasilar disease are at high risk for recurrence if systolic blood pressure is lowered too aggressively (e.g., <140 mm Hg), as this can exacerbate low-flow states.

IV. Diagnostic Grading: The NASCET Calculation

For extracranial carotid disease, the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria serve as the standardized method for grading stenosis via CT angiography (CTA) or MR angiography (MRA).

- **Calculation:** The degree of stenosis is the ratio of the luminal diameter at the narrowest diseased segment to the luminal diameter of the normal distal cervical internal carotid artery (ICA).

Grade	Stenosis Range	Clinical Significance
Mild	<50%	Low recurrence risk; medical management
Moderate	50–69%	Revascularization considered based on patient-specific factors
Severe	70–99%	Highest risk for early recurrence; revascularization highly effective

Table 4.2 — NASCET grading scale for carotid stenosis.

Imaging Modality Selection

Circulation	Preferred Modality	Notes
Extracranial	Carotid duplex ultrasound	Cost-effective, accurate screening tool but cannot visualize intracranial or posterior circulation vessels; CTA/MRA provide anatomic detail for surgical planning
Intracranial	CTA (preferred in emergency setting)	MRA is an alternative for renal impairment/contrast allergy but is less accurate for moderate stenosis and more susceptible to motion artifact
Gold standard (either)	Digital subtraction angiography (DSA)	Definitive for differentiating small aneurysms from infundibula and precisely measuring stenosis; reserved for complex cases due to invasiveness and small procedural stroke risk

Table 4.3 — Imaging modalities for LAA.

V. Intensive Medical and Metabolic Parameters

Blood Pressure Targets

Population	Target
Symptomatic extracranial disease	<130/80 mm Hg
Symptomatic intracranial stenosis	<140/90 mm Hg (more conservative — aggressive targets of <120 or <130 mm Hg are avoided as they are associated with larger infarct volumes and higher recurrence rates)

Table 4.4 — Blood pressure targets in large artery atherosclerosis.

Intensive Lipid Management

- **LDL targets:** Standard secondary prevention target is <70 mg/dL (Treat Stroke to Target trial). For very high-risk intracranial disease, European guidelines and recent studies suggest a target of <55 mg/dL.

Pharmacotherapy Escalation Steps

Step	Therapy	Notes / Evidence
1	High-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg)	First-line therapy at maximally tolerated doses
2	Ezetimibe	Add as adjunct if <70 mg/dL target not achieved on statins alone (IMPROVE-IT trial)
3	PCSK9 inhibitors (alirocumab, evolocumab)	For patients intolerant to statins or failing to reach targets on maximal statin/ezetimibe combination

Table 4.5 — Lipid-lowering escalation pathway.

VI. Antithrombotic Protocols (POINT, SAMMPRIS, and CAPTIVA)

- **Minor stroke / high-risk TIA:** For NIHSS ≤ 3 or ABCD² ≥ 4 , initiate DAPT with aspirin and clopidogrel for 21 days, followed by antiplatelet monotherapy.
- **Severe symptomatic intracranial stenosis (70–99%):** Based on the SAMMPRIS trial, DAPT with aspirin and clopidogrel is mandated for 90 days in conjunction with intensive risk factor management.
- **CAPTIVA trial:** Currently investigating whether 1-year dual antithrombotic combinations (ASA + clopidogrel vs. ASA + ticagrelor vs. ASA + rivaroxaban) are superior for preventing recurrence in severe intracranial disease.

VII. Surgical and Endovascular Selection (CEA vs. CAS)

Symptomatic Extracranial Carotid Disease

- **Optimal timing:** Revascularization should occur once the patient is stable, ideally 2 days to 2 weeks from the index event. Revascularization within 48 hours is generally discouraged as it can increase 30-day stroke/death risk.

Stenosis	Recommendation
≥70%	Revascularization (CEA/CAS) is highly effective (NNT = 6)
50–69%	Considered based on patient-specific factors (age, sex, comorbidities); benefit is less robust in women

Table 4.6 — Revascularization thresholds for symptomatic extracranial carotid disease.

CEA vs. CAS Selection

Scenario	Preferred Approach
Age <70 years	Either CEA or CAS is acceptable
Age ≥70 years	CEA preferred (lower rates of periprocedural stroke and death)
Contralateral occlusion, prior neck radiation/surgery, tracheostomy, or severe medical comorbidity	CAS preferred

Table 4.7 — CEA vs. CAS decision factors.

Asymptomatic Extracranial Carotid Disease

- Routine screening is not recommended.
- **Revascularization criteria:** May be considered for 70–99% stenosis in patients with low perioperative risk, male sex, and life expectancy >5 years (CREST-2; NNT = 31 to prevent an event at 4 years).

Symptomatic Intracranial Stenosis Consensus

✗ PITFALL

Percutaneous transluminal angioplasty and stenting is NOT recommended as first-line treatment for symptomatic intracranial stenosis. Randomized trials (SAMMPRIS, VISSIT, CASSISS) consistently showed higher 30-day stroke/death rates in the stenting group (up to 15–25%) compared to aggressive medical therapy alone (6–7%). Intensive medical management is the superior strategy.

◆ CLINICAL PEARL

Do not chase intracranial stenting for symptomatic intracranial atherosclerosis — the evidence base (SAMMPRIS, VISSIT, CASSISS) consistently favors aggressive medical therapy (DAPT × 90 days, high-intensity statin, BP <140/90 mm Hg) over endovascular intervention.

CHAPTER 5

Cerebral Venous Thrombosis and Vascular Malformations

I. Cerebral Venous Thrombosis (CVT)

Pathophysiology and Localization

- **Mechanism:** CVT involves the formation of a thrombus within the dural venous sinuses or cortical veins, leading to increased venous pressure, disrupted blood-brain barrier, and potentially focal parenchymal injury or hemorrhage.

Site	Clinical Significance
Sagittal and transverse sinuses	Common sites; thrombus may extend from the superior sagittal sinus into the transverse and sigmoid sinuses
Deep venous system (internal cerebral veins, straight sinus)	High-risk feature associated with worse prognostic outcomes
Cavernous sinus	Involvement in CVT can lead to specific cranial neuropathies

Table 5.1 — Anatomical distribution of CVT and clinical relevance.

Clinical Presentation

- **Increased ICP and papilledema:** Presenting symptoms typically reflect elevated intracranial pressure, which can manifest as gradual-onset headache and papilledema. Acetazolamide is the first-line treatment for associated papilledema.
- **Ocular signs:** In severe cases, patients may exhibit proptosis, visual disturbances, or cranial nerve deficits.
- **Acute complications:** Seizures occur in approximately 10% of survivors, with status epilepticus and intracranial hemorrhage serving as baseline predictors.

Diagnostic Markers

- **Neuroimaging:** Dedicated vascular imaging via MR Venography (MRV) or CT Venography (CTV) is required for confirmation.
- **The “empty delta sign”:** A hallmark radiographic marker on contrast-enhanced CT or CTV, representing a central filling defect within a dural sinus (e.g., the superior sagittal or sigmoid sinus).
- **Laboratory evaluation:** D-dimer testing lacks sufficient sensitivity to reliably exclude CVT in the clinical workflow.

✗ PITFALL

Do not rely on a negative D-dimer to rule out CVT — sensitivity is insufficient for this purpose. If clinical suspicion is present, proceed directly to MRV/CTV.

II. Arteriovenous Malformations (AVMs)

Anatomy and Etiology

- **Structure:** AVMs are characterized by direct arterial-to-venous shunting through a nidus, bypassing the normal capillary bed. Components include feeding arteries, the nidus, and draining veins.
- **Origin:** Most are congenital anomalies of the capillary network, though de novo formation is documented.

Classification: The Spetzler-Martin Grading Scale

This scale assesses the risk associated with open surgical resection based on three parameters:

Parameter	Category	Points
Size of nidus	Small (<3 cm)	1
	Medium (3–6 cm)	2
	Large (>6 cm)	3
Eloquence of brain tissue	Non-eloquent	0
	Eloquent (e.g., motor, sensory, or visual cortex)	1
Venous drainage	Superficial only	0
	Deep venous drainage present (e.g., internal cerebral veins, straight sinus)	1

Table 5.2 — Spetzler-Martin AVM grading scale (Grade = sum of points, range I–V).

Clinical Presentation

Presentation	Frequency / Risk
Hemorrhage	Most frequent and severe presentation (58%), carrying a 40% rate of poor outcomes. Rupture risk increases to at least 6% in the first year following an initial bleed
Seizures	Occur in 34% of patients; the 5-year risk of epilepsy after a first seizure is approximately 58%
Steal phenomenon	Progressive neurologic deterioration due to flow-steal from surrounding parenchymal tissue or gliosis

Table 5.3 — AVM clinical presentation and natural history.

Management Options

Modality	Indication / Evidence
Observation	The ARUBA trial demonstrated that medical management is superior to interventional therapy for unruptured, asymptomatic AVMs
Microsurgical resection	Preferred option for low-grade (Spetzler-Martin I and II) symptomatic lesions in accessible areas
Stereotactic radiosurgery	Highly effective for small-to-moderate volume lesions (<12 cm ³ or ≤3 cm) in deep or eloquent regions
Endovascular embolization	Can achieve radiologic cure in selected cases with few arterial feeders; often used as an adjunct to surgery

Table 5.4 — AVM management strategies.

◆ CLINICAL PEARL

ARUBA changed practice: for unruptured, asymptomatic AVMs, medical management (observation with risk factor control) outperforms prophylactic intervention. Reserve intervention for ruptured or symptomatic lesions.

III. Intracranial Aneurysms and Subarachnoid Hemorrhage

Epidemiology and Screening

- **Prevalence:** Approximately 3.2% of the general population.
- **High-risk localization:** The Anterior Communicating (ACoM), Middle Cerebral (MCA), and Posterior Communicating (PCoM) arteries are the most common sites for ruptured aneurysms.
- **Screening criteria:** Indicated for patients with two or more first-degree relatives with aneurysms/SAH, or those with systemic conditions like Autosomal Dominant Polycystic Kidney Disease (ADPKD), Ehlers-Danlos syndrome (Type IV), or Marfan syndrome.

Risk Stratification Scores

Score	Purpose
PHASES score	Estimates the 5-year absolute risk of rupture based on population, hypertension, age, size, prior SAH, and site
UIATS	A multidimensional framework to guide decisions between serial imaging surveillance and active repair (surgical or endovascular)

Table 5.5 — Unruptured aneurysm risk stratification tools.

Acute SAH Complications

- **Delayed cerebral ischemia (DCI):** Occurs in 20–30% of patients with aneurysmal SAH and is a primary predictor of poor functional outcome.
- **Vasospasm window:** Management includes rigorous monitoring for vasospasm, which typically manifests between Day 3 and Day 14 post-rupture.
- **Nimodipine protocol:** Standard hyperacute management for SAH includes blood pressure control and prevention of secondary complications like vasospasm.

✗ EMERGENCY

Vasospasm surveillance (clinical exam ± transcranial Doppler ± angiography) should be maintained through the full Day 3–14 window after aneurysmal SAH, as delayed cerebral ischemia is a leading driver of poor outcome during this period.

Management

- **Surgical clipping:** Preferred for younger patients and easily accessible sites, such as MCA bifurcation aneurysms.
- **Endovascular coiling / flow diversion:** The majority of unruptured aneurysms are now treated endovascularly, with average complication rates around 5%.

★ MEMORY TIP / MNEMONIC

The three most common aneurysm sites spell out the anterior circle of Willis hotspots: AComm, MCA bifurcation, PComm — over 85% of saccular aneurysms arise from the anterior circulation.

CHAPTER 6

Intracerebral Hemorrhage Management

I. Acute Management and Surgical Protocols

Hyperacute Blood Pressure Management

Presentation	Target
Standard presentation	SBP controlled to goal <140 mm Hg within 1–2 hours of presentation
SBP >220 mm Hg on arrival	Slightly higher goal of <160 mm Hg may be considered

Table 6.1 — Hyperacute blood pressure targets in ICH.

Current guidelines recommend antihypertensive pharmacotherapy and lifestyle modifications for any patient with a baseline SBP ≥ 130 mm Hg or diastolic BP ≥ 80 mm Hg.

Minimally Invasive Surgery (ENRICH Trial)

- **Trial paradigm:** The ENRICH trial compared standard medical management to early surgical hematoma evacuation using Minimally Invasive Parafascicular Surgery (MIPS).
- **Inclusion/exclusion impact:** The trial demonstrated significant benefits for lobar hemorrhage in terms of functional recovery and survival.
- **Outcomes:** Patients undergoing MIPS for lobar ICH showed continued improvement in functional outcomes through 6 months post-procedure. Outcomes for deep ICH were less definitive, and the trial emphasized the need for careful patient selection.

★ HIGH YIELD

ENRICH: benefit of minimally invasive hematoma evacuation was seen specifically for LOBAR hemorrhage, not deep hemorrhage. Location matters for surgical decision-making.

II. Chronic Microangiopathy and Diagnostic Criteria

MRI Markers of Small Vessel Disease (SVD)

- **Cerebral microbleeds (CMBs):** Small, rounded areas of signal void on susceptibility-sensitive sequences. Burden is categorized by number (e.g., 2–4 vs. >4) and location (strictly lobar vs. deep/mixed).
- **Cortical superficial siderosis (cSS):** Characterized by linear blood residues within cortical sulci arising from amyloid-laden cortical and leptomeningeal end arteries.

cSS Subtype	Definition	Significance
Focal cSS	Restricted to three or fewer sulci	Lower recurrence risk
Disseminated cSS	Affecting four or more sulci	Most important imaging predictor for lobar ICH recurrence

Table 6.2 — Cortical superficial siderosis subtypes.

Modified Boston Criteria v2.0 for CAA Diagnosis

Diagnosis of Probable Cerebral Amyloid Angiopathy (CAA) requires one of the following two paradigms:

Paradigm	Requirements
Multiple hemorrhagic markers	Multiple strictly lobar ICHs, CMBs, or cSS foci in any combination
Single hemorrhage + white matter markers	A single lobar ICH AND either: enlarged perivascular spaces (>20 visible in the centrum semiovale of one hemisphere), OR WMH multispot pattern (>10 small hyperintense lesions on T2-FLAIR in bilateral subcortical white matter)

Table 6.3 — Modified Boston Criteria v2.0 for probable CAA.

Neuroimmunology Risk and ARIA

- **Therapeutic risk:** Anti-amyloid monoclonal antibodies (e.g., lecanemab, donanemab) used for Alzheimer disease are currently contraindicated in patients with a history of primary ICH or markers of CAA.

ARIA Subtype	Description	Incidence
ARIA-E (edema)	Vasogenic edema	~25% of treated patients
ARIA-H (hemorrhage)	Intracranial micro- or macrohemorrhages	18% of treated patients

Table 6.4 — Amyloid-Related Imaging Abnormalities (ARIA).

⚠ WARNING

ARIA pathophysiology closely resembles CAA-related inflammation, suggesting shared mechanisms of amyloid-laden vessel destabilization during plaque removal. CAA markers on baseline imaging are a key exclusion criterion for anti-amyloid immunotherapy.

III. Secondary Prevention and Resumption Landmark Trials

ICH Recurrence Risk

Category	Annual Recurrence Risk
Overall	1.2–3% per year
Lobar recurrence	7.4% per year (primarily due to CAA)
Deep recurrence	1.1% per year (primarily due to arteriolosclerosis)

Table 6.5 — ICH recurrence risk by location.

Other risk factors: older age, high CMB burden, disseminated cSS, poorly controlled hypertension, Asian or Black race, and APOE $\epsilon 2/\epsilon 4$ alleles.

Landmark Resumption Trials: Antiplatelets

Trial	Protocol	Outcome
RESTART	Resuming antiplatelet therapy at a median of 76 days post-ICH	Did not increase risk of recurrent ICH, even in patients with lobar ICH or high CMB burden
E-START	Postoperative aspirin: early (Day 3) vs. delayed (Day 30)	Early initiation significantly reduced new ischemic events (20.1% vs. 31.1%) at 90 days with no increase in intracranial bleeding (1% vs. 3%)

Table 6.6 — Antiplatelet resumption trials after ICH.

Landmark Resumption Trials: Anticoagulants

- **PRESTIGE-AF trial:** Compared DOAC to no anticoagulation in patients with AF and a history of small ICH. Median enrollment at 49 days post-ICH. Ischemic stroke was significantly lower with DOAC (0.83 vs. 8.60 per 100 patient-years), but recurrent ICH risk was substantially increased (RR 11.2).
- **LAAO alternative:** Left atrial appendage occlusion is noninferior to anticoagulation in some AF trials and may be superior for reducing non-procedure-related bleeding.

✗ PITFALL

PRESTIGE-AF demonstrates a stark tradeoff: DOAC resumption after ICH in AF patients reduces ischemic stroke but massively increases recurrent ICH risk (RR 11.2). Anticoagulation decisions after ICH require careful individualized risk-benefit discussion, and LAAO should be considered as an alternative.

Statins after ICH

- **SPARCL consideration:** Post-hoc analysis suggested high-dose atorvastatin and very low LDL levels (<70 mg/dL) might be associated with increased ICH recurrence.
- **SATURN trial:** Ongoing trial specifically comparing continuation vs. discontinuation of statins in ICH survivors to resolve existing variability in observational data.

IV. Recovery and Neurorehabilitation Trajectories

Neurorehabilitation Paradigms

- **Timing:** Evaluation should begin within 24–48 hours. However, very early mobilization (sitting/standing) within the first 24 hours is discouraged due to increased mortality risk seen in the AVERT trial.

Functional Trajectory

- Recovery is slower and more protracted than in ischemic stroke.
- Among survivors with mRS 4–5 at Day 30, >40% achieved mRS 0–3 (good outcome) by 1 year.
- One-third of these patients achieved functional independence (mRS 0–2) within that same timeframe.

Cognitive and Mood Trajectories

- **Biphasic cognition:** Early impairment is common; improvement often occurs in the first 1–2 years, followed by potential progressive decline in those with high SVD burden or APOE risk.
- **Poststroke depression:** Affects 20–36% of survivors. Independently associated with slower functional recovery and lower quality of life, necessitating serial screening.

✦ CLINICAL PEARL

Do not mobilize ICH patients within the first 24 hours (AVERT trial showed increased mortality with very early mobilization) — but do begin formal rehabilitation evaluation within 24–48 hours. These are not contradictory: evaluate early, mobilize cautiously.

CHAPTER 7

Neurologic and Systemic Complications of Stroke

I. Neurologic Complications

1. Hemorrhagic Transformation (HT) of AIS

- **Hyperacute risk:** Symptomatic hemorrhagic transformation is the most significant risk of IV thrombolysis, estimated to occur in 2–7% of treated patients.

Agent / Scenario	Hemorrhage Risk Profile
Tenecteplase (0.25 mg/kg)	Higher likelihood of excellent 90-day functional outcomes compared to alteplase, with a comparable safety profile
Reteplase	Better 90-day outcomes than alteplase but a significantly increased incidence of hemorrhage
Tirofiban (after IV thrombolysis)	Improves outcomes in noncardioembolic stroke but carries a higher incidence of symptomatic ICH
Extended window (EXTEND, 4.5–9h)	Clinical benefit shown, but a trend toward increased hemorrhage risk in later windows

Table 7.1 — Hemorrhagic transformation risk by agent/scenario.

2. Malignant MCA Syndrome and Cerebral Edema

- **Pathophysiology:** Ischemia triggers a cascade from cytotoxic edema (intracellular water accumulation) to vasogenic edema (blood-brain barrier disruption).
- **Monitoring:** Early complications such as cerebral edema and mass effect require close assessment and potential treatment modification in the first week.

Large Core Infarction Management

- Patients with ASPECTS 3–5 and a proximal large vessel occlusion (LVO) are now recommended for mechanical thrombectomy, as it improves functional independence despite the large core.
- For very large core infarcts (ASPECTS 0–2), thrombectomy may be considered in select patients under 80 years old within 6 hours of onset.
- **Decompressive hemicraniectomy:** Indicated for life-threatening mass effect; in the setting of CVT, approximately one-third of patients requiring decompression achieve functional independence at 1 year.

✗ EMERGENCY

Malignant MCA edema typically peaks between days 2–5 post-stroke. Close neurologic and imaging monitoring during this window is essential — decompressive hemicraniectomy is a life-saving intervention when mass effect becomes life-threatening.

3. Post-Stroke Seizures and Epilepsy

- **Perinatal/neonatal stroke:** Seizures are the hallmark clinical presentation, often occurring in the absence of focal deficits.
- **CVT survivors:** Approximately 10% develop epilepsy.
- **Vascular malformations:** Seizures occur in 34% of AVM patients; the 5-year risk of epilepsy after a first-ever seizure is 58%. Intervention does not reliably reduce seizure frequency in unruptured AVMs.

Risk Factors for Post-Stroke Epilepsy

Recognized risk factors include acute symptomatic seizures, status epilepticus, intracranial hemorrhage/subdural hematoma, decompressive hemicraniectomy, and older age.

4. Central Fever

- **Acute impact:** Fever in the first 7 days post-stroke is associated with worse long-term functional outcomes.
- **Management:** Formalized stroke units reduce mortality by implementing bundled protocols for rapid fever reduction.

II. Systemic and Medical Complications

1. Aspiration Pneumonia and Dysphagia

- **Prevalence:** Dysphagia affects nearly 50% of all stroke survivors.
- **Screening and outcomes:** Early swallow assessments in stroke units are standard components demonstrated to reduce post-stroke mortality.
- **Rehabilitation:** Group programs utilizing oropharyngeal exercises and swallow-breathing coordination significantly reduce aspiration rates.

EXAM TIP

Bedside swallow screening should occur before any oral intake (including medications) in all acute stroke admissions — dysphagia affects nearly half of stroke survivors and aspiration pneumonia is a leading preventable complication.

2. Cardiac Dysfunction and Neurogenic Complications

- **General cardiac risk:** Cardiac complications, including arrhythmia and myocardial infarction, are life-threatening early risks.
- **Pregnancy-specific:** Peripartum cardiomyopathy (EF <45% in late pregnancy or first 5 months postpartum) carries a 4% embolic risk, particularly if EF <35%.
- **Secondary ischemia:** Survivors of ICH have a fourfold higher risk of major adverse cardiovascular events compared to controls, including myocardial infarction and ischemic stroke.

3. DVT and PE Prophylaxis

- **Risk timing:** The risk of thrombotic events remains significantly elevated for 12 weeks after delivery in pregnant patients.
- **Prevention:** Early initiation of antiplatelets (e.g., E-START trial) reduces the burden of deep vein thrombosis without increasing intracranial bleeding risk. For CVT in pregnancy, LMWH (enoxaparin) is the preferred agent due to its safety profile.

4. Central SIADH and Metabolic Shifts

- **Assessment:** Rapid assessment of electrolytes and creatinine is mandatory in pregnant or postpartum patients complicated by hypertensive disorders before thrombolysis, to rule out preeclampsia-associated metabolic imbalances.
- **Management:** Hyperglycemia treatment and electrolyte monitoring are core stroke unit practices demonstrated to reduce mortality.

5. Post-Stroke Depression

Parameter	Finding
Overall prevalence	Approximately one-third of all stroke survivors; linked to a 46% increase in mortality
ICH vs. AIS	Risk is twofold higher in ICH (20–36%) than in ischemic stroke
Risk factors	Female sex, Hispanic ethnicity, cognitive impairment, and inability to return home within one month. APOE ε2 and APOE ε4 alleles are associated with persistent symptoms
Pharmacotherapy	SSRIs are effective but may slightly increase ICH recurrence risk. SNRIs have not been associated with increased stroke or ICH risk in general anxiety/depression studies

Table 7.2 — Post-stroke depression: prevalence, risk factors, and treatment considerations.

✦ CLINICAL PEARL

Screen every stroke survivor for depression at follow-up — post-stroke depression affects up to a third of survivors, is independently linked to a 46% increase in mortality, and is often underrecognized because symptoms overlap with post-stroke fatigue and cognitive changes.

CHAPTER 8

Stroke Prevention and Risk Factor Management

I. Risk Prediction Tools and Targets

Comprehensive Risk Prediction Tools

Tool	Components	Key Outcomes Predicted
AHA Life's Essential 8	100-point scale: 4 behavioral factors (diet, exercise, nicotine exposure, sleep) + 4 health factors (weight, cholesterol, blood sugar, blood pressure)	Stroke, all-cause dementia (HR 1.50 lowest quartile), vascular dementia (HR 1.86), late-life depression
McCance Brain Care Score	Life's Essential 8 parameters plus stress, social engagement, and purpose in life	Composite brain health measure: stroke, dementia, late-life depression
AHA PREVENT Calculator	Validated ages 30–79; incorporates HbA1c, eGFR, and Social Deprivation Index; removes racial modifiers used in prior models	10- or 30-year risk of composite cardiovascular and atherosclerotic events

Table 8.1 — Comprehensive cardiovascular/brain health risk prediction tools.

Targeted Physiological Thresholds

Parameter	Target
Primary prevention SBP	<130 mm Hg (35% reduction in stroke risk)
Prevention of MCI/dementia	<120 mm Hg (more aggressive control)
Secondary prevention SBP	<130 mm Hg
LDL — secondary prevention (atherosclerosis)	<70 mg/dL
LDL — high-risk intracranial atherosclerosis	<55 mg/dL (European guidelines / observational data)

Table 8.2 — Blood pressure and lipid targets for stroke prevention.

Statins (e.g., atorvastatin 40–80 mg or rosuvastatin 20–40 mg) are first-line therapy. Ezetimibe or PCSK9 inhibitors (alirocumab, evolocumab) are indicated for patients intolerant to statins or those failing to reach targets on maximally tolerated statin doses.

II. Cardiometabolic and Atrial Fibrillation Management

Cardiometabolic Recommendations

- **GLP-1 receptor agonists:** Indicated for patients with Type 2 diabetes and high cardiovascular risk (or established CVD) with an HbA1c $\geq 7\%$. Semaglutide has been shown to reduce nonfatal stroke risk (HR 0.84). In patients with CVD and overweight/obesity without diabetes, weekly subcutaneous semaglutide 2.4 mg reduces composite cardiovascular outcomes.
- **Bariatric surgery:** Associated with a 64% reduction in total stroke risk and a 37% reduction in ischemic stroke risk compared to medical care alone in patients with obesity and Type 2 diabetes.

Atrial Fibrillation (AF) Protocols

- **Anticoagulant selection:** DOACs (dabigatran, apixaban, rivaroxaban, edoxaban) are generally recommended over warfarin due to a lower risk of ICH. Warfarin remains indicated for patients with mechanical heart valves.
- **Subclinical AF detection:** Long-term monitoring is recommended for patients with unexplained stroke (ESUS). Device-detected subclinical AF of at least 6 minutes occurs in one-third of high-risk patients within 2 years.

Atrial Fibrillation Scoring Systems

Criterion	CHADS2 Points	CHA2DS2-VASc Points
Congestive heart failure	1	1
Hypertension	1	1
Age 65–74	—	1
Age ≥ 75	1	2
Diabetes	1	1
Stroke/TIA/systemic embolism	2	2
Vascular disease history	—	1
Sex category (female)	—	1

Table 8.3 — CHADS2 vs. CHA2DS2-VASc scoring for AF stroke risk.

Anticoagulation is recommended for an elevated risk score ($\geq 2\%$ per year), defined as ≥ 2 for men and ≥ 3 for women (CHA2DS2-VASc).

III. Revascularization and Antiplatelet Strategies

Carotid Stenosis Intervention Criteria

Population	Stenosis Threshold	Notes
Symptomatic	>70%	CEA or stenting recommended
Symptomatic	50–69%	Considered in selected patients
Asymptomatic	>60%	Revascularization may reduce annual risk from 2% to 1%; absolute benefit modest. Screening not currently recommended for the general population

Table 8.4 — Carotid revascularization criteria.

Optimal timing for intervention is between 2 days and 2 weeks following the index event.

Antiplatelet Timing and Indications

- **Primary prevention:** Initiation of low-dose aspirin is individualized for adults aged 40–59 years with a $\geq 10\%$ 10-year ASCVD risk. Recommended against in patients ≥ 60 years old. Not supported for incidentally discovered “silent” infarcts.

Secondary Prevention (AIS/TIA)

Scenario	Regimen
Immediate	Aspirin 160–325 mg (or 300 mg) started as soon as possible after symptom onset
Minor stroke (NIHSS ≤ 3) / high-risk TIA (ABCD ² ≥ 4)	Clopidogrel (300/600 mg load, 75 mg maintenance) plus aspirin for 21–90 days, followed by single-agent therapy
Intracranial stenosis (symptomatic, 70–99%)	DAPT with aspirin and clopidogrel for 90 days

Table 8.5 — Secondary prevention antiplatelet regimens by scenario.

i NOTE

Colchicine 0.5–0.6 mg daily is associated with a reduction in cardiovascular events in patients with stroke and recent myocardial infarction, reflecting the growing role of anti-inflammatory therapy in secondary prevention.

IV. High-Risk Scenarios and Cryptogenic Stroke

Patent Foramen Ovale (PFO) Management

RoPE Score Calculator

Criterion	Points
No hypertension	1
No diabetes	1
No prior stroke/TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age 18–29	5
Age 30–39	4
Age 40–49	3
Age 50–59	2
Age 60–69	1
Age ≥70	0

Table 8.6 — RoPE score for cryptogenic stroke risk of paradoxical embolism.

PASCAL Classification System

Category	Criteria
Probable	High RoPE score (≥7) AND high-risk PFO feature (ASA or large shunt)
Possible	High RoPE score (≥7) OR high-risk PFO feature
Unlikely	Low RoPE score (<7) AND no high-risk PFO feature

Table 8.7 — PASCAL classification for PFO-attributable stroke.

High-risk PFO features are defined as Atrial Septal Aneurysm (ASA) with ≥10 mm excursion, or a large shunt (>20 bubbles on bubble study).

◆ CLINICAL PEARL

PFO closure inclusion: patients <60 years old with an unexplained (cryptogenic) stroke and a Probable pathogenic PFO (RoPE ≥7 AND high-risk anatomical feature) derive the greatest benefit from closure.

Embolic Stroke of Undetermined Source (ESUS)

- **Current paradigm:** Antiplatelet agents (e.g., aspirin) remain the antithrombotics of choice.

- **Trial outcomes:** Trials (NAVIGATE ESUS, RE-SPECT ESUS) comparing DOACs (rivaroxaban, dabigatran) to aspirin did not show a general benefit for anticoagulation in ESUS.
- **Special considerations:** Anticoagulation may benefit specific subgroups, such as those with a left atrial diameter >4.6 cm or elderly patients (>75 years). Routine management includes aggressive long-term cardiac monitoring for subclinical AF.

✗ PITFALL

Do not default to anticoagulation for ESUS. Despite the embolic-appearing pattern, large randomized trials (NAVIGATE ESUS, RE-SPECT ESUS) show no general benefit of DOACs over aspirin — anticoagulation should be reserved for specific high-risk subgroups.

CHAPTER 9

Pregnancy and Stroke Risk Management

I. Epidemiology, Pathophysiology, and Headache Red Flags

Epidemiology and Timing

- **Incidence:** Approximately 30 per 100,000 pregnancies.

Period	Relative Risk (RR)	Definition
Antepartum	0.7 (lowest)	Before labor
Peripartum	27.3 (peak)	2 days before to 1 day after delivery
Postpartum	3.2 (elevated)	1 day to 6 weeks after delivery

Table 9.1 — Relative risk of stroke across the pregnancy timeline.

- **Thromboembolic window:** The risk of thrombotic events remains significantly elevated for the first 12 weeks after delivery.

Relative Incidence by Stroke Type

Stroke Type	Risk in Pregnancy vs. Nonpregnant
Ischemic stroke	Similar to nonpregnant women
Hemorrhagic stroke	Higher (IRR 1.4)
Cerebral venous thrombosis (CVT)	Highest (IRR 8.1)

Table 9.2 — Stroke subtype risk in pregnancy.

Pathophysiology (Virchow Triad and Pregnancy Adaptations)

Virchow Component	Pregnancy-Related Change
Hypercoagulability	Procoagulant shift to protect against childbirth hemorrhage. Increased: fibrinogen (Factor I), von Willebrand factor, Factors V, VIII, and XII. Reduced: natural anticoagulants protein C and protein S
Venous stasis	Expanding uterus compresses the inferior vena cava and iliac veins (predominantly left side). Progesterone-driven vascular relaxation reduces venous tone
Vascular injury	Endothelial trauma occurs during vaginal or cesarean delivery, particularly in pelvic veins

Table 9.3 — Virchow triad in pregnancy-associated thrombosis.

Cardiovascular adaptations: systemic vasodilation begins at 5 weeks, with blood pressure reaching its nadir at 20 weeks' gestation. Cardiac output increases by 45% by the second trimester and surges 60–80% during labor.

Headache Red Flags: The “SCAN-ME” Mnemonic

Letter	Red Flag
S	Sudden / Severe / Seizure
C	Change in position or quality
A	Altered mental status
N	Neurological deficits / Nausea and vomiting
M	Medications without relief
E	Elevated blood pressure or temperature

Table 9.4 — SCAN-ME mnemonic for headache red flags in pregnancy.

★ MEMORY TIP / MNEMONIC

SCAN-ME: any pregnant or postpartum patient whose headache triggers one of these six features warrants urgent neuroimaging and stroke/preeclampsia workup.

II. Diagnostic Imaging and Acute Interventions Safety

Imaging Safety Guidelines

Allowable fetal radiation exposure threshold: 50 mGy.

Modality	Fetal Exposure	Safety Notes
Noncontrast head CT	0.001–0.01 mGy	Safe. Do not use abdominal shielding — it may interfere with CT sensors and increase radiation
CTA / CT perfusion	0.01–0.66 mGy	Use clinical judgment in pregnancy; safe in lactation. Iodinated contrast does not require interruption of breastfeeding
Brain MRI (1.5T or 3.0T)	None (no ionizing radiation)	Safe without gadolinium

Table 9.5 — Fetal radiation exposure by imaging modality.

Contrast Agents

- **Gadolinium:** Water-soluble and crosses the placenta. Exposure should be limited unless benefits outweigh risks (use clinical judgment).
- **Lactation:** Both iodinated and gadolinium-based contrasts are safe and do not require interrupting breastfeeding.

Acute Interventions

- **IV thrombolysis:** Reasonable for disabling symptoms. Alteplase and tenecteplase (59,000 Da) do not cross the placenta and pose no direct bleeding risk to the fetus. Caution is required in the early postpartum period (<14 days) due to risk of maternal hemorrhage.
- **Mechanical thrombectomy:** Indicated for large vessel occlusions within 24 hours of last known well. Transradial approach preferred; continuous fetal monitoring recommended in the third trimester.

Acute Hemorrhage Management

Parameter	Target / Agent
BP target — initial	<160/110 mm Hg
BP target — subsequent	<140/90 mm Hg
First-line therapeutics	IV labetalol, IV hydralazine, oral nifedipine

Table 9.6 — Acute hemorrhage BP management in pregnancy.

- **CVT management:** LMWH is the primary treatment; it is safe even if ICH is present. Duration: continue for at least 6 weeks postpartum, for a total minimum treatment of 3 months.

III. Hypertensive Disorders and Specific Conditions

Diagnostic Classifications

Condition	Definition
Gestational hypertension	BP $\geq$ 140/90 mm Hg; onset $\geq$ 20 weeks gestation; no proteinuria or end-organ involvement
Chronic hypertension	Onset <20 weeks gestation
Preeclampsia	Hypertension onset $\geq$ 20 weeks with proteinuria or end-organ dysfunction
Eclampsia	Preeclampsia plus seizures. Treat with magnesium for seizure prevention
HELLP syndrome	Severe complication of preeclampsia: Hemolysis, Elevated Liver enzymes, Low Platelets

Table 9.7 — Hypertensive disorders of pregnancy classification.

⚠ WARNING

Thrombocytopenia in HELLP syndrome is a contraindication to IV thrombolysis.

Specific Cerebrovascular Conditions

Condition	Key Features	Management
RCVS	Thunderclap headache; postpartum period is a major trigger. Triggers: SSRIs, triptans, pseudoephedrine	Remove triggers; calcium channel blockers may reduce headache intensity
PRES	Vasogenic edema in parieto-occipital regions; associated with 97% of eclampsia cases	Treat underlying hypertension/preeclampsia
Cervical artery dissection	Risk is highest postpartum (IRR 5.5)	Thrombolysis should not be withheld in eligible patients
Peripartum cardiomyopathy	Systolic heart failure, EF <45% in late pregnancy or first 5 months postpartum; embolic risk 4% (higher if EF <35%)	Standard heart failure management; consider anticoagulation if EF <35%

Table 9.8 — Pregnancy-specific cerebrovascular conditions.

★ MEMORY TIP / MNEMONIC

RCVS and PRES frequently coexist in the peripartum period and share overlapping triggers (hypertension, vasoactive medications) — both should be considered in a postpartum patient with thunderclap headache or seizures.

IV. Long-Term Risk and Medication Safety

Primary Prevention Protocol (Preeclampsia)

- **Aspirin dosing:** 81 mg daily.
- **Timing:** Initiate between 12 and 28 weeks' gestation (ideally before 16 weeks) and continue until delivery.
- **Inclusion:** Women at high risk for preeclampsia (chronic hypertension, prior preeclampsia, diabetes, renal disease, autoimmune disorders like lupus/APS, or multiple gestation).

Medication Safety Profiles

Antihypertensives

Category	Pregnancy	Lactation
First-line	Labetalol, nifedipine extended-release	Nifedipine ER, enalapril, amlodipine, labetalol, hydralazine, spironolactone, verapamil (RID <10%)
Alternatives	Alpha-methyldopa, clonidine, hydrochlorothiazide, hydralazine	Caution/limited data: chlorthalidone, lisinopril, losartan, valsartan
Contraindicated	ACE inhibitors, ARBs, direct renin inhibitors, mineralocorticoid receptor antagonists	—

Table 9.9 — Antihypertensive safety in pregnancy and lactation.

Antithrombotics

Agent	Pregnancy	Lactation
Aspirin (<100 mg)	Safe (first-choice antiplatelet)	Safe
LMWH / unfractionated heparin	Safe (first-choice anticoagulant)	Safe
Clopidogrel	Use for shortest duration; limited human data	Safe
Warfarin	Teratogenic in first trimester; may be used later for mechanical valves	Safe
DOACs (dabigatran, rivaroxaban, apixaban)	Insufficient data; generally avoided	Insufficient data
Statins	Assess risk-benefit; no evidence of teratogenicity	Not recommended (potential disruption of infant lipid metabolism)

Table 9.10 — Antithrombotic and statin safety in pregnancy and lactation.

◆ CLINICAL PEARL

Warfarin is teratogenic specifically in the first trimester but is safe during lactation — a common source of confusion. LMWH remains first-choice throughout pregnancy for both CVT and thromboprophylaxis given its predictable, safe profile.

CHAPTER 10

Stroke in Children and Young Adults

I. Age Classifications and Epidemiology

The epidemiology of cerebrovascular disease in earlier life is categorized by distinct developmental periods, each with unique incidence patterns and risk profiles.

Period	Definition	Incidence / Notes
Perinatal	Early gestation through the first 28 days of life	One of the highest-risk periods for stroke in a person's life: 1 in 1600–3000 full-term births
Neonatal	Often used interchangeably with perinatal for acute presentations	Typically manifests as acute symptomatic seizures or encephalopathy, frequently without focal neurologic deficits
Childhood	After the first 28 days of life through 18 years	Global incidence 13–180 per 1 million people per year
Young adult	Age cutoff of 50–55 years	Incidence rising due to conventional risk factors (especially >35 years); non-atherosclerotic mechanisms remain highly prevalent

Table 10.1 — Age-based classification of stroke across the lifespan.

II. Non-Atherosclerotic Etiologies

Unlike stroke in older populations, the young often experience strokes driven by a confluence of underlying genetic susceptibility and inciting triggers.

Category	Examples
Cardioembolic	Complex congenital heart disease (CHD), such as cyanotic lesions (e.g., transposition of the great arteries), and cardiac shunts like patent foramen ovale (PFO)

Category	Examples
Metabolic and genetic	Sickle cell disease (SCD), Fabry disease, and genetically mediated small vessel diseases such as COL4A1- or COL4A2-related disorders and deficiency of adenosine deaminase 2 (ADA2)
Infectious	Acute triggers such as otitis media, mastoiditis, sinusitis, and meningitis — recognized contributors to both arterial ischemic stroke and cerebral venous thrombosis (CVT)
Arterial dissection	Accounts for 25% of strokes in adults younger than 50 years and up to 20% of spontaneous dissections in children related to monogenic connective tissue disorders

Table 10.2 — Non-atherosclerotic etiologies of stroke in the young.

III. Pathophysiology of Pediatric Arteriopathies

1. Focal Cerebral Arteriopathy (FCA)

- **Clinical features:** Typically affects school-aged children presenting with acute stroke; rare in young adults.
- **Imaging:** Characterized by unilateral focal or segmental arterial stenosis of the distal internal carotid artery (ICA) and proximal anterior (ACA) or middle cerebral arteries (MCA).
- **Subtypes:** Includes dissection-type (often trauma-related) and inflammation-type (active or postinfectious).
- **Management:** Inflammation-type FCA can progress over days to weeks, with a 25% recurrence rate during this high-risk window; corticosteroids are a proposed treatment.

2. Moyamoya Disease

- **Clinical features:** Bimodal onset peaking at 5–15 years and 35–45 years. Symptoms include ischemic stroke, TIA, seizures, movement disorders, and headaches.
- **Imaging:** Progressive steno-occlusion of terminal ICAs with compensatory basal collaterals (“puff of smoke”).
- **Management:** Temporization includes IV fluids and fludrocortisone for recurrent spells. Chronic medical therapy includes cilostazol (reduced mortality in a major Korean study) and aspirin. Surgical revascularization (direct or indirect anastomosis) is indicated for symptomatic patients or those with impaired hemodynamic reserve.

★ MEMORY TIP / MNEMONIC

Moyamoya = Japanese for “puff of smoke”, describing the characteristic angiographic appearance of the fine collateral vessel network that develops as the terminal ICAs progressively occlude.

3. Antithrombotic Management for Cervical Artery Dissection

- Thrombolysis should not be withheld in eligible patients with cervical artery dissection and AIS.

Cervical Artery Dissection Algorithm

Bleeding Risk	Radiology	Recommended Regimen
Elevated bleeding risk	Any	Antiplatelet monotherapy
Not elevated	High-risk (intraluminal thrombus, occlusive dissection) — low bleeding risk	Parenteral anticoagulation followed by oral anticoagulation
Not elevated	High-risk — moderate bleeding risk	DAPT with loading dose for 21–90 days, then single agent
Not elevated	Absence of high-risk features — low bleeding risk	DAPT for 21–90 days, then single agent
Not elevated	Absence of high-risk features — moderate bleeding risk	Antiplatelet monotherapy

Table 10.3 — Antithrombotic selection algorithm for cervical artery dissection.

i NOTE

For intracranial artery dissection, antiplatelet agents are generally preferred over anticoagulants, unlike the more anticoagulant-inclusive approach used for cervical (extracranial) dissection.

IV. Sickle Cell Disease and Congenital Heart Disease Protocols

Sickle Cell Disease (SCD)

Phase	Management
Primary prevention	Routine transcranial Doppler (TCD) screening; treatment with regular blood transfusions and hydroxyurea
TCD velocity thresholds	High-risk children are identified for transition to hydroxyurea only after TCD velocities have normalized on chronic transfusions
Acute management	Suspected or confirmed AIS must be treated with exchange transfusion, even if symptoms are transient or resolving
Secondary prevention	Regular exchange transfusions to maintain target hemoglobin of 9 g/dL and hemoglobin S level <30%

Table 10.4 — Sickle cell disease stroke management protocol.

✗ EMERGENCY

Suspected or confirmed AIS in a patient with sickle cell disease requires exchange transfusion even if symptoms are transient or resolving — do not defer transfusion pending symptom resolution.

Patent Foramen Ovale (PFO) and PASCAL Classification

- **Closure criteria:** PFO closure is highly beneficial for young adults with cryptogenic stroke and a Probable pathogenic PFO according to PASCAL.

PASCAL Category	Criteria
Probable	High RoPE score (≥ 7) AND high-risk PFO feature (ASA or large shunt)
Possible	High RoPE score (≥ 7) OR high-risk PFO feature
Unlikely	Low RoPE score (< 7) AND no high-risk PFO feature

Table 10.5 — PASCAL classification scoring breakdown.

High-risk anatomical features are defined as Atrial Septal Aneurysm (ASA, ≥ 10 mm excursion) or a Large Shunt (> 20 bubbles on echocardiography).

Congenital Heart Disease (CHD) Brain Injury Contributors

Life Stage	Brain Injury Contributors
In utero	Altered cerebral blood flow and oxygenation
At birth	White matter injury and delayed brain maturation
Life course	Surgical iatrogenesis, hypoxemia, inflammation, thromboembolic events, and premature brain aging

Table 10.6 — Congenital heart disease brain injury contributors across the lifespan.

V. Pediatric Cerebral Venous Thrombosis (CVT)

Prognostic Indicators

Adverse baseline indicators include older age, altered level of consciousness, deep venous involvement, status epilepticus, and intracranial hemorrhage.

Acute Anticoagulation

- Guidelines recommend parenteral anticoagulation (typically LMWH over unfractionated heparin), followed by oral therapy with direct oral anticoagulants (DOACs) or vitamin K antagonists.

⚠ WARNING

Intracranial hemorrhage is NOT a contraindication to anticoagulation in CVT.

Monitoring and Recanalization

Up to 70% of patients show recanalization within the first week of anticoagulation; however, little additional recanalization occurs after 3–6 months.

Long-Term Anticoagulation Duration

Scenario	Duration
Primary phase (most patients)	3 to 12 months
Transient risk factors present	May be limited to 3 to 6 months

Table 10.7 — Duration of anticoagulation for pediatric CVT.

Long-term sequelae: approximately 10% of pediatric CVT survivors develop epilepsy.

✦ CLINICAL PEARL

Unlike other intracranial hemorrhage scenarios, ICH complicating CVT is not a contraindication to anticoagulation — the underlying venous hypertension mechanism means anticoagulation is still indicated to promote recanalization and prevent thrombus propagation.

NEUROCRITICAL CARE

CHAPTER 1

Intracranial Hypertension, Advanced Neuromonitoring, and Traumatic Brain Injury

This chapter presents evidence-based protocols for the pathophysiology and stepwise management of elevated intracranial pressure (ICP), osmotherapy, advanced multimodal neuromonitoring, and specialist review of traumatic brain injury (TBI), consistent with the Brain Trauma Foundation (BTF) Guidelines (4th Edition) and Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) recommendations.

I. Pathophysiology of ICP and CPP

1. The Monro–Kellie Doctrine

The cranium is a rigid, non-compliant vault containing brain parenchyma, blood, and cerebrospinal fluid (CSF). Because these components are incompressible, an increase in the volume of one — or the addition of a pathological mass (hematoma, edema) — must be compensated by an equal decrease in the volume of the others.

Once adaptive mechanisms (CSF displacement and venous shunting) are exhausted, intracranial compliance fails, leading to an exponential rise in ICP and, ultimately, herniation.

🔍 MEMORY TRICK / MNEMONIC

The Monro–Kellie Doctrine can be remembered as "Three-in-a-Box": Brain + Blood + CSF must always sum to a constant volume within the rigid skull. If one goes up, another must go down — or ICP rises.

2. Perfusion Formulas and Thresholds

Parameter	Formula / Threshold	Notes
Cerebral Perfusion Pressure (CPP)	$CPP = MAP - ICP$	Primary determinant of cerebral blood flow when autoregulation is impaired.
Standard ICP treatment threshold	Treat if ICP > 22 mmHg (adults)	Sustained elevation, not an isolated transient spike.
Standard CPP target	60–70 mmHg	Avoid aggressive CPP-directed therapy above this range (risk of ARDS from vasopressors/fluids).
SBP target — age 15–49 or > 70 years	$SBP \geq 110$ mmHg	Age-stratified BTF thresholds.
SBP target — age 50–69 years	$SBP \geq 100$ mmHg	Age-stratified BTF thresholds.

3. Autoregulation and Cerebral Blood Flow (CBF)

CBF is normally kept constant across a range of mean arterial pressures (MAP) via pressure autoregulation. After TBI or hypoxic-ischemic injury, this curve is often right-shifted (requiring a higher MAP to maintain flow) or absent/pressure-passive (CBF fluctuates directly with MAP).

- **Pressure Reactivity Index (PRx):** a continuous, moving correlation coefficient between ICP and MAP. A PRx < 0.2 indicates intact autoregulation; higher (more positive) values indicate impaired or absent autoregulation.

CLINICAL PEARL

A positive PRx identifies a pressure-passive cerebral circulation — in these patients, aggressively raising MAP to boost CPP may simply raise ICP in parallel without improving perfusion, and individualized "optimal CPP" targets (CPPopt) should guide management where available.

II. Stepwise Management of Elevated ICP

Management follows a tiered escalation strategy. "Tier 0" measures are universal and applied to all patients; subsequent tiers are added sequentially only if ICP remains refractory to the preceding tier.

Table 1.1 — Tiered ICP Treatment Protocol

Tier	Intervention	Clinical Specifications & Targets
Tier 0	Universal Stabilization	Intubation/ventilation, normothermia, euvolemia, and basic analgesia/sedation for all patients with severe TBI and intracranial hypertension.
Tier 1	First-Line Medical Therapy	HOB: > 30°, head in neutral position to optimize venous drainage. Ventilation: target normocapnia (PaCO ₂ 35–45 mmHg). CSF Drainage: External Ventricular Drain (EVD) placement. Temporary Bridge: mild hyperventilation (PaCO ₂ 30–34 mmHg) only as a bridge to surgery or Tier 2 therapy.
Tier 2	Hemodynamic & Osmotic Therapy	Osmotherapy: intermittent boluses of Mannitol or Hypertonic Saline. Hemodynamics: vasopressors to maintain CPP 60–70 mmHg if autoregulation is impaired.
Tier 3	Refractory Measures	Barbiturate Coma: pentobarbital titrated to EEG burst suppression. Hypothermia: moderate cooling (35°C to 36°C). Surgery: secondary decompressive craniectomy for late refractory ICP. Positioning: verticalization therapy (standing position) in select centers.

WARNING

Tier	Intervention	Clinical Specifications & Targets
Prophylactic severe hyperventilation ($\text{PaCO}_2 < 25$ mmHg) is contraindicated. Even the "temporary bridge" range (PaCO_2 30–34 mmHg) should be used for the shortest duration necessary, as excessive vasoconstriction can precipitate cerebral ischemia		
★ HIGH YIELD Escalation is sequential — do not skip tiers except in acute herniation, where hyperosmolar therapy and emergent neurosurgical consultation take priority regardless of tier.		

III. Osmotherapy Manual

Table 1.2 — Osmotherapy Dosing and Monitoring

Agent	Preparation	Dose / Rate	Monitoring & "Caps"
Mannitol	20% solution	1 g/kg IV every 6 hours	Osmolar gap: hold dose if gap > 20 mOsm/kg (risk of acute kidney injury).
Hypertonic Saline (HS)	3% or 23.4%	Bolus or continuous infusion	Serum sodium: limit to 160 mEq/L. Favored in patients with hemorrhagic shock or hypotension (does not cause diuresis).
⚠ PITFALL Mannitol is an osmotic diuretic and can worsen hypotension in hemodynamically unstable patients — hypertonic saline is generally preferred when concurrent hypotension or hemorrhagic shock is present.			

IV. Advanced Neuromonitoring

Table 1.3 — Neuromonitoring Metrics and Targets

Modality	Parameter	Normal / Pathological Threshold	Clinical Interpretation
EVD	ICP / Drainage	ICP ≤ 22 mmHg	Level at the tragus; drain at 15–20 cm H ₂ O to avoid premature herniation.
Parenchymal Probe	PbtO ₂	Target > 20 mmHg	Hypoxia < 20 mmHg; severe ischemia < 15 mmHg.

Modality	Parameter	Normal / Pathological Threshold	Clinical Interpretation
Jugular Bulb	SjO ₂	Target > 50%	Measures global hemispheric oxygen saturation.
TCD	Mean Flow Velocity (mfv), MCA	> 120 cm/s (mild); > 150 (moderate); > 200 (severe)	Elevated mfv suggests vasospasm or hyperemia.
TCD	Lindegaard Ratio	MCAmfv / ICAMfv	< 3: hyperemia; > 3: mild vasospasm; > 5: severe vasospasm.
CLINICAL PEARL Multimodal monitoring (ICP + PbtO₂ ± SjO₂) allows detection of "covert" cerebral ischemia even when ICP itself is within target range — treat the physiology, not a single number.			

V. Traumatic Brain Injury (TBI) Specialist Review

1. Brain Trauma Foundation (BTF) Surgical Guidelines

Table 1.4 — Surgical Evacuation Thresholds

Lesion	Evacuation Criteria
Epidural Hematoma (EDH)	Evacuate if volume > 30 mL, or if thickness > 15 mm / midline shift > 5 mm with GCS < 9.
Subdural Hematoma (SDH)	Evacuate if thickness > 10 mm or midline shift > 5 mm.
Parenchymal Lesions	Evacuate if volume > 50 mL, or with progressive clinical deterioration.

2. Diffuse Axonal Injury (DAI)

Injury to axons occurs via rotational/shearing forces, most commonly at gray–white matter junctions, the corpus callosum, and the dorsolateral brainstem.

- **Imaging:** often CT-negative; best seen on MRI (susceptibility-weighted imaging [SWI], gradient echo [GRE], and FLAIR sequences).
- **Grades:** Grade 1 (diffuse, gray–white junction); Grade 2 (corpus callosum involvement); Grade 3 (rostral brainstem involvement).

MEMORY TRICK / MNEMONIC

DAI grading mnemonic — "Grade goes deeper": Grade 1 = lobar/gray-white junction, Grade 2 = corpus callosum (more central), Grade 3 = brainstem (deepest and most severe).

3. Paroxysmal Sympathetic Hyperactivity (PSH)

PSH commonly occurs approximately one week post-injury as sedation is weaned.

- **Clinical signs:** tachycardia, hypertension, tachypnea, fever, and extensor posturing, characteristically triggered by non-painful stimuli.
- **Management:** propranolol, bromocriptine, clonidine, gabapentin, and opioids.

4. BTF Pharmacological Standards

Table 1.5 — Pharmacological Standards in Severe TBI

Agent / Intervention	Recommendation
Corticosteroids	Strongly contraindicated — increase mortality (CRASH trial). Must not be used for ICP control in TBI.
Seizure Prophylaxis	7 days of levetiracetam or phenytoin to reduce the risk of early seizures (< 7 days). No proven benefit for late (> 7 days) post-traumatic seizure prevention.
Amantadine	100–200 mg twice daily; used to accelerate recovery of consciousness, typically between weeks 4–16 post-injury.
EMERGENCY Corticosteroids must never be administered for ICP control after TBI — this is a "never event" supported by high-quality randomized trial evidence (CRASH trial) demonstrating increased mortality.	

CHAPTER 2

Acute Ischemic Stroke and Spontaneous Intracerebral Hemorrhage

This chapter is a board-level reference for the ICU management of Acute Ischemic Stroke (AIS) and Spontaneous Intracerebral Hemorrhage (ICH), distilled from current evidence-based standards including AHA/ASA guidelines and pivotal trial data.

I. Acute Ischemic Stroke (AIS) in the ICU

1. Monitoring Protocols (Post-Reperfusion)

Following intravenous thrombolysis (IV rtPA/tenecteplase) or endovascular thrombectomy (EVT), meticulous monitoring is required to detect clinical changes indicating secondary events.

- **Neurologic examination frequency:** every 15 minutes immediately post-procedure, spaced to every 1–2 hours by 8 hours post-procedure.

- **Imaging:** routine repeat non-contrast head CT within 24 hours of reperfusion therapy, or immediately upon neurologic deterioration.

2. Hemorrhagic Transformation (HT) Management

Hemorrhage risk is determined by infarct size and blood–brain barrier permeability.

Table 2.1 — Heidelberg Classification of Hemorrhagic Transformation

Class	Type	Clinical Significance
1a / 1b	Hemorrhagic infarction (HI) of infarcted tissue	Minimal impact (1a: petechiae; 1b: confluent petechiae).
1c (PH1)	Parenchymal Hematoma 1	Hematoma < 30% of infarct volume with minimal mass effect; worsened short-term recovery.
2 (PH2)	Parenchymal Hematoma 2	Hematoma ≥ 30% of infarct volume with mass effect; associated with worse 90-day outcomes.
3	ICH outside infarcted tissue	Variable impact (3a: remote parenchymal hematoma; 3b: intraventricular hemorrhage; 3c: subarachnoid hemorrhage; 3d: subdural hemorrhage).

Table 2.2 — Conceptual Reversal Protocol for rtPA-Related Hemorrhage

Action	Medication / Intervention	Dose / Target
Stop rtPA	Discontinue infusion	Immediate discontinuation (for alteplase).
Inhibit thrombolysis	Tranexamic acid OR aminocaproic acid	Tranexamic acid: 1 g IV infused over 1–20 minutes. Aminocaproic acid: 5 g IV over 1 hour, then 1 g/h if required.
Restore fibrinogen	Cryoprecipitate	10 units over 10–30 minutes; repeat until fibrinogen > 150 mg/dL.
Supply clotting factors	PCC or FFP	PCC: 2000 units IV.
🚨 EMERGENCY Suspected symptomatic hemorrhagic transformation after thrombolysis is a neurologic emergency: stop the rtPA infusion immediately, obtain emergent non-contrast head CT, send fibrinogen/coagulation studies, and begin the reversal protocol above without delay.		

3. Malignant MCA Syndrome (Cerebral Edema)

Malignant edema carries a mortality rate of 80% if untreated.

- **Clinical predictors:** younger age, NIHSS ≥ 20 (dominant hemisphere) or ≥ 15 (non-dominant), nausea/vomiting within 24 hours, SBP > 180 mmHg within 12 hours, and early decrease in alertness.

- **Imaging predictors:** infarct volume > 1/3 of the MCA territory, progressive midline shift, or diffusion-weighted imaging (DWI) lesion volume > 82 mL.

Surgical Intervention (Decompressive Hemicraniectomy)

- **Age ≤ 60 years:** perform within 24–48 hours for infarcts encompassing > 2/3 of the MCA territory with reduced consciousness.
- **Age 60–80 years:** lifesaving but carries a high risk of severe residual disability; requires shared decision-making with the family.
- **Surgical criteria:** bone flap defect must be at least 12 cm × 9 cm and extend to the floor of the middle fossa.

★ HIGH YIELD

The pivotal trials underpinning early hemicraniectomy for malignant MCA infarction (DECIMAL, DESTINY, HAMLET pooled analysis) consistently demonstrate a mortality benefit but at the cost of increased survival with moderate-to-severe disability — informed consent and goals-of-care discussion are essential before proceeding, especially in patients over 60.

II. Ischemic Stroke Blood Pressure (BP) Management

Table 2.3 — BP Targets in Reperfusion Therapy

Clinical Scenario	Systolic BP (SBP) Target	Rationale
Pre-rtPA / EVT	< 185 mmHg	Reduces hemorrhage risk during thrombolysis.
Post-successful recanalization	< 185 mmHg	Intensive lowering to 100–129 mmHg did not improve functional outcomes in the BP-TARGET trial.
No recanalization (permissive hypertension)	Up to 220 mmHg	Preserves perfusion of the ischemic penumbra via autoregulation.
Hemorrhagic transformation	< 140 or < 160 mmHg	Balances hemorrhage expansion risk against maintenance of cerebral perfusion.
○ IMPORTANT NOTE Nicardipine and clevidipine infusions are the preferred titratable agents for BP control in AIS. The source material does not provide a specific titration starting-dose table for these agents in this context; refer to institutional protocols or the current AHA/ASA Guidelines for exact infusion parameters.		

III. Spontaneous Intracerebral Hemorrhage (ICH)

1. The ICH Score (Prognostic Grading)

Table 2.4 — ICH Score Components

Component	Clinical Feature	Points
GCS Score	3–4 (2 pts); 5–12 (1 pt); 13–15 (0 pts)	0–2
Age	≥ 80 years	1
ICH Volume	≥ 30 cm ³	1
IVH	Presence of intraventricular blood	1
Location	Infratentorial origin	1
Total Score	—	0–6

MEMORY TRICK / MNEMONIC

"GAIL" mnemonic for the ICH Score: GCS, Age ≥ 80, IVH present, Location infratentorial — plus ICH Volume ≥ 30 cm³. Higher scores correlate strongly with increased 30-day mortality.

2. Blood Pressure Control (INTERACT-2 / ATACH-2 Principles)

- **Target SBP:** 130–150 mmHg.
- **Timing:** initiate within 2 hours of symptom onset to reduce hematoma expansion.
- **Standard:** avoid peaks and variability in BP; use titratable drips such as nicardipine.

3. Reversal of Anticoagulants

Table 2.5 — Hemostatic Reversal for ICH

Anticoagulant	Reversal Agent	Exact Dosing Protocol
Warfarin	4-Factor PCC + Vitamin K	PCC: INR 1.3–1.9 → 10–20 IU/kg; INR ≥ 2.0 → 25–50 IU/kg. Vitamin K: 10 mg IV (prevents rebound INR elevation).
Dabigatran	Idarucizumab	Specific reversal agent of choice.
Factor Xa Inhibitors (Apixaban/Rivaroxaban)	Andexanet alfa OR 4-Factor PCC	Andexanet alfa: modified recombinant factor Xa decoy. 4-Factor PCC: alternative if andexanet is unavailable.
Antiplatelet agents	Platelet transfusion	Only if urgent neurosurgery is planned; harmful in conservative (non-surgical) management.

PITFALL

Empiric platelet transfusion in antiplatelet-associated ICH without a planned surgical intervention is harmful and should be avoided — this is a commonly tested and commonly violated principle.

IV. Intraventricular Hemorrhage (IVH) and Hydrocephalus

1. Hydrocephalus Management

- **EVD indication:** recommended for ICH with moderate-to-large IVH and impaired consciousness to facilitate CSF drainage and alleviate ICP.
- **Leveling:** level at the tragus; drain at a gradient of 20–25 cm H₂O to avoid premature herniation or rebleeding.

2. CLEAR-III Trial Applications (Intraventricular Thrombolysis)

- **Protocol:** serial administration of rtPA directly into the ventricles via EVD.
- **Outcomes:** improved survival and reduced mortality, but functional recovery at 90 days was neutral in the primary trial analysis.
- **Subgroup benefit:** better functional outcomes noted when initiated within 48 hours and in patients with large IVH (> 20 mL).

CLINICAL PEARL

CLEAR-III demonstrates that intraventricular tPA is a survival-improving, but not necessarily function-improving, therapy in the overall trial population — counsel families accordingly, while noting the more favorable subgroup signal with early treatment of large-volume IVH.

CHAPTER 3

Aneurysmal Subarachnoid Hemorrhage and Acute Neurovascular Emergencies

This chapter compiles evidence-based grading, aneurysm securement protocols, and management of delayed complications in aneurysmal subarachnoid hemorrhage (aSAH), reflecting current AHA/ASA guidance.

I. Diagnostic and Prognostic Grading Scales

Standardized scales are used to quantify injury severity, predict the risk of delayed cerebral ischemia (DCI), and inform family communication.

Table 3.1 — Clinical Severity Grading (Hunt and Hess & WFNS)

Grade	Hunt and Hess Scale (Surgical Risk)	World Federation of Neurosurgical Societies (WFNS)
1	Asymptomatic or mild headache; slight nuchal rigidity.	GCS 15; no motor deficit.
2	Moderate to severe headache; stiff neck; no focal deficit except cranial nerve palsy.	GCS 13–14; no motor deficit.
3	Drowsy or confused; mild focal neurologic deficit.	GCS 13–14; with motor deficit.
4	Stupor; moderate or severe hemiparesis.	GCS 7–12; with or without motor deficit.
5	Deep coma; decerebrate posturing.	GCS 3–6; with or without motor deficit.

Table 3.2 — Radiographic and Outcome Grading

Scale	Feature	Criteria / Scoring
Modified Fisher	Risk of DCI / vasospasm	1: focal/thin SAH, no IVH. 2: focal/thin SAH, with IVH. 3: thick/diffuse SAH, no IVH. 4: thick/diffuse SAH, with IVH.
Ogilvy & Carter	Surgical outcome prediction	1 point each for: age > 50; Hunt & Hess 4–5; Fisher 3–4; aneurysm size > 10 mm; giant posterior aneurysm (≥ 25 mm).

Table 3.3 — Radiographic "Tightness" (Marshall & Rotterdam Scores)

While primarily developed for TBI, these scales define intracranial compliance and mortality risk that are also relevant to catastrophic SAH.

Marshall Score	Radiographic Feature	Rotterdam Component	Feature (Points)
I	No visible pathology.	Cisterns	Normal (0), Compressed (1), Absent (2).
II	Pathology present; midline shift ≤ 5 mm.	Midline Shift	≤ 5 mm (0), > 5 mm (1).
III (Swelling)	Cisterns compressed; shift ≤ 5 mm.	Epidural Mass	Present (0), Absent (1).
IV (Shift)	Midline shift > 5 mm.	Blood (IVH/SAH)	Absent (0), Present (1).
V / VI	Evacuated / non-evacuated mass lesion.	Total Score	Sum of component scores + 1.

II. Acute Management and Aneurysm Securing

1. Pre-Securement Stabilization

- **Blood pressure containment:** the goal is to avoid extremes of BP to reduce rebleeding risk while maintaining cerebral perfusion.
 - **AHA/ASA (2023):** emphasizes MAP ≥ 65 mmHg; use serial neurologic exams to ensure adequate perfusion.
 - **NCS/AHA (prior guidelines):** targeted SBP < 160 mmHg (2012) or SBP < 180 mmHg (ESO 2013) to reduce rebleeding.
- **Antifibrinolytic therapy:** enthusiasm for short-course tranexamic acid (TXA) has waned following the ULTRA trial, which showed no outcome benefit if aneurysm securement occurs within 24 hours.
- **CSF shunting:** acute hydrocephalus should be treated with an EVD. Before securement, keep the drain at a high gradient (20–25 cm H₂O above the tragus) to avoid overdrainage and transmural pressure changes that could provoke rebleeding.

2. Aneurysm Securement Selection (ISAT Insights)

- **Timing:** securement should ideally occur within 24 hours to prevent rerupture (risk: 8%–23%).
- **Clipping vs. coiling:**
 - **Coiling:** generally preferred for posterior circulation aneurysms and equally amenable anterior circulation aneurysms (better 1-year functional outcomes per ISAT).
 - **Clipping:** may offer a long-term durability benefit for patients younger than 40 years.
- **Flow diversion / stents:** used for ruptured wide-neck, fusiform, or blister aneurysms; typically requires delayed antiplatelet initiation.

WARNING

Rebleeding is the single most modifiable determinant of early mortality in aSAH. Delays in securement beyond 24 hours meaningfully increase rerupture risk (8%–23%) — expedite angiography and neurosurgical/endovascular consultation.

III. Complications and ICU Management

1. Delayed Cerebral Ischemia (DCI) and Vasospasm

DCI typically occurs between days 4 and 10 after hemorrhage.

Prophylaxis — Oral Nimodipine

- **Mainstay:** 21-day course.
- **Standard dose:** 60 mg every 4 hours.
- **Adjustment:** if hypotension occurs, use more frequent, lower doses (30 mg every 2 hours).

Monitoring

- **TCD thresholds (mfv):** > 120 cm/s (mild), > 150 cm/s (moderate), > 200 cm/s (severe).
- **Lindegaard ratio (MCAmfv / ICAMfv):** > 3 (vasospasm), > 5 (severe vasospasm).

Active Management — Induced Hypertension

- **First-line treatment** for symptomatic DCI.
- **Targets:** SBP up to 230 mmHg or MAP 130 mmHg.
- **Norepinephrine** is the most frequently utilized agent.

Refractory DCI

- **Intra-arterial (IA) vasodilators:** IA verapamil or nicardipine administered during angiography.
- **Milrinone:** IA or IV (phosphodiesterase-3 inhibitor) as an inodilator; may require vasopressor support for systemic BP maintenance.

MEMORY TRICK / MNEMONIC

Vasospasm timing mnemonic — "4 to 10, watch it grow": DCI risk window is days 4–10 post-hemorrhage, peaking around day 7.

2. Medical Complications Matrix

Table 3.4 — Systemic Medical Complications of aSAH

Complication	Findings & Clinical Pattern	Management Protocol
Neurogenic Myocardium Stunned	Apical hypokinesis; decreased LVEF (21%–30%); T-wave inversions/QT prolongation.	Avoid excessive fluid administration; tailor vasopressor choice (e.g., dobutamine over norepinephrine if cardiac function is failing).
Neurogenic Edema Pulmonary	Rapid-onset interstitial/alveolar fluid post-ictus; increased capillary permeability.	Supplemental O ₂ ; avoid diuresis unless the patient is euvolemic.

Complication	Findings & Clinical Pattern	Management Protocol
Hyponatremia	Na < 135 mEq/L. Differentiate SIADH (euvolemic) from cerebral salt wasting (hypovolemic).	Target euvolemia. Rescue: bolus 3% NaCl for acute severe deficits (e.g., Na 122 mEq/L).
⚠ PITFALL SIADH and cerebral salt wasting (CSW) both cause hyponatremia after aSAH but require opposite fluid management — SIADH is euvolemic/hypervolemic (fluid restriction may be appropriate), whereas CSW is hypovolemic (requires volume and sodium replacement, never restriction). Misdiagnosis can worsen cerebral perfusion.		

CHAPTER 4

Status Epilepticus and Neurotoxicological/Metabolic ICU Emergencies

This chapter synthesizes ILAE operational definitions, tiered pharmacotherapy, and management of metabolic brain failure in the neurocritical care unit.

I. Status Epilepticus: Definitions and Timelines

The 2015 ILAE operational definition establishes two critical time points to emphasize that treatment should be started emergently and not delayed until neuronal injury has commenced.

- **T₁ (time to treat):** the point at which a seizure typically does not cease spontaneously and has the potential to become continuous.
- **T₂ (time of permanent damage):** the point at which seizures may result in long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks.

Table 4.1 — Operational Timelines for Status Epilepticus

Seizure Type	T ₁ (Start Treatment)	T ₂ (Neuronal Damage)
Bilateral Tonic-Clonic (GCSE)	5 minutes	30 minutes
Focal SE (with impaired consciousness)	10 minutes	60 minutes
Absence Status Epilepticus	10–15 minutes	Unknown

Clinical Stages of Progression

Stage	Definition
Stage 1 — Impending	Continuous or intermittent seizures > 5 minutes without full recovery of consciousness.
Stage 2 — Established	10–30 minutes after onset; non-responsive to benzodiazepines.
Stage 3 — Refractory	Seizures persist after two medications, including an adequate benzodiazepine dose.
Stage 4 — Super-Refractory	SE continuing for ≥ 24 hours after initiation of anesthetics.
Prolonged Refractory	Persists ≥ 7 days despite management without anesthetics.
Prolonged Refractory Super-Refractory	Persists ≥ 7 days including ongoing need for anesthetics.
MEMORY TRICK / MNEMONIC GCSE mnemonic — "5 to stop, 30 to harm": treat bilateral tonic-clonic seizures by 5 minutes (T_1); irreversible neuronal injury risk begins by 30 minutes (T_2).	

II. Tiered Status Epilepticus Pharmacotherapy Protocols

Table 4.2 — Tier 1: Emergent Initial Therapy (Benzodiazepines)

Medication	Route & Exact Dosing	Max Limits / Frequency
Lorazepam	IV: 0.1 mg/kg	Max 4 mg per dose; may repeat once.
Midazolam	IM: 10 mg (if > 40 kg)	Single dose; IM route has good absorption.
Midazolam	IV: 0.2 mg/kg	Max 10 mg.
Diazepam	IV: 0.15–0.2 mg/kg	May repeat once.
Diazepam	Rectal: 0.2–0.5 mg/kg	Max 15–20 mg per dose.

CLINICAL PEARL

Underdosing is the primary cause of Stage 1 treatment failure. Appropriate benzodiazepine dosing does not necessarily increase respiratory depression — untreated status epilepticus carries a higher incidence of respiratory failure than adequately treated status epilepticus.

Table 4.3 — Tier 2: Urgent Control (Non-Sedating IV Anti-Seizure Medications)

Medication	Loading Dose (Exact)	Max Infusion Rate	Maintenance Dose
Levetiracetam	60 mg/kg	Max 4500 mg total	1000–6000 mg/day
Fosphenytoin	20 mg PE/kg	150 mg/min	5–7 mg PE/kg/day

Medication	Loading Dose (Exact)	Max Infusion Rate	Maintenance Dose
Valproate Sodium	40 mg/kg	60 mg/kg/min	10–15 mg/kg/day
Lacosamide	8 mg/kg	Max 600 mg total	200–300 mg q12h
Phenobarbital	20 mg/kg	60 mg/min	1–3 mg/kg/day
⚠ WARNING Do not use lacosamide if the PR interval is > 200 ms. Avoid concurrent valproate and carbapenem antibiotics — carbapenems precipitate a dramatic, clinically significant drop in valproate levels.			

Table 4.4 — Tier 3: Refractory SE (Continuous Anesthetic Infusions)

Medication	Loading Dose	Infusion Rate (Maintenance)	Systemic Side Effects / Monitoring
Midazolam	0.2 mg/kg IV	0.1–2.9 mg/kg/h	Hypotension; active metabolites are renally cleared (accumulation in renal failure).
Propofol	1–2 mg/kg IV	20–200 µg/kg/min	PRIS risk: monitor CK, triglycerides, and for metabolic acidosis, especially at rates > 80 µg/kg/min.
Ketamine	1.5 mg/kg q5–10min	1–10 mg/kg/h	Hypertension, tachycardia, hypersalivation.
Pentobarbital	10 mg/kg IV	1–4 mg/kg/h	Hypotension (requires vasopressor support), ileus, immune suppression.
⚠ EMERGENCY Propofol Infusion Syndrome (PRIS) is a life-threatening complication of high-dose or prolonged propofol infusion, characterized by metabolic acidosis, rhabdomyolysis, hyperkalemia, cardiac failure, and hepatomegaly. Monitor creatine kinase, triglycerides, and acid-base status closely, particularly at infusion rates above 80 µg/kg/min.			

Titration targets: maintain electrographic seizure cessation for a minimum of 24–48 hours. Pentobarbital is usually reserved for failure of midazolam or propofol.

Super-Refractory Status Epilepticus — Additional Options

- **Ketogenic diet:** anticonvulsant effect via increased glutamine and GABA; avoid hidden carbohydrate sources.
- **Magnesium:** bolus 4 g, then 2–6 g/h; target serum level 3.5 mmol/L.
- **Immunomodulation:** consider early for suspected NORSE (new-onset refractory status epilepticus) — steroids, IVIg, plasma exchange (PLEX).
- **Neuromodulation:** electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or vagus nerve stimulation (VNS).

III. Metabolic and Toxic Encephalopathies

1. Hepatic and Uremic Encephalopathy

- **Patterns:** often associated with metabolic myoclonus (irregular, diffuse).
- **Management:** ammonia-clearing protocols involve lactulose and rifaximin.

○ IMPORTANT NOTE

Exact dosing schedules for lactulose and rifaximin are referenced in standard ICU care but were not provided as a specific dosing table in the source excerpt.

2. Wernicke Encephalopathy

- **ICU protocol:** high-dose IV thiamine must be administered before any glucose-containing fluids to prevent precipitating acute Wernicke-Korsakoff syndrome.

🚨 EMERGENCY

Never administer dextrose-containing fluids before thiamine in a patient at risk for thiamine deficiency — glucose loading can precipitate or worsen Wernicke encephalopathy by accelerating depletion of thiamine-dependent cofactors.

3. Hyponatremia and Osmotic Demyelination Syndrome (ODS)

- **Acute rescue:** bolus 3% NaCl is indicated for severe symptomatic hyponatremia ($\text{Na} \approx 122 \text{ mmol/L}$).
- **Correction metrics:** slow correction of serum osmolarity is mandatory during rewarming or recovery to prevent central pontine myelinolysis. Intraparenchymal ICP monitors may be used to gauge ICP responses during metabolic shifts.

🚨 PITFALL

Overly rapid correction of chronic hyponatremia is a preventable cause of osmotic demyelination syndrome. General guidance limits correction to no more than 8 mEq/L in any 24-hour period (lower limits in high-risk patients) — always confirm against current institutional protocol.

4. Pyridoxine (Vitamin B₆) Deficiency

- **ICU impact:** found in up to 80% of patients with established status epilepticus.
- **Management:** consider empiric thiamine and pyridoxine infusion in patients refractory to benzodiazepines.

CHAPTER 5

Neuromuscular Respiratory Failure, Acute Spinal Cord Critical Care, and Temperature/Autonomic Emergencies

This chapter focuses on evidence-based stabilization, crisis intervention dosing, and hemodynamic targets for neuromuscular respiratory failure, spinal cord injury, and systemic autonomic/temperature emergencies.

I. Neuromuscular Respiratory Failure

1. Pathophysiology of Respiratory Collapse

Neuromuscular coordination of breathing requires functional bulbar and upper airway muscles (to clear secretions and prevent aspiration) and adequate strength of the diaphragm, intercostal, and accessory muscles (to maintain ventilation).

Respiratory failure in Guillain-Barré syndrome (GBS) and myasthenic crisis manifests primarily as hypoventilation (hypercarbic failure), though hypoxia may occur secondary to aspiration or atelectasis. Both hypercarbia and hypoxia are late manifestations; intervention must be based on bedside mechanics before blood gas deterioration occurs.

2. Bedside Evaluation and the "20/30/40 Rule"

- **Bedside proxy:** neck flexion strength is the most reliable clinical bedside test to approximate diaphragmatic strength.
- **Visual markers:** tachypnea, increased work of breathing, diaphoresis, and paradoxical breathing patterns (thoracoabdominal desynchrony).
- **Single-breath counting:** a count of less than 20 (after a maximal deep breath) indicates respiratory compromise.

Table 5.1 — Reference Metrics for Prophylactic Intubation ("20/30/40 Rule")

Parameter	Threshold for High Risk / Intubation	Rationale
Forced Vital Capacity (FVC)	< 20 mL/kg (or < 1500 mL)	Inability to meet gas exchange requirements.
Maximal Inspiratory Pressure (MIP/NIF)	Weaker than -30 cm H ₂ O (e.g., -20 cm H ₂ O)	Sensitive marker of diaphragmatic weakness.
Maximal Expiratory Pressure (MEP)	< 40 cm H ₂ O	Inadequate cough strength and secretion clearance.

Parameter	Threshold for High Risk / Intubation	Rationale
Dynamic Trend	> 30% reduction within 24 hours	Suggests rapid progression and imminent respiratory failure.
📌 MEMORY TRICK / MNEMONIC "20/30/40 Rule": FVC < 20 mL/kg, MIP weaker than -30 cm H ₂ O, MEP < 40 cm H ₂ O — any one of these merits close monitoring for impending ventilatory failure and consideration of elective intubation.		
★ HIGH YIELD Do not wait for hypoxia or hypercarbia on arterial blood gas to intubate a patient with neuromuscular respiratory failure — by the time gas exchange abnormalities appear, decompensation may be imminent. Trend bedside pulmonary function tests serially		

II. Crisis Therapy Dosing Schedules

Table 5.2 — Induction Immunosuppression Protocols

Therapy	Dosing and Volume	Administration & Monitoring
Intravenous Immunoglobulin (IVIG)	2 g/kg total dose	Dosed by ideal body weight; administered as 0.4 g/kg/day for 5 days. Monitor for: renal failure, thrombosis, aseptic meningitis, and hyponatremia.
Plasma Exchange (PLEX)	5 exchanges total	1 to 1.5 plasma volumes per session, usually every other day. Replacement fluid: 5% albumin or crystalloid-colloid. Monitor for: low fibrinogen (replace with cryoprecipitate), hypocalcemia, and hypotension.

Myasthenic Crisis — High-Stakes Drug Contraindications

Clinicians must strictly avoid or use extreme caution with the following agents in patients with myasthenia gravis:

Agent / Class	Risk in Myasthenia Gravis
Fluoroquinolones (e.g., ciprofloxacin)	Boxed warning for worsening MG.
Telithromycin	Contraindicated; associated with fatal worsening of MG.
Magnesium (IV)	Potentially dangerous; use only if absolutely necessary.
Beta-blockers	May worsen weakness; use cautiously.
Aminoglycosides (e.g., gentamicin)	May worsen myasthenic weakness.

Agent / Class	Risk in Myasthenia Gravis
Corticosteroids	Use with care — up to 26% of patients have transient worsening within the first 2 weeks of initiation.
EMERGENCY IV magnesium and telithromycin are especially dangerous in myasthenic crisis and can precipitate acute respiratory failure by impairing neuromuscular transmission — verify the myasthenia gravis diagnosis and screen the medication list before administering any new agent in these patients.	

III. Acute Spinal Cord Injury (SCI)

1. Neurogenic vs. Spinal Shock — Diagnostic Matrix

Table 5.3 — Neurogenic Shock vs. Spinal Shock

Entity	Classification	Characteristic Features
Neurogenic Shock	Hemodynamic / distributive shock	Results from loss of sympathetic tone (injury at T5 level or above). Characterized by hypotension and bradycardia.
Spinal Shock	Neurologic syndrome	Hyperacute loss of spinal cord function below the level of injury. Characterized by flaccid paralysis and areflexia.
PITFALL Neurogenic shock and spinal shock are distinct entities that are frequently confused: neurogenic shock is a hemodynamic diagnosis (hypotension/bradycardia from sympathetic disruption), while spinal shock is a neurologic diagnosis (transient areflexia and flaccidity). A patient can have either, both, or neither.		

2. Hemodynamic Optimization and Perfusion

- **MAP targets:** maintain 85–90 mmHg for 7 days using volume resuscitation followed by vasopressors.
- **Vasopressor selection:** norepinephrine is preferred due to its balanced alpha- and beta-adrenergic effects, treating both vasoplegia and bradycardia.

3. Autonomic Dysreflexia and Secondary Deterioration

- **Paroxysmal Sympathetic Hyperactivity (PSH):** recurrent surges of tachycardia, hypertension, tachypnea, and fever triggered by minor stimuli.
- **Management:** avoidance of known triggers; treatment with beta-blockers, bromocriptine, clonidine, gabapentin, or opioids.

IV. Temperature Management and Heat Syndromes

1. Targeted Temperature Management (TTM)

- **Target:** fever avoidance is the minimum standard of care (each degree above 37°C worsens neurologic outcomes); therapeutic hypothermia (32°C to 36°C) is a reasonable strategy for select patients.
- **Shivering suppression:** crucial for achieving temperature goals. Use short-acting sedation (fentanyl, propofol, dexmedetomidine); benzodiazepines are generally avoided as they delay awakening. Neuromuscular blockade may be required for refractory shivering.

2. Heat and Autonomic Syndromes (Toxidromes)

- **Neuroleptic malignant syndrome (NMS), serotonin syndrome, and malignant hyperthermia:** these are "must-not-miss" neurocritical toxidromes involving autonomic instability.

○ IMPORTANT NOTE

The source material identifies NMS, serotonin syndrome, and malignant hyperthermia as critical emergencies but does not explicitly tabulate mg/kg dosing for their specific antidotes (e.g., dantrolene for malignant hyperthermia/NMS, cyproheptadine for serotonin syndrome). Confirm exact dosing against current institutional protocols or a pharmacology reference before administration.

Table 5.4 — Differential Diagnosis of Hyperthermic Autonomic Toxidromes

Syndrome	Typical Trigger	Classic Features
Neuroleptic Malignant Syndrome (NMS)	Dopamine antagonists (antipsychotics) or abrupt dopaminergic withdrawal	Lead-pipe rigidity, hyperthermia, autonomic instability, altered mental status; onset over days.
Serotonin Syndrome	Serotonergic agents (SSRIs, MAOIs, tramadol, linezolid, etc.)	Clonus, hyperreflexia, tremor, agitation, hyperthermia; onset over hours.
Malignant Hyperthermia	Volatile anesthetics or succinylcholine in genetically susceptible patients	Rapid-onset severe hyperthermia, muscle rigidity, hypercarbia, rhabdomyolysis; onset intraoperative/minutes.

CHAPTER 6

Systemic Complications, Brain Death Determination, and Neuro-Prognostication

This chapter emphasizes the "death of therapeutic nihilism," the rigorous medical prerequisites for determination of death by neurological criteria, and the ethical imperative of shared decision-making in neurocritical care.

I. Cardiopulmonary and Systemic Interfaces

1. Ventilator Management and Cerebral Physiology

In neurocritical patients, mechanical ventilation must balance lung-protective strategies with the maintenance of cerebral homeostasis.

- **PEEP and ICP:** positive end-expiratory pressure (PEEP) can potentially increase ICP by impeding venous return from the head. However, in patients with decreased lung compliance (e.g., ARDS), PEEP is often necessary to maintain oxygenation.

Targeted Ventilation

- **PaO₂:** target 75–100 mmHg. Avoid both hypoxia and severe hyperoxia (> 200 mmHg), as the latter induces oxidative stress.
- **PaCO₂:** target normocapnia (35–45 mmHg).
 - **Hypocapnia:** causes cerebral vasoconstriction and ischemia.
 - **Hypercapnia:** causes cerebral vasodilation and can exacerbate ICP.
- **Airway protection:** tracheal intubation for depressed consciousness (GCS < 8) alone is no longer recommended; decisions should be based on objective signs of airway obstruction or inability to manage secretions.

★ HIGH YIELD

The dogma "GCS < 8, intubate" has been revised — current evidence favors an individualized decision based on airway protective reflexes and secretion management rather than an isolated GCS cutoff.

2. Paroxysmal Sympathetic Hyperactivity (PSH) — Pharmacological Summary

PSH is a hyperadrenergic syndrome common after severe TBI, typically emerging as sedation is weaned (approximately 1 week post-injury).

Table 6.1 — Pharmacological Management of PSH

Medication Class	Example Agent(s)	Clinical Application
Beta-Blockers	Propranolol	Blunts tachycardia and hypertension.
Alpha-2 Agonists	Clonidine	Centrally acting agent to reduce sympathetic surge.
GABA-ergics	Gabapentin	Used for preventive and abortive symptom control.
Dopamine Agonists	Bromocriptine	Specifically targets diencephalic centers implicated in PSH.
Opioids	Fentanyl / Morphine	Used to manage paroxysmal surges triggered by noxious or non-noxious stimuli.

II. Determination of Death by Neurological Criteria

Table 6.2 — Medical and Legal Prerequisites for Brain Death Evaluation

Prerequisite	Technical Requirement / Parameter
Etiology	Must have a clear, irreversible, catastrophic proximate cause demonstrated on CT/MRI.
Confounder Exclusion	Rule out severe metabolic, endocrine, or acid-base derangements.
Hypothermia	Core temperature must be $\geq 36^{\circ}\text{C}$ (96.8°F), or $\geq 36.5^{\circ}\text{C}$ (97.7°F) per some protocols.
Hypotension	Maintain SBP ≥ 100 mmHg (vasopressors may be used).
Drug Clearance	Absence of sedatives or neuromuscular blockers — must be within 5 half-lives of the last dose.
Neuromuscular Blockade	Must demonstrate 4 of 4 twitches on Train-of-Four (TOF) monitoring before proceeding.
EMERGENCY Determination of death by neurological criteria is a rigorous, high-stakes diagnosis with significant legal and ethical weight. Every prerequisite above must be confirmed and documented before proceeding to clinical examination and apnea testing.	

III. Clinical Examination and Apnea Testing Protocol

1. Clinical Examination of Brainstem Reflexes

The formal examination requires the absence of all brainstem reflexes and zero motor response to noxious stimuli (excluding spinally mediated reflexes).

Table 6.3 — Brainstem Reflex Examination

Reflex	Expected Finding (Consistent with Brain Death)
Pupillary	No response to bright light; automated pupillometry may be used for precision.
Corneal	No blink response to tactile stimulation.
Oculovestibular	No eye movement following ice-water irrigation of the ear canal.
Gag / Cough	No response to posterior pharynx stimulation or deep tracheal suctioning.

2. The Apnea Test Protocol

The apnea test is designed to determine whether PaCO₂ can rise high enough to stimulate the medullary respiratory center in the absence of spontaneous breaths.

Table 6.4 — Apnea Testing Checklist and Diagnostic Thresholds

Step / Parameter	Clinical Target / Metric
Pre-oxygenation	100% O ₂ for 10 minutes to target PaO ₂ ≥ 200 mmHg.
Baseline PaCO ₂	Normal baseline (35–45 mmHg).
Termination Criteria	Abort the test if: SBP falls < 90 mmHg, SpO ₂ desaturates significantly, or a cardiac arrhythmia occurs.
Confirmation (pH)	pH < 7.30 (per World Brain Death Project 2020 standards).
Confirmation (CO ₂)	PaCO ₂ ≥ 60 mmHg OR a rise of 20 mmHg from baseline.
Requirement	Zero respiratory effort observed throughout the rise in CO ₂ .
 WARNING The apnea test carries real physiological risk (hypoxemia, arrhythmia, hemodynamic instability) and must be performed with continuous monitoring and a pre-defined abort protocol. If the test cannot be safely completed, proceed to ancillary testing rather than repeating an unsafe test.	

3. Ancillary Testing Mandates

Ancillary tests are not required when the clinical examination and apnea test can be completed. They are mandated only when:

- Confounding factors cannot be adequately cleared.
- The apnea test cannot be performed or is medically unsafe (e.g., severe hypoxemia).
- **Acceptable modalities:** CT angiography (CTA), nuclear medicine cerebral perfusion study (gold standard), or conventional cerebral angiography.

IV. Neuro-Prognostication Ethics

1. Avoiding Early Nihilism and Premature Withdrawal of Life-Sustaining Therapy (WLST)

Prognostic pessimism is the primary driver of premature WLST. Current evidence emphasizes a "wait-and-see" approach for at least 72 hours before firm prognostic statements are made.

Table 6.5 — Recovery Timelines That Argue Against Early Nihilism

Clinical Scenario	Observation
Cardiac Arrest	Awakening can be delayed up to 2 weeks in the setting of sedation or targeted temperature management.
Severe TBI	15% of patients with favorable outcomes at 6 months did not follow commands until after 2 weeks post-injury.
ICH	40% of patients with initial "poor" 30-day outcomes recover to functional independence by 1 year.
CLINICAL PEARL A minimum observation period of 72 hours — and often substantially longer, particularly after cardiac arrest, severe TBI, or ICH — is essential before rendering a definitive poor-prognosis statement. Early neurologic examination findings systematically underestimate the potential for meaningful recovery.	

2. Shared Decision-Making and the Disability Paradox

- **The Disability Paradox:** patients often report a higher quality of life with their "new normal" than clinicians or surrogates predict based on bedside examination alone.
- **Prognostic communication:** surrogates prefer precise numeric estimates (e.g., "5 out of 100 people like this survive") over vague qualitative terms like "poor" or "guarded."
- **Decision aids:** tools such as icon arrays are recommended to help surrogates visualize probabilities and mitigate the "self-fulfilling prophecy" effect of clinical severity scores.

★ HIGH YIELD

The self-fulfilling prophecy of prognostication: pessimistic prognostic scores can prompt early WLST, which in turn "confirms" the poor prognosis in outcome studies — this circularity is a recognized bias when interpreting severity-of-illness scores as predictors of outcome after WLST decisions.

APPENDIX

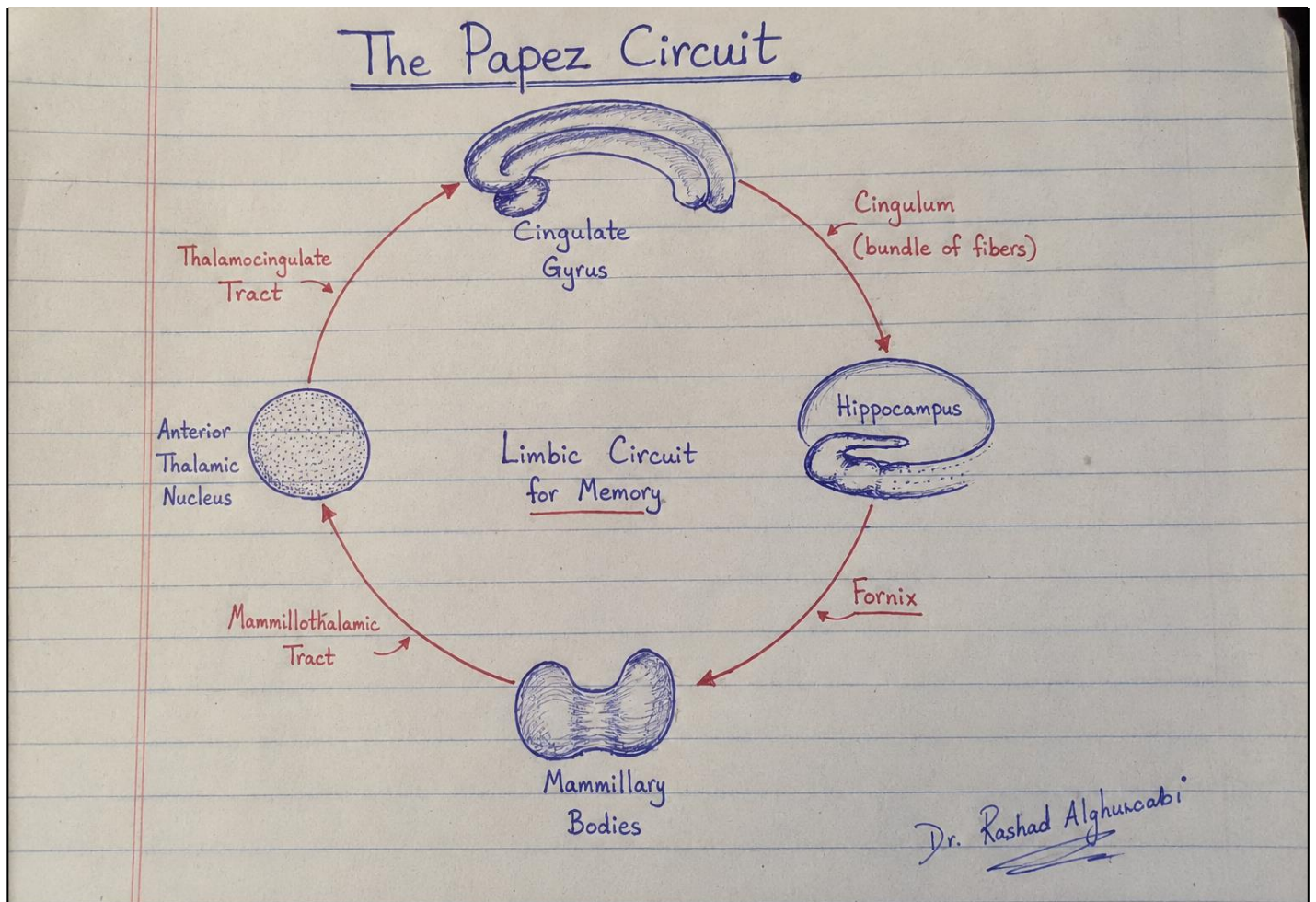
Abbreviations

Abbreviation	Definition
AIS	Acute Ischemic Stroke
aSAH	Aneurysmal Subarachnoid Hemorrhage
BTF	Brain Trauma Foundation
CBF	Cerebral Blood Flow
CPP	Cerebral Perfusion Pressure
CSF	Cerebrospinal Fluid

Abbreviation	Definition
CSW	Cerebral Salt Wasting
DAI	Diffuse Axonal Injury
DCI	Delayed Cerebral Ischemia
EVD	External Ventricular Drain
EVT	Endovascular Thrombectomy
FVC	Forced Vital Capacity
GBS	Guillain-Barré Syndrome
GCS	Glasgow Coma Scale
GCSE	Generalized Convulsive Status Epilepticus
HT	Hemorrhagic Transformation
ICH	Intracerebral Hemorrhage
ICP	Intracranial Pressure
ILAE	International League Against Epilepsy
IVH	Intraventricular Hemorrhage
IVIG	Intravenous Immunoglobulin
MAP	Mean Arterial Pressure
MCA	Middle Cerebral Artery
MEP	Maximal Expiratory Pressure
MIP/NIF	Maximal Inspiratory Pressure / Negative Inspiratory Force
NMS	Neuroleptic Malignant Syndrome
NORSE	New-Onset Refractory Status Epilepticus
ODS	Osmotic Demyelination Syndrome
PbtO ₂	Brain Tissue Oxygen Tension
PCC	Prothrombin Complex Concentrate
PEEP	Positive End-Expiratory Pressure
PLEX	Plasma Exchange
PRIS	Propofol Infusion Syndrome
PRx	Pressure Reactivity Index
PSH	Paroxysmal Sympathetic Hyperactivity
SBP	Systolic Blood Pressure

Abbreviation	Definition
SCI	Spinal Cord Injury
SDH	Subdural Hematoma
SE	Status Epilepticus
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion
SjO ₂	Jugular Venous Oxygen Saturation
TBI	Traumatic Brain Injury
TCD	Transcranial Doppler
TOF	Train-of-Four
TTM	Targeted Temperature Management
TXA	Tranexamic Acid
WFNS	World Federation of Neurosurgical Societies
WLST	Withdrawal of Life-Sustaining Therapy

DEMENTIA



PART 1

The Molecular Framework, Fluid Biomarkers, Neuroimaging, and Pathology of Dementia

I. The ATN Multi-Biomarker Framework

The **ATN classification system** is a biological framework for the diagnosis of Alzheimer disease (AD), originally established in 2016, that defines biomarker-based criteria independent of clinical findings. This framework was **updated in 2024** to incorporate additional dimensions: inflammation (I), synucleinopathy (S), and vascular damage (V), forming the extended **AT(N)IVS** schema. Core categories classify biomarkers into those that define the disease itself (A and T) and those that are nonspecific or reflect copathology (N, I, V, and S).

Table 1.1 — Revised Staging and Core Biomarker Categories

Category	Process	CSF Analytes	Plasma Analytes	Imaging
A	Amyloid- β ($A\beta$)	$A\beta$ 42, $A\beta$ 42/ $A\beta$ 40 ratio	$A\beta$ 42, $A\beta$ 42/ $A\beta$ 40 ratio	Amyloid-PET (Florbetapir, Florbetaben, Flutemetamol)
T ₁	Tau proteinopathy (phosphorylated/secreted)	p-tau217, p-tau181, p-tau231	p-tau217, p-tau181, p-tau231	N/A
T ₂	Tau proteinopathy (aggregated)	p-tau205, MTBR-tau243	N/A	Tau-PET (Flortaucipir)
N	Neurodegeneration	Neurofilament light (NfL), t-tau	NfL	Structural MRI (atrophy), FD (hypometabolism)
I	Inflammation	GFAP, YKL-40	GFAP	N/A
V	Vascular injury	N/A	N/A	MRI (infarcts, WMH, PVS), (microbleeds)
S	α -Synuclein	α -synuclein SAA (seed amplification assay)	N/A	N/A

Diagnostic Sensitivity, Specificity, and Fluid Biomarker Utility

- **$A\beta$ 42/40 Ratio:** Patients with AD have lower CSF $A\beta$ 42 levels due to sequestration within plaques. The $A\beta$ 42/40 ratio has excellent diagnostic value in CSF (~50% difference between AD and controls) but only a ~20% difference in plasma, necessitating high-precision mass spectrometry for plasma measurement.

- **Phosphorylated Tau (p-tau217):** Measured by mass spectrometry in plasma, this is the most effective biomarker for AD progression, showing accuracy equivalent to FDA-approved CSF biomarkers in predicting amyloid PET status.
- **Neurofilament Light (NfL):** A marker of neuroaxonal loss; sensitive to neurodegeneration but nonspecific for a particular diagnosis — elevated in AD, FTD, stroke, and traumatic brain injury.
- **Glial Fibrillary Acidic Protein (GFAP):** A marker of astrocytic activation; plasma GFAP distinguishes healthy individuals from those with AD pathology and predicts future conversion from MCI to AD.

Table 1.2 — Verified Fluid Biomarker Cut-offs (Representative Values)

Biomarker	Specimen	Normal Range	AD-Supportive Range
Aβ42	CSF	> 834 pg/mL	< 834 pg/mL
p-tau181	CSF	≤ 21.6 pg/mL	> 21.6 pg/mL
p-tau217	Plasma	High accuracy	Highly predictive of PET amyloid status
Aβ42/40 ratio	Plasma	Higher	Depressed (low)
Amyloid-Tau Index (ATI)	CSF	High	Low (< 0.8)

CLINICAL PEARL

Plasma p-tau217 is rapidly becoming the preferred first-line blood test for AD pathology screening because its accuracy for predicting amyloid-PET positivity rivals CSF testing — without the need for lumbar puncture

II. Molecular & Structural Neuroimaging

Table 1.3 — Structural MRI Atrophy Patterns by Disease

Diagnosis	Precise Pattern of Regional Atrophy
Typical AD	Mesial temporal (hippocampus, entorhinal cortex), lateral temporal, and parietal lobes; global atrophy in advanced stages.
Posterior Cortical Atrophy (PCA)	Marked posterior atrophy: occipital lobe, visual association areas, posterior parietal, and mesial parietal.
Logopenic PPA (lvPPA)	Asymmetric (usually left) temporoparietal region and superior temporal gyrus.
Behavioral variant FTD (bvFTD)	Frontal and temporal lobes, insula, anterior cingulate, and orbitofrontal cortex; asymmetric in TDP-43 cases.
Semantic Dementia	Significant focal atrophy in ventrolateral anterior temporal lobe (temporal pole); markedly worse on the left.
Nonfluent/agrammatic PPA (nfvPPA)	Left posterior frontal region, anterior insula, and left pars opercularis.

Diagnosis	Precise Pattern of Regional Atrophy
Lewy Body Disease (DLB/PDD)	Cortical atrophy (insula, cingulate) with relative sparing of the hippocampus.
Progressive Supranuclear Palsy (PSP)	Midbrain atrophy ("Hummingbird sign") out of proportion to the pons; subthalamic nucleus and substantia nigra.
Multiple System Atrophy (MSA)	Cerebellum, pons, and brainstem; "Hot Cross Bun" sign in the pons.
CADASIL	Confluent T2 white-matter hyperintensities involving the external capsule and anterior temporal poles.

Table 1.4 — FDG-PET Hypometabolism Distributions

Disease	Hypometabolism Distribution	Pathognomonic / Supportive Sign
Alzheimer disease	Bitemporal and biparietal cortices; posterior cingulate	Classic temporoparietal pattern
DLB	Occipital cortex; relative sparing of the posterior cingulate	Cingulate island sign
PCA	Occipital and parietal lobes; relative frontal hypermetabolism	Cingulate island sign (even without DLB)
bvFTD	Prominent frontal and anterior temporal lobes	Frontal-predominant
lvPPA	Left temporal and parietal areas	Temporoparietal (language network)
svPPA	Asymmetric anterior temporal lobe (usually left)	Ventrolateral anterior temporal focus
nfvPPA	Left inferior frontal and peri-insular regions	Broca area involvement
PSP	Prefrontal cortex, caudate, and subthalamic nucleus	Subcortical / midbrain focus

Table 1.5 — Molecular Imaging Ligands

Tracer Type	Specific Tracers	Indications / Key Findings
Amyloid-PET	Florbetapir (¹⁸ F), Florbetaben (¹⁸ F), Flutemetamol (¹⁸ F), PiB (¹¹ C)	Eligibility for anti-amyloid therapy; widespread cortical uptake in AD
Tau-PET	Flortaucipir (AV-1451), PI-2620, RO948	Staging disease severity (Braak staging); signal in mesial/lateral temporal and parietal lobes
Dopamine transporter (DAT)	¹²³ I-FP-CIT SPECT (DaTscan), ¹⁸ F-DOPA	Indicative biomarker for LBD; decreased striatal uptake (putamen)
α-Synuclein	ACI-12589 (experimental)	Uptake in cerebellar white matter in MSA; distinguishes MSA from DLB/PDD

Tracer Type	Specific Tracers	Indications / Key Findings
Noradrenergic	¹²³ I-MIBG (cardiac)	Low cardiac uptake indicative of LBD/PDD (autonomic denervation)

III. Neuropathological Hallmarks

Pathological Staging Systems

- **Braak Staging (Tau):** Begins in the transentorhinal cortices (Stage I–II), spreads to the anterior hippocampus (Stage III–IV), and finally involves the associative and unimodal neocortex (Stage V–VI).
- **Thal Phases (Amyloid):** Begins in the neocortex, spreads to the hippocampus, then basal ganglia, then brainstem, and finally the cerebellum.
- **LATE Staging (TDP-43):** Stage 1 (amygdala) → Stage 2 (hippocampus) → Stage 3 (middle frontal gyrus).

MEMORY TIP / MNEMONIC

"BATH" — **B**raak = tau; **A**myloid follows **T**hal phases; **T**DP-43 follows **L**ATE staging; **H**ippocampus is a common early waypoint for both Thal and LATE staging, but NOT for Braak (which starts in transentorhinal cortex).

Table 1.6 — Microscopic Features of Key Inclusions

Hallmark	Feature	Microscopic Detail
Amyloid plaques	Diffuse	Early stage; non-fibrillar Aβ deposition
Amyloid plaques	Neuritic	Highly aggregated Aβ core surrounded by tau-positive dystrophic neurites and activated glia
Tau inclusions	Neurofibrillary tangles (NFTs)	Hyperphosphorylated tau in paired helical filaments; intraneuronal
Tau inclusions	Pick bodies	Round, perinuclear 3R tau inclusions; hallmark of Pick disease
Tau inclusions	Tufted astrocytes	Hallmark of PSP (4R tau)
Tau inclusions	Astrocytic plaques	Hallmark of CBD (4R tau)
α-Synuclein	Lewy bodies	Brainstem type: eosinophilic core with pale halo. Cortical type: less distinct, requires immunohistochemistry
α-Synuclein	Lewy neurites	Threadlike α-synuclein aggregates in neuronal processes
α-Synuclein	Glial cytoplasmic inclusions (GCIs)	Inclusions in oligodendrocytes; hallmark of MSA
TDP-43	LATE-NC	Aberrantly localized and phosphorylated TDP-43 in the limbic system; Type A-like pattern

TDP-43 Histopathologic Subtypes in FTLD-TDP

Type	Microscopic Pattern	Genetic Association
Type A	Neuronal cytoplasmic inclusions (NCIs) chiefly in cortical layer II; short, thick dystrophic neurites	GRN mutations; some C9orf72
Type B	Diffuse granular NCIs throughout all neocortical layers and hippocampal dentate lamina	C9orf72; MND/ALS
Type C	Long, dystrophic neurites in superficial cortical layers	Typical of Semantic Dementia (usually sporadic)
Type D	Numerous neuronal intranuclear inclusions (NIIs) and short dystrophic neurites	VCP mutations

Isoform Specificity in Tauopathies

Tau Isoform	Diseases
3R tau	Pick disease (intraneuronal Pick bodies)
4R tau	PSP (tufted astrocytes), CBD (astrocytic plaques), argyrophilic grain disease (spindle-shaped grains), globular glial tauopathy
3R + 4R tau	Alzheimer disease, chronic traumatic encephalopathy (CTE), primary age-related tauopathy (PART)
★ HIGH YIELD Tau isoform (3R vs. 4R vs. mixed) is one of the highest-yield discriminators between tauopathies on exams — always link the isoform to its signature histologic inclusion	

PART 2

Genetic Architecture, Clinical Phenotypes, and Advanced Therapeutics in Alzheimer Disease

I. Clinical Phenotypes and Atypical AD Variants

Alzheimer disease (AD) is a multidimensional illness that often transcends the classic amnesic profile. While memory impairment is the most salient feature in typical AD, atypical variants exhibit unique functional neuroanatomy and management requirements.

Table 2.1 — Clinical Characteristics of AD Phenotypes

Phenotype	Core Clinical Features	Primary Functional Neuroanatomy
Typical amnesic AD	Gradual onset of short-term memory loss; "short-term/long-term paradox" (retained remote memories)	Mesial temporal lobes (hippocampus, entorhinal cortex), precuneus, and parietal lobes
Posterior Cortical Atrophy (PCA)	Higher-order visual dysfunction (alexia, simultanagnosia, optic ataxia); relative sparing of memory early on	Occipital lobe, visual association areas, posterior parietal/temporal regions
Logopenic variant PPA (lvPPA)	Word retrieval failures in spontaneous speech/naming; impaired repetition of sentences	Superior temporal gyrus and temporoparietal junction of the language-dominant hemisphere
Dysexecutive AD	Primary executive dysfunction; profound trouble with planning, organization, and multitasking	Heteromodal association cortex, particularly parietal-dominant with frontal involvement
Behavioral variant AD (bvAD)	Personality shifts, social inappropriateness, blunted affect, and loss of motivation; mimics bvFTD	Anterior temporal lobes and medial frontal regions
Corticobasal Syndrome (CBS)	Asymmetric rigidity, limb apraxia, dystonia, and alien limb phenomenon	Asymmetric atrophy of primary motor/sensory cortices, midbrain, and basal ganglia
 WARNING CBS is a clinical syndrome, not a single pathology — while it can result from underlying AD, it is more frequently caused by corticobasal degeneration (4R tauopathy) or other tauopathies. Pathological confirmation is required for certainty.		

II. Genetic Architecture: Monogenic vs. Risk Modifiers

The genetic liability for AD is estimated at **70%** based on twin studies. Genetic architecture is split between rare, deterministic mutations causing **early-onset AD (EOAD)** and common risk modifiers for **late-onset AD (LOAD)**.

Table 2.2 — Monogenic Early-Onset AD (Deterministic)

Gene	Chromosome	Molecular Pathophysiology	Inheritance
APP	21	Overproduction of A β or decreased solubility; triggered by Trisomy 21 triplication	Autosomal dominant
PSEN1	14	Most common cause of monogenic AD; alters γ -secretase to increase A β 42	Autosomal dominant
PSEN2	1	Similar to PSEN1; results in increased A β peptide formation	Autosomal dominant

LOAD Risk Modifier: APOE Polymorphisms

The **APOE ε4 allele** is the strongest common genetic risk factor for LOAD.

Allele / Genotype	Effect on AD Risk
APOE ε2	Protective allele; associated with decreased lifetime risk of AD
APOE ε3	Neutral / most common allele
APOE ε4 (heterozygous, 1 copy)	~3-fold increased risk compared to the general population
APOE ε4 (homozygous, 2 copies)	~15-fold increased risk compared to the general population
🔍 MEMORY TIP / MNEMONIC "2 vs. 4": ε2 = protects (think "2 good"); ε4 = "4 times the trouble" — each copy compounds risk roughly geometrically (3× → 15×, not 6×).	

III. Symptomatic Therapeutics and Dosing

Symptomatic therapies do not alter the underlying pathology but provide a delay in decline typically ranging from **9 to 12 months**.

Table 2.3 — Pharmacologic Dosing for Symptomatic AD

Drug	Initial Dose	Titration Speed	Target Maintenance	Max Dose
Donepezil (oral)	5 mg/d	After 4–6 weeks	10 mg/d	23 mg/d (moderate/severe)
Rivastigmine (patch)	4.6 mg/24h	Every 4 weeks	9.5 mg/24h	13.3 mg/24h
Rivastigmine (oral)	1.5 mg BID	Every 2–4 weeks	3–6 mg BID	12 mg/d
Galantamine (ER)	8 mg/d	Every 4 weeks	16 mg/d	24 mg/d
Memantine (IR)	5 mg/d	+5 mg/d weekly	10 mg BID	20 mg/d
Memantine (ER)	7 mg/d	+7 mg/d weekly	28 mg/d	28 mg/d
📌 IMPORTANT NOTE The first four agents are cholinesterase inhibitors (ChEIs); memantine is an NMDA-receptor antagonist. Combination ChEI + memantine therapy is standard in moderate-to-severe AD.				

IV. Disease-Modifying Therapies (DMT): Monoclonal Antibodies

Anti-amyloid monoclonal antibodies clear cortical plaques and show **25% to 35% slowing** of clinical progression over 18 months.

Protocol: Lecanemab (Leqembi) and Donanemab (Kisunla)

- **Mandatory Patient Selection:** Must have early AD (MCI due to AD, or mild AD dementia).
- **Pathology Verification:** Mandatory confirmation of amyloid positivity via amyloid-PET or CSF (A β 42/40 ratio or ATI).
- **APOE Genotyping:** Required to stratify ARIA risk; ϵ 4 homozygotes have the highest risk.
- **Lecanemab dosing:** 10 mg/kg IV infusion every 2 weeks.
- **Donanemab dosing:** IV infusion every 4 weeks (monthly). Efficacy is highest in low-to-medium tau-burden cohorts.

V. ARIA Safety and Management

Amyloid-Related Imaging Abnormalities (ARIA) are the primary safety concern for monoclonal antibodies, involving fluid leakage or hemorrhage.

Table 2.4 — ARIA Radiological Grading and Monitoring

Feature	ARIA-E (Edema / Effusion)	ARIA-H (Hemorrhage)
MRI signature	T2/FLAIR hyperintensity; parenchymal edema or sulcal effusion	T2 GRE or SWI hypointensity; microhemorrhages (≤ 10 mm) or siderosis
Exclusion criteria	Pre-existing vasogenic edema	>4 microhemorrhages, any macrohemorrhage (>10 mm), or superficial siderosis
Surveillance MRI	Before infusions: 5th, 7th, 14th, and 26th	Same as ARIA-E protocol

ARIA Management Algorithm

- **Asymptomatic / Mild:** Typically resolves in 4 months; treatment may continue or be briefly held depending on lesion size.
- **Symptomatic / Moderate–Severe:** Immediately suspend infusions. Radiological "moderate" is defined as parenchymal edema (e.g., ~ 6 cm in diameter).
- **Medical intervention for severe edema:** High-dose corticosteroids — IV methylprednisolone 1000 mg for 5 days, followed by a prolonged oral prednisone taper.
- **Permanent discontinuation:** Required for any macrohemorrhage (>10 mm), severe symptomatic ARIA, or recurrent ARIA-E.

 **EMERGENCY / BLACK BOX WARNING**

ARIA can be clinically silent. Surveillance MRI at defined infusion intervals is mandatory for all patients on anti-amyloid monoclonal antibody therapy — do not rely on symptoms alone.

PART 3

Frontotemporal Lobar Degeneration (FTLD), Behavioral and Language Syndromes, and Motor Neuron Disease Associations

I. Behavioral Variant Frontotemporal Dementia (bvFTD)

Behavioral variant FTD is the most common of the FTD core syndromes. It is characterized by progressive changes in personality and interpersonal conduct, often emerging between ages **40 and 65**.

Table 3.1 — Diagnostic Criteria Checklist for Possible / Probable bvFTD

Possible bvFTD requires ≥ 3 of the following 6 criteria:

Criterion	Specific Manifestations
Disinhibition	Socially inappropriate behavior, loss of manners/decorum, or impulsive/rash actions
Apathy / inertia	Loss of interest in hobbies or lack of drive to initiate activities
Loss of empathy	Diminished response to others' needs/feelings; loss of personal warmth
Compulsive / ritualistic behavior	Simple repetitive movements, complex ritualistic behaviors, or stereotyped speech
Hyperorality	Altered food preferences (e.g., sweets), binge eating, increased smoking/alcohol, or pica
Executive deficits	Impaired planning/flexibility with relative sparing of episodic memory and visuospatial skills
Structural imaging	Probable bvFTD requires frontal and/or anterior temporal atrophy on MRI/CT, or hypometabolism on FDG-PET

Neuroanatomical Hallmarks

- **Fronto-insular atrophy:** Typically involves the anterior cingulate, ventral anterior insula, and orbitofrontal cortex.
- **Asymmetry:** Right-sided atrophy correlates more strongly with severity of disinhibition.
- **Salience network:** The clinical features reflect breakdown of the salience network, which integrates external/internal stimuli to deploy appropriate behaviors.

II. Primary Progressive Aphasia (PPA)

PPA is a language-based dementia in which language erosion is the primary feature for at least the first **two years** of the disease.

Table 3.2 — Clinical, Linguistic, and Anatomical Differentiation of PPAs

Variant	Core Linguistic Differentiators	Neuroanatomical Epicenter	Likely Molecular Pathology
Nonfluent/agrammatic (nfvPPA)	Agrammatism (omitting suffixes/function words); effortful/halting speech; apraxia of speech; impaired complex syntax comprehension	Left posterior fronto-insular region; left pars opercularis	Tauopathy (FTLD-Tau, e.g., Pick disease)
Semantic (svPPA)	Loss of word meaning; impaired object naming; surface dyslexia (cannot read irregular words such as "yacht" or "colonel"); spared repetition	Asymmetric anterior temporal lobe (usually left); temporal pole	TDP-43 Type C (>80% of cases)
Logopenic (lvPPA)	Impaired single-word repetition; phonemic paraphasias; word-finding pauses; spared word meaning	Left temporoparietal junction; superior temporal gyrus	Alzheimer disease (~70% of cases)
MEMORY TIP / MNEMONIC "SNAG the PPA": Semantic = anterior Naming loss (TDP-43 Type C); Agrammatic = Anterior/frontal (tauopathy); Logopenic = often underlying Grey-matter AD pathology at the temporoparietal junction.			

III. FTLD Tauopathies vs. TDP-43 Proteinopathies

FTLD is classified by the primary molecular defect identified at autopsy.

Table 3.3 — Molecular Correlation of FTLD Syndromes

Pathology Class	Key Subtypes & Isoforms	Clinical Associations	Genetic Drivers
FTLD-Tau	3R tau: Pick bodies	Pick disease; bvFTD, nfvPPA	MAPT
FTLD-Tau	4R tau: tufted astrocytes (PSP); astrocytic plaques (CBD)	PSP, CBD; atypical parkinsonism syndromes	MAPT
FTLD-TDP-43	Type A: NCIs in layer II; short neurites	bvFTD; nfvPPA	GRN, C9orf72
FTLD-TDP-43	Type B: diffuse granular NCIs	FTD-MND/ALS; bvFTD	C9orf72

Pathology Class	Key Subtypes & Isoforms	Clinical Associations	Genetic Drivers
FTLD-TDP-43	Type C: long dystrophic neurites	Semantic variant PPA	Sporadic (usually)
FTLD-FUS	NCIs in middle/deep layers	Very young-onset bvFTD; pica; caudate atrophy	Sporadic

IV. FTD–Motor Neuron Disease (MND) Complex and Related Syndromes

- **FTD-ALS Overlap:** Approximately 15% of FTD patients have ALS, and 30% of ALS patients have FTD.
- **Genetic driver:** The GGGGCC hexanucleotide repeat expansion in C9orf72 is the chief cause of inherited FTD-ALS and is associated with more psychotic features (delusions/hallucinations).
- **Progressive Supranuclear Palsy (PSP):** A 4R-tau phenotype featuring globose tangles and tufted astrocytes. Hallmark imaging is the "Hummingbird sign" (midbrain atrophy out of proportion to the pons).
- **Corticobasal Degeneration (CBD):** A 4R-tau phenotype featuring astrocytic plaques and ballooned neurons. Features asymmetric rigidity, limb apraxia, and alien limb phenomenon.

V. Treatment Compass: Behavioral Strategies

WARNING

There are no FDA-approved disease-modifying therapies for FTD; management is entirely symptomatic.

Table 3.4 — Symptomatic Pharmacotherapy in FTD

Medication Class	Agent & Target Symptoms	Representative Dose
SSRIs	Sertraline, paroxetine, fluoxetine, citalopram — for disinhibition, irritability, and compulsions	Sertraline: 25–200 mg/d; Citalopram: 20–30 mg/d
Other serotonergic	Trazodone — for irritability, agitation, and disordered eating	50–200 mg/d
Antipsychotics	Quetiapine, olanzapine, aripiprazole, risperidone — off-label for severe agitation/psychosis	Quetiapine: 25–200 mg/d; Risperidone: 0.5–2 mg/d
Mood stabilizers	Carbamazepine, lamotrigine — for inappropriate sexual or physically violent behavior	Lamotrigine: 50–200 mg/d

Explicit Warnings

- **Cholinesterase Inhibitors:** Generally not recommended; they lack efficacy in FTD and may actually worsen behavioral symptoms.

- **Traditional Neuroleptics:** Patients with FTLD are hypersensitive to extrapyramidal side effects; classic agents (e.g., haloperidol) should be avoided due to the risk of life-threatening reactions.
- **NMDA Antagonists:** Memantine is well-tolerated but has shown no benefit in FTD clinical trials.

EMERGENCY / BLACK BOX WARNING

Avoid conventional (typical) antipsychotics in all FTLD-spectrum patients — the risk of severe extrapyramidal and life-threatening reactions parallels the neuroleptic sensitivity seen in Lewy body disease.

PART 4

Dementia with Lewy Bodies (DLB), Parkinson Disease Dementia (PDD), and Vascular Cognitive Impairment and Dementia (VCID)

I. Lewy Body Dementia (LBD): DLB vs. PDD

Lewy body dementia (LBD) is an umbrella term encompassing two clinical diagnoses — dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) — which share the common pathologic substrate of α -synuclein aggregation into Lewy bodies and Lewy neurites.

The "One-Year Rule" and Chronology

The distinction between DLB and PDD is based entirely on the temporal relationship between the onset of cognitive and motor symptoms.

- **DLB:** Dementia manifests before, or within one year of, the onset of spontaneous parkinsonism.
- **PDD:** Dementia develops in the context of established Parkinson disease (PD), specifically manifesting more than 12 months after the onset of motor signs.

MEMORY TIP / MNEMONIC

"1-Year Rule": cognition before or within 1 year of parkinsonism = DLB. Cognition arriving after >1 year of established PD = PDD. Same underlying pathology, different clinical sequence.

Table 4.1 — Core Clinical Features of DLB

Feature	Clinical Description
Fluctuating cognition	Spontaneous waxing and waning of attention, alertness, and arousal; may present as "staring spells" or periods of illogical thinking
Visual hallucinations	Recurrent, well-formed, colorful, and detailed (e.g., people or animals); often non-threatening and non-distressing

Feature	Clinical Description
REM sleep behavior disorder (RBD)	Lack of normal muscle atonia during REM sleep, leading to acting out dreams (vocalizations, violent movements); may precede cognitive decline by decades
Spontaneous parkinsonism	Bradykinesia, rigidity, and postural instability; typically bilateral at onset with prominent axial involvement; resting tremor less common than in idiopathic PD

II. Diagnostic Biomarkers for LBD

Table 4.2 — Indicative and Emerging Biomarkers

Biomarker Type	Assessment Method	Diagnostic Finding in LBD
Dopaminergic system	¹²³ I-FP-CIT SPECT (DaTscan)	Reduced dopamine transporter (DAT) uptake in the basal ganglia (posterior putamen)
Noradrenergic system	¹²³ I-MIBG myocardial scintigraphy	Low cardiac uptake reflecting postganglionic sympathetic denervation
Sleep physiology	Polysomnography (PSG)	Confirmation of REM sleep without atonia
α-Synuclein pathology	CSF seed amplification assay (SAA / RT-QuIC)	Detection of misfolded α-synuclein seeds; sensitivity 92–95%
Peripheral tissue	Skin biopsy	Detection of phosphorylated α-synuclein in dermal nerve fibers; specificity near 100%

III. Extreme Neuroleptic Sensitivity and Therapeutics

EMERGENCY / BLACK BOX WARNING

Patients with DLB exhibit life-threatening neuroleptic sensitivity in 30% to 50% of cases. Reactions include sudden onset of acute confusion, impaired alertness, and severe exacerbation of parkinsonian features (rigidity and immobility), which can lead to death within days. Avoid typical/conventional antipsychotics (e.g., haloperidol) entirely.

Table 4.3 — Specialized Pharmacotherapy and Dosing Guidelines

Target Symptom	Medication	Recommended Dosing / Notes
Psychosis / agitation	Quetiapine	25–200 mg/d; often first-line but literature support is weak

Target Symptom	Medication	Recommended Dosing / Notes
Psychosis / agitation	Pimavanserin	34 mg/d; approved for PD psychosis; inverse serotonin 2A agonist
Psychosis / agitation	Clozapine	Effective for PD psychosis but requires strict hematopoietic monitoring
Psychosis / agitation	Brexpiprazole	0.5–3 mg/d; recently approved for agitation in AD
Parkinsonism	Carbidopa/levodopa	Initiated only if motor symptoms interfere with function; monitor for drug-induced psychosis
Cognitive symptoms	ChEIs (donepezil/rivastigmine)	Standard AD dosing; potentially more effective in LBD due to severe cholinergic loss
RBD (sleep)	Melatonin	3–9 mg nightly; maximum doses of 15–20 mg
RBD (sleep)	Clonazepam	0.25–1 mg nightly; second-line due to risk of falls and confusion
Autonomic (overactive bladder)	Mirabegron	β 3-agonist preferred over antimuscarinics to avoid cognitive worsening

IV. Vascular Cognitive Impairment and Dementia (VCID)

VCID is inclusive of all forms of vascular-related cognitive decline, including mixed pathologies.

VCID Subtypes

- **Multi-infarct dementia:** Cognitive decline resulting from multiple large or territorial cortical infarcts.
- **Strategic single-infarct dementia:** Cognitive impairment following a single event in critical regions — left frontotemporal lobe, left thalamus, or right parietal lobe.
- **Subcortical Ischemic Vascular Dementia (SIVD):** Also known as Binswanger disease; characterized by small vessel disease, chronic hypoperfusion, and slowly progressive decline in executive function and processing speed.

Table 4.4 — MRI Markers of Small Vessel Ischemic Disease

MRI Marker	Radiologic Description / Thresholds
White matter hyperintensities (WMH)	T2/FLAIR signal; periventricular or deep subcortical; Fazekas grade 3 is severe
Lacunar infarcts	Small subcortical T1 hypointensities; seen in up to 23% of older individuals
Cerebral microbleeds	Small foci of hypointensity on SWI or T2 GRE
Perivascular spaces (PVS)	Enlarged spaces within the centrum semiovale (>20 per hemisphere is severe in CAA)
Cortical superficial siderosis	Linear hemosiderin deposits in cortical sulci; indicative of CAA

V. Hereditary Vascular Dementias

Hereditary arteriopathies should be suspected when small vessel disease burden is disproportionate to vascular risk factors.

Table 4.5 — Genetic, Clinical, and Pathological Features

Disorder	Genetic Locus / Mutation	Pathological / Imaging Hallmarks
CADASIL	NOTCH3 (Chr 19), cysteine-altering variants	Confluent T2 WMH involving external capsule and anterior temporal poles; recurrent subcortical strokes and migraines with aura
CARASIL	HTRA1 gene (autosomal recessive)	Subcortical infarctions and leukoencephalopathy
Dutch-type CAA	APP point variations	Hereditary cerebral hemorrhage with amyloidosis; young-onset stroke
CARTS	GRN (rs5848) polymorphism	Risk factor for hippocampal sclerosis independent of TDP-43

VCID Management Strategies

- Secondary stroke prevention is mandatory for post-stroke cases.
- For SIVD, memantine and donepezil have demonstrated off-label efficacy in improving cognitive function.
- Aggressive blood pressure control (systolic <120 mm Hg per SPRINT-MIND) reduces risk for MCI and dementia.

PART 5

Rapidly Progressive Dementias (RPD), Prion Diseases, and Autoimmune / Paraneoplastic Cognitive Syndromes

I. Prion Diseases: Clinical and Pathological Phenotypes

Prion diseases are unique neurodegenerative disorders characterized by the accumulation of the abnormal, self-propagating **PrP protein**. They often manifest as rapidly progressive dementia (RPD) accompanied by multi-system neurologic dysfunction.

Table 5.1 — Clinical and Pathological Profiles of Prion Diseases

Disease Entity	Primary Clinical Features	Pathological Hallmarks
Sporadic CJD (sCJD)	Rapid cognitive decline, myoclonus, ataxia, extrapyramidal/pyramidal signs, and visual disturbances	Spongiotic change (microvacuolization) in gray matter; predominantly affects the neocortex
Familial CJD (fCJD)	Similar to sCJD but caused by PRNP gene mutations; variable age of onset based on specific mutation	PrP protein aggregates; distribution of atrophy is often discontinuous
Fatal Familial Insomnia (FFI)	Early progressive insomnia and profound dysautonomia	Spongiotic changes and atrophy localized primarily to the thalamus
Gerstmann-Sträussler-Scheinker (GSS)	Chronic ataxia and rapidly progressive cognitive decline	Multicentric plaques containing abnormal PrP protein, primarily in the cerebellar cortex

II. CJD Diagnostic Criteria & Biomarkers

The diagnosis of CJD has shifted from clinical observation to high-precision fluid and imaging biomarkers. While total tau and 14-3-3 are sensitive markers of neuronal injury, they are nonspecific and may be elevated in other conditions such as stroke or encephalitis.

Table 5.2 — Diagnostic Utility of CSF Biomarkers for CJD

Biomarker	Diagnostic Value	CJD-Supportive Finding
RT-QuIC	Gold standard; amplifies aggregated prion protein	Positive (high sensitivity and specificity)
14-3-3 protein	Empirical marker of rapid neuronal injury	High (interpreted with caution — nonspecific)
Total tau	Marker of massive axonal/neuronal damage	Very high (exceeds typical AD levels)
Amyloid / p-tau	Used to rule out AD mimics	Typically within normal limits

Neuroimaging & EEG Signs

- **MRI (DWI/FLAIR):** Crucial for detecting cortical ribboning (hyperintensity in the cerebral cortex) and the "hockey-stick sign" (hyperintensity in the pulvinar and dorsomedial thalamus).
- **EEG:** Historically used to detect periodic sharp wave complexes (PSWCs), though it may lack the sensitivity of RT-QuIC and MRI.

★ HIGH YIELD

RT-QuIC on CSF is now the single highest-yield test for confirming CJD — it has largely superseded 14-3-3 and total tau due to markedly superior specificity.

III. Autoimmune & Paraneoplastic Dementias / Encephalopathies

Autoimmune encephalopathies are critical RPD mimics because they are potentially **reversible**. While some present with subacute cognitive decline, others can mimic focal neurodegenerative syndromes like primary progressive aphasia (PPA).

Table 5.3 — Profiles of Inflammatory and Autoimmune Mimics

Syndrome	Key Cognitive / Clinical Phenotype	Associated Features
Anti-NMDAR encephalitis	Can present as a mimic of progressive aphasia	Often associated with ovarian teratomas; psychiatric features and dyskinesias
Anti-AMPA encephalitis	Another inflammatory mimic of progressive aphasia syndromes	Limbic encephalitis phenotype
CAA-related inflammation (CAA-ri)	Subacute cognitive decline, headaches, focal deficits, or seizures	Associated with APOE $\epsilon 4/\epsilon 4$ homozygosity; reflects an autoimmune response to vascular amyloid
○ IMPORTANT NOTE Detailed antibody-specific features (e.g., faciobrachial dystonic seizures in LGI1 encephalitis, or Anti-Hu/Ma2 malignancy associations) were not present in the source material for this handbook and should be verified against a dedicated autoimmune neurology reference before clinical use		
.		

IV. Immunomodulatory Induction & Maintenance Dosing

Treatable inflammatory cognitive syndromes, such as CAA-related inflammation, require aggressive immunosuppression. Clinical and MRI follow-up is necessary to monitor for the resolution of vasogenic edema.

Table 5.4 — Dosing Protocols for Inflammatory Cognitive Syndromes

Therapy Tier	Medication	Dosing Protocol
First-line induction	Methylprednisolone	1000 mg IV daily for 5 days
First-line maintenance	Prednisone	Following IV pulse, initiate a prolonged oral taper (e.g., 1-month duration)
Seizure rescue	Levetiracetam	750 mg twice daily (standard starting dose for CAA-ri–associated seizures)
Refractory cases	Second-line agents (Rituximab, Cyclophosphamide, IVIG)	Regimens are being standardized to minimize inpatient stay; specific dosing requires independent verification

Radiological Monitoring (Safety MRI)

For patients receiving immunomodulatory therapies (or those undergoing ARIA monitoring during anti-amyloid therapy), MRI must be scheduled at specific intervals:

- Weeks 9–10 (before 5th infusion)
- Weeks 13–14 (before 7th infusion)
- Weeks 27–28 (before 14th infusion)
- At 1 year

PART 6

Reversible Cognitive Syndromes, Traumatic Encephalopathies, and Management of Behavioral and Psychological Symptoms of Dementia (BPSD)

I. Reversible Cognitive Impairment: Clinical Matrix

Neurologists must systematically exclude reversible causes of cognitive decline, as these conditions are common in older adults and may significantly contribute to or simulate a neurodegenerative process.

Normal Pressure Hydrocephalus (NPH)

- **Clinical presentation:** NPH is a disorder of CSF dynamics that may occur in association with, or mimic, Alzheimer disease. It typically manifests with a classic triad of gait dysfunction, urinary urgency/incontinence, and cognitive decline.
- **Neuroimaging:** Structural MRI is the preferred modality to exclude NPH, evaluating for disorders of CSF dynamics and hydrocephalus ex vacuo (longitudinal increases in temporal horn size). Evan's index and callosal angle are standard adjunct clinical metrics.
- **Management:** High-volume lumbar puncture (tap test) and shunting criteria are used to determine whether cognitive and motor symptoms are secondary to potentially reversible CSF dynamics.

MEMORY TIP / MNEMONIC

NPH triad — "Wet, Wobbly, and Wacky": urinary incontinence (wet), gait apraxia (wobbly), and cognitive decline (wacky).

Endocrine, Metabolic, and Nutritional Disorders

- **Wernicke-Korsakoff Syndrome:** Nutritional deficits are potentially modifiable risk factors for dementia.

- **Vitamin B₁₂ Deficiency:** Serum B₁₂ is mandatory in the baseline workup for all patients with emergent cognitive decline, as deficiency can produce cognitive symptoms that may precede hematological changes.
- **Hypothyroidism:** Thyroid function tests (TSH) are essential; severe hypothyroidism is a common and reversible contributor to cognitive impairment in the elderly.

Table 6.1 — Mandatory Screening for Reversible Contributors

Assessment	Condition Target	Rationale in Dementia Workup
Brain MRI	NPH, strokes, tumors	Exclude occult lesions or disorders of CSF dynamics
Vitamin B ₁₂	Nutritional deficiency	Cognitive symptoms may precede anemia
TSH / free T4	Hypothyroidism	Relatively common reversible cause of cognitive symptoms
Depression screen	Pseudodementia	Depression can mimic or exacerbate cognitive decline
 WARNING A structural MRI, vitamin B₁₂ level, and thyroid function panel should be obtained in essentially every patient presenting with new cognitive decline before a neurodegenerative diagnosis is finalized		
.		

II. Chronic Traumatic Encephalopathy (CTE)

CTE is a primary age-related tauopathy associated with repetitive mild traumatic brain injury (TBI).

- **Pathophysiology:** Characterized by intracellular aggregation of hyperphosphorylated three-repeat (3R) and four-repeat (4R) tau isoforms.
- **Anatomic localization:** Tau pathology shows a unique perivascular distribution at the depths of the cortical sulci, primarily in the frontal cortex.
- **Phases of decline:** TBI is a modifiable risk factor that can lead to progressive neurobehavioral dysregulation and eventually symptomatic cognitive decline.

III. BPSD Treatment Manual

Behavioral and psychological symptoms of dementia (BPSD) are core features of all dementias and often have a greater impact on clinical outcomes than cognitive loss itself.

Table 6.2 — BPSD Pharmacotherapy: Agitation and Psychosis

Medication	Target Symptom	Starting Dose	Titration / Maintenance	Max Dose
Brexpiprazole	AD agitation	0.5 mg/d	Gradual titration	3 mg/d
Risperidone	Agitation, psychosis	0.5 mg/d	Weekly/monthly reassessment	2 mg/d
Olanzapine	Psychosis, anxiety	2.5 mg/d	"Start low, go slow"	10 mg/d
Aripiprazole	Agitation, psychosis	2 mg/d	Monitor for akathisia	15 mg/d
Quetiapine	Psychosis, sleep	25 mg/d	Used for nighttime disturbances	200 mg/d
Pimavanserin	PD psychosis	34 mg/d	Approved specifically for PD	34 mg/d
⚠ EMERGENCY / BLACK BOX WARNING FDA Black Box Warning: Atypical antipsychotics are associated with a greater than 1.5-fold increased risk of death and cerebrovascular disease in elderly patients with dementia. Mortality risk is expressed early in treatment and increases with higher doses. Use only when non-pharmacologic strategies have failed and risks/benefits are discussed with the patient/family				

Table 6.3 — Management of Depression, Apathy, and Sleep

Medication	Indication	Starting Dose	Clinical Nuance / Safety
Citalopram	Depression, agitation	20 mg/d	Max 30 mg/d due to QTc prolongation risk
Escitalopram	Depression, anxiety	5 mg/d	Max 20 mg/d; monitor for QTc prolongation
Sertraline	Depression, irritability	25 mg/d	Preferred over paroxetine (which is anticholinergic)
Methylphenidate	Apathy	5 mg/d	Can improve global functioning but may reduce appetite
Trazodone	Insomnia, agitation	50 mg/d	Target 50–200 mg/d; helpful for nocturnal agitation
Suvorexant	AD insomnia	Standard dosing	Only FDA-approved agent for AD sleep disturbance
Melatonin	RBD	3 mg	Maintenance 3–9 mg; max cap 15–20 mg
Clonazepam	RBD	0.25 mg	Target 0.25–1 mg; monitor for falls/confusion

Neurochemical & Safety Considerations

- **Serotonergic effects:** SSRIs may actually worsen apathy while treating mood symptoms.
- **Cholinesterase inhibitors:** Before using psychotropic agents in AD, ChEIs (donepezil/rivastigmine) should be optimized, as they reduce overall BPSD burden.
- **Lewy body sensitivity:** Patients with DLB/PDD are extremely sensitive to traditional neuroleptics (e.g., haloperidol), which can cause life-threatening reactions and should be avoided.

CLINICAL PEARL

Always optimize a cholinesterase inhibitor before reaching for an antipsychotic in BPSD management — it addresses the underlying cholinergic deficit driving many behavioral symptoms and carries a far more favorable safety profile.

APPENDIX

Master Differential Diagnosis, Diagnostic Criteria Reference, and Abbreviations

A. Master Differential Diagnosis of Dementia Syndromes

The following table consolidates the major dementia syndromes covered in this handbook by their dominant clinical presentation, to aid rapid bedside differential diagnosis.

Dominant Presentation	Leading Diagnoses	Distinguishing Clue
Amnestic (episodic memory)	Typical AD; hippocampal sclerosis; LATE	Retained remote memory vs. recent memory loss; mesial temporal atrophy on MRI
Visuospatial / visual	Posterior Cortical Atrophy; DLB	Alexia, simultanagnosia, optic ataxia (PCA) vs. fluctuating cognition and hallucinations (DLB)
Language	nvPPA, svPPA, lvPPA	Agrammatism (nvPPA) vs. semantic loss (svPPA) vs. repetition deficit (lvPPA)
Behavioral / personality	bvFTD; bvAD	Disinhibition, apathy, hyperorality with frontal atrophy vs. AD biomarker positivity
Motor + cognitive (parkinsonism)	DLB, PDD, PSP, CBD, MSA	Timing of dementia vs. parkinsonism onset (1-year rule); hummingbird sign (PSP); hot cross bun sign (MSA)
Rapidly progressive (weeks–months)	CJD/prion disease; autoimmune encephalitis; CAA-ri	Myoclonus and cortical ribboning (CJD) vs. potentially reversible inflammatory markers
Stepwise / vascular risk factors	VCID (multi-infarct, SIVD/Binswanger, strategic infarct)	WMH burden, infarcts on MRI; executive/processing-speed predominant in SIVD

Dominant Presentation	Leading Diagnoses	Distinguishing Clue
Gait + incontinence + cognitive decline	Normal Pressure Hydrocephalus (NPH)	Classic triad; ventriculomegaly out of proportion to atrophy; improvement with CSF drainage
Reversible / metabolic	B ₁₂ deficiency, hypothyroidism, pseudodementia (depression)	Correctable laboratory abnormality or mood disorder history

B. Diagnostic Criteria Quick Reference

NIA-AA Research Framework for Alzheimer Disease (Biological Definition)

AD is defined biologically by the presence of amyloid pathology (A+) together with tau pathology (T+), independent of clinical symptoms. This allows classification along the AD continuum:

- **A+T−**: Alzheimer pathologic change
- **A+T+**: Alzheimer disease (biologically defined)
- **A−T+**: Non-AD pathologic change (e.g., PART, LATE)
- **A−T−**: Normal AD biomarkers

○ IMPORTANT NOTE

This ATN-based biological staging framework (NIA-AA, updated 2018 and expanded 2024) is included here as an essential contextual classification for interpreting the biomarker tables in Part 1; it underpins modern clinical trial eligibility and diagnostic practice for anti-amyloid therapy.

C. Key Abbreviations

Abbreviation	Meaning
AD	Alzheimer disease
ARIA	Amyloid-related imaging abnormalities
ATN	Amyloid / Tau / Neurodegeneration biomarker framework
bvFTD	Behavioral variant frontotemporal dementia
CAA(-ri)	Cerebral amyloid angiopathy (-related inflammation)
CBD / CBS	Corticobasal degeneration / corticobasal syndrome
ChEI	Cholinesterase inhibitor
CJD	Creutzfeldt-Jakob disease
CTE	Chronic traumatic encephalopathy
DLB	Dementia with Lewy bodies
FTLD	Frontotemporal lobar degeneration

Abbreviation	Meaning
GFAP	Glial fibrillary acidic protein
LATE	Limbic-predominant age-related TDP-43 encephalopathy
lvPPA / nfvPPA / svPPA	Logopenic / nonfluent-agrammatic / semantic variant primary progressive aphasia
NfL	Neurofilament light chain
NPH	Normal pressure hydrocephalus
PART	Primary age-related tauopathy
PCA	Posterior cortical atrophy
PDD	Parkinson disease dementia
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
RBD	REM sleep behavior disorder
RPD	Rapidly progressive dementia
SIVD	Subcortical ischemic vascular dementia
VCID	Vascular cognitive impairment and dementia
WMH	White matter hyperintensities

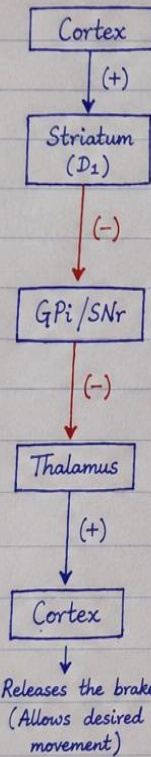
MOVEMENT

DISORDERS

Basal Ganglia Pathways

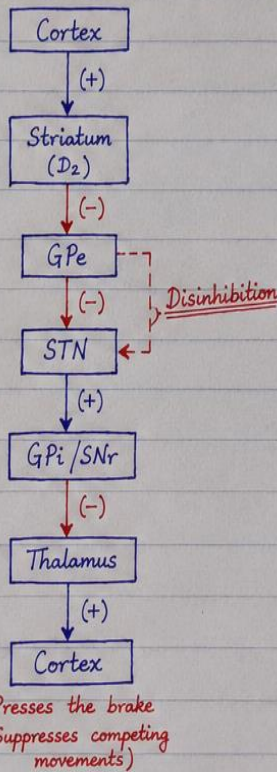
(+) = excitatory
(glutamatergic)
(-) = inhibitory
(GABAergic)

DIRECT PATHWAY (Facilitates movement)



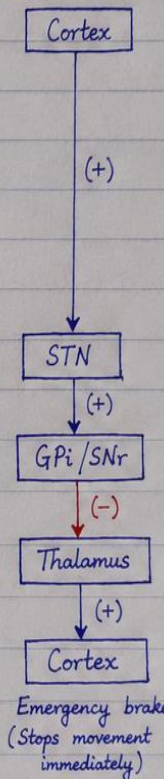
Net effect:
↑ Movement

INDIRECT PATHWAY (Suppresses movement)



Net effect:
↓ Movement

HYPERDIRECT PATHWAY (Fast brake - Stops movement rapidly)



Net effect:
Immediate suppression of movement

Key Players

- Cortex → Striatum: Glutamate (+)
- Striatum → Targets: GABA (-)
- STN → GPi/SNr: Glutamate (+)
- GPi/SNr → Thalamus: GABA (-)
- Thalamus → Cortex: Glutamate (+)

DOPAMINE (from SNc)

- D₁ receptors: Excite direct pathway → ↑ Movement
- D₂ receptors: Inhibit indirect pathway → ↑ Movement

Overall effect of dopamine:
Facilitates movement

SUMMARY			
Pathway	Effect on GPi/SNr	Effect on Thalamus	Result
Direct	↓ (Inhibits)	↑ (Disinhibits)	↑ Movement
Indirect	↑ (Excites)	↓ (Inhibits)	↓ Movement
Hyperdirect	↑ (Excites strongly)	↓ (Inhibits rapidly)	Stops movement immediately

Think of:

- GPi/SNr = Brake pedal
- Thalamus = Accelerator
- Direct = Release brake
- Indirect = Press brake
- Hyperdirect = Emergency brake

Dr. Rashad Alghurabi

CHAPTER 1

Movement Disorders: Phenomenology, Functional Anatomy, and Clinical Approach

I. Phenomenological Classification

Movement disorders are clinically divided into hypokinetic (parkinsonism) and hyperkinetic/kinetic syndromes based on the character of the involuntary motor activity.

A. Hypokinetic / Bradykinetic Disorders (Parkinsonism)

Term	Definition
Parkinsonism	A syndrome of bradykinesia combined with at least one additional cardinal motor feature: resting tremor or rigidity.
Bradykinesia	Slowness of movement associated with a progressive reduction in amplitude or speed during repetitive actions.
Rigidity	Increased resistance during passive movement of a joint, independent of the direction or velocity of the movement.
Postural Instability	Inability to execute postural adjustments in response to changing support, often leading to falls.
Freezing of Gait (FOG)	An episodic gait pattern characterized by an inability to step, occurring during gait initiation, turning, or environmental transitions.

B. Kinetic / Hyperkinetic Disorders

Tremor: an involuntary, rhythmic, oscillatory movement of a body part produced by alternating contractions of antagonist muscle groups.

Tremor Subtypes

Subtype	Description
Rest tremor	Occurs when the limb is fully supported and at rest (e.g., 4–6 Hz in Parkinson's disease).
Postural tremor	Elicited by sustaining a posture against gravity.
Kinetic tremor	Occurs during any voluntary movement.
Intention tremor	A type of kinetic tremor in which amplitude increases as the limb approaches a target.
Task-specific tremor	Triggered only by a highly specific activity (e.g., primary writing tremor).

Other Hyperkinetic Phenomena

Phenomenon	Description
Chorea	Involuntary movements that are random, purposeless, unpredictable, brief, abrupt, and free-flowing from one body part to another.
Ballism	A severe, high-amplitude form of chorea involving proximal joints, appearing as violent flinging movements of the limbs.
Dystonia	Sustained or intermittent muscle contractions causing abnormal, often repetitive, twisting movements or fixed postures.
Myoclonus	Simple, sudden muscle jerks; typically non-rhythmic and lacking the flowing quality of chorea.
Polyminimyoclonus	Low-amplitude, frequent, jerky postural movements, often seen in neurodegenerative conditions such as MSA.
Tics	Quick, recurrent, non-rhythmic movements (motor tics) or sounds (phonic tics) that are typically suppressible and preceded by a premonitory urge.
Ataxia	Incoordination of voluntary movement, typically causing wide-based gait, imbalance, and dysmetria (inaccurate distance modulation).

MEMORY TIP

"TRAP" for parkinsonism cardinal features: Tremor (rest), Rigidity, Akinesia/bradykinesia, Postural instability.

II. Functional Anatomy & Pathophysiology

The basal ganglia (BG) are a collection of subcortical nuclei responsible for the modulation of volitional movement through complex circuitry.

A. Core Circuitry & Pathways

- **Striatum (Caudate and Putamen):** the primary input station of the basal ganglia, receiving glutamatergic projections from the cortex and dopaminergic input from the substantia nigra pars compacta (SNc).

Pathway	Receptor	Mechanism	Net Effect
Direct pathway (facilitatory)	D1	Striatal projections inhibit GPi/SNr, which disinhibits the thalamus.	Increased thalamocortical drive → facilitates movement
Indirect pathway (inhibitory)	D2	Striatal projections inhibit GPe, which disinhibits the STN; STN excites GPi/SNr.	Increased thalamic inhibition →

Pathway	Receptor	Mechanism	Net Effect
			reduced motor output

Adenosine A2A receptors are located in the indirect pathway; A2A antagonists (e.g., istradefylline) are thought to reduce excessive indirect-pathway inhibition to improve motor control in Parkinson's disease.

B. Neurochemical Imbalances

Hypokinetic State (Parkinsonism)

The prime contributor is degeneration of dopaminergic cells in the SNc, leading to loss of striatal dopaminergic neurotransmission and over-activity of the indirect pathway.

Hyperkinetic State (Chorea / Dyskinesia)

Locus	Mechanism
Presynaptic	Excess dopamine packaging into vesicles (mediated by VMAT2) or increased dopamine release.
Postsynaptic	Over-sensitivity or over-stimulation of postsynaptic D2 receptors; conversely, blocking these receptors (neuroleptics) can induce parkinsonism or tardive dyskinesia.

📌 IMPORTANT NOTE

Paroxysmal movement disorders often result from ion channelopathies (K^+ , Na^+ , Ca^{2+} channels), synaptopathies (vesicle fusion proteins such as PRRT2), or transportopathies (e.g., GLUT1 deficiency).

III. Red Flags & Examination Pearls

A. Parkinsonism Examination & Red Flags

- **Retropulsion Pull-Test:** a standardized method to assess postural stability. The examiner stands behind the patient and pulls briskly on the shoulders; taking more than two steps backward, or requiring capture, is abnormal.

Red Flags Suggesting Atypical Parkinsonism

Red Flag	Clinical Significance
Rapid gait progression requiring a wheelchair within 5 years	Suggests atypical parkinsonism rather than idiopathic PD

Red Flag	Clinical Significance
Early bulbar dysfunction (dysarthria, dysphagia) or inspiratory stridor	Suggests MSA or PSP
Severe autonomic failure (orthostatic hypotension, urinary incontinence) within 5 years	Suggests MSA
Recurrent unprovoked falls within 3 years of onset	Highly suggestive of PSP
Symmetric onset of symptoms or lack of progression over 5 years	Atypical for idiopathic PD

CLINICAL PEARL

Hummingbird Sign: disproportionate midbrain atrophy on midsagittal MRI — a key imaging biomarker for PSP.

B. Hyperkinetic Examination Pearls

Ocular Motor Signs (PSP)

Slowed vertical downward saccades are more specific than restricted upgaze. Look for the "round-the-house" sign (curved downward saccades) and square-wave jerks.

Dystonia Clues

Sign	Description
Sensory trick (geste antagoniste)	A specific maneuver (e.g., touching the chin) that temporarily improves dystonic posture.
Task specificity	Dystonia emerging only during a specific action, such as writer's cramp or mirror dystonia (affected limb mimics posture when the contralateral side performs a task).

Chorea / Huntington Disease Pearls

Sign	Description
Motor impersistence	Inability to maintain a sustained contraction; tested via "milkmaid's grip" or tongue protrusion ("trombone tongue").
Forehead chorea	Involuntary movements of the frontalis/eyebrows; useful for distinguishing Huntington disease from tardive dyskinesia.

C. Functional Movement Disorder (FMD) "Rule-In" Maneuvers

Sign	Description
Distractibility	Involuntary movements (e.g., tremor) diminish or stop when the patient performs a complex task with another limb.
Entrainment	A functional tremor shifts its frequency to match the rhythm of a voluntary repetitive movement performed by a different body part.
Hoover sign	For functional leg weakness: weakness of hip extension returns to normal strength when the patient is asked to flex the contralateral hip against resistance (demonstrates normal automatic movement).
Overflow	In functional dystonia, posturing may involve the entire limb or spread inconsistently, unlike the patterned movements of organic dystonia.

★ HIGH YIELD

FMD diagnosis should be a "rule-in" diagnosis based on positive signs (distractibility, entrainment, Hoover sign), not a diagnosis of exclusion.

CHAPTER 2

Parkinson's Disease: Etiology, Diagnostic Criteria, and Clinical Manifestations

I. Pathology & Genetics

Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder resulting from complex interactions between genetic and environmental factors.

Neuropathology

Feature	Detail
α -synucleinopathy	The pathologic hallmark is accumulation of misfolded α -synuclein protein in the form of Lewy bodies and Lewy neurites.
Dopaminergic loss	Degeneration occurs primarily in the substantia nigra pars compacta, causing loss of dopaminergic neurotransmission in the striatum.
Progression threshold	An estimated 50–70% of dopaminergic neurons are lost by the time motor symptoms become clinically evident.
Pathology mapping	Lewy body pathology is categorized as brainstem-predominant, limbic (transitional), neocortical, amygdala-predominant, or olfactory-bulb-only.

Genetic Profiles

Monogenic Forms

Gene (Locus)	Inheritance	Phenotype
LRRK2 (PARK8)	Autosomal dominant	Most common monogenic form; resembles idiopathic PD with fewer non-motor symptoms.
SNCA (PARK1/4)	Autosomal dominant	Duplications resemble idiopathic PD; triplications cause early-onset, rapidly progressive disease with cognitive decline.
VPS35 (PARK17)	Autosomal dominant	Resembles tremor-predominant PD.
PRKN (PARK2)	Autosomal recessive	12.5% of recessive PD; early onset (20–40 years); associated with lower-limb focal dystonia and freezing of gait.
PINK1 (PARK6)	Autosomal recessive	Early onset; slow progression; prominent gait/balance issues.
DJ-1 (PARK7)	Autosomal recessive	Early onset; includes dystonic symptoms.

Major Genetic Risk Factor

- **GBA variants:** the most common genetic risk factor (found in 5–10% of patients). Associated with earlier disease onset, a more aggressive motor course, and significantly earlier/more prominent cognitive decline.

CLINICAL PEARL

Genetic testing is critically indicated for patients with onset before age 50 or a positive family history.

II. MDS Clinical Diagnostic Criteria

The International Parkinson and Movement Disorders Society (MDS) criteria prioritize objective clinical findings to enhance diagnostic accuracy, achieving approximately 84% accuracy among specialists.

Core Feature: Parkinsonism

Bradykinesia (slowness plus a progressive reduction in speed or amplitude) PLUS at least one of the following:

- Resting tremor (typically 4–6 Hz), OR
- Rigidity (increased resistance independent of velocity)

Supportive Criteria (Required for "Clinically Established" Status)

Supportive Criterion
Dramatic response to dopaminergic therapy
Presence of levodopa-induced dyskinesias
Resting tremor of a limb
Olfactory loss (anosmia/hyposmia) or cardiac sympathetic denervation on MIBG scintigraphy

⚠ WARNING

Red Flags Suggesting an Alternative Diagnosis:

- Rapid progression — gait impairment requiring a wheelchair within 5 years
- Early prominent dysarthria/dysphagia or inspiratory stridor
- Severe autonomic failure (orthostatic hypotension or urinary incontinence) within 5 years
- Recurrent falls within 3 years of onset
- Bilateral symmetric disease at onset

Absolute Exclusion Criteria

Exclusion Criterion
Unequivocal cerebellar signs (e.g., limb ataxia)
Downward vertical supranuclear gaze palsy, or selective slowing of downward saccades (suggests PSP)
Dementia (bvFTD or PPA) occurring within 5 years of motor onset
Treatment with dopamine receptor blockers/depleters (drug-induced parkinsonism)
No response to high-dose levodopa (≥ 600 mg/day)
Unequivocal cortical sensory loss or limb ideomotor apraxia
Normal presynaptic dopaminergic imaging (e.g., DaTscan)

III. Non-Motor Symptoms & Prodrome

Non-motor symptoms often affect quality of life more significantly than motor symptoms and can emerge decades before motor onset.

Prodromal Markers

Marker	Detail
REM sleep behavior disorder (RBD)	Dream enactment with loss of normal muscle atonia. The most potent biomarker for synucleinopathy, with a 40–60% risk of conversion to a neurodegenerative disorder within 10 years of diagnosis.
Olfactory dysfunction	Anosmia or hyposmia is common and differentiates PD from atypical syndromes such as MSA.
Constipation	Occurs in up to 66% of patients; a key early prodromal feature.

Dysautonomia

- **Orthostatic hypotension (OH):** defined as a drop of ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic within 3 minutes of standing; caused by postganglionic noradrenergic denervation.
- **Urinary/sexual:** nocturia, urinary frequency, and erectile dysfunction.

Neuropsychiatric & Cognitive Complications

Complication	Detail
Apathy	Present in approximately 40% of patients across all disease stages.
Depression/anxiety	Affects up to 35% of patients.
PD psychosis	Well-formed hallucinations (people, animals) and delusions; risk increases with disease progression and dopaminergic medication use.
Impulse control disorders (ICD)	Binge eating, compulsive shopping, gambling, or hypersexuality; most commonly associated with dopamine agonists.
PD dementia (PDD)	Cognitive impairment progresses from mild cognitive impairment (seen in $\frac{1}{3}$ of patients) to PDD, typically with executive, attentional, and visuospatial deficits.

IMPORTANT NOTE

The "1-Year Rule": if dementia occurs within 1 year of motor onset, the diagnosis is Dementia with Lewy Bodies (DLB) rather than PD Dementia (PDD).

Pharmacological Management of Parkinson's Disease: Mechanisms, Dosing, and Complications

This chapter provides a detailed pharmacological reference for the management of Parkinson's disease based on current clinical standards.

I. Levodopa Formulations

Levodopa (3,4-dihydroxy-L-phenylalanine) remains the most effective symptomatic treatment for PD, serving as a precursor to dopamine to address striatal deficiency.

Mechanism & Kinetics

Levodopa is usually combined with carbidopa to inhibit peripheral metabolism, which increases central dopamine delivery and reduces side effects such as nausea.

IMPORTANT NOTE

Absorption Pearl: clinical efficacy can be hindered by unpredictable intestinal absorption. Infusion therapies are used when oral absorption is unreliable; levodopa also competes for transport via large neutral amino acid transporters in the gut.

Dosing Strategies

Strategy	Regimen
Diagnostic challenge (confirm dopamine responsiveness)	Start low and titrate up to 2–3 tablets of 25/100 mg per dose; often requires total daily levodopa-equivalent dose (LED) ≥ 600 mg/day.
Standard starting dose	One tablet of 25/100 mg three times daily.
Maintenance (advanced disease)	Highly individualized; advanced patients may require regimens such as two tablets five times daily to maintain "on" time.

Advanced Delivery Systems

System	Description
Intestinal gel (DUOPA)	Continuous infusion bypassing the stomach; provides stable plasma levels and typically increases daily "on" time by ≥ 2 hours.
Subcutaneous infusion	Newly approved pump delivering continuous foscarbidopa/foslevodopa.
Inhalational levodopa	Used for intermittent rescue of "off" periods.

II. Dopamine Agonists (DA)

Dopamine agonists are synthetic compounds that directly stimulate postsynaptic D2 receptors.

Formulations & Dosing

Route	Agent(s)
Oral	Pramipexole, Ropinirole
Transdermal	Rotigotine patch (continuous delivery)
Rescue / infusion	Apomorphine (subcutaneous injection for "off" rescue, or continuous subcutaneous pump)

Clinical Complications & Pearls

Complication	Detail
Impulse control disorders (ICD)	Occur in approximately 1 in 6 patients; includes binge eating, hypersexuality, shopping, and gambling. Risk is significantly higher with DAs than with levodopa.
Sleep attacks & edema	Associated with excessive somnolence, sudden sleep onset, and lower-extremity edema.
DA withdrawal syndrome (DAWS)	A severe syndrome (anxiety, depression, drug craving, pain) that can emerge during tapering. DAs must be weaned slowly to prevent DAWS.

⚠️ WARNING

Dopamine agonists must always be tapered slowly — abrupt discontinuation risks DA withdrawal syndrome (DAWS).

III. MAO-B and COMT Inhibitors

These agents function as "levodopa extenders" by inhibiting the breakdown of dopamine.

MAO-B Inhibitors

Drug	Dosing	Notes
Rasagiline	1 mg daily	Inhibits MAO-B in glial cells to increase synaptic dopamine.
Selegiline	—	Same class mechanism

Drug	Dosing	Notes
Safinamide	—	Same class mechanism

CLINICAL PEARL

Risk of serotonin syndrome with SSRIs is exceedingly rare with MAO-B–selective agents compared to MAO-A inhibitors.

COMT Inhibitors

Drug	Dosing / Notes
Entacapone	Commonly used for end-of-dose wearing-off; blocks peripheral levodopa metabolism.
Opicapone	Administered once daily.
Tolcapone	Blocks peripheral and central levodopa metabolism; carries a boxed warning for liver toxicity requiring frequent monitoring.

IV. Amantadine and Anticholinergics

Amantadine

Attribute	Detail
Mechanism	Noncompetitive NMDA antagonist; also stimulates dopamine release and blocks cholinergic receptors.
Primary indication	Suppressing levodopa-induced dyskinesia. Both immediate-release and extended-release versions are used.
Side effects	Livedo reticularis (splotchy leg rash), visual hallucinations, confusion, peripheral edema.

Anticholinergics

Attribute	Detail
Drugs	Trihexyphenidyl, Benztropine
Use	Targeted specifically at tremor control.
Age restriction	Avoid in older patients; use generally limited to younger, cognitively intact patients due to high risk of confusion and long-term cognitive decline.

V. Motor Complications Management

As PD progresses, the therapeutic window narrows, leading to motor fluctuations.

"Wearing-Off" (Off States)

Strategy	Approach
1	Increase dosing frequency (administer doses closer together).
2	Add adjuvant therapies — MAO-B inhibitors, COMT inhibitors, or dopamine agonists.
3	Add istradefylline (adenosine A2A antagonist) to reduce indirect-pathway inhibition.

Peak-Dose Levodopa-Induced Dyskinesia (LID)

Strategy	Approach
1	Use smaller levodopa doses, more frequently.
2	Add amantadine — the established treatment for LID.
3	Reduce or stop MAO-B or COMT inhibitors.

"Delayed-On" & Unpredictable Absorption

Utilize infusion therapies (intestinal gel or subcutaneous pumps) to provide continuous drug delivery and bypass gastric emptying issues.

VI. Other Symptomatic Adjuncts

Psychosis

If visual hallucinations occur, reduce or stop medications in this order:

Anticholinergics → Dopamine agonists → Amantadine → COMT inhibitors → Levodopa

Antipsychotic	Notes
Pimavanserin	FDA-approved for PD psychosis; does not worsen motor function.
Clozapine	Effective but requires CBC monitoring.
Quetiapine (low-dose)	Alternative agent.

Orthostatic Hypotension

If behavioral changes fail, initiate pharmacologic therapy:

- Droxidopa
- Fludrocortisone 0.1–0.2 mg
- Midodrine up to 5 mg three times daily
- Pyridostigmine

Levodopa-Equivalent Drug Summary Table

Drug Class	Representative Agents	Typical Starting Dose	Key Caution
Levodopa/carbidopa	25/100 mg tablets	1 tab TID	Unpredictable absorption; on/off fluctuations
Dopamine agonists	Pramipexole, Ropinirole, Rotigotine	Low-dose titration	ICD, sleep attacks, DAWS on withdrawal
MAO-B inhibitors	Rasagiline	1 mg daily	Rare serotonin syndrome risk with SSRIs
COMT inhibitors	Entacapone, Opicapone, Tolcapone	Per agent	Tolcapone: hepatotoxicity (boxed warning)
Amantadine	IR/ER formulations	Per agent	Livedo reticularis, hallucinations, edema
Anticholinergics	Trihexyphenidyl, Benztropine	Low-dose	Avoid in elderly — cognitive decline risk

CHAPTER 4

Atypical Parkinsonism (Parkinson-Plus) Reference Manual

I. Progressive Supranuclear Palsy (PSP)

PSP is the most common form of atypical parkinsonism, pathologically classified as a 4-repeat (4R) tauopathy.

Neuropathology & Genetics

- Hallmarks include aggregated tau in tufted astrocytes, globose neurofibrillary tangles, and coiled bodies in oligodendrocytes.
- Pathology primarily affects the subthalamic nucleus, globus pallidus, substantia nigra, and dentate nucleus.
- **The MAPT H1 haplotype** (specifically H1c) increases disease risk at least fivefold.

Cardinal Clinical Features

- Prominent early gait impairment with unexplained, often backward, falls within 3 years of onset.
- Vertical supranuclear gaze palsy (selective slowing of downward saccades is more specific and sensitive than restricted upgaze).
- Axial-predominant rigidity and retrocollis.
- Frontal-executive dementia featuring slowed processing (bradyphrenia) and reduced verbal fluency.

Rare Signs & Differentiators

Sign	Description
Rocket sign	Motor impulsivity — the patient "rocks" out of a chair without assistance, leading to falls.
Sunglass sign	Indoor use of sunglasses due to marked photosensitivity.
Round-the-house sign	Inability to make straight vertical downward saccades; the gaze instead follows a lateral arc.
Applause sign	Perseveration on the three-clap test — the patient claps more than three times despite instructions.
Procerus sign	Furrowing of the brow with a wide-eyed "worried" or "astonished" expression.

Phenotypic Variants

Variant	Features
Richardson's syndrome (PSP-RS)	Classic presentation with early falls and vertical gaze palsy.
PSP-Parkinsonism (PSP-P)	Comprises ⅓ of cases; mimics PD with asymmetric tremor and early levodopa response, but progresses to classic PSP.
PSP-Gait Freezing (PSP-PGF)	Early, progressive, levodopa-resistant gait freezing.

Imaging Signatures

Sign	Modality / Finding
Hummingbird sign	Disproportionate midbrain atrophy on midsagittal MRI.
Mickey Mouse / Morning Glory sign	Midbrain atrophy on axial MRI.
MR Parkinsonism Index (MRPI) 2.0	Objective ratio of pons-to-midbrain area and peduncle widths, used to differentiate PSP from PD.

II. Multiple System Atrophy (MSA)

MSA is a sporadic, rapidly progressive α -synucleinopathy characterized by glial cytoplasmic inclusions (GCIs) in oligodendrocytes.

Core Diagnostic Criteria (MDS 2022)

- Requires autonomic failure (neurogenic orthostatic hypotension $\geq 20/10$ mmHg, or unexplained urinary incontinence/retention).
- Must feature either levodopa-resistant parkinsonism or a cerebellar syndrome.

Clinical Phenotypes

Phenotype	Predominant Features
MSA-P	Parkinsonian features (bradykinesia, rigidity) predominate.
MSA-C	Cerebellar features (gait/limb ataxia, scanning speech, ocular dysfunction) predominate.

Rare Signs & Differentiators

Sign	Description
Disproportionate anterocollis	Severe forward flexion of the neck; present in over 40% of patients.
Polyminimyoclonus	Low-amplitude, jerky, postural/action movements of the hands.
Stridor	High-pitched, harsh inspiratory sound during sleep or wakefulness.
Pisa syndrome	Severe lateral flexion of the spine.
Autonomic clues	Cold, discolored hands/feet and impaired sweating (preganglionic localization).
Orofacial dystonia	Levodopa-induced "risus sardonicus" (lower facial grimacing) without limb dyskinesia.

🚨 EMERGENCY

Stridor in MSA is a potential marker of increased mortality risk and warrants prompt sleep medicine / ENT evaluation.

Imaging Signatures

Sign	Finding
Hot cross bun sign	Cruciate pontine T2-signal hyperintensity.
Putaminal rim sign	Hyperintense rim bordering the atrophic putamen on T2 MRI.
Middle cerebellar peduncle (MCP) atrophy	Marker for the cerebellar type (MSA-C).

⚠️ WARNING

MSA-associated stridor is a red flag for potential nocturnal sudden death and may warrant sleep study evaluation and consideration of tracheostomy or CPAP in advanced cases.

III. Corticobasal Degeneration (CBD / CBS)

Corticobasal Syndrome (CBS) refers to the clinical phenotype, while Corticobasal Degeneration (CBD) is the specific underlying 4R tauopathy.

Pathology

Pathognomonic astrocytic plaques, tau-positive threads, and ballooned neurons.

Cardinal Clinical Features

Feature	Description
Extreme asymmetry	Marked lateralization of motor and cortical signs.
Apraxia	Early limb-kinetic apraxia (loss of dexterity) or ideomotor apraxia (inability to mime tasks such as using a screwdriver).
Alien limb phenomenon	Feeling of estrangement from a limb that performs involuntary movements such as posturing or grasping.
Cortical sensory loss	Agraphesthesia or astereognosis despite intact basic sensation.

Rare Signs & Differentiators

- Stimulus-sensitive myoclonus — focal jerking triggered by touch or action.
- Atypical coarse tremor — a jerky rest-action tremor, often treatment-resistant.
- Preserved semantic memory — memory is often spared until late, unlike Alzheimer's disease.

Imaging Signature

Asymmetric frontoparietal atrophy, particularly involving the perirolandic gyri contralateral to the most affected limb.

IV. Dementia with Lewy Bodies (DLB)

DLB is the second most common neurodegenerative dementia, defined as an α -synucleinopathy.

CLINICAL PEARL

The "1-Year Rule": dementia must occur before or within 1 year of the onset of parkinsonian motor symptoms to distinguish DLB from Parkinson's Disease Dementia (PDD).

Core Clinical Features

Feature	Description
Fluctuating cognition	Pronounced variations in attention and alertness (e.g., staring blankly for periods).
Recurrent visual hallucinations	Typically well-formed, detailed images of people, children, or animals.
REM sleep behavior disorder (RBD)	Dream enactment behavior that often precedes cognitive decline.
Spontaneous parkinsonism	Bradykinesia, rest tremor, or rigidity.

Rare Signs & Differentiators

- Neuroleptic sensitivity — severe, potentially fatal reactions to even standard doses of antipsychotics.
- Capgras syndrome — the systematized delusion that a familiar person has been replaced by an identical imposter.
- Minor hallucinations — "passage hallucinations" (shadows in the periphery) or a "sense of presence" (feeling someone is nearby).

WARNING

Neuroleptic sensitivity in DLB can be severe and potentially fatal. Avoid typical antipsychotics; if treatment for psychosis is required, use quetiapine, clozapine, or pimavanserin with caution.

Biomarkers & Imaging

Biomarker	Finding
Dopamine transporter imaging	Reduced uptake on SPECT or PET.
Cardiac sympathetic denervation	Low uptake on I-123 MIBG myocardial scintigraphy (highly specific vs. Alzheimer's disease).
Cingulate island sign	Occipital hypometabolism with relative sparing of the posterior cingulate on FDG-PET.
EEG changes	Posterior slow-wave activity (frequencies < 8 Hz).

Differential Diagnosis: Atypical Parkinsonian Syndromes

Feature	PSP	MSA	CBD/CBS	DLB
Pathology	4R Tau	α -synuclein (GCIs)	4R Tau	α -synuclein (Lewy bodies)
Key early sign	Early falls, vertical gaze palsy	Autonomic failure $\pm$ ataxia	Asymmetric apraxia/alien limb	Fluctuating cognition, hallucinations
Levodopa response	Poor	Poor	Poor	Modest
Classic imaging	Hummingbird sign	Hot cross bun / putaminal rim	Asymmetric frontoparietal atrophy	Occipital hypometabolism, cingulate island sign
Cognitive pattern	Frontal-executive (bradyphrenia)	Relatively spared (early)	Apraxia; memory spared late	Fluctuating attention, visuospatial

CHAPTER 5

Tremor Syndromes Reference Guide

I. MDS Consensus Classification

The International Parkinson and Movement Disorder Society (MDS) utilizes a two-axis classification system to standardize the characterization of tremor syndromes.

Axis 1: Clinical Features

Historical Features

Age at onset, temporal onset and evolution (sudden vs. gradual), past medical history, family history of movement disorders, and sensitivity of the tremor to alcohol and drugs.

Tremor Characteristics

Documented by body distribution (upper limbs, head, voice, jaw, legs), activation conditions, and frequency.

Category	Description
Rest tremor	Occurs when the limb is fully supported and not activating muscles against gravity.
Postural tremor	Elicited by sustaining a posture against gravity.
Kinetic tremor	Occurs during any voluntary movement.
Intention tremor	A type of kinetic tremor where amplitude increases as the limb approaches a target.
Task-specific tremor	Triggered only by a highly specific activity (e.g., writing).

Associated signs: presence of other neurologic features such as bradykinesia, rigidity, dystonia, or ataxia, as well as signs of systemic illness or "soft signs" of uncertain significance.

Axis 2: Etiology

Classification of the underlying cause as acquired, genetically defined, or idiopathic (further divided into familial or sporadic).

II. Essential Tremor (ET) vs. ET-Plus

Distinguishing isolated ET from ET-plus is critical for both clinical management and research stratification.

Isolated Essential Tremor (ET) — Diagnostic Criteria

- An isolated tremor syndrome consisting of bilateral upper-limb action tremor.
- At least 3 years' duration.
- With or without tremor in other locations (e.g., head, voice, or lower limbs).
- Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.

Essential Tremor-Plus (ET-Plus)

Tremor with the core characteristics of ET but accompanied by additional neurological signs of uncertain significance ("soft signs"), including impaired tandem gait, questionable dystonic posturing, memory impairment, or rest tremor in the absence of other parkinsonian features.

MEMORY TIP

ET = 3+ years, bilateral, upper limb, action tremor, NO other neurological signs. Add any "soft sign" and it becomes ET-Plus.

III. Other Tremor Types

Tremor Type	Key Features
Dystonic tremor	Jerky, irregular tremor. Key diagnostic feature: the "null point," where the tremor significantly diminishes or disappears when the body part is moved into a specific direction or rotation.
Holmes tremor (midbrain/rubral tremor)	Low-frequency (< 4.5–5 Hz), combining rest, postural, and intention tremor. Usually caused by midbrain or brainstem lesions involving the dentato-olivary pathway.
Orthostatic tremor	High-frequency tremor uniquely occurring in the legs and trunk immediately upon standing. Diagnosis requires surface EMG demonstrating a pathognomonic frequency of 13–18 Hz.
Enhanced physiological tremor	High-frequency (8–13 Hz), low-amplitude (<0.5 cm) action tremor. Typically visible only when amplified by stress, caffeine, anxiety, muscle fatigue, or hyperthyroidism.

IV. Pharmacological Treatment & Dosing

Oral pharmacotherapies are the mainstay for upper-limb tremor, though they are often less effective for head and voice tremor.

Drug Summary Table

Drug	Line	Starting Dose	Maintenance / Effective Range	Key Cautions
Propranolol	First-line	10 mg TID	120–240 mg/day total (e.g., 40–80 mg TID)	Contraindicated in asthma, COPD, diabetes (masks hypoglycemia)
Primidone	First-line	12.5–25 mg nightly	50–1000 mg/day (titrate 25 mg/week up to 250 mg nightly)	Acute ataxia/confusion at low doses; interacts

Drug	Line	Starting Dose	Maintenance / Effective Range	Key Cautions
				with warfarin and DOACs
Topiramate	Second-line	—	25–400 mg/day (Level B evidence; effective >200 mg/day)	Paresthesias, weight loss, cognitive impairment
Gabapentin	Second-line	—	1200–3600 mg/day in divided doses	Level B evidence; some guidelines find efficacy inconclusive

⚠ WARNING

Avoid propranolol in patients with asthma, COPD, or diabetes — nonselective beta-blockade can precipitate bronchospasm and mask hypoglycemic symptoms.

CHAPTER 6

Huntington's Disease and Hyperkinetic Chorea Syndromes

I. Huntington's Disease (HD)

Huntington's disease is the most common inherited cause of chorea in adults, characterized by a clinical triad of motor, cognitive, and psychiatric symptoms.

Genetics & Pathophysiology

Feature	Detail
Gene & chromosome	Triplicate CAG expansion in the HTT gene (also called IT15), located on the short arm of chromosome 4.
Genetic anticipation	Offspring develop the disease earlier or with more severe symptoms.
Paternal transmission bias	CAG repeat expansion occurs more frequently during spermatogenesis; children of affected fathers are at higher risk for early-onset disease.
Neuropathology	Degeneration of GABAergic medium spiny neurons in the direct and indirect pathways of the basal ganglia.

CAG Repeat Thresholds & Interpretation

CAG Repeat Number	Interpretation
≤ 26	Normal range; individual will not develop HD.
27–35 (intermediate)	Generally asymptomatic, but risk of expansion in offspring (anticipation).
36–39 (reduced/incomplete penetrance)	May or may not develop symptoms, typically with later age of onset.
≥ 40 (full penetrance)	Individual will develop HD if they live a normal lifespan.
≥ 60	Typically associated with juvenile-onset HD.

MEMORY TIP

CAG thresholds — think "26 is normal, 40 is full penetrance, 60 is juvenile." 27–35 sits in the gray zone of anticipation risk without personal disease.

The Clinical Triad

Motor Features

Feature	Description
Chorea	Random, purposeless, unpredictable, and free-flowing involuntary movements.
Motor impersistence	Inability to maintain a sustained posture; tested via "milkmaid's grip" (fluctuating grip intensity) or tongue darting (inability to sustain protrusion for 10 seconds).
Forehead chorea	Involuntary movements of the frontalis/eyebrows; a helpful differentiator from tardive dyskinesia.
Ocular motor findings	Slowed/delayed saccades and saccadic intrusion of smooth pursuit.

Cognitive & Psychiatric Features

- **Cognitive:** progressive subcortical dementia and frontal-executive decline.
- **Psychiatric:** high rates of anxiety, depression, irritability, aggression, and psychosis.

WARNING

Suicide risk in HD is substantial. Suicidal ideation occurs in up to 30% of patients, and suicide is the third most common cause of death (6.6%). Screen for mood and suicidality at every visit.

Westphal Variant (Juvenile HD)

Defined by onset in childhood or early adulthood (typically ≥ 60 repeats). Manifests as rigidity, parkinsonism, dystonia, and seizures rather than chorea.

II. HD Management and Pharmacology

Treatment is symptomatic and focuses on depleting dopamine either presynaptically or postsynaptically.

Presynaptic Dopamine Depletion — VMAT2 Inhibitors

Mechanism: targets Vesicular Monoamine Transporter 2 (VMAT2) to block the packaging of dopamine into presynaptic vesicles.

Drug	Starting Dose	Maintenance / Max	Dosing Frequency	Key Pearls / Risks
Tetrabenazine	12.5 mg/day	50 mg/day (HD); 75 mg/day (TD)	TID	Black box warning: depression and suicidal ideation in HD patients
Deutetrabenazine	12 mg/day	48 mg/day	BID	Longer half-life, fewer sedation effects than tetrabenazine; boxed warning for depression/suicidality; rare QTc prolongation
Valbenazine	40 mg/day	80 mg/day	Once daily	Approved for HD chorea in 2023; boxed warning for depression/suicidality; QTc prolongation risk

⚠️ WARNING

All three VMAT2 inhibitors (tetrabenazine, deutetrabenazine, valbenazine) carry a boxed warning for depression and suicidal ideation in HD patients — screen mood before initiation and at follow-up.

Postsynaptic Dopamine Depletion — Neuroleptics

Mechanism: blocks postsynaptic D2 receptors on striatonigral neurons.

- **Drugs:** Olanzapine (high D2 affinity), Risperidone, and Aripiprazole.
- **Use case:** often preferred as off-label treatment when comorbid psychiatric issues (e.g., aggression, psychosis) are present.
- **Other agents:** amantadine (NMDA antagonist) has limited evidence for success in HD chorea.

III. Other Chorea Syndromes

A systematic approach to non-HD chorea involves assessing acuity, age, and body distribution.

Sydenham's Chorea

Attribute	Detail
Mechanism	Autoimmune (post-streptococcal); antibodies against group A streptococcus target basal ganglia antigens.
Clinical	Most common cause of acute chorea in children; can be asymmetrical or hemichorea.
Management	Antibiotics (penicillin), corticosteroids, and valproic acid.

- **Chorea gravidarum:** a recurrence of chorea during pregnancy or with the use of birth control, often in patients with a history of Sydenham chorea.

Neuroacanthocytosis Syndromes

Rare genetic causes featuring acanthocytes (spiculated RBCs) on peripheral smear.

Syndrome	Inheritance / Gene	Features
Chorea-acanthocytosis	Autosomal recessive (VPS13A)	Orobuccolingual chorea, tongue-protrusion dystonia, feeding dystonia, seizures, elevated CK.
McLeod syndrome	X-linked recessive (XK), affects males	Reduced Kell antigen expression.

📌 IMPORTANT NOTE

HD should be considered in any adult with chronic chorea — even without a clear family history — as "senile chorea" often represents an unrecognized HD phenocopy or late-presenting HD.

Key Differential Differentiators

Condition	Key Distinguishing Feature
Wilson disease	Treatable copper transport disorder (ATP7B gene); MRI shows "face-of-the-giant-panda" sign in the midbrain.
Benign hereditary chorea (Brain-Lung-Thyroid syndrome)	Caused by NKX2-1 variants; includes chorea, ataxia, and pulmonary/thyroid issues.
Nonketotic hyperglycemia	Common cause of acute hemichorea in adults; MRI shows T1 hyperintensity in the contralateral putamen.

CHAPTER 7

The Dystonias: Classification, Genetics, and Therapeutic Interventions

I. Classification Framework

Dystonia is a variable movement disorder characterized by sustained or intermittent muscle contractions that cause abnormal, often repetitive, twisting movements or postures. Diagnostic classification follows a two-axis system established by the 2013 International Consensus Group.

A. Axis 1: Clinical Characteristics

Age of Onset

Category	Age Range
Infancy	Birth to 2 years
Childhood	3 to 12 years
Adolescence	13 to 20 years
Early adulthood	21 to 40 years
Late adulthood	Older than 40 years

Body Distribution

Distribution	Description
Focal	Affects a single body part (e.g., neck, eyelids, voice, jaw, or a limb).
Segmental	Affects two or more contiguous body parts (e.g., cervical plus oromandibular).
Multifocal	Affects two or more non-contiguous body parts.
Generalized	Affects the trunk and at least two other sites; typically starts in a limb and spreads.
Hemidystonia	Involves only one side of the body; often suggests an acquired structural lesion.

Temporal Pattern

Characteristics include the disease course (static vs. progressive) and variability (persistent, action-specific, diurnal, or paroxysmal).

B. Axis 2: Etiology

- Nervous system pathology: identification of structural brain abnormalities (via MRI) or degenerative changes (e.g., basal ganglia mineralization).
- Inherited vs. acquired: differentiates monogenic causes (e.g., TOR1A, GCH1) from acquired causes such as hypoxic-ischemic injury, traumatic brain injury, or drug-induced tardive dystonia.
- Idiopathic: used when no clear etiology, structural change, or genetic marker is identified.

II. Genetic Dystonias

Inherited dystonias exhibit significant variability in onset, distribution, and therapeutic response.

Gene (Former Name)	Inheritance	Key Clinical Features
TOR1A (DYT1)	Autosomal dominant	Early-onset isolated generalized dystonia; mean onset age 13, usually beginning in a lower limb before generalizing. Caused by a specific 3-bp (GAG) deletion; reduced penetrance — manifestation unlikely if symptoms have not emerged by age 26.
THAP1 (DYT6)	Autosomal dominant	Most commonly childhood-onset (25% present in adulthood); often segmental or generalized distribution. Initial site frequently neck or limbs; may include tremor or, rarely, myoclonus.
GCH1 (dopa-responsive dystonia / Segawa disease)	Autosomal dominant	"Treatable" form; typically starts in childhood in the lower limbs. Characterized by diurnal variation (worsens through the day, improves with sleep); may develop parkinsonian features later. Dramatic, sustained response to low-dose levodopa.

★ HIGH YIELD

Any child with lower-limb dystonia and diurnal variation should receive a levodopa trial — dopa-responsive dystonia (GCH1) is dramatically and durably treatable.

III. Focal Dystonias

Adult-onset isolated dystonia most commonly presents focally, frequently featuring the presence of sensory tricks (geste antagoniste).

Focal Dystonia	Description
Cervical dystonia	The most common focal dystonia; involves patterned and repetitive head/neck movements (torticollis, tilt, or laterocollis). Sensory tricks such as touching the face or chin can temporarily normalize head posture.

Focal Dystonia	Description
Blepharospasm	Stereotyped, bilateral, synchronous orbicularis oculi spasms. Sometimes mistaken for tics but distinguished by the inability to voluntarily suppress the spasms.
Oromandibular dystonia / Meige syndrome	Involuntary mouth or jaw movements (e.g., clenched-fist jaw, tongue protrusion). When blepharospasm co-occurs with lower facial or jaw dystonia, it is considered segmental dystonia (Meige syndrome).
Writer's cramp (task-specific)	Focal limb dystonia causing excessive flexion of fingers and thumb only when picking up a pen.
Musician's dystonia (task-specific)	Can involve focal hand or embouchure dystonia (laryngeal/vocal cords); may be career-ending.

IV. Treatment Strategies & Dosing

Therapeutic selection depends on the dystonia distribution, etiology, and patient age.

Botulinum Toxin (BoNT)

BoNT is the mainstay of treatment for focal dystonia. It acts by inhibiting the release of acetylcholine at the neuromuscular junction to cause localized muscle relaxation.

Formulation	FDA-Approved Indications
OnabotulinumtoxinA	Blepharospasm, cervical dystonia
IncobotulinumtoxinA	Blepharospasm, cervical dystonia
AbobotulinumtoxinA	Cervical dystonia
RimabotulinumtoxinB	Cervical dystonia
DaxibotulinumtoxinA-ianm	Cervical dystonia (longer-acting)

Injections are typically performed every 3 months, often using guidance techniques such as ultrasound or EMG for precise targeting.

Anticholinergics

Primarily used for generalized or multifocal dystonia.

- **Trihexyphenidyl:** adults are often limited by side effects (confusion, cognitive impairment); children may tolerate high doses of 100 mg or more per day, though these high pediatric doses are associated with decreased academic performance.

Baclofen

A GABA-B receptor agonist used both orally and intrathecally. Occasionally effective for secondary generalized dystonia in the pediatric population or for painful muscle contractions.

Deep Brain Stimulation (DBS)

A robust surgical option for medication-refractory generalized or segmental dystonia, particularly in TOR1A-associated dystonia (often achieving >50% improvement). Primary targets include the globus pallidus internus (GPI) or the subthalamic nucleus.

⚠ WARNING

High-dose trihexyphenidyl in children, while sometimes tolerated at doses ≥ 100 mg/day, is associated with measurable decreases in academic performance — weigh symptomatic benefit against cognitive/educational cost.

CHAPTER 8

Myoclonus, Tics, and Tourette Syndrome Reference Guide

I. Myoclonus: Classification and Treatment

Myoclonus is a brief, lightning-like jerk characterized as the quickest movement a body part can produce, typically lasting 50–200 milliseconds. It is categorized by physiology, distribution, and relationship to stimuli.

A. Anatomical & Neurophysiological Classification

Type	Origin / Distribution	Burst Duration	Notes
Cortical	Sensorimotor cortex; face and distal limbs	< 100 ms	Spontaneous, action-induced, or stimulus-sensitive; giant SEPs and positive back-averaging on electrophysiology
Subcortical (brainstem/reticular)	Generalized or synchronous axial jerks; proximal limbs	> 100 ms	Simultaneous rostral and caudal muscle activation
Spinal — segmental	A few contiguous spinal levels	> 100 ms	Often spontaneous, unaffected by sleep
Spinal — propriospinal	Axial muscles; mid-thoracic origin	> 100 ms	Slow propagation (5–15 m/s); lying down often provoking

Type	Origin / Distribution	Burst Duration	Notes
Peripheral	Peripheral nerve or myotome distribution	< 50 ms	Associated with fasciculations and muscle atrophy

B. Post-Hypoxic Myoclonus Variants

Variant	Description
Lance-Adams syndrome	A chronic form of post-anoxic myoclonus, predominantly action-induced, that can significantly impair mobility.
Myoclonic status epilepticus	Occurs in the acute phase of severe encephalopathy; jerks are often generalized and indicate a poor neurologic prognosis.

C. Pharmacotherapy Protocols & Dosing

Drug	Indication	Starting Dose	Maintenance / Max
Clonazepam	First-line for stimulus-induced startle (hyperekplexia) and myoclonus-dystonia	0.25–0.5 mg/day	Up to 2 mg/day, typically divided BID
Levetiracetam	Cortical myoclonus and tics	250 mg/day or 20 mg/kg/day	Up to 2000 mg/day or 60 mg/kg/day, in two divided doses
Valproate	Primary myoclonic epilepsies and Sydenham chorea	250 mg BID (adults); weight-based in children	Monitor for hepatotoxicity and weight gain

⚠ WARNING

Myoclonic status epilepticus in the post-anoxic setting, particularly with generalized jerks, indicates a poor neurologic prognosis and should prompt urgent EEG and critical-care neurology involvement.

II. Tics and Tourette Syndrome (TS)

Tics are stereotyped, recurrent, non-rhythmic movements or sounds that are typically preceded by an urge and are suppressible.

A. DSM-5 Diagnostic Criteria for Tourette Syndrome

1. Multiple motor tics AND at least one vocal (phonic) tic must be present at some time during the illness (not necessarily concurrently).

2. Duration: tics must occur for more than 1 year since the first tic onset.
3. Onset: must manifest before age 18.
4. Exclusion: not attributable to the physiological effects of a substance or another medical condition.

B. Clinical Features and Phenomena

Feature	Description
Premonitory urge	A somatic (e.g., itch, tension) or psychosomatic (e.g., inner restlessness) sensation relieved by performing the tic.
Suppression	A hallmark feature — patients can transiently stop tics, though the urge typically builds until release.
Rostrocaudal progression	Tics typically begin as simple motor tics (90% initially eye blinking) and progress downward to the face, neck, trunk, and extremities.

Complex Phenomena

Phenomenon	Description
Coprolalia	Involuntary use of socially inappropriate words (present in only 10–30% of cases).
Echolalia / echopraxia	Repeating others' words or mimicking their gestures.
Palilalia	Repeating one's own words.

CLINICAL PEARL

Coprolalia is present in only 10–30% of Tourette syndrome patients — it is not required for diagnosis, a common misconception.

III. Management of Tics

Management is indicated when tics are painful, disruptive to learning, or cause significant social impairment.

A. Behavioral Therapy (First-Line)

- **Comprehensive Behavioral Intervention for Tics (CBIT):** has efficacy similar to pharmacotherapy.
- **Protocol:** eight sessions over 10 weeks (typically 6 weekly sessions followed by 2 bi-weekly).
- **Components:** awareness training, competing-response training (habit reversal), relaxation training, and functional intervention.

B–C. Pharmacotherapy Drug Summary Table

Class / Drug	Age	Starting Dose	Maintenance / Max	Notes
Guanfacine (α_2 -agonist, first-line)	—	0.5–1 mg/day	1–4 mg/day, may be divided BID	Preferred for less sedation
Clonidine (α_2 -agonist, first-line)	—	0.025–0.05 mg/day, 1–2 divided doses	0.6 mg/day max (up to QID); max single dose 0.2 mg	Useful if sleep disturbance is a major comorbidity
Haloperidol	≥ 3 yr	0.5 mg/day	2–10 mg/day (titrate 0.25–0.5 mg weekly)	FDA-approved antipsychotic
Pimozide	≥ 12 yr	0.05 mg/kg/day	0.2 mg/kg/day (max 10 mg/day)	FDA-approved antipsychotic
Aripiprazole	6–17 yr	1.25–2.5 mg/day	2.5–20 mg/day, typically divided	FDA-approved antipsychotic
Topiramate	—	25 mg/day	50–200 mg/day	Adjunct
Baclofen	—	10 mg/day	80 mg/day max (3–4 divided doses)	Adjunct

D. Other Therapeutic Interventions

- **Ecopipam (selective D1 antagonist):** a novel agent that met primary endpoints for tic reduction.
- **Botulinum toxin:** considered for focal tics (face/neck) or those at risk of self-injury (e.g., neck-snapping).

CHAPTER 9

Movement Disorder Emergencies and Drug-Induced Syndromes

This chapter details the clinical recognition, diagnostic criteria, and emergency protocols for movement disorder emergencies and drug-induced syndromes.

I. Acute Drug-Induced Syndromes

Acute reactions typically occur shortly after exposure to dopamine receptor-blocking agents (DRBAs), such as typical/atypical antipsychotics and antiemetics.

Acute Dystonic Reactions

Attribute	Detail
Clinical presentation	Unremitting muscle contractions including laryngeal dystonia, blepharospasm, cervical dystonia, oculogyric crisis, and focal limb dystonia.
Epidemiology	Most common in young men.
Timeline	Usually begins within 24 hours of exposure; 90% of reactions occur within the first 5 days.

EMERGENCY

Emergency Treatment — Acute Dystonic Reaction:

- IV Benztropine mesylate 1–2 mg, OR
- IV Diphenhydramine 25–50 mg (highly effective for rapid relief)
- Maintenance: a short oral anticholinergic course (4–7 days) may be required to prevent recurrence

Akathisia

Attribute	Detail
Definition	A hyperkinetic state of subjective and objective restlessness.
Etiology	Associated with peak doses of levodopa in PD, or as a side effect of dopamine depleters such as tetrabenazine.
Treatment note	Documented primarily as a side effect to monitor when using VMAT2 inhibitors; propranolol and mirtazapine are used clinically for symptomatic control.

II. Tardive Syndromes

Tardive syndromes result from chronic exposure to dopamine receptor-blocking drugs (neuroleptics).

Tardive Dyskinesia (TD)

Phenomenology: characterized by involuntary, repetitive movements, most commonly orobuccolingual chorea (mouth and tongue movements).

Prevention & First-Line Management

- Careful removal of the offending dopamine receptor-blocking drug is the primary step.
- If a psychiatric indication persists, switching to a drug with lower D2 receptor affinity (e.g., clozapine) is recommended.

Pharmacologic Treatment — VMAT2 Inhibitors

Drug	Starting Dose	Maintenance / Max	Dosing Frequency
Valbenazine	40 mg/day	80 mg/day	Once daily
Deutetrabenazine	12 mg/day	48 mg/day	Twice daily
Tetrabenazine	12.5 mg/day	75 mg/day (for TD)	Three times daily

III. Movement Disorder Emergencies

These are life-threatening conditions requiring rapid diagnosis and often intensive care unit (ICU) admission.

Neuroleptic Malignant Syndrome (NMS)

EMERGENCY

The Tetrad of NMS:

- Fever (may be delayed)
- Rigidity ("lead-pipe")
- Mental status changes (confusion, agitation)
- Autonomic dysfunction (tachycardia, labile blood pressure, diaphoresis)

Attribute	Detail
Pathophysiology	Hypothalamic D2 blockade disrupts the temperature set point; nigrostriatal blockade causes rigidity.
Laboratory hallmarks	Elevated creatine phosphokinase (CPK), leukocytosis, and elevated liver enzymes (ALT/AST).

NMS Treatment Protocol

- Immediate discontinuation of all dopamine receptor-blocking agents and ICU stabilization.
- **Dantrolene:** 3–5 mg/kg IV, three to four times daily (TID–QID).
- **Bromocriptine:** 5 mg four times daily (QID).
- Other options: levodopa, benzodiazepines, or apomorphine have shown efficacy.
- Reintroduction: delay restarting antipsychotics for at least 2 weeks after symptom resolution (6 weeks for depot formulations).

Serotonin Syndrome (SS)

Attribute	Detail
Clinical presentation	Triad of altered mental status, autonomic instability, and neuromuscular excitation (tremor, myoclonus, hyperreflexia, clonus).
Etiology	Excessive serotonin stimulation, often from SSRIs, SNRIs, or interactions with MAO inhibitors.
Differentiation from NMS	Unlike NMS, SS typically does not feature severely elevated CPK, leukocytosis, or low serum iron.
Treatment	Removal of offending agents, supportive care, and cyproheptadine (5-HT1A antagonist).

Parkinsonism-Hyperpyrexia Syndrome (PHS)

Attribute	Detail
Etiology	Results from abrupt withdrawal or reduction of dopaminergic medications (e.g., levodopa).
Clinical features	Indistinguishable from NMS but occurs in patients with pre-existing parkinsonism.
Emergency protocol	Supportive measures and immediate reinstitution of dopaminergic therapy. Bromocriptine and dantrolene may be added as adjuncts.

⚠ WARNING

Never abruptly discontinue dopaminergic therapy in a Parkinson's disease patient (e.g., before surgery) without a bridging plan — this can precipitate parkinsonism-hyperpyrexia syndrome, a condition indistinguishable from NMS.

IV. Comparison Table: NMS vs. Serotonin Syndrome

Feature	Neuroleptic Malignant Syndrome	Serotonin Syndrome
Onset	Acute (minutes to hours)	Subacute (days)
Resolution	Gradual (average 9 days)	Fast (improves in <24 hours)
Muscle rigidity	Present (>90%)	Present (50%)
Hyperreflexia	Rare	Common (50%)
Myoclonus	Rare	Common (50%)

Feature	Neuroleptic Malignant Syndrome	Serotonin Syndrome
CPK level	Elevated (>90%)	Normal (<20% elevated)
Leukocytosis	Present (>90%)	Uncommon (<15%)

CHAPTER 10

Advanced Therapeutics (DBS) and Functional Movement Disorders

I. Deep Brain Stimulation (DBS) in Movement Disorders

Deep brain stimulation is a neurosurgical intervention that delivers circuit-based neuromodulation to specific basal ganglia or thalamic targets to symptomatically improve motor function.

A. Selection Criteria for Parkinson's Disease

Criterion	Detail
Disease stage & duration	Candidates typically have idiopathic PD with emergent troublesome or disabling motor fluctuations (off periods) or levodopa-induced dyskinesias (LID) no longer fully controlled with optimized pharmacotherapy.
Dopaminergic responsiveness	A clear and dramatic response to dopaminergic therapy is a critical supportive criterion and a predictor of DBS success.
Early intervention threshold	DBS has shown efficacy in patients with early-onset PD (onset approximately age 50) within 1–2 years of the emergence of motor fluctuations.
Cognitive & screening factors	Successful outcomes require an intact cognitive profile and an experienced multidisciplinary screening team to ensure readiness for the procedure and device optimization.

B. Anatomical Targets and Indications

Target	Indication
Subthalamic nucleus (STN)	Primary target for PD; particularly effective for reducing motor fluctuations and allowing reduction of dopaminergic medication.
Globus pallidus internus (GPi) — for PD	Standard target alongside the STN; often favored when suppression of dyskinesias is the primary goal.

Target	Indication
Globus pallidus internus (GPi) — for dystonia	Mainstay surgical target for generalized or segmental dystonia, offering sustained benefit, particularly in TOR1A-associated dystonia.
Ventral intermediate nucleus of the thalamus (Vim)	Primary target for essential tremor; also effective for tremor-predominant PD when tremor is the most disabling feature.

C. Side Effects and Complications

Category	Detail
Surgical risks	Cerebral hemorrhage is uncommon but serious; infections are more frequent but typically occur outside the brain, sometimes requiring device removal.
Stimulation-induced: speech & sensation	Dysarthria (slurred speech) or sensory disturbances.
Stimulation-induced: motor incoordination	Stimulation-induced ataxia or dysmetria may emerge if stimulation settings are too high while attempting to alleviate kinetic tremor.
Long-term factors	Loss of benefit may occur over time, likely due to underlying disease progression rather than device failure.

DBS Target Selection — Quick Reference

Disorder	Preferred DBS Target
Parkinson's disease (fluctuations)	STN
Parkinson's disease (dyskinesia-predominant)	GPi
Tremor-predominant PD	Vim (or STN)
Essential tremor	Vim
Generalized / segmental dystonia (incl. TOR1A)	GPi

II. Functional Movement Disorders (FMD)

Functional movement disorders are characterized by a disorder of voluntary movement or motor agency, manifest by impaired voluntary movement in the presence of normal automatic movement.

A. Clinical Diagnostic Features

Feature	Description
Onset and progression	Often an abrupt or sudden onset with rapid progression to maximal disability.
Phenomenology	Movements are typically variable and inconsistent over time, often triggered by emotional or physical stressors.
Remissions	Symptoms may feature spontaneous remissions or a placebo response to non-potent interventions.
Distractibility	The involuntary movement (e.g., tremor or jerk) diminishes or ceases when the patient's attention is directed elsewhere, such as performing a complex task with another limb.

B. Positive Signs on Examination ("Rule-In" Signs)

Sign	Description
Hoover's sign	For functional leg weakness: weakness of hip extension briefly returns to normal strength when the patient is asked to flex the contralateral hip against resistance.
Tremor entrainment test	A functional tremor shifts its frequency to match the rhythm of a voluntary repetitive movement performed by a different body part.
Improved automatic movements	Patients may show improved gait when walking faster or backward, or when using a treadmill, despite severe difficulty with normal forward walking.
Mirror feedback	Many patients are surprised by the appearance of their abnormal posture when viewing it in a full-length mirror or on video.

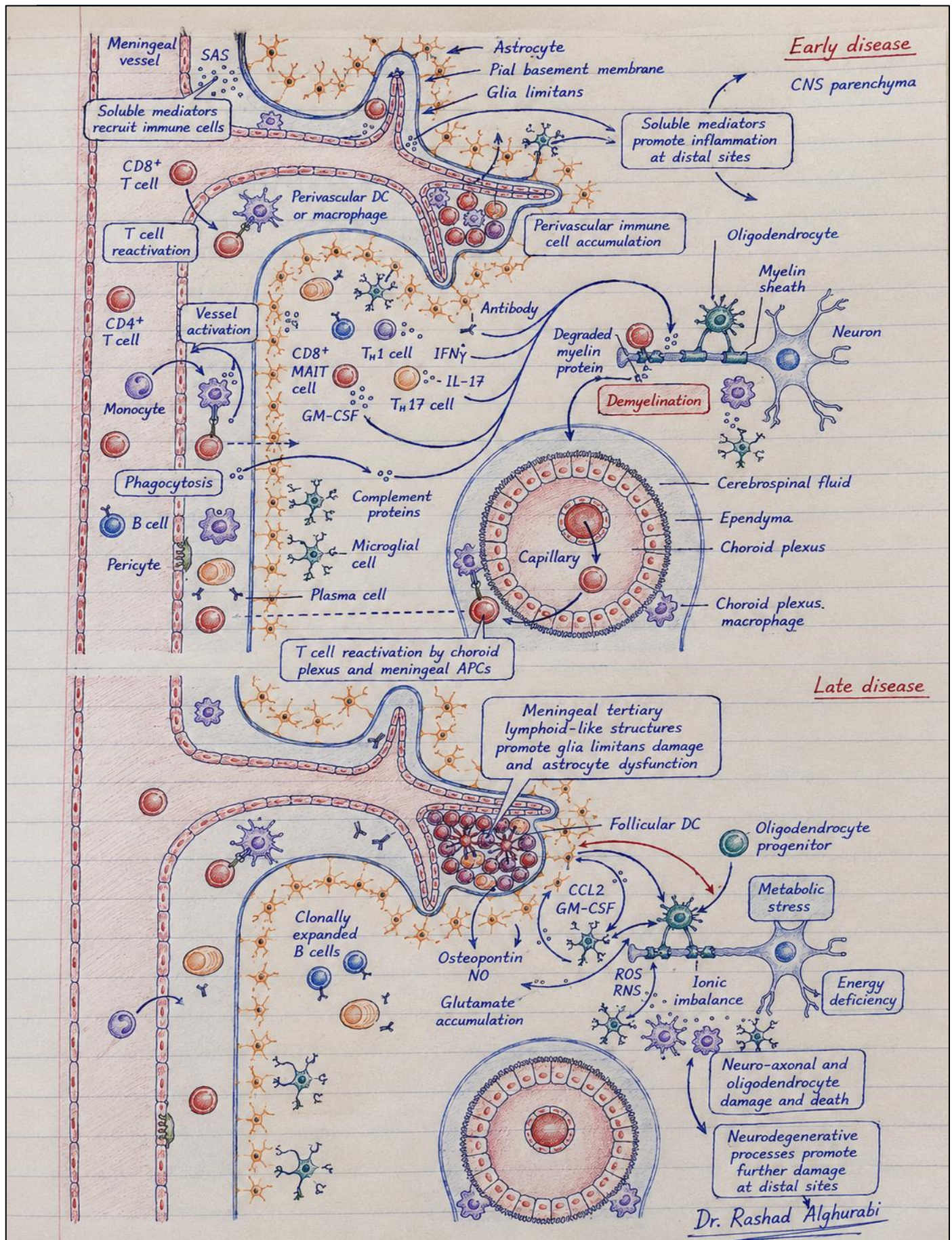
C. Management Principles

- **Multidisciplinary approach:** management requires a team including neurologists, psychiatrists, and specialized rehabilitation therapists (physiotherapists, speech therapists, occupational therapists).
- **"Rule-in" diagnosis:** diagnosis should be based on positive clinical features (e.g., entrainment) rather than a diagnosis of exclusion because other tests are normal.
- **Patient education:** therapy is unlikely to succeed unless the patient is confident in the explanation (e.g., "the software is fine, but the system is out of tune") and is an active partner in treatment.
- **Avoiding invasive diagnostics:** investigations are appropriate to look for comorbidities but are not necessary to make the primary diagnosis of FMD.
- **Rehabilitative strategies:** FND-specific physiotherapy promotes automatic movement while suppressing abnormal voluntary pathways.

★ HIGH YIELD

FMD is a "rule-in" diagnosis based on positive signs (Hoover's sign, entrainment, distractibility) — not a diagnosis of exclusion. Communicating this clearly to patients improves engagement with rehabilitation.

MULTIPLE SCLEROSIS



Immunopathogenesis, Pathology, and Clinical Phenotypes of Multiple Sclerosis

I. Immunopathogenesis and Pathology

Multiple sclerosis (MS) is a chronic immune-mediated disease of the **central nervous system (CNS)** characterized by a triad of **inflammation, demyelination, and neurodegeneration**. The **immunopathogenesis** involves a complex interplay of peripheral immune activation and compartmentalized CNS processes.

Cellular Pathophysiology

- **T-cell and CD8+ infiltration:** The disease is driven by infiltration of the CNS by peripheral immune cells, including **CD8+ T-cell infiltrates**, a hallmark of MS pathology.
- **Th17 cells:** T-helper 17 (Th17) cells play a crucial role by supporting immunoglobulin synthesis and cytokine secretion.

B-Cell Mechanisms

- **Meningeal B-cell follicles:** The involvement of **B-cell follicles** within the meninges is a recognized driver of **progressive disease biology**. These **meningeal lymphoid-like follicles** contribute to the localized inflammatory environment.

Glial Activation and Astrogliosis

- Chronic lesions are characterized by **astrocytic damage, gliosis**, and activation of **microglia**.
- **Paramagnetic rim lesions (PRLs):** Visualized on susceptibility-weighted imaging, these represent **chronic active “smoldering” lesions** surrounded by a rim of **iron-laden activated microglia**.

Neurodegeneration and Axonal Pathology

- Permanent disability is attributed to **axonal injury, denuded axons**, and **retrograde axonal degeneration**.
- **Driving mechanisms:** Energetic failure, oxidative stress, mitochondrial changes, and glutamate excitotoxicity.

Cortical Demyelination

- MS pathology features **confluent cortical demyelination**, which can occur independently of white matter involvement and is highly specific for the disease.

Smoldering MS and PIRA

The concept of **Progression Independent of Relapse Activity (PIRA)** highlights that progressive neurodegeneration occurs as a **continuum across all forms of MS**, often early in the disease course, rather than being confined to a late phase.

★ HIGH YIELD

Smoldering MS reflects compartmentalized CNS inflammation — driven by meningeal B-cell follicles, chronic active (PRL) lesions, and diffuse microglial activation — that persists **independently of peripheral immune activity** and is largely invisible to conventional relapse-based monitoring.

II. Clinical Phenotypes (2024/2026 Updates)

The 2024 McDonald criteria emphasize a **unified diagnostic framework** across the lifespan, integrating clinical and paraclinical findings.

MS Phenotype Classification

Phenotype	Definition	Key Features
Clinically Isolated Syndrome (CIS)	Monophasic clinical episode reflecting a monofocal or multifocal inflammatory demyelinating CNS event	Symptoms must last ≥ 24 hours in the absence of fever or infection
Relapsing-Remitting MS (RRMS)	Multifocal clinical relapses over time	Periods of stability (remission) between attacks
Secondary Progressive MS (SPMS)	Slowly accumulating neurodegeneration and disability worsening	Typically occurs years after an initial relapsing-relmitting course
Primary Progressive MS (PPMS)	Steadily increasing, objectively documented neurologic disability independent of relapses	Progression present for ≥ 12 months

📌 IMPORTANT NOTE

2024 Diagnostic Update — Progressive Onset: In patients with progressive onset, **two or more spinal cord lesions** are now sufficient to demonstrate **dissemination in space (DIS)**, even if brain MRI is normal.

Defining Disease Activity and Progression

Term	Definition
Active disease	Punctuated by acute/subacute clinical relapses, or new/newly enlarging T2-weighted or gadolinium-enhancing lesions on MRI
Not active	Absence of relapses and absence of new/enlarging T2 or gadolinium-enhancing lesions
With progression	Steady, objective neurologic worsening independent of relapses
Without progression	No steady objective neurologic worsening independent of relapses

III. Classic Syndromes and Clinical Pearls

Optic Neuritis (ON)

Typically presents with **mild-to-moderate unilateral visual loss**, a **central scotoma**, and **retro-orbital pain** that worsens with eye movement.

◆ CLINICAL PEARL

Examination often reveals a **relative afferent pupillary defect (RAPD)**, also known as a **Marcus Gunn pupil**. The optic disc may appear normal or mildly swollen.

Internuclear Ophthalmoplegia (INO)

Results from a lesion in the **medial longitudinal fasciculus (MLF)**.

◆ CLINICAL PEARL

On lateral gaze, there is **failure of adduction** in the ipsilateral eye and **nystagmus** in the contralateral abducting eye. **Bilateral INO in a young patient is highly suggestive of MS.**

Classic Sensory and Motor Signs

Sign	Description	Clinical Significance
Lhermitte's Sign	Electrical sensation or tingling arising from the neck and radiating down the back and into the limbs, triggered by neck flexion	Indicates a cervical spinal cord lesion
Uhthoff's Phenomenon	Temporary flare or worsening of neurologic symptoms with increased core body temperature (exercise, fever, hot bath)	Reflects conduction block in demyelinated axons; not a true relapse
Pulfrich Effect	Distorted spatial perception of moving objects	Associated with unilateral conduction delay in the optic nerve
MS Hug	Tight, band-like sensation around the chest or abdomen	Associated with spinal cord demyelination
McArdle Sign	Transient reversibility of upper limb weakness specifically with neck flexion	Highly specific for an MS cervical cord lesion

Transverse Myelitis (TM) in MS

Typical MS spinal cord lesions are **short-segment** (less than two vertebral segments), **eccentric/peripherally located** (often dorsolaterally), and occupy **less than one-half of the cord's cross-sectional area**.

📌 MEMORY TIP / MNEMONIC

"SHORT and OFF-CENTER" — typical MS cord lesions are Short-segment, Off-center (eccentric/dorsolateral), and occupy less than half the cord cross-section. Contrast this with NMOSD's LETM, which is Long (≥ 3 segments) and Central.

Diagnostic Criteria (McDonald 2024), Neuroimaging Protocols, and Biomarkers

I. McDonald Diagnostic Criteria (2024 Revisions)

The 2024 McDonald criteria provide a **unified diagnostic framework** applicable across the lifespan, incorporating advanced imaging and fluid biomarkers to facilitate earlier diagnosis while maintaining high specificity.

Dissemination in Space (DIS)

Verification requires the presence of one or more T2-hyperintense lesions in at least **two of five characteristic anatomic locations**:

#	Anatomic Location	Notes
1	Periventricular	Round-to-ovoid lesions ≥ 3 mm in direct contact with lateral ventricles, axis perpendicular to the ventricle ("Dawson's fingers")
2	Cortical or juxtacortical	White matter lesions in contact with or within the cortex; DIR or PSIR sequences required for precise visualization
3	Infratentorial	Ovoid lesions in the brainstem (often peripheral/subpial) or cerebellum
4	Spinal cord	Short-segment (< 2 vertebral segments), eccentric/dorsolateral, < 50% of cord cross-sectional area
5	Optic nerve (new in 2024)	See below — MRI, OCT, or VEP criteria

★ **HIGH YIELD**

Optic Nerve — the New Fifth Topography: Optic nerve involvement can now be demonstrated via MRI (short-segment intrinsic lesions), **optical coherence tomography (OCT)** (pRNFL inter-eye difference ≥ 6 μm or mGCIPL difference ≥ 4 μm), or **visual evoked potentials (VEP)** (unilateral latency prolongation).

📌 **IMPORTANT NOTE**

Progressive Onset Framework: In patients with ≥ 12 months of objective progression, DIS can be satisfied by **two or more spinal cord lesions**, even if brain imaging is normal.

Dissemination in Time (DIT)

- A new clinical attack;
- The presence of one or more new T2 lesions on follow-up MRI; or

- Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions on any single scan.

Paraclinical Substitutes for DIT

Positive CSF findings — specifically **CSF-restricted oligoclonal bands (OCBs)** or an elevated **kappa free light chain (kFLC) index (≥ 6.1)** — can substitute for the requirement of radiologic or clinical DIT.

Radiologically Isolated Syndrome (RIS) as MS

Asymptomatic patients with incidental MRI findings meeting DIS in ≥ 2 locations can be diagnosed with MS if they also demonstrate **DIT, positive CSF, or Select-6 CVS positivity**.

Exclusion Criteria and Red Flags

MS remains a **diagnosis of exclusion**, requiring reasonable elimination of mimics.

Category	Red Flags
Clinical	Transient symptoms < 24 hours; bilateral or severe unilateral optic neuritis with poor recovery (consider NMOSD/MOGAD); isolated headache or meningismus
MRI (MIMICS mnemonic)	Meningeal enhancement • Indistinct/increasing lesions • Macro/microbleeds • Infarcts • Cavities/complete ring enhancement • Symmetric or longitudinally extensive cord lesions (≥ 3 segments)
MEMORY TIP / MNEMONIC MIMICS — M: Meningeal enhancement • I: Indistinct/increasing lesions • M: Macro/microbleeds • I: Infarcts • C: Cavities/complete ring enhancement • S: Symmetric or longitudinally extensive (≥ 3 -segment) cord lesions. Any of these should trigger a search for an MS mimic.	

II. Neuroimaging Protocols and Radiological Signatures

High-field **3T MRI** is the preferred platform for diagnosis, though 1.5T remains acceptable with optimized parameters.

Technical Requirements for Advanced Biomarkers

Biomarker	Required Sequence
Central Vein Sign (CVS)	3D T2*-weighted echo-planar imaging (EPI) or optimized 3D susceptibility-weighted imaging (SWI) with magnitude-filtered phase
Paramagnetic Rim Lesions (PRLs)	Susceptibility-based phase imaging to detect iron-laden activated microglia; filtered phase images are superior for detection

Critical Discriminators

- **Select-6 CVS Criteria:** Positive if ≥ 6 white matter lesions demonstrate a central vein; if < 10 lesions are present, the majority must be CVS-positive.
- **PRL Presence:** Highly specific for MS; characterized by a discrete, continuous paramagnetic rim around $\geq 2/3$ of a non-enhancing T2-hyperintense lesion edge.

III. CSF Analysis and Peripheral Biomarkers

Paraclinical laboratory evidence is now considered **essential** in most diagnostic pathways to prevent misdiagnosis.

Intrathecal Immunoglobulin Synthesis

Marker	Interpretation
IgG Index	Values > 0.700 typically indicate intrathecal production
Oligoclonal Bands (OCBs)	≥ 2 unique CSF-restricted bands (Type 2: CSF-restricted; Type 3: CSF-restricted with shared bands in serum/CSF)
Kappa Free Light Chain (kFLC) Index	Ratio-based quantitative metric (cutoff ≥ 6.1); interchangeable with OCBs in the 2024 criteria due to observer-independent results

Peripheral Blood Biomarkers and Kinetics

Biomarker	Reflects	Kinetics
Serum Neurofilament Light Chain (NfL)	Axonal damage	Peaks ~ 5 weeks post-attack; declines slowly over 20 weeks
Glial Fibrillary Acidic Protein (GFAP)	Astrocytic/glial injury	Peaks rapidly within 1 week of attack; declines sharply over the following 12 weeks

★ HIGH YIELD

MS vs. NMOSD by Biomarker Profile: Higher GFAP levels (z-score > 3.0) and elevated GFAP/NfL ratios are highly suggestive of **NMOSD astrocytopathy**, in contrast to the primarily axonal/demyelinating biomarker profile of MS.

Disease-Modifying Therapies (DMTs) in Multiple Sclerosis

This chapter consolidates DMT classification, mechanism of action, and the **complete pharmacotherapy reference** — exact dosing, pre-treatment clearance, and monitoring protocols — for MS, NMOSD, and MOGAD therapeutics.

I. Platform Therapies (Low Efficacy)

Platform therapies are generally utilized for mild-to-moderate MS and are characterized by a favorable long-term safety profile with minimal infection risk.

Interferon Beta-1a & 1b

- **Mechanism:** Immunomodulatory cytokine therapy.
- **Dosing:** Interferon beta-1a — intramuscular (IM) or subcutaneous (SC); Interferon beta-1b — SC; Peginterferon beta-1a — SC.
- **Monitoring:** Generally not associated with increased infection risk. Rarely associated with development of sarcoidosis.

Glatiramer Acetate

- **Mechanism:** Glatiramoid; acts as a decoy for myelin basic protein.
- **Dosing:** SC administration.
- **Monitoring:** No increased risk of opportunistic infections. Clinical monitoring for injection-site lipoatrophy is essential.

II. Disease-Modifying Therapy Classes — Mechanism Overview

Oral Therapies (Moderate to High Efficacy)

Oral DMTs offer enhanced efficacy over platform agents but require more stringent laboratory and clinical monitoring.

S1P Receptor Modulators (Fingolimod, Siponimod, Ozanimod, Ponesimod)

- **Mechanism:** Sequesters lymphocytes within lymphoid organs by preventing egress into systemic circulation.
- **Cardiac:** Baseline EKG and first-dose observation (FDO) protocols required to monitor for bradycardia and AV block.
- **Ophthalmic:** Periodic screening for macular edema is mandatory.
- **Infections:** High risk for varicella-zoster virus (VZV), herpes simplex virus (HSV), Cryptococcus (including meningitis), Toxoplasmosis, and atypical mycobacteria.

⚠ WARNING

Washout Trap: Abrupt discontinuation of S1P modulators is strictly discouraged due to the risk of a severe clinical rebound of MS activity.

Fumarates (Dimethyl Fumarate, Diroximel Fumarate)

- **Mechanism:** Activates the Nrf2 antioxidant response pathway; immunomodulatory and neuroprotective potential.
- **Hematologic:** Monitor for leukopenia and lymphopenia.
- **Infections:** PML risk is elevated in patients with prolonged grade 2/3 lymphopenia.
- **Tolerability:** Flushing and GI distress are common; diroximel fumarate may offer improved GI tolerability.

Teriflunomide

- **Mechanism:** Inhibits dihydroorotate dehydrogenase (DHODH), halting de novo pyrimidine synthesis in proliferating T and B cells.

- **Hepatic:** Severe hepatotoxicity risk; requires monthly LFT monitoring for the first 6 months.
- **Hematologic:** Monitor for neutropenia in the first few weeks.
- **Other:** Monitor for alopecia and tuberculosis reactivation.

✗ EMERGENCY

Category X Teratogen: Requires an accelerated elimination protocol using cholestyramine or activated charcoal for patients planning pregnancy or following accidental exposure.

Cladribine

- **Mechanism:** Purine analog inducing transient depletion of B and T cells; categorized as an immune reconstitution/induction therapy.
- **Dosing:** Weight-based oral administration, divided into two yearly treatment cycles.
- **Monitoring:** Requires strict lymphocyte tier gating before and after each cycle. Carries a warning for potential malignancy risk.

Injectable Monoclonal Antibodies (High Efficacy)

Monoclonal antibodies represent the most potent DMT class, targeting specific cell surface markers or trafficking molecules.

Anti-CD20 Infusions (Ocrelizumab, Ofatumumab, Rituximab, Ublituximab)

- **Mechanism:** Selective depletion of CD20+ B cells.
- **Screening:** Mandatory baseline screening for Hepatitis B (HBsAg and HBcAb) due to reactivation risk. Screen for hypogammaglobulinemia (IgG/IgM levels) and tuberculosis.
- **Vaccination:** Vaccines should be administered at least 4 weeks prior to initiation. Antibody responses are blunted, but T-cell responses remain robust.

Natalizumab

- **Mechanism:** Anti-alpha-4 integrin; blocks interaction with VCAM-1, preventing lymphocyte trafficking across the blood–brain barrier.
- **PML Stratification:** Risk tiered by JCV antibody index (thresholds > 0.9 or > 1.5), prior immunosuppressant use, and treatment duration (> 24 months). JCV status rechecked every 6 months.

⚠ WARNING

Rebound Risk: High risk of severe inflammatory rebound if natalizumab is discontinued without prompt bridging to another DMT.

Alemtuzumab

- **Mechanism:** Anti-CD52; causes rapid, profound depletion of nearly all lymphocyte subsets.
- **Monitoring:** Requires 48 months of monthly safety monitoring (blood/urine) post-final dose.

⚠ WARNING

Secondary Autoimmunity: High risk of ITP, anti-GBM disease (Goodpasture syndrome), and thyroiditis.

Emerging Therapies — BTK Inhibitors

- **Tolebrutinib, Evobrutinib, Fenebrutinib:** CNS-penetrant inhibitors targeting microglia, monocytes, and B cells.
- **Current Data:** Tolebrutinib demonstrated a statistically significant 24% to 31% reduction in confirmed disability progression in nonrelapsing SPMS.
- **Safety Signal:** Associated with a risk of aspergillosis.

Clinical Monitoring Summary Table

DMT Class	Target Lymphocyte / Safety Threshold	Primary Monitoring Parameter
Fumarates	Avoid if lymphocytes < 500/ μ L chronically	Absolute Lymphocyte Count (ALC)
Teriflunomide	Accelerated elimination if pregnancy planned	ALT/AST, Neutrophils, TB Screen
S1P Modulators	Monitor for lymphopenia-associated infections	FDO EKG, Macular OCT, VZV/HSV status
Anti-CD20	Monitor for IgG < 400–500 mg/dL	Hepatitis B status, Quantitative Igs
Natalizumab	Risk increases significantly with JCV index > 0.9	JCV Index (q6 months), MRI (PML surveillance)
Cladribine	Cycle gating based on ALC recovery	Yearly ALC cycles, Malignancy screen

III. Complete Pharmacotherapy Reference — Exact Dosing, Pre-Clearance, and Safety Protocols

This section provides comprehensive dosing profiles for therapies utilized in Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorder (NMOSD), and Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease (MOGAD).

Oral Disease-Modifying Therapies

Drug	Exact Dosage	Pre-Clearance Screening	Monitoring
Fingolimod	Starting/maintenance: 0.5 mg PO daily. Pediatric (< 40 kg): 0.25 mg PO daily.	Baseline EKG, LFTs, VZV serology (vaccinate if seronegative $\geq$ 1 month before start). Baseline macular edema screening via OCT.	FDO: 6-hour EKG monitoring for bradycardia/AV block for initial dose and if treatment missed $\geq$ 2 weeks. Repeat macular OCT at 3–4 months. Monitor for VZV, HSV, Cryptococcus, atypical mycobacteria.
Siponimod	5-day titration; maintenance based on CYP2C9 genotype — 2 mg daily (most genotypes) or 1 mg daily	Mandatory CYP2C9 genotyping (contraindicated in CYP2C9*3/*3). Baseline EKG and LFTs.	FDO required only for patients with specific preexisting cardiac conditions.

Drug	Exact Dosage	Pre-Clearance Screening	Monitoring
	(specific variants). Max 2 mg daily.		
Ozanimod & Ponesimod	Multi-day titration schemes to maintenance; PO daily thereafter.	Baseline LFTs and EKG.	Periodic LFT monitoring.
Dimethyl Fumarate / Diroximel Fumarate	Starting: 120 mg BID × 7 days. Maintenance: 240 mg BID.	Baseline CBC with differential (ALC).	Monitor ALC every 6 months. Discontinue/hold if ALC < 500/ μ L persists > 6 months (PML risk). Monitor flushing/GI distress.
Teriflunomide	7 mg or 14 mg PO daily.	LFTs, CBC (neutrophils), BP, TB screen. Pregnancy test (Category X).	Monthly LFTs for first 6 months. Accelerated elimination: cholestyramine 8 g TID × 11 days OR activated charcoal 50 g BID × 11 days to reach plasma level < 0.02 mg/L.
Cladribine	3.5 mg/kg total body weight, divided into two yearly treatment cycles.	TB screen, Hepatitis B/C, VZV serology, malignancy screening.	Strict ALC tier gating before each yearly cycle and at 2 and 6 months after each cycle.

Infusion and Injectable Monoclonal Antibodies

Drug	Exact Dosage	Pre-Medication / Pre-Clearance	Monitoring
Ocrelizumab	Initial: 300 mg IV Day 0 and Day 14 (split infusion). Maintenance: 600 mg IV every 6 months.	Methylprednisolone 100 mg IV plus antihistamines pre-infusion. Hepatitis B panel (HBsAg + HBcAb mandatory), TB screen, HIV, quantitative Igs.	Monitor for hypogammaglobulinemia; hold if IgG < 400–500 mg/dL or severe/recurrent infections.
Ublituximab	IV infusion every 6 months.	Same as Ocrelizumab.	Same as Ocrelizumab.
Ofatumumab	Starting: 20 mg SC at Weeks 0, 1, 2. Maintenance: 20 mg SC monthly.	Same as anti-CD20 infusions (Hepatitis B, TB, Igs).	Monitor for hypogammaglobulinemia.
Natalizumab	Standard: 300 mg IV every 4 weeks. Extended Interval Dosing (EID): 300 mg IV every 6 weeks (reduces PML risk).	Baseline JCV antibody index.	JCV stratification: Low risk < 0.9; High risk > 1.5. Recheck JCV index every 6 months. Increased MRI surveillance frequency if JCV index > 0.9 and duration > 24 months.

Drug	Exact Dosage	Pre-Medication / Pre-Clearance	Monitoring
Alemtuzumab	Course 1: 12 mg/day IV × 5 consecutive days. Course 2: 12 mg/day IV × 3 consecutive days, 12 months after Course 1.	—	Mandatory 48-month post-treatment protocol — Monthly: CBC with differential, serum creatinine, urinalysis (screen for ITP and anti-GBM/Goodpasture disease). Every 3 months: Thyroid function tests.

Acute Relapse Management and Comprehensive Symptomatic Pharmacotherapy

I. Acute Relapse Management

IMPORTANT NOTE

Clinical Relapse Definition: New or worsening neurologic symptoms attributable to MS, lasting at least **24 hours**, in the absence of fever or infection, and preceded by clinical stability for at least **30 days**.

High-Dose Corticosteroid Protocols

Population / Regimen	Dosage
Standard IV Methylprednisolone (adults)	1000 mg IV daily for 3 to 5 days
Alternative IV regimen (MS)	500 mg IV daily for 5 days
Oral bioequivalent (adults)	1250 mg oral Prednisone once daily for 5 days (equally effective in hastening recovery)
Pediatric (ADEM/MOGAD)	30 mg/kg/day IV (Max 1 g/day) for 3 to 5 days; oral equivalent 500 mg oral Methylprednisolone
Corticosteroid taper (post-pulse)	Oral Prednisone taper, e.g., starting at 40 mg, over 4 to 6 weeks, to prevent early rebound relapses

Plasma Exchange (PLEX) / Immunoabsorption

- **Indications:** First-line rescue for steroid-refractory fulminant attacks or severe presentations where complete recovery is not achieved with steroids alone.
- **Schedule:** 5 to 7 exchanges, typically performed every other day.
- **Exchange volume:** 1 to 1.5 plasma volumes per treatment.

II. Spasticity and Gait Impairment

Dalfampridine (Gait Impairment)

- **Mechanism:** Voltage-gated potassium channel blocker that improves action potential conduction in demyelinated axons.
- **Dosing:** 10 mg PO twice daily, administered exactly 12 hours apart (Max 20 mg/day).

✗ EMERGENCY

Absolute Contraindications: History of seizures OR creatinine clearance (CrCl) $\leq$ 50 mL/min.

Spasticity Agents

Drug	Dosing	Key Monitoring / Caution
Baclofen	Starting: 10 mg PO BID; titrate to clinical effect	Balance spasticity reduction against systemic weakness and sedation. Intrathecal pumps reserved for severe, refractory spasticity.
Tizanidine	Minimum effective dose	Mandatory LFT monitoring — hepatotoxicity risk

III. Paroxysmal Symptoms, Pain, and Fatigue

Paroxysmal Symptoms (Tonic Spasms & Trigeminal Neuralgia)

Sodium channel-blocking antiseizure medications are the gold standard. **Carbamazepine** and **Oxcarbazepine** are highly effective for painful, stereotyped unilateral muscle contractions (tonic spasms) or lancinating trigeminal neuralgia.

Central Neuropathic Pain

- **Gabapentin:** Used for bodily pain and eye movement abnormalities (nystagmus, vertigo) at a total daily dose of 1200 mg.
- **Pregabalin & Duloxetine:** First-line systemic therapies for generalized neuropathic pain syndromes.

MS Fatigue Management

- **Amantadine, Modafinil, Armodafinil:** Carry low levels of evidence; use requires caution due to potential side effects. Limit stimulants when the patient is already taking sedating medications.
- **Melatonin:** 0.5 mg to 3 mg may be used for comorbid sleep disruption contributing to secondary fatigue.

IV. Neurogenic Bladder and Bowel Management

Neurogenic Bladder

Dysfunction	Management
Detrusor hyperreflexia (urgency/frequency)	Anticholinergics/antimuscarinics (Oxybutynin, Solifenacin — risk of confusion/constipation; Tolterodine — lower dry-mouth risk). β 3-adrenergic agonists (Mirabegron, Vibegron) preferred for a more favorable cognitive profile.

Dysfunction	Management
Detrusor-sphincter dyssynergia (retention)	Indicated if postvoid residual (PVR) > 100 mL. Intermittent self-catheterization is primary management; alpha-blockers or suprapubic catheters in complex cases.
Refractory detrusor overactivity	OnabotulinumtoxinA — direct bladder injections

Neurogenic Bowel

- **Mild constipation:** Bulking agents (bran, psyllium) or surfactant laxatives (docusate).
- **Chronic constipation:** Osmotic laxatives — polyethylene glycol, lactulose, or magnesium salts.
- **Enemas:** Use is generally limited in the MS population.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, severe, relapsing inflammatory disorder of the CNS that is distinct from multiple sclerosis.

I. Pathophysiology and Diagnostic Criteria

Astrocytopathy Mechanism

NMOSD is primarily an **autoimmune astrocytopathy** driven by **AQP4-IgG antibodies**, which target the **aquaporin-4 (AQP4) water channel** concentrated on astrocyte endfeet.

Cellular Cascade and Pathologic Hallmarks

- Binding of AQP4-IgG triggers **complement-dependent cytotoxicity (CDC)** and **antibody-dependent cellular cytotoxicity (ADCC)**, leading to primary astrocytic injury, secondary demyelination, and neuronal loss.
- Active lesions demonstrate **AQP4 loss**, **C9neo complement deposition**, and infiltrates rich in **neutrophils** and **eosinophils**.

Antibody Screening

Cell-based assays (CBA), either fixed or live, are the gold standard for detection due to superior sensitivity and specificity. **ELISA and Western blot** are discouraged given a higher risk of false results. Retesting is indicated only in highly suggestive seronegative cases or if the initial sample was taken during immunosuppression.

IPND 2015 Diagnostic Criteria

Category	Requirements
NMOSD with AQP4-IgG	≥ 1 core clinical characteristic + positive CBA for AQP4-IgG + exclusion of alternative diagnoses
Seronegative NMOSD	≥ 2 core clinical characteristics from one or more attacks (≥ 1 must be ON, LETM, or APS) + dissemination in space + additional MRI requirements

Core Clinical Manifestations

Manifestation	Key Features
Optic Neuritis (ON)	Often severe (visual acuity $\leq 20/200$); frequently bilateral
Acute Myelitis	Characterized by longitudinally extensive transverse myelitis (LETM)
Area Postrema Syndrome (APS)	Intractable hiccups, nausea, or vomiting
Acute Brainstem Syndrome	Ocular motor disorders, facial palsy, or vestibular dysfunction
Diencephalic Syndrome	Hypersomnia, narcolepsy, hyperphagia, or SIADH-induced hyponatremia
Symptomatic Cerebral Syndrome	Encephalopathic symptoms with NMOSD-typical brain lesions

II. Neuroimaging Characteristics

- **Optic nerve:** Posterior involvement frequently extending into the optic chiasm or tract; lesions are longitudinally extensive, involving more than half the nerve's length.
- **Spinal cord (LETM):** T2-hyperintense intramedullary lesion extending over ≥ 3 contiguous vertebral segments. Central cord swelling and “bright spotty lesions” (intralesional T2-hyperintensities brighter than CSF) are common; ring-like or lens-shaped enhancement may occur acutely.
- **APS:** Lesions localized to the dorsal medulla or area postrema.
- **Periependymal lesions:** Signal abnormalities surrounding the third and fourth ventricles, in regions of high AQP4 expression.
- **Cloud-like enhancement:** Acute brain lesions may demonstrate blurred, “cloud-like” margins.

📌 MEMORY TIP / MNEMONIC

LETM = Longitudinally Extensive Transverse Myelitis (≥ 3 vertebral segments) — the hallmark spinal cord signature that distinguishes NMOSD from the short-segment lesions typical of MS.

III. High-Yield Targeted Therapies and Dosing

✖ EMERGENCY

Critical Safety Warning: Standard MS DMTs — **Interferon-beta, Fingolimod, and Natalizumab** — are known to **exacerbate NMOSD** and can trigger fulminant, life-threatening relapses. NMOSD management differs critically from MS.

Acute Attack Management

- **High-dose steroids:** IV Methylprednisolone 1 g daily for 3 to 7 days.
- **PLEX:** Rapid escalation to plasma exchange (5 to 7 sessions every other day) is an emergency mandate if steroids fail to produce immediate improvement.

Maintenance Targeted Therapeutics

Agent	Mechanism	Dosing
Rituximab (off-label, Anti-CD20)	Selective B-cell depletion	1000 mg IV, repeated at 2 weeks, then maintenance 1000 mg every 6 months
Inebilizumab (Anti-CD19)	Targets CD19 to deplete B cells, plasmablasts, and plasma cells	300 mg IV Day 0 and Day 14, then 300 mg every 6 months
Eculizumab (C5 complement inhibitor)	Blocks cleavage of C5 to prevent terminal complement activation	900 mg IV weekly × 4 weeks, 1200 mg at Week 5, then 1200 mg every 2 weeks
Ravulizumab (C5 complement inhibitor)	Long-acting C5 inhibitor	Weight-based IV infusion every 8 weeks
Satralizumab (IL-6 receptor antagonist)	Inhibits IL-6-mediated inflammation and AQP4-IgG production	120 mg SC at Weeks 0, 2, 4 (loading), then 120 mg SC every 4 weeks
Tocilizumab (off-label, IL-6 receptor antagonist)	Anti-IL-6 receptor monoclonal antibody	8 mg/kg IV every 4 weeks

⚠ WARNING

Vaccine Mandate: Meningococcal vaccination is required at least 2 weeks prior to initiating C5 complement inhibitors (Eculizumab, Ravulizumab) due to the high risk of **Neisseria meningitidis** infection.

Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease (MOGAD) and Acute Disseminated Encephalomyelitis (ADEM)

MOGAD is a recently characterized inflammatory CNS demyelinating disease driven by pathogenic **MOG-IgG** antibodies. It is distinct from multiple sclerosis (MS) and aquaporin-4 antibody–positive NMOSD (AQP4+NMOSD).

I. MOGAD Phenotypes and Diagnostic Criteria

Cellular Pathophysiology

MOGAD is an **oligodendrogliaopathy**. MOG is a protein specifically localized to the surface of **oligodendrocytes** and the outermost layers of the myelin sheath.

International Consensus Diagnostic Criteria (2023)

Diagnosis requires fulfillment of three criteria (A, B, and C):

Criterion	Requirement
(A) Core clinical manifestation	At least one of: acute/subacute optic neuritis, myelitis, ADEM, cerebral monofocal/polyfocal deficits, brainstem/cerebellar deficits, or cerebral cortical encephalitis with seizures
(B) MOG-IgG positivity (cell-based assay)	Clear positive: titer $\geq 1:100$ (fixed CBA) or ≥ 2 doubling dilutions above cutoff (live CBA). Low positive: titers 1:10–1:100 (fixed CBA) — requires additional supporting clinical/MRI features (e.g., bilateral ON, conus lesion, H-sign) and a negative AQP4-IgG test
(C) Exclusion of alternative diagnoses	Specifically MS and other mimics

Clinical Phenotypes — High-Yield Features

Phenotype	Key Features
Optic Neuritis (ON)	Most common attack type in adults. Severe visual loss (median nadir: hand movement); bilateral in 33–50% of cases. Optic disc swelling present in up to 86%.
Acute Myelitis	Often severe — 75% of patients require gait aids at nadir. Hallmark: predilection for the conus medullaris.
Cerebral Cortical Encephalitis (CCE)	Headache, seizures, fever, and cortical dysfunction (e.g., aphasia). MRI shows cortical T2 hyperintensity and swelling.
Brainstem/Cerebellar Syndrome	Diplopia or ataxia, typically part of a multifocal presentation rather than an isolated event.

II. ADEM and Multiphasic Variants

Acute Disseminated Encephalomyelitis (ADEM)

- **Definition:** A “polyfocal” clinical CNS event with a presumed inflammatory etiology, requiring encephalopathy and multifocal brain lesions.
- **MOGAD association:** 30–50% of children presenting with ADEM test positive for MOG-IgG.
- **Multiphasic variants:** Defined as a second ADEM event occurring at least 3 months after the first.

Radiological Signatures (MRI)

Region	Signature
Brain	Large, poorly marginated, “fluffy” T2 lesions involving deep gray matter (thalamus, basal ganglia) and deep white matter. Leptomeningeal enhancement occurs in up to 33% of cerebral attacks.
Spinal cord	70% of myelitis cases demonstrate LETM (≥ 3 segments). Axial T2 images typically show a central H-sign, representing selective gray matter involvement.
Optic nerve	Long-segment enhancement ($> 50\%$ of nerve length) with frequent perineural “tram-track” enhancement and intraorbital fat involvement.

Region	Signature
Lesion dynamics	70–80% of parenchymal T2 lesions resolve by 1 year — a critical differentiator from MS plaques.
📌 MEMORY TIP / MNEMONIC H-sign on axial spinal cord T2 imaging reflects selective gray matter involvement and is characteristic of MOGAD myelitis — distinct from the peripheral, eccentric white matter lesions of MS.	

III. Acute and Maintenance Therapy

Acute Relapse Management

Therapy	Dosing / Notes
High-dose corticosteroids (adults)	1000 mg IV Methylprednisolone daily for 5 days, or 1250 mg oral Prednisone
High-dose corticosteroids (children)	30 mg/kg/day (Max 1 g) for 5 days
Plasma Exchange (PLEX)	Second-line for severe/refractory attacks — 5 to 7 sessions every other day
IVIG (acute)	1–2 g/kg total dose over 2–5 days; third-line rescue, particularly in children
Corticosteroid taper	Prednisone taper starting at 40 mg or 1 mg/kg, over 4–6 weeks, to prevent early rebound relapses

Maintenance Attack-Prevention Therapy

Maintenance therapy is reserved for **relapsing disease** (≥ 2 attacks) or severe monophasic events with poor recovery, as up to **50% of patients have a monophasic course**.

Agent	Dosing	Notes
IVIG	1 g/kg every 3–4 weeks	Currently shows the most promise in retrospective data
Tocilizumab (IL-6 receptor blocker)	4–8 mg/kg IV every 4 weeks, or 162 mg SC weekly	—
Mycophenolate Mofetil	Titrated to maintenance of 1000 mg BID (adults)	—
Azathioprine	Titrated to 2–3 mg/kg total daily dose	—
Rituximab (Anti-CD20)	1000 mg IV, repeated at 2 weeks, then every 6 months	Higher proportion of patients relapse on Rituximab compared to NMOSD

Childhood vs. Adult Variations

- **Age predilection:** MOGAD accounts for ~1/3 of pediatric CNS demyelinating syndromes.
- **Attack type:** ADEM is dominant in children < 12; optic neuritis is dominant in adults.
- **Prognosis:** Most disability is accumulated during the first attack; unlike MS, there is no evidence of a progressive disease phase in MOGAD.

Rare Demyelinating Variants and Inflammatory Mimics of the CNS

I. Rare Demyelinating Variants

Rare variants of MS and atypical demyelinating syndromes often present as diagnostic challenges due to their fulminant nature or unique radiological signatures.

Balo's Concentric Sclerosis

- **Pathophysiology:** Large (typically > 1 cm) demyelinating lesions composed of concentric layers of demyelination alternating with relatively preserved myelin.
- **MRI:** "Onion-skin" or target-shaped appearance. Concentric demyelinated layers are T2-hyperintense; interspersed preserved myelin is T2-isointense.
- **Kinetics:** Expanding lesions show a leading edge of restricted diffusion that precedes gadolinium enhancement at the inner aspect of the lesion edge.
- **Ancillary data:** CSF-restricted OCBs present in approximately 20% to 30% of cases.

Tumefactive Demyelination

- **Definition:** Large demyelinating lesions (> 2 cm) often mistaken for neoplasms, infections, or infarcts.
- **MRI:** Typically characterized by open ring enhancement, with the open side facing the cortex or deep gray matter (specificity of 98% vs. primary neoplasm).
- **Advanced features:** Minimal perilesional edema/mass effect relative to lesion size, a T2-hypointense rim, and a peripheral rim of restricted diffusion. Typically hypometabolic on FDG-PET with reduced cerebral blood volume on CT perfusion.

Marburg Variant and Schilder's Disease

📌 IMPORTANT NOTE

These two entities are not explicitly detailed in the original source material. The following summaries reflect general, well-established clinical neuroimmunology standards and should be corroborated with current primary literature.

- **Marburg Variant:** An acute, fulminant form of MS characterized by rapid, progressive neurologic decline and extensive, destructive demyelinating lesions throughout the CNS.
- **Schilder's Disease:** Traditionally described as diffuse sclerosis, presenting as large, bilateral, symmetric areas of demyelination, most common in children or young adults.

II. Inflammatory and Autoimmune Mimics

These disorders can present with clinical and radiological features that satisfy dissemination in space (DIS) and time (DIT), necessitating rigorous exclusion before an MS diagnosis is rendered.

1. Neuro-Behçet Disease

- **Anatomic predilection:** Large inflammatory lesions typically localized to the brainstem, often extending into the thalamus and basal ganglia.
- **Radiological signature:** On coronal T2-weighted MRI, diencephalic lesions contiguous with the upper brainstem create the “Waterfall sign.”
- **Clinical presentation:** Systemic evaluation often reveals orogenital ulceration, acneiform rash, or uveitis. Most prevalent in populations of Turkish ancestry or along the “Silk Road.”

📌 IMPORTANT NOTE

Specific dosing for Behçet disease is not detailed in the source text; the text acknowledges the use of corticosteroids and anti-TNF therapies (Infliximab, Adalimumab) in neuroinflammatory contexts.

2. Neurosarcoidosis

- **MRI:** Leptomeningeal enhancement (often in the basal cisterns) and cranial neuropathies (CN VII most common).
- **Spinal cord:** Characteristic dorsal subpial linear enhancement on post-gadolinium sequences. Axial sequences at the lesion level may demonstrate a three-pronged “Trident sign.”
- **Clinical:** May involve the hypothalamus or pituitary gland, leading to hypothalamic-pituitary dysfunction or diencephalic syndromes.
- **Ancillary data:** CSF ACE levels and whole-body CT/PET to identify systemic lymphadenopathy are standard diagnostic adjuncts.

📌 IMPORTANT NOTE

Specific neurosarcoidosis dosing is not provided in the source; common agents mentioned for autoimmune management include corticosteroids, Methotrexate, and Infliximab.

3. Primary CNS Vasculitis (PACNS)

- **Clinical profile:** Often presents with a triad of headache, cognitive decline, and multifocal focal deficits.
- **MRI:** Lesions are often heterogeneous, with “cloudy” enhancement and marked areas of restricted diffusion, most prominent at the lesion edges.
- **Diagnosis:** Angiography can show characteristic “beading,” but brain biopsy remains the gold standard for definitive diagnosis, as MRI findings can mimic tumefactive demyelination.

Differential Diagnosis Summary Table

Disorder	Key MRI Clue	Key Clinical Clue
Balo's Concentric Sclerosis	"Onion-skin" / target-shaped lesion	May present with acute, tumor-like fulminant course
Tumefactive Demyelination	Open ring enhancement (open toward cortex/gray matter)	Mimics neoplasm; minimal mass effect for lesion size
Neuro-Behçet Disease	"Waterfall sign" (diencephalic-brainstem lesion continuity)	Orogenital ulcers, uveitis; Turkish/Silk Road ancestry
Neurosarcoidosis	"Trident sign"; dorsal subpial spinal enhancement; basal leptomeningeal enhancement	CN VII palsy; hypothalamic-pituitary dysfunction
Primary CNS Vasculitis (PACNS)	Angiographic "beading"; heterogeneous restricted diffusion at lesion edges	Headache, cognitive decline, multifocal deficits; biopsy is gold standard

Red Flags for Rare Variants and Mimics

Category	Red Flags
Clinical	Hyperacute presentation (< 4 hours); absence of pain in optic neuritis; purely progressive course without relapses
MRI (MIMICS mnemonic)	Meningeal enhancement • Indistinct/increasing lesions • Macro/microbleeds • Infarcts • Cavities/complete ring enhancement • Symmetric lesions or longitudinally extensive cord lesions

MS in Special Populations — Pregnancy, Lactation, Vaccinations, and Quality Metrics

This chapter details clinical management and risk stratification for patients with multiple sclerosis and related neuroinflammatory disorders (NMOSD, MOGAD) during critical life stages and long-term surveillance.

I. Pregnancy and Lactation Management

The management of neuroinflammatory disease during pregnancy requires balancing maternal disease stability against potential fetal risks.

Natural History and Relapse Risk Drivers

- In MS, the **relapse rate decreases significantly during pregnancy**, particularly in the **third trimester**, followed by a **rebound surge in the first 3 months postpartum**.
- Contemporary population-based studies indicate a **postpartum relapse risk of approximately 27%** within the first year, with an annualized relapse rate (ARR) of 0.27 in the first trimester postpartum.
- In **NMOSD**, postpartum relapse risk is increased and strongly correlated with **discontinuation of immunosuppressive treatment** and **AQP4-antibody seropositivity**.

- **Primary risk driver:** Relapses or MRI activity in the year preceding pregnancy are the primary predictors of postpartum disease activity.

DMT Safety Tiers and Protocols

Tier	Agents	Guidance
Tier 1 — Pregnancy-compatible	Glatiramer acetate, Interferon-beta	Can be continued until conception or throughout pregnancy; do not cross the placenta in significant concentrations; not associated with rebound activity upon cessation
Active MS management	Natalizumab	Continuing throughout pregnancy is often justified to prevent rebound relapses; final dose typically administered at 30 to 34 weeks gestation
Tier 2 — Induction/durable efficacy	CD20-antibody therapies (Ocrelizumab, Rituximab), Cladribine	Provide durable disease control; relapse rates remain suppressed during pregnancy even if treatment is paused
Tier 3 — Absolute restrictions/washout	S1P modulators (Fingolimod); Teriflunomide; Cladribine (contraception requirement)	See below

✗ EMERGENCY

S1P Modulators (Fingolimod): Strictly contraindicated due to teratogenicity (4.9% to 12.5% malformation risk); must be switched to a pregnancy-compatible DMT before attempting conception.

⚠ WARNING

Teriflunomide: Requires an accelerated elimination protocol if pregnancy is planned or confirmed.

⚠ WARNING

Cladribine: Both males and females must use effective contraception for 6 months following each treatment course.

Postpartum and Lactation Protocols

- **Relapse prevention:** Early resumption of DMTs is mandatory for those at highest risk of relapse, specifically those who discontinued Natalizumab or S1P modulators.
- **Ineffective interventions:** Corticosteroids or IVIG to prevent postpartum relapses are not recommended.

- **Breastfeeding safety:** All monoclonal antibodies (Anti-CD20, Natalizumab, Anti-C5, Anti-IL-6) are suitable during breastfeeding as they enter milk at minimal concentrations and are not systemically absorbed by the infant gut.
- **Restart timing:** For CD20 antibodies paused during pregnancy, wait at least 2 weeks postpartum to restart, to minimize transfer via colostrum.

II. Vaccination Protocols in MS

Vaccination efficacy and safety are governed by the patient's current or planned degree of immunosuppression.

Vaccine Type Guidance

Vaccine Type	Examples	Guidance
Live-attenuated	Measles, Mumps, Rubella, Varicella, Yellow Fever, Intranasal Influenza	Strictly contraindicated once immunosuppressive DMTs (Anti-CD20, S1P modulators, Cladribine, Alemtuzumab) have started
Inactivated	—	Considered safe and recommended; do not increase the risk of MS relapses

Timing Protocols Relative to DMTs

Scenario	Timing
Pre-DMT initiation	Complete inactivated vaccines ≥ 2 weeks and live vaccines ≥ 4 to 6 weeks before starting DMT
During CD20 therapy (6-month dosing)	Administer vaccines at least 3 months after the last infusion and at least 4 weeks before the next, to maximize response
Neonate/in utero exposure	For infants exposed to monoclonal antibodies in the third trimester, postpone live vaccines (BCG, Rotavirus) for 6 months or until infant B cells are within normal range
C5 inhibitor initiation	Meningococcal vaccination (A, C, W, Y, and B strains) required ≥ 2 weeks prior to initiating Eculizumab or Ravulizumab

III. Long-Term Monitoring and Prognosis

Continuous tracking of multi-domain health metrics is essential for optimizing long-term quality of life.

Cognitive and Functional Tracking

- **Symbol Digit Modalities Test (SDMT):** Recommended for routine periodic screening.

SDMT Decline	Clinical Significance
≥ 4 points	Predicts challenges in employment
≥ 8 points or 2 SD below population average	Indicates meaningful cognitive decline

Clinical Phenotype Transitions

Most permanent disability in MS occurs during the **secondary progressive phase**; however, **progression independent of relapse activity (PIRA)** can occur early.

Safety and Systemic Monitoring

- **Bone health:** Long-term or frequent use of high-dose corticosteroids significantly increases the risk of osteoporosis and hip avascular necrosis.
- **Malignancy screening:** Cladribine carries a specific warning for potential malignancy risk, requiring adherence to age-appropriate screening guidelines.
- **Driving and employment:** Specific legal driving limits vary by jurisdiction; meaningful cognitive decline (SDMT decline ≥ 4 points) is a known driver for loss of employment.
- **Quality metrics:** MS management should adhere to the 2020 MS Quality Measurement Set to improve performance in value-based payment programs.

NEURO-INFECTIOUS DISEASES

Part 1 — Acute Bacterial Meningitis, Brain Abscesses, and Suppurative Intracranial Infections

1. Acute Bacterial Meningitis: Epidemiology and Risk Groups

Acute bacterial meningitis is a neurologic emergency in which outcomes are significantly worsened by delays in treatment. The annual incidence in the United States is approximately **5–10 per 100,000**.

EMERGENCY

Every hour of delay in antibiotic administration increases mortality. Do not delay empiric antibiotics for neuroimaging or lumbar puncture if either is expected to take time — draw blood cultures first, then start antibiotics + dexamethasone immediately.

Age- and Risk-Stratified Pathogens

Risk Group	Most Common Pathogens	Clinical Pearls
Neonates	- Streptococcus agalactiae (Group B Strep) - Escherichia coli - Listeria monocytogenes	Acquired via the birth canal; Group B Strep is the single most common cause.
Children and Adults	- Streptococcus pneumoniae - Neisseria meningitidis	H. influenzae is now rare due to vaccination but remains a consideration in unvaccinated or older adults.
Elderly (>50–65 yr) / Immunocompromised	S. pneumoniae N. meningitidis - Listeria monocytogenes	Listeria risk factors include alcohol use disorder and impaired cell-mediated immunity.
Post-Neurosurgical / Trauma	- Staphylococcus aureus - Gram-negative rods (e.g., Pseudomonas aeruginosa)	Results from skin or environmental breaches; S. aureus is common in shunt infections.

MEMORY TIP / MNEMONIC

Neonatal meningitis pathogens — “GEL”: Group B Strep, E. coli, Listeria — the three organisms crossing the birth canal or gut barrier in the very young and very old (extremes-of-age immunity gaps).

2. CSF Diagnostic Matrix for Acute Meningitis

The **CSF-to-blood glucose ratio of <0.4** is a critical metric, carrying a **likelihood ratio of 18** for bacterial meningitis.

Parameter	Bacterial	Viral	Tuberculous / Fungal
Opening pressure	Often elevated (>20 cm H ₂ O)	Usually normal or mildly elevated	Often markedly elevated in Cryptococcus
WBC count (cells/mm ³)	>500 (often >1000)	10–500	10–1000

Parameter	Bacterial	Viral	Tuberculous / Fungal
Cell predominance	Polymorphonuclear (PMN)	Lymphocytic	Lymphocytic
Protein (mg/dL)	>100	<120	>50 (can be markedly high)
Glucose	<40% of serum (or <40 mg/dL)	>40% of serum	<40% of serum

Diagnostic Sensitivity and Specificity

- **Gram stain:** test of choice for rapid identification; sensitivity for *Listeria* is notably low.
- **CSF culture:** positive in 70–85% of cases; blood cultures are positive in ~70%.
- **FilmArray ME panel (multiplex PCR):** 97.5% sensitivity for bacterial pathogens; 90.1% sensitivity for viral pathogens. Evaluates 6 organisms — *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *L. monocytogenes*, *S. agalactiae*, *E. coli K1*.
- **Latex agglutination:** rapidly evaluates microbial antigens but is increasingly supplanted by PCR.

CLINICAL PEARL

A CSF glucose ratio <0.4 combined with a WBC >1000/mm³ and protein >100 mg/dL is essentially diagnostic of bacterial meningitis — this triad should trigger immediate empiric therapy while awaiting culture confirmation.

3. Empiric and Targeted Antimicrobial Pharmacotherapy

Empiric therapy must be initiated **immediately** upon suspicion of meningitis, ideally after blood cultures but **before** lumbar puncture if imaging delays are expected.

Empiric Regimens for Adults

Clinical Context	Recommended Regimen	Exact Dosing & Max Caps
Community-acquired (adults <50)	Vancomycin + Ceftriaxone	Vancomycin: 15–20 mg/kg IV q8–12h (max 2 g/dose; total daily max 60 mg/kg) AND Ceftriaxone: 2 g IV q12h.
Community-acquired (adults >50, alcoholism, immunosuppressed)	Vancomycin + Ceftriaxone + Ampicillin	Add Ampicillin 2 g IV q4h to cover <i>Listeria</i> .
Nosocomial (post-op, shunt, trauma)	Vancomycin + antipseudomonal beta-lactam	Cefepime 2 g IV q8h OR Ceftazidime 2 g IV q8h OR Meropenem 2 g IV q8h.

Adjunctive Dexamethasone Protocol

- **Dose:** 10 mg IV every 6 hours for 4 days.
- **Timing:** must be initiated before or with the first dose of antibiotics.
- **Benefits:** reduces mortality in adults with *S. pneumoniae* and reduces sensorineural hearing loss in children with *H. influenzae*.

WARNING / PITFALL

Dexamethasone is generally discontinued if the causative organism is found to be something other than *S. pneumoniae*, as benefit has not been consistently shown for other pathogens.

Targeted Treatment Durations

Organism	Duration
<i>Neisseria meningitidis</i>	7 days
<i>Haemophilus influenzae</i>	7–10 days
<i>Streptococcus pneumoniae</i>	10–14 days
Group B <i>Streptococcus</i>	14–21 days
<i>Listeria monocytogenes</i> / Gram-negative bacilli	21 days

4. Focal Intracranial Suppurative Infections

Brain Abscess: Pathogenesis and Stages

Bacterial inoculation of the brain progresses through four distinct stages:

1. **Early cerebritis** — localized necrosis, edema, and PMN accumulation.
2. **Late cerebritis** — macrophage and lymphocyte infiltration with developing central necrosis.
3. **Early capsule** — formation of a vascularized fibrotic capsule that sequesters the infection.
4. **Late capsule** — well-defined wall; the capsule is often thinner on the ventricular surface, explaining the high risk of intraventricular rupture, which is often fatal.

Neuroimaging Hallmarks

- **CT:** hypodense center with variable enhancement.
- **MRI (modality of choice):** ring-enhancing lesions with central diffusion restriction on DWI/ADC — this restriction distinguishes abscesses from most tumors.

CLINICAL PEARL

Central diffusion restriction (bright on DWI, dark on ADC) is the single most useful imaging feature separating a pyogenic abscess from a necrotic/cystic tumor, which typically shows facilitated diffusion centrally.

Surgical and Medical Management

- **Surgical indications:** abscesses >2.5 cm, significant mass effect, or lesions abutting the ventricle. Minimally invasive stereotactic aspiration is now preferred over excision.
- **Antibiotic duration:** typically 6–8 weeks of IV therapy.
- **Empiric regimen:** Ceftriaxone (or Cefotaxime) + Metronidazole (anaerobic coverage); add Vancomycin if there is a history of trauma or neurosurgery.

Suppurative Collections: Epidural and Subdural

Entity	Key Features
Spinal epidural abscess	• Neurologic emergency requiring urgent decompression if deficits are present • Most common pathogen: <i>S. aureus</i> (>2/3 of cases)
Subdural empyema	• Often associated with sinusitis or neurosurgery • Can be more fulminant than brain abscess because infection is not contained by a capsule

Part 2 — Viral Encephalitis, Aseptic Meningitis, and Chronic Neurotropic Viral Syndromes

1. Acute Viral Encephalitis Pathogens

Viral encephalitis involves inflammation of the brain parenchyma, manifesting as altered mental status, seizures, and focal deficits.

Pathogen Class	Specific Pathogens	Key Clinical & Epidemiological Features
Herpesviruses	• HSV-1 • HSV-2 • VZV • CMV • EBV • HHV-6	HSV-1 is the most common sporadic cause globally. VZV is the second most common; rash is absent in 33% of cases. CMV occurs mainly in patients with AIDS (CD4 <50).
Arboviruses	• West Nile virus (WNV) • Japanese encephalitis • La Crosse • Powassan	WNV is the most common epidemic viral encephalitis in the US. Japanese encephalitis is the primary cause in Asia, often affecting children.
Enteroviruses	• EV-71 • EV-D68 • Poliovirus	Often associated with outbreaks of acute flaccid myelitis and brainstem encephalitis.
Other viruses	• Measles • Rabies • SARS-CoV-2	Rabies is almost 100% fatal once symptomatic. SARS-CoV-2 rarely causes direct encephalitis; it more commonly leads to encephalopathy or ADEM.

2. Diagnostic and Imaging Hallmarks

Neuroimaging, specifically MRI, provides essential clues to viral etiology based on regional tropism.

Pathogen	Clinical Hallmark	Neuroimaging Pattern (MRI)
HSV-1	• Olfactory hallucinations • Aphasia • PLEDs on EEG (periodic discharges)	Asymmetric T2/FLAIR hyperintensity in temporal lobes, insula, and orbitofrontal regions. Restricted diffusion common early; hemorrhage may appear later.
West Nile virus	• Parkinsonism, tremors • Asymmetric flaccid paralysis (anterior horn cell injury)	T2 hyperintensity in the deep gray matter (thalami and basal ganglia). Spinal MRI may show ventral cord/gray matter signal changes.
VZV	• Stroke-like presentations • Painful dermatomal rash (shingles)	Multifocal infarcts at the gray–white matter junction; arterial beading on angiography.
HHV-6	• Amnesia and SIADH	Symmetric T2 hyperintensity in bilateral medial temporal lobes/limbic structures.

Pathogen	Clinical Hallmark	Neuroimaging Pattern (MRI)
	Occurs weeks post-hematopoietic stem cell transplant	
CMV	Often occurs with retinitis, colitis, or ventriculitis in AIDS	Periventricular white matter changes and subependymal/ependymal enhancement.
CLINICAL PEARL HSV encephalitis + temporal lobe involvement + PLEDs on EEG is a classic triad. Never withhold empiric IV acyclovir while awaiting HSV PCR — treat first, confirm later.		

3. HSV and VZV Pharmacotherapy

Prompt initiation of empiric therapy is critical, as delays significantly worsen cognitive and survival outcomes.

Medication	Indication	Dosing	Mechanism & Monitoring
Acyclovir (IV)	Proven or suspected HSV or VZV encephalitis	10 mg/kg IV q8h for 14–21 days	Nucleoside analogue. Adjust for renal function/creatinine clearance. Maintain aggressive hydration to prevent crystalline nephropathy (occurs in up to 20% of patients).
Ganciclovir (IV)	CMV encephalitis or HHV-6	5 mg/kg IV q12h	Monitor for bone marrow suppression (neutropenia).
Foscarnet (IV)	CMV ventriculoencephalitis; resistant HSV/VZV	90 mg/kg IV q12h for 21 days	Frequently associated with electrolyte depletion (calcium, magnesium) and nephrotoxicity.
⚠ WARNING / PITFALL Acyclovir-induced crystalline nephropathy occurs in up to 20% of patients — always ensure aggressive IV hydration and infuse slowly over at least one hour.			

4. Chronic Viral Proteinopathies and Infections

These conditions represent subacute or chronic neurologic decline driven by persistent viral replication or reactivation.

A. Progressive Multifocal Leukoencephalopathy (PML)

- **Pathogen:** reactivation of the JC virus.
- **Mechanism:** lytic infection of oligodendrocytes leading to multifocal demyelination.
- **Imaging:** asymmetric T2 hyperintensities in juxtacortical white matter and subcortical U-fibers; typically lacks mass effect or enhancement.
- **Risk link:** associated with monoclonal antibodies, most notably Natalizumab. Risk increases with duration (>24 months) and prior immunosuppressant exposure.

- **Treatment:** immediate drug withdrawal and immune reconstitution; caution for PML-IRIS, which may require steroids.

B. Subacute Sclerosing Panencephalitis (SSPE)

- **Pathogen:** persistent, defective measles virus.
- **Presentation:** chronic, progressive brain inflammation following initial measles infection, even if subsequently vaccinated.
- **Outcome:** almost uniformly fatal.

C. HIV-Associated Neurocognitive Disorders (HAND)

- **Spectrum:** Asymptomatic Neurocognitive Impairment (ANI), Minor Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD).
- **Pathogenesis:** microglial activation and release of neurotoxic viral proteins (e.g., Tat).
- **Clinical:** HAD presents as a subcortical dementia with psychomotor slowing, though a "cortical" phenotype with memory loss is increasing in the ART era.
- **Treatment:** strict adherence to Antiretroviral Therapy (ART) to achieve plasma and CSF virologic suppression.

5. Diagnostic PCR and Serology Thresholds

Test Type	Pathogen	Target / Threshold	Diagnostic Value
CSF PCR	HSV-1 / HSV-2	Viral DNA	High sensitivity (96%) and specificity (99%)
CSF PCR	JC virus	Viral DNA	Sensitivity varies (74–93%)
CSF serology	West Nile virus	IgM in CSF	More sensitive than PCR; diagnostic of intrathecal synthesis
CSF serology	VZV	IgG (reduced serum:CSF ratio)	93% sensitivity for vasculitis (PCR is only 30% sensitive here)
FilmArray ME panel	Multiple	Multiplex PCR	Fast but has known false negatives for HSV-1, HSV-2, and Enterovirus

★ HIGH YIELD — EXAM FOCUS

VZV vasculitis is a classic exam trap: CSF PCR for VZV DNA is often negative (only ~30% sensitive) despite active vasculitis. CSF VZV IgG antibody testing is far more sensitive (93%) and should be sent when VZV vasculopathy is suspected clinically or radiologically.

Part 3 — Neuro-HIV Manifestations, Opportunistic Infections, and Neurosyphilis

1. Acute and Chronic HIV CNS Manifestations

Neurologic manifestations of HIV can occur at any point from acute infection to advanced immunosuppression.

A. Acute Manifestations (Seroconversion)

- **Primary HIV meningitis:** aseptic meningitis may occur during initial infection, often accompanied by a flulike illness and rash.
- **Cranial neuropathy:** unilateral or bilateral facial (CN VII) paralysis is the most common, occurring at a median of 15 days post-clinical onset.
- **Other seroconversion syndromes:** rarely, Guillain-Barré syndrome (with CSF pleocytosis), acute transverse myelitis, or acute disseminated encephalomyelitis (ADEM).

B. Chronic Manifestations

Syndrome	Key Features
HIV-associated vacuolar myelopathy	• Late manifestation, typically in advanced AIDS • Slowly progressive spastic paraparesis, sensory ataxia (dorsal column), bowel/bladder dysfunction • Imaging: spinal cord atrophy and T2 hyperintensities, most severe in mid-lower thoracic cord
Distal symmetric polyneuropathy (DSPN)	• Most common HIV-related neurologic complication • Sensory-predominant "stocking-glove" distribution with pain, paresthesia, diminished ankle reflexes
Immune reconstitution inflammatory syndrome (IRIS)	• Paradoxical clinical worsening after ART initiation as immune system recovers • Criteria: increasing CD4+ count and decreasing viral load between 2 and 25 weeks after starting ART
📌 IMPORTANT NOTE CSF escape refers to ongoing viral replication in the CNS despite plasma virologic suppression. While ART regimens with high CNS penetration effectiveness (CPE) are studied, plasma virologic suppression remains the paramount treatment goal.	

2. Opportunistic CNS Infections: CD4-Tiered Reference

The risk of specific opportunistic infections is strictly tied to the degree of immunodeficiency as measured by the CD4+ T-cell count.

Pathogen	CD4 Threshold	Neuroimaging Hallmarks	First-Line Regimen
Cerebral toxoplasmosis	<100/ μ L (often <200)	Multiple ring-enhancing lesions in basal ganglia/cortex. Eccentric target	Pyrimethamine (load 200 mg, then 50–75 mg/day) + Sulfadiazine (1–1.5

Pathogen	CD4 Threshold	Neuroimaging Hallmarks	First-Line Regimen
		sign (asymmetric nodule along the wall) is highly specific.	g q6h) + Leucovorin (10–25 mg/day). Alt: trimethoprim-sulfamethoxazole.
Cryptococcal meningitis	<100/ μ L	Often normal MRI. May show "soap bubble" appearance (gelatinous pseudocysts in basal ganglia); nodular basilar enhancement.	Induction: liposomal Amphotericin B (3–4 mg/kg/day) + Flucytosine (100 mg/kg/day) for ≥ 2 weeks. Consolidation: Fluconazole (400–800 mg/day) for 8 weeks.
Primary CNS lymphoma (PCNSL)	<50/ μ L	Often a single, large, homogeneously or ring-enhancing lesion with restricted diffusion. Sparing of susceptibility (unlike toxoplasmosis).	High-dose Methotrexate + ART. Rituximab may be added.
Progressive multifocal leukoencephalopathy (PML)	<200/ μ L	Asymmetric, confluent T2 hyperintensities involving subcortical U-fibers; lacks mass effect and (usually) enhancement.	Immune reconstitution (reducing/stopping immunosuppressants or starting ART).

Diagnostic Differentiation: PCNSL vs. Toxoplasmosis

Feature	PCNSL	Toxoplasmosis
PET/SPECT metabolism	Hypermetabolic	Hypometabolic
CSF EBV PCR	Highly sensitive for PCNSL in immunocompromised patients	Negative
Treatment response window	No response to empiric anti-Toxoplasma therapy within 10–14 days → biopsy for PCNSL	Expected radiologic improvement within 10–14 days

CLINICAL PEARL

A ring-enhancing lesion that fails to improve on empiric anti-toxoplasmosis therapy after 10–14 days should prompt brain biopsy to rule out PCNSL — do not simply escalate antimicrobial therapy indefinitely.

Cryptococcal Opening Pressure Management

- **Management:** markedly elevated opening pressure (>20 cm H₂O) occurs in 70% of cases.
- **Therapeutic LP:** serial lumbar punctures are often required to manage pressure; refractory cases may require a ventriculoperitoneal shunt.

3. Neurosyphilis (*Treponema pallidum*)

Neurosyphilis can occur at any stage of infection and is particularly common in patients with HIV.

Phenotype	Timing Post-Infection	Clinical Presentation
Asymptomatic	Early	No symptoms, but detectable <i>T. pallidum</i> or inflammatory profile in CSF.

Phenotype	Timing Post-Infection	Clinical Presentation
Meningovascular	Weeks to months (early)	Subacute meningitis followed by ischemic stroke (vasculitis of small or medium arteries).
General paresis	Years to decades (late)	Chronic encephalitis presenting as dementia, personality changes, and psychiatric symptoms.
Tabes dorsalis	Decades (late)	Sensory gait ataxia, impaired proprioception, lancinating pains, and Argyll Robertson pupils.
Syphilitic amyotrophy	Variable (late)	Progressive degeneration of anterior horn cells leading to wasting of hand or leg muscles.
📌 MEMORY TIP / MNEMONIC Argyll Robertson pupil — “Prostitute’s pupil”: accommodates but does not react (to light). Classic for tabes dorsalis.		

CSF Diagnostic Matrix

- **CSF VDRL:** the primary diagnostic test — highly specific but poorly sensitive (30–70%).
- **CSF FTA-ABS / TPPA:** very sensitive; a negative result helps rule out neurosyphilis, but a positive result does not distinguish active from treated infection.
- **TPPA titer cutoff:** a CSF TPPA titer >1:320 is increasingly recognized as a supporting criterion for diagnosis.

4. Neurosyphilis Therapeutic Protocol

Penicillin remains the gold standard of therapy. In cases of severe allergy, desensitization is preferred.

Drug	Dosing & Frequency	Duration
Aqueous Penicillin G (IV)	18–24 million units daily; given as 3–4 million units q4h OR via continuous infusion	10–14 days
Procaine Penicillin (IM) + Probenecid	2.4 million units IM daily PLUS Probenecid 500 mg orally 4 times daily	10–14 days
Ceftriaxone (IV) — alternative	2 g daily IV (used for penicillin allergy)	10–14 days
📌 IMPORTANT NOTE Monitoring cure: a fourfold decline in serum nontreponemal (RPR) titer correlates with treatment success. Serial CSF examinations every 6 months are recommended until pleocytosis resolves.		

Part 4 — Tuberculous Meningitis, Endemic Mycoses, and Parasitic Neuro-Infections

1. Tuberculous Meningitis (TBM): Pathophysiology and CSF Profile

TBM is the most severe form of tuberculosis, with mortality reaching **60%** in low-resource settings.

Pathophysiology Hallmarks

- **Rich focus rupture:** disease originates from hematogenous spread of mycobacteria to the brain parenchyma or meninges, forming microscopic granulomatous foci called Rich foci. Their rupture into the subarachnoid space triggers TBM.
- **Thick basal exudates:** a defining feature is thick, gelatinous inflammatory exudate in the basal cisterns. These exudates entrap cranial nerves (VI most common, followed by VII and III) and obstruct CSF flow.
- **Vasculitis and the "tuberculous zone":** TBM causes proliferative and necrotizing vasculitis. Infarctions occur in 30–60% of cases, primarily in the basal ganglia, thalami, and internal capsule, due to involvement of medial striate and thalamoperforating arteries.

CSF Diagnostic Matrix

Parameter	TBM Characteristic Profile
Opening pressure	Elevated in >50% of cases
WBC count	10–500 cells/mm ³ (rarely >1000)
Cell predominance	Mononuclear (lymphocytic or monocytic)
Protein	Markedly elevated (>100 mg/dL); can exceed 200 mg/dL
Glucose	Markedly low (<40 mg/dL) or <50% of serum glucose

2. TBM Pharmacotherapy and Corticosteroid Protocols

Standard Antimicrobial Regimen

Treatment is divided into two phases to manage slow-growing *M. tuberculosis*.

Phase	Duration	Regimen
Intensive	2 months	Rifampicin + Isoniazid + Pyrazinamide + Ethambutol
Continuation	7–10 months	Rifampicin + Isoniazid
Adjunctive B6	Entire course	Pyridoxine 50 mg daily — MUST be co-prescribed with Isoniazid to prevent painful peripheral neuropathy

📌 IMPORTANT NOTE

For drug resistance, clinicians may use Levofloxacin, Bedaquiline, Linezolid, or Clofazimine. Isoniazid is a potent CYP450 inhibitor, while Rifampicin is a potent inducer — careful drug level monitoring is required for co-administered medications (e.g., anticonvulsants, ART).

Mandatory Adjunctive Corticosteroid Taper

- Steroids reduce mortality, severe disability, and relapse.
- **Protocol:** tapered over 6–8 weeks.
- **Timing:** initiated with or before starting antituberculous therapy.
- **Example dosing:** 2 weeks IV Dexamethasone (MRC Grade 1) or 4 weeks IV Dexamethasone (Grades 2–3), followed by a 4-week oral Prednisone taper.

3. Neurocysticercosis (*Taenia solium*): Clinical Stages and Management

Neurocysticercosis (NCC) is the most common cause of acquired epilepsy worldwide.

Clinical and Radiologic Stages

Stage	Imaging Features
Vesicular	Viable, non-inflamed cyst with liquid content (CSF-like signal); scolex often seen as an eccentric nodule
Colloidal vesicular	Degenerating cyst with thick fluid; intense ring enhancement and perilesional edema
Granular nodular	Cyst collapses into an inflammatory nodule; decreasing enhancement/edema
Calcified	Inflammatory nodule disappears and reappears as a calcified scar (30–40% of cases)

Anthelmintic Therapeutic Algorithm

⚠ WARNING / PITFALL

High-dose corticosteroids **MUST** be started **BEFORE** anthelmintics to mitigate the catastrophic inflammatory response triggered by parasite death (a potentially fatal peri-cyst inflammatory reaction and cerebral edema).

- **Monotherapy:** for a single viable parenchymal cyst — Albendazole 15 mg/kg/day for 7–15 days.
- **Dual therapy:** for multiple viable parenchymal cysts — Albendazole 15 mg/kg/day + Praziquantel 50 mg/kg/day for 10 days (superior efficacy).

4. Endemic Mycoses and Amoebic Neuro-Infections

Endemic Fungal Meningitis Profiles

Fungal Agent	Endemic Region	Diagnostic Keys
Coccidioidomycosis	Southwestern US	CSF antibody and antigen are diagnostic. Treatment is lifelong azoles.
Histoplasmosis	Mississippi / Ohio River valleys	CSF antigen is more sensitive than antibodies. Requires Amphotericin B induction.
Blastomycosis	Great Lakes; Mississippi/Ohio valleys	CNS disease often accompanied by pulmonary infection.

Amoebic Infections: PAM and GAE

Entity	Organism	Key Features
Primary amebic meningoencephalitis (PAM)	<i>Naegleria fowleri</i>	Enters via nasal passages after swimming in warm freshwater. Rapidly fatal due to profound tissue necrosis.
Granulomatous amebic encephalitis (GAE)	<i>Acanthamoeba</i> or <i>Balamuthia mandrillaris</i>	Subacute progressive encephalopathy, necrotic mass lesions, and hydrocephalus.

Experimental/survival regimen: multidrug protocols including Miltefosine (associated with several rare survivals), Pentamidine, Sulfadiazine, Flucytosine, and Fluconazole.

5. Critical Care Metrics: Shunting and Resistance

- **Neurosurgical shunting — TBM:** indicated for hydrocephalus. Endoscopic third ventriculostomy is an option but has success rates <60%.
- **Neurosurgical shunting — NCC:** VP shunt placement is critical for hydrocephalus associated with racemose (subarachnoid grape-like) cysts or intraventricular cysts.
- **Resistance markers:** the Xpert MTB/RIF assay rapidly detects both *M. tuberculosis* and rifampicin resistance via nucleic acid amplification.
- **TBM complication management:** hyponatremia (seen in 40–50% of TBM cases) must be aggressively differentiated between Cerebral Salt Wasting and SIADH for proper critical care.

CLINICAL PEARL

Distinguishing Cerebral Salt Wasting from SIADH in TBM hinges on volume status: CSW patients are volume-depleted (treat with salt/fluid replacement), whereas SIADH patients are euvolemic (treat with fluid restriction). Treating CSW as SIADH can worsen hyponatremia and precipitate cerebral infarction.

Part 5 — Lyme Neuroborreliosis, Tick-Borne Encephalitides, and Emerging Zoonotic Neuro-Infections

1. Lyme Neuroborreliosis (*Borrelia burgdorferi*)

Neurologic manifestations (neuroborreliosis) occur in approximately 3–12% of patients with Lyme disease. In the United States, it is caused by *B. burgdorferi*; in Europe, *B. afzelii* and *B. garinii* are also prevalent.

Clinical Triad: Bannwarth Syndrome

While more common in Europe, the classic triad of early neuroborreliosis includes:

5. **Lymphocytic meningitis** — often presents with headache; fever and meningismus may be mild or absent.
6. **Painful radiculoneuropathy** — sharp, shooting pains in single or multiple nerve root distributions.
7. **Cranial neuropathy** — most commonly unilateral or bilateral facial nerve (VII) palsy.

MEMORY TIP / MNEMONIC

Bannwarth syndrome = “MRC”: Meningitis (lymphocytic) + Radiculopathy (painful) + Cranial neuropathy (facial palsy).

Diagnostic Criteria and Laboratory Assays

Diagnostic Step	Metric / Criteria
Initial screen	ELISA for antibodies to <i>B. burgdorferi</i> . If negative, Lyme is excluded.
Confirmatory test	Western blot for IgM and IgG if ELISA is positive or borderline.
CSF profile	Typically demonstrates lymphocytic pleocytosis.
Antibody index	$(\text{anti-Borrelia IgG in CSF} / \text{serum}) \div (\text{total IgG in CSF} / \text{serum})$. A result >1.3 – 1.5 verifies intrathecal synthesis.
CSF CXCL13	A B cell-attracting chemokine that increases rapidly in early neuroborreliosis; concentrations fall rapidly after starting antibiotics.

2. Lyme Pharmacotherapy

The 2020 guidelines from the AAN, IDSA, and ACR recommend the following for neuroborreliosis:

Indication	Preferred Regimen	Dosing & Duration
Lyme meningitis, cranial neuritis, or radiculoneuropathy	Ceftriaxone (IV)	2 g IV once daily for 14–28 days
Alternative (meningitis/neuritis)	Doxycycline (oral)	100 mg orally twice daily for 14–28 days. European studies show oral doxycycline is as effective as IV antibiotics.
Severe manifestations (encephalitis/myelitis)	IV antibiotics	Ceftriaxone 2 g daily OR Cefotaxime 2 g q8h OR Penicillin G 18–24 million units daily
High-risk tick bite prophylaxis	Doxycycline (single dose)	200 mg for adults; 4.4 mg/kg (max 200 mg) for children

3. Other Tick-Borne and Vector Pathogens

Rocky Mountain Spotted Fever (RMSF — *Rickettsia rickettsii*)

- **Clinical:** abrupt onset of fever, severe headache, and delirium. A distinctive spotted rash appears 3–5 days after fever onset, initially on wrists and ankles.
- **Neuroimaging:** "starry sky" appearance on MRI in children — scattered punctate areas of T2 hyperintensity and restricted diffusion in the deep gray and white matter.
- **Management:** Doxycycline should be initiated empirically if a rickettsial disorder is suspected.

⚠ WARNING / PITFALL

Never withhold doxycycline in suspected RMSF while awaiting confirmatory serology, even in children — delayed treatment dramatically increases mortality, and the rash may not yet be present at first evaluation.

Emerging Arboviruses

- **West Nile virus (WNV):** the most common epidemic viral encephalitis in the US. Deep gray matter (basal ganglia/thalamus) involvement causes parkinsonism or tremors; tropism for anterior horn cells leads to asymmetric flaccid paralysis.

Diagnostic: CSF IgM is the test of choice; PCR is only 50% sensitive in CSF.

- **Powassan virus:** increasing incidence; neuroimaging abnormalities are often multifocal and variable.

4. Prion and Rabies Protocols

Rabies Encephalitis

- **Pathophysiology:** virus enters the CNS via retrograde axonal transport after a bite.

Form	Clinical Presentation
Furious form	Extreme agitation, hydrophobia, delirium, and seizures
Paralytic form	Ascending paralysis followed by coma
📌 IMPORTANT NOTE The "Milwaukee Protocol" has not been proven effective and is not a validated treatment strategy for symptomatic rabies.	

Rabies Post-Exposure Prophylaxis (PEP)

📌 EMERGENCY

PEP must be administered before neurologic symptoms manifest — once symptomatic, rabies is nearly 100% fatal.

8. **Human Rabies Immune Globulin (HRIG):** administered to provide immediate passive antibodies.
9. **Vaccine schedule:** a series of vaccinations to induce active immunity.

5. Serological Testing Pitfalls and Molecular Diagnostics

Potential Pitfall	Scientific Detail
Lyme IgM false positives	Isolated IgM Western blots have a high false-positive rate and are only useful within the first 3–6 weeks of symptoms.
Lyme serology time-lag	IgG antibodies may be negative in the very earliest period of infection, requiring CSF analysis for diagnosis.
WNV IgM persistence	WNV IgM can persist for longer than 1 year — a positive result may reflect previous exposure rather than acute neuroinvasive disease.
FilmArray ME panel	Known false negatives for pathogens including <i>Borrelia</i> (not included on panel) and can miss low-titer viral infections.
Metagenomic sequencing	An emerging, hypothesis-free technique for identifying rare/unexpected pathogens in the CSF of immunocompromised patients.

Part 6 — Healthcare-Associated Infections, Spinal Cord Neuro-Infections, and Infectious Mimics

This section covers infections related to neurosurgical interventions and devices, spinal cord infections, and the critical differentiation of infectious syndromes from non-infectious mimics.

1. Healthcare-Associated Ventriculitis and Meningitis

Healthcare-associated (nosocomial) infections typically occur following neurosurgical procedures, head trauma, or placement of indwelling devices such as external ventricular drains (EVDs) or ventriculoperitoneal (VP) shunts.

Pathogen Class	Specific Organisms	Clinical Context
Gram-positive (skin flora)	• <i>S. epidermidis</i> • <i>S. aureus</i> • <i>C. acnes</i>	Most common in VP shunt and EVD infections.
Gram-negative (nosocomial)	• <i>Pseudomonas aeruginosa</i> • <i>E. coli</i> • <i>Klebsiella</i>	Associated with recent neurosurgery or hospital stay.
Fungal (rare)	• <i>Candida</i> species	Risk increases with indwelling IV lines or neutropenia.

📌 IMPORTANT NOTE

CSF sampling nuance: when interpreting CSF drawn from a ventricular device, remember that CSF protein is normally lower and glucose normally higher in the ventricles compared to the lumbar sac — do not apply standard lumbar reference ranges

2. Device Infection Pharmacotherapy

Management of device-associated infections requires aggressive IV therapy and, frequently, removal of the hardware.

- **IV empiric regimen:** must cover both resistant Staphylococci (MRSA) and *Pseudomonas* — Vancomycin PLUS an antipseudomonal beta-lactam (Cefepime, Ceftazidime, or Meropenem).
- **Intraventricular (IT) therapy:** considered when infection responds poorly to systemic therapy alone or when systemic drug penetration is inadequate.

⚠️ WARNING / PITFALL

Infected CNS devices (EVDs, VP shunts) must be removed to achieve sterilization of the CSF — antibiotics alone rarely clear device-associated biofilm infections.

Medication	Route	Dosing	Notes
Vancomycin	IV	15–20 mg/kg q8–12h	Max 2 g/dose; adjust for renal function
Cefepime	IV	2 g q8h	Standard antipseudomonal dose
Meropenem	IV	2 g q8h	Broad aerobic/anaerobic coverage
Ceftazidime	IV	2 g q8h	Alternative antipseudomonal agent
Amphotericin B	Intrathecal	0.01–0.5 mg	For fungal device infections that cannot be removed

📌 IMPORTANT NOTE

Intraventricular dosing of Vancomycin and Gentamicin is used clinically for resistant device infections; exact intrathecal milligram doses for these agents are institution- and protocol-specific and should be confirmed with neurosurgery/infectious disease pharmacy guidance.

3. Spinal Cord Neuro-Infections

Spinal Epidural Abscess (SEA)

EMERGENCY

SEA is a neurologic emergency due to the risk of irreversible cord compression. Immediate surgical decompression (laminectomy/debridement) is indicated for patients with acute or progressive neurologic deficits.

The clinical triad: back pain, fever, and neurologic deficits (weakness, sensory loss, or sphincter dysfunction). This full triad is present in only 2–33% of patients at presentation.

Evolutionary Stages

10. Localized spinal pain
 11. Radicular pain (shooting pain)
 12. Myelopathic symptoms (weakness, bowel/bladder dysfunction)
 13. Paralysis
- **Diagnostic mandate:** urgent spinal MRI with contrast is the modality of choice.
 - **Most common pathogen:** *S. aureus* (>2/3 of cases).

WARNING / PITFALL

Conservative (non-surgical) management may fail in patients over age 65, those with MRSA infection, or those with highly elevated CRP (>115 mg/L) — a lower threshold for surgery should be applied in these groups.

Infectious Myelitis and Myeloradiculitis

Pathogen	Characteristic Tropism	Key Clinical Features
Varicella-zoster (VZV)	Dorsal root ganglia / spinal cord	Acute/subacute asymmetric weakness; often follows shingles rash (though "sine herpete" presentation without rash occurs).
HTLV-1 (HAM/TSP)	Dorsolateral columns	Slowly progressive spastic paraparesis, bladder dysfunction, and impaired proprioception.
Schistosomiasis	Conus medullaris / T11–L1	Lower limb weakness, low back pain, and sphincter dysfunction; eggs lodge in Batson's plexus.

4. Non-Infectious Mimics

Infectious CNS syndromes can be closely mimicked by systemic inflammatory or autoimmune disorders. Differentiation is critical for proper management (steroids vs. antimicrobials).

Mimic Syndrome	Clues for Differentiation	Radiologic / Laboratory Hallmarks
Neurosarcoidosis	History of pulmonary sarcoid; chronic headache	Basilar meningeal enhancement; may cause hypoglycorrhachia mimicking TB/fungal infection
Behçet's disease	Oral/genital ulcers; systemic inflammation	Meningoencephalitis or longitudinally extensive transverse myelitis (LETM)
Neoplasia (carcinomatous meningitis)	Weight loss; known primary malignancy	Leptomeningeal metastases; low CSF glucose and elevated protein
Autoimmune encephalitis	Rapidly progressive cognitive/psychiatric changes	Limbic (medial temporal) T2 hyperintensities; requires specialized antibody testing
📌 IMPORTANT NOTE Additional non-infectious mimics worth considering, though not detailed extensively in the source material: GFAP astrocytopathy (autoimmune meningoencephalomyelitis with perivascular radial enhancement) and CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids). Both should be part of the differential for steroid-responsive, infection-negative CNS inflammatory syndromes.		
★ HIGH YIELD — EXAM FOCUS Whenever CSF shows low glucose with a lymphocytic predominance and infectious workup is negative, systematically screen for the “chronic lymphocytic meningitis” differential: TB, fungal, carcinomatous meningitis, neurosarcoidosis, and CNS lymphoma — the pattern alone cannot distinguish these.		

CHILD NEUROLOGY

PART 1

Neonatal Neurology & Early-Onset Encephalopathies

I. Neonatal Encephalopathy & Hypoxic-Ischemic Encephalopathy (HIE)

Neonatal encephalopathy is a heterogeneous clinical syndrome defined by disrupted CNS function in the first days of life, presenting with altered mental status, seizures, hypotonia, and respiratory or feeding disturbances. Hypoxic-ischemic encephalopathy (HIE) refers specifically to neonatal encephalopathy caused by global hypoxia-ischemia, and is the most common identifiable cause.

A. Sarnat Clinical Staging of HIE

The severity of HIE is classified as mild (Stage I), moderate (Stage II), or severe (Stage III), based on the worst degree of encephalopathy observed on serial neurological examinations.

Feature	Stage I (Mild)	Stage II (Moderate)	Stage III (Severe)
Consciousness	Irritability, hyperalertness	Lethargy, decreased responsiveness	Coma, stupor
Muscle Tone	Normal or slightly increased	Hypotonia	Flaccid or generalized hypotonia
Reflexes	Depressed or abnormal	Depressed primitive reflexes	Absent primitive reflexes
Seizures	Typically absent	Common	Frequent; status epilepticus common
Prognosis	Excellent survival	Intermediate rates of death/disability	High mortality; near-total disability in survivors

CLINICAL PEARL

Sarnat staging should be based on the worst stage reached over serial examinations in the first days of life, not a single snapshot — encephalopathy severity typically evolves over 24–72 hours.

B. Therapeutic Hypothermia Protocol

Therapeutic hypothermia is the standard of care for infants ≥ 36 weeks gestational age with suspected or confirmed moderate-to-severe HIE.

Parameter	Specification
Inclusion Criteria	≥ 36 weeks gestational age; Apgar score < 5 at 10 minutes; fetal umbilical artery pH < 7.00 OR base deficit ≥ 12 mmol/L
Clinical Entry	Evidence of moderate-to-severe encephalopathy
Implementation Window	Must be initiated within 6 hours after birth
Target Temperature	33.5 °C (92.3 °F)
Duration	72 hours
Methodology	Whole-body cooling is preferred; head cooling is an equally accepted alternative
Adjuvant Care	Sedation (e.g., morphine) to prevent shivering and cold stress
Rewarming Rate	Slow, controlled rewarming is standard; longer or deeper cooling (120 hours / 32 °C) confers no additional benefit

⚠ WARNING

Delayed initiation of cooling beyond the 6-hour window significantly reduces neuroprotective efficacy. Time-to-cooling should be tracked as a quality metric in every unit managing suspected HIE.

📌 EXAM TIP

Deeper or longer cooling protocols (32 °C or 120 hours) have been studied and shown NOT to improve outcomes compared with standard 33.5 °C / 72-hour cooling — a frequently tested distractor.

II. Primitive Reflexes & Developmental Milestones

Assessment of primitive reflexes (Moro, palmar grasp, tonic neck, rooting) is an essential part of the neonatal neurologic examination. Their depression or absence is a hallmark finding in HIE and other causes of neonatal encephalopathy.

A. Developmental Milestone Timeline

Developmental milestones provide the framework against which regression or delay is measured, and are used as specifiers for neurodevelopmental diagnoses.

Age	Language & Communication	Social-Emotional
2–3 months	Cooing; onset of babbling	Social smile
6 months	Responds to name	Consistently alerts to social bid
6–12 months	Imitates gestures	Enjoys interactive games (peekaboo, pat-a-cake)
12 months	First words; uses pointing/gestures	Imitates actions of others
12–24 months	Verbal turn-taking	—
18 months	—	Simple pretend play; wider range of emotions
3 years	Complex make-believe/imaginary play	—
4 years	—	Cooperative play; follows rules

B. Developmental Regression: Red Flags

- **Loss of previously acquired skills** — e.g., cessation of babbling, loss of purposeful hand use.
- **Global developmental delay** — failure to meet milestones in ≥ 2 developmental domains.
- **Acquired auditory agnosia** — word deafness presenting in school-age children (Landau-Kleffner syndrome).
- **Regression after a period of normal development** — classic for Rett syndrome or an evolving metabolic crisis.

EMERGENCY

Any child with true developmental regression (loss of previously acquired skills, as opposed to a plateau) warrants urgent evaluation for neurometabolic disease, neurodegenerative disorders, epileptic encephalopathy (e.g., Landau-Kleffner), or Rett syndrome.

III. Neonatal Seizures

Neonatal seizures are frequently the first clinical sign of an underlying brain injury, including stroke, HIE, or a structural malformation.

A. Pathophysiology and EEG Patterns

- **Electroclinical dissociation:** seizures frequently occur without clinical correlates (subclinical seizures); clinical observation alone is unreliable for detection.

- **Occult (electromechanical uncoupling) seizures:** common after anticonvulsant administration, where clinical signs stop but electrographic seizure activity continues.

EEG Signatures

Pattern	Description	Classic Association
Burst-suppression	High-voltage bursts alternating with flat (suppressed) periods	Early Infantile Epileptic Encephalopathy (Ohtahara syndrome) and Early Myoclonic Encephalopathy
Hypsarrhythmia	Chaotic, high-voltage slow activity with multifocal spikes	Infantile spasms (West syndrome)
Theta pointu alternant	Shifting focal theta rhythm with superimposed sharp waves	Benign neonatal seizures ('fifth-day fits')

B. Acute Management & Dosing

Medication	Loading Dose	Maintenance Dose	Notes
Phenobarbital	20 mg/kg IV	3–5 mg/kg/day	First-line agent; monitor for respiratory depression
Levetiracetam	40–60 mg/kg IV	—	Second-line; limited efficacy data specific to neonates
Fosphenytoin	20 mg PE/kg IV	—	Preferred over phenytoin; loading dose expressed in phenytoin equivalents (PE)
Midazolam	100–200 mcg/kg load	100–800 mcg/kg/hour infusion	Reserved for refractory status epilepticus

C. Pyridoxine-Dependent Epilepsy (PDE) Trial

In any neonate with refractory status epilepticus unresponsive to conventional anticonvulsants, a trial of pyridoxine (vitamin B6) is mandatory to exclude pyridoxine-dependent epilepsy.

- **Protocol:** administer 100 mg pyridoxine IV (up to 500 mg) under continuous EEG monitoring.
- **Response:** clinical cessation of seizures and normalization of the EEG background typically occurs within 10 minutes.

⚠ WARNING

Pyridoxine administration must occur under continuous cardiorespiratory and EEG monitoring, as apnea and bradycardia have been reported with intravenous administration.

💡 MEMORY TIP / MNEMONIC

"Refractory neonatal seizures — always B6 before you give up." Any neonate failing first- and second-line anticonvulsants deserves an empiric pyridoxine trial before the diagnosis is abandoned.

IV. Congenital Malformations of the CNS

Structural malformations of the CNS are categorized according to the embryologic stage at which development was disrupted. This framework allows the clinician to predict the pattern of associated anomalies from the timing of the insult.

A. Disorders of Neurulation (Weeks 3–4)

- **Myelomeningocele:** incomplete caudal neural tube fusion; approximately 90% have associated hydrocephalus.
- **Arnold-Chiari malformation, Type II:** caudal displacement of the cerebellar tonsils and vermis through the foramen magnum, with elongation of the medulla; classically associated with myelomeningocele.

B. Disorders of Prosencephalic Development (Weeks 5–6)

- **Holoprosencephaly:** failure of hemispheric cleavage; subtypes in order of severity are alobar (most severe), semilobar, and lobar.
- **Septo-optic dysplasia:** optic nerve hypoplasia, hypopituitarism, and absent septum pellucidum.

C. Disorders of Neuronal Proliferation & Migration

Malformation	Mechanism	Key Features / Genetics
Microcephaly / microlissencephaly	Decreased neuronal proliferation	Genetic (e.g., ASPM gene) or acquired/infectious (e.g., congenital Zika virus)
Hemimegalencephaly	Unilateral hemispheric overgrowth	Unilateral enlargement of a hemisphere; universally associated with epilepsy
Lissencephaly (classical / Type I)	Neuronal migration arrest — 'smooth brain'	Agyria or pachygyria; often due to LIS1 or DCX mutations

Malformation	Mechanism	Key Features / Genetics
Cobblestone malformation (Type II)	Neuronal overmigration through a defective glia limitans	Neurons migrate into the subarachnoid space (e.g., Walker-Warburg syndrome)
Periventricular nodular heterotopia	Failed radial migration	Ectopic neuronal clusters lining the ventricles; often due to FLNA mutations

D. Disorders of Postmigrational Development

- **Polymicrogyria:** disruption of late migration or early cortical organization (e.g., bilateral perisylvian syndrome).
- **Focal cortical dysplasia (FCD):** disorganized cortical lamination; Type IIb is characterized by dysmorphic 'balloon cells' and carries the highest epileptogenic potential.

🔖 MEMORY TIP / MNEMONIC

Malformation timing mnemonic — "NPMP": Neurulation (wk 3–4) → Prosencephalic cleavage (wk 5–6) → Proliferation/Migration (wk 6–16 wks and beyond) → Postmigrational organization (late gestation onward). Matching the malformation to its embryologic window narrows the differential rapidly.

PART 2

Pediatric Epilepsy & Neuro-Ophthalmology

This chapter distills clinical diagnostic criteria, EEG signatures, and therapeutic protocols for pediatric epilepsy syndromes and neuro-ophthalmologic disease.

I. Age-Dependent Pediatric Epilepsy Syndromes

Pediatric epilepsy syndromes are classified by age of onset, which in turn dictates the diagnostic approach and management strategy.

A. Neonatal and Infantile Syndromes

Syndrome	Age of Onset	EEG Hallmark	Genetics / Etiology	Treatment & Notes
Benign neonatal seizures	Days 4–6 ('fifth-day fits')	Theta pointu alternant: shifting focal theta with sharp waves	Non-familial; cause unknown	Self-limited; acute management only
Benign familial neonatal epilepsy	Days 2–3	Background often normal	KCNQ2, KCNQ3 (autosomal dominant)	High penetrance; ~10% risk of later epilepsy
West syndrome (infantile epileptic spasms syndrome)	3–12 months	Hypsarrhythmia: chaotic, high-voltage slow waves with multifocal spikes	TSC, CDKL5, ARX, or acquired injury (e.g., HIE)	First-line: ACTH or high-dose prednisolone; vigabatrin preferred for TSC
Dravet syndrome	< 12 months	3–4 Hz generalized spike-wave (emerges later in course)	SCN1A mutation (> 80%)	Triggered by fever/heat; avoid sodium-channel blockers

B. Childhood and Adolescent Syndromes

Syndrome	Age of Onset	EEG Hallmark	Clinical Features	Management
Childhood absence epilepsy (CAE)	4–10 years (peak 5–7)	3 Hz generalized spike-wave, abrupt onset/offset	Brief staring spells; triggered by hyperventilation	Ethosuximide (first-line); valproate if GTCs present

Syndrome	Age of Onset	EEG Hallmark	Clinical Features	Management
Benign rolandic epilepsy (BECTS)	4–11 years (peak 7–8)	Centrotemporal spikes with tangential dipole; activated by sleep	Orofacial paresthesias, drooling, nocturnal focal seizures	Often untreated; carbamazepine or levetiracetam if frequent
Lennox-Gastaut syndrome (LGS)	1–6 years	Slow spike-wave (1–2.5 Hz); paroxysmal fast activity in sleep	Triad: multiple seizure types (tonic, atonic, absence), slow spike-wave, intellectual disability	Rufinamide/clobazam for drop attacks; VNS or corpus callosotomy
Juvenile myoclonic epilepsy (JME)	12–18 years	4–6 Hz generalized polyspike-wave ('inverted W')	Myoclonus on awakening; triggered by sleep deprivation/alcohol	Valproate (gold standard); lifelong treatment usually required

🔍 MEMORY TIP / MNEMONIC

Age-of-onset mnemonic for the epilepsy syndromes — think in ascending age bands: Days (BFNE) → Weeks–months (West) → Infancy (Dravet) → Early childhood (LGS) → Mid-childhood (CAE, BECTS) → Adolescence (JME). Anchoring age narrows the syndromic differential immediately.

II. Pediatric Status Epilepticus (SE) Protocols

Status epilepticus management in the pediatric ICU requires rapid, staged escalation to prevent secondary neuronal injury.

A. Step-by-Step Rescue & Urgent Control

Stage	Timeline	Medication & Dosage	Notes
Emergent (Stage 1)	0–5 min	Lorazepam 0.1 mg/kg IV (max 4 mg)	Alternative: intranasal midazolam or rectal diazepam
Urgent (Stage 2)	5–20 min	Fosphenytoin 20 mg PE/kg IV load	Alternative: levetiracetam 40–60 mg/kg or valproate
Refractory (Stage 3)	> 20 min	Midazolam infusion; load 100–200 mcg/kg	Begin continuous EEG monitoring immediately

B. Refractory Status Epilepticus Infusion Parameters

Medication	Loading Dose	Titration Parameters	Goal
Midazolam	100–200 mcg/kg	Increase by 50 mcg/kg/h every 15 min to a max of 600–800 mcg/kg/h	Cessation of seizures or burst suppression
Pentobarbital	6–8 mg/kg	Maintenance 1–4 mg/kg/h	Titrate to burst suppression (24–48 hours)

EMERGENCY

Failure to escalate therapy on schedule is a major contributor to poor neurologic outcome in status epilepticus. Continuous EEG monitoring must begin no later than the onset of refractory status (Stage 3) to detect ongoing electrographic seizures once clinical convulsive activity has stopped.

III. Pediatric Neuro-Ophthalmology & Autonomic Systems

Neuro-ophthalmic findings are frequently the earliest indicator of increased intracranial pressure or an underlying genetic syndrome.

A. Differential Diagnosis of Optic Nerve Pathology

Papilledema vs. Pseudopapilledema

Feature	Papilledema	Pseudopapilledema
Mechanism	True optic disc swelling due to elevated intracranial pressure	Structural disc anomaly, most commonly optic disc drusen
Clinical Significance	In Tuberous Sclerosis Complex, acute headache with papilledema suggests a SEGA causing obstructive hydrocephalus at the foramen of Monro	Benign; may mimic true disc edema on fundoscopy
Confirmatory Testing	Neuroimaging and formal ICP assessment as indicated	Ocular ultrasound or optical coherence tomography (OCT) to avoid unnecessary ICP workup

Optic Pathway Gliomas (OPG)

- **Association:** occur in 15–20% of children under age 6 with neurofibromatosis type 1 (NF1).
- **Signs:** decreased visual acuity, proptosis, and pupillary abnormalities.
- **Surveillance:** annual ophthalmologic examination until age 8; routine screening MRI remains controversial in asymptomatic NF1 patients.

B. Nystagmus and Pupillary Abnormalities

Condition	Key Features
Septo-optic dysplasia (SOD)	Presents in infancy with nystagmus or poor visual engagement, optic nerve hypoplasia, and hypopituitarism
Chiari II malformation (myelomeningocele)	Brainstem compression can produce nystagmus, stridor, and vocal cord paralysis
Vigabatrin toxicity	Used for West syndrome; causes irreversible peripheral vision loss and visual field constriction. Regular monitoring with electroretinography or formal visual field testing is mandatory
Congenital Zika virus infection	Macular scarring and pigmentary retinal mottling alongside severe microcephaly

⚠ WARNING

Vigabatrin-associated visual field loss is often irreversible and may be asymptomatic until advanced. Baseline and periodic ophthalmologic monitoring (electroretinogram or perimetry) is mandatory for the duration of treatment.

C. Autonomic Systems in Epilepsy

- **Panayiotopoulos syndrome:** characterized by profound autonomic symptoms — recurrent vomiting, pallor, and pupillary changes — occurring during seizures.
- **Paroxysmal sympathetic hyperactivity:** 'sympathetic storms' (tachycardia, hypertension, hyperthermia) following severe traumatic brain injury or cardiac arrest.

PART 3

Neurometabolic Disorders & Neurocutaneous Syndromes

This chapter focuses on precise biochemical profiles, genetic markers, and targeted therapeutic protocols for inborn errors of metabolism, mitochondrial and storage disorders, and the phakomatoses.

I. Inborn Errors of Metabolism (IEM) in Childhood

Inborn errors of metabolism are individually rare but collectively occur in approximately 1 in 1,000 births. Early recognition of biochemical 'red flags' is essential to prevent irreversible neurological injury.

A. Acute Metabolic Crisis Laboratory Profiles

Acute presentations often mimic sepsis but can be distinguished by specific patterns of metabolic derangement.

Clinical Finding	Associated Biochemical Profile	Suspected Disorder Group(s)
Hyperammonemia	Ammonia > 150 $\mu\text{mol/L}$; early respiratory alkalosis; normal or low BUN	Urea cycle defects; organic acidurias (secondarily inhibiting the urea cycle)
Metabolic acidosis	Elevated anion gap; ketonuria; hypoglycemia	Organic acidurias (e.g., methylmalonic, propionic acidemia)
Lactic acidosis	Elevated blood/CSF lactate; low N-acetylaspartate (NAA) on MR spectroscopy	Mitochondrial disorders; pyruvate metabolism defects
Hypoglycorrachia	Low CSF glucose (< 60 mg/dL) with normal blood glucose; normal or low CSF lactate	GLUT-1 deficiency syndrome

B. Aminoacidopathies & Organic Acidurias

These disorders typically feature a symptom-free interval immediately after birth, reflecting placental clearance of toxic metabolites in utero.

Disorder	Genetic Target / Enzyme	Characteristic Biomarkers	Treatment
Phenylketonuria (PKU)	PAH gene; phenylalanine hydroxylase	Elevated phenylalanine	Lifelong phenylalanine-restricted diet

Disorder	Genetic Target / Enzyme	Characteristic Biomarkers	Treatment
Maple syrup urine disease (MSUD)	Branched-chain α -ketoacid dehydrogenase	Elevated leucine, isoleucine, and valine in plasma/CSF	Acute: BCAA-free TPN. Chronic: low-protein diet; thiamine cofactor trial
Methylmalonic acidemia	Methylmalonyl-CoA mutase (or cobalamin metabolism defects)	Elevated methylmalonic acid and homocysteine	Protein restriction; cobalamin (B12) injections if B12-responsive
Propionic acidemia	Propionyl-CoA carboxylase	Elevated 3-hydroxypropionate and methylcitrate	Protein restriction; biotin supplementation

CLINICAL PEARL

A well-appearing neonate who deteriorates after 24–72 hours of life — coinciding with the introduction of protein feeds — should immediately raise suspicion for an inborn error of metabolism, particularly a urea cycle defect or organic aciduria.

II. Mitochondrial and Storage Disorders

A. Mitochondrial and Energy Metabolism Disorders

Mitochondrial disease should be suspected in cases of multi-system involvement or recurrent 'metabolic strokes.'

- **Pyruvate dehydrogenase complex (PDHC) deficiency:** commonly caused by PDHA1 mutations (X-linked). Features neonatal lactic acidosis and brain malformations, including cystic lesions and agenesis of the corpus callosum.

The 'Mitochondrial Cocktail' & Management

- **Ketogenic diet:** provides ketone bodies as an alternative fuel source, bypassing defective glucose/pyruvate oxidation pathways.
- **Biotin-thiamine-responsive basal ganglia disease (BTBGD):** caused by SLC19A3 mutations; requires high-dose biotin (5–10 mg/kg/day) and thiamine (300–900 mg/day).

WARNING

Valproate is strictly contraindicated in suspected or confirmed mitochondrial disease. It interferes with respiratory chain function and can precipitate fulminant liver failure in patients with POLG-1 variants (Alpers syndrome).

B. Peroxisomal and Lysosomal Storage Diseases (Leukodystrophies)

Disorder	Genetic / Biochemical Target	Diagnostic Hallmark	Therapeutic Protocol
X-linked adrenoleukodystrophy	ABCD1 gene (Xq28); peroxisomal membrane transporter protein	Elevated very long chain fatty acids (VLCFA), specifically C26:0 and the C26:C22 ratio	HSCT for early cerebral form (Loes score < 10); mandatory adrenal function monitoring
Metachromatic leukodystrophy	ARSA gene; arylsulfatase A	Low ARSA enzyme activity plus elevated urinary sulfatides	HSCT for asymptomatic or early juvenile forms; lentiviral gene therapy in clinical trials
Krabbe disease	GALC gene; galactosylceramidase	Enzyme activity < 5%; elevated CSF protein; elevated psychosine	Umbilical cord blood transplant if performed in the asymptomatic neonate (before ~7 weeks of age)

★ HIGH YIELD

Presymptomatic hematopoietic stem cell transplantation (HSCT) is disease-modifying across several leukodystrophies (X-ALD, MLD, Krabbe) — this underlies the rationale for newborn screening programs targeting these conditions.

III. Neurocutaneous Syndromes (Phakomatoses)

A. Neurofibromatosis Type 1 and Type 2

Feature	Neurofibromatosis Type 1 (NF1)	Neurofibromatosis Type 2 (NF2)
Genetics	NF1 gene (17q11.2); encodes neurofibromin (a Ras-GTPase-activating protein)	NF2 gene (22q12.2); encodes merlin/schwannomin
Diagnostic Criteria	≥ 2 of: 6+ café-au-lait macules; 2+ neurofibromas (or 1 plexiform); axillary/inguinal freckling; optic glioma; 2+ Lisch nodules; sphenoid wing dysplasia; first-degree relative with NF1	Manchester criteria: bilateral vestibular schwannomas OR a first-degree relative with NF2 plus a unilateral vestibular schwannoma or two other NF2-associated tumors (meningioma, glioma, etc.)
Targeted Therapy	MEK inhibitors for symptomatic, inoperable plexiform neurofibromas	Bevacizumab (anti-VEGF) for progressive vestibular schwannomas
Surveillance	Annual vision and blood pressure checks; annual ophthalmology through age 8; brain MRI only if symptomatic	MRI of brain and spine at diagnosis; regular audiology; high risk of somatic mosaicism

B. Tuberous Sclerosis Complex (TSC)

TSC results from loss-of-function mutations in TSC1 or TSC2, leading to overactivation of the mTOR signaling pathway.

Category	Clinical Criteria	Targeted Management
Major criteria	Hypomelanotic macules (≥ 3); angiofibromas (≥ 3); shagreen patch; subependymal giant cell astrocytoma (SEGA); cortical tubers; cardiac rhabdomyoma; angiomyolipoma	Everolimus (mTOR inhibitor): first-line for SEGAs > 5–10 mm and asymptomatic renal angiomyolipomas > 3 cm
Minor criteria	'Confetti' skin lesions; dental enamel pits (> 3); intraoral fibromas (≥ 2); multiple renal cysts	Vigabatrin: preferred first-line agent for TSC-associated infantile spasms

C. Sturge-Weber Syndrome (SWS)

A sporadic condition caused by a somatic mosaic mutation in GNAQ.

- **Port-wine birthmark:** typically follows a V1 and V2 trigeminal nerve distribution.
- **Leptomenigeal angiomatosis:** often parieto-occipital in location; causes chronic ischemia, progressive hemiatrophy, and 'stroke-like' episodes.

- **Glaucoma risk:** 50% if both eyelids are involved by the port-wine stain; screening is recommended every few months in infancy and annually thereafter, for life.
- **Management:** standard medical management for epilepsy; low-dose aspirin (3–5 mg/kg/day) is used, though controversially, to reduce the frequency of stroke-like episodes.

🔖 MEMORY TIP / MNEMONIC

The phakomatoses and their signature 'stigmata' — NF1: café-au-lait macules & Lisch nodules. TSC: ash-leaf (hypomelanotic) macules & angiofibromas. Sturge-Weber: port-wine stain in a trigeminal distribution. Matching the skin finding to the syndrome anchors the differential at the bedside.

PART 4

Neuromuscular Disorders, Cerebral Palsy & Movement Disorders

📌 IMPORTANT NOTE

Pediatric primary muscle disease (e.g., the congenital and limb-girdle muscular dystrophies) receives comprehensive treatment in dedicated neuromuscular reference volumes and is intentionally not duplicated in full here; this chapter emphasizes general neuromuscular principles, gene-modifying therapies, and metabolic movement disorders most relevant to the general neurologist.

I. Pediatric Neuromuscular Disorders

A. Spinal Muscular Atrophy (SMA) and Gene-Modifying Therapy

SMA is a landmark condition in the implementation of antisense oligonucleotide (ASO) and gene-replacement therapy for a genetic neuromuscular disease.

- **ASO mechanism:** therapy modifies splicing of the SMN2 gene to increase production of functional survival motor neuron (SMN) protein, compensating for the deleted or non-functional SMN1 gene.
- **Nusinersen:** an intrathecally administered antisense oligonucleotide with demonstrated efficacy in altering the natural history of SMA.
- **Genetic testing:** molecular genetic analysis (PCR) for homozygous deletion of the SMN1 gene is the first-tier investigation, and often obviates the need for invasive muscle biopsy.

B. Genetic Muscular Dystrophies (DMD/BMD)

Duchenne muscular dystrophy (DMD) is a prime example of the clinical importance of exon-level deletions, which account for up to 70% of pathogenic mutations in the DMD gene.

Therapeutic Category	Protocol / Agent	Notes
Glucocorticoids	Prednisone / deflazacort	Standard of care to slow functional decline; a key consideration during transition to adult care
Gene-modifying therapy	Exon-skipping oligonucleotides antisense	Mutation-specific (exon-targeted); represents the frontier of targeted therapy for DMD
Supportive care	Physical and occupational therapy	Essential for maximizing independence and preventing joint contractures

C. Neuromuscular Junction (NMJ) Disorders

- **Congenital myasthenic syndromes:** may present as primary movement disorders or with a 'cerebral-palsy-like' phenotype, making them an important mimic to consider.
- **Diagnostic approach:** nerve conduction studies (NCS) and electromyography (EMG) are required to differentiate axonal from demyelinating neuropathy before proceeding to targeted genetic testing.

II. Cerebral Palsy (CP) and Functional Classification

Many treatable metabolic conditions can masquerade as cerebral palsy. A central diagnostic task is distinguishing 'static' CP from progressive neurometabolic disease.

A. Motor Classification and Treatable Mimics

- **Dopa-responsive dystonia (DYT5):** can present with CP-like features but responds dramatically to low-dose levodopa.
- **GLUT-1 deficiency syndrome:** can likewise mimic static CP but is treated effectively with a ketogenic diet.
- **Comorbidities:** autism spectrum disorder and epilepsy are frequent in CP populations; up to 20% of children with autism spectrum disorder may have co-occurring epilepsy.

PITFALL

Any child labeled with 'cerebral palsy' whose motor findings are progressive, rather than static, or who has atypical features (diurnal fluctuation, an unusually preserved cognitive profile, or a family history of a movement disorder) should be re-evaluated for a treatable metabolic mimic before the CP label is accepted as final.

B. Gross Motor Function Classification System (GMFCS)

The GMFCS is the internationally accepted standard for describing functional motor severity in cerebral palsy and guides prognostic discussion and the transition of care.

GMFCS Level	Functional Description
Level I	Walks without limitations
Level II	Walks with limitations (e.g., difficulty with uneven surfaces, inclines, or in crowds)

GMFCS Level	Functional Description
Level III	Walks using a hand-held mobility device (e.g., walker, crutches)
Level IV	Self-mobility with limitations; may use powered mobility
Level V	Transported in a manual wheelchair; limited ability to maintain head and trunk posture against gravity

? IMPORTANT NOTE

The GMFCS I–V table above reflects the internationally accepted, standard definitions (Palisano et al.) supplied here to complete the classification framework, as it is essential for clinical staging and communication but was not exhaustively tabulated in the source material.

III. Pediatric Movement Disorders

Pediatric movement disorders are usefully categorized by the presence of an underlying metabolic or structural trigger. Neurotransmitter diseases are high-stakes diagnostic 'misses' in this population, as many are treatable.

A. Treatable Dystonias and Chorea

Disorder	Clinical Hallmark	Treatment / Titration Profile
Dopa-responsive dystonia	Diurnal fluctuation (worsening symptoms in the evening)	Oral levodopa: 1–10 mg/kg/day
Wilson disease	Kayser-Fleischer rings; 'double panda' sign on brain MRI	D-penicillamine: 10–20 mg/kg/day
Biotin-thiamine-responsive basal ganglia disease	Recurrent encephalopathy/dystonia triggered by febrile illness	Biotin 5–10 mg/kg/day AND thiamine 300–900 mg/day
Sydenham chorea	Associated with prior group A streptococcal infection	Requires secondary penicillin prophylaxis to prevent recurrence

★ HIGH YIELD

Neurotransmitter and cofactor-responsive movement disorders (dopa-responsive dystonia, BTBGD, Wilson disease) are dramatically treatable and must be actively excluded in any child with an atypical or progressive movement disorder before it is labeled idiopathic or attributed to CP.

B. Tic Disorders and Tourette Syndrome

- **Characteristics:** stereotyped, involuntary, briefly suppressible movements.
- **Diagnostic testing:** unlike many other pediatric movement disorders, Tourette syndrome and essential tremor currently require no specific genetic testing for diagnosis or management.
- **Comorbidities:** tics are common in children with ADHD and autism spectrum disorder.

C. Neuromuscular and Movement Disorder Genetic Targets

Target Gene	Associated Condition	Therapeutic Intervention
SMN1 / SMN2	Spinal muscular atrophy (SMA)	Nusinersen (antisense oligonucleotide)
DMD	Duchenne muscular dystrophy	Exon-skipping antisense oligonucleotides (mutation-specific)
GCH1	Dopa-responsive dystonia	Levodopa, titrated by weight
SLC2A1	GLUT-1 deficiency syndrome	Ketogenic diet (provides an alternative CNS fuel source)
ABCD1	X-linked adrenoleukodystrophy	Hematopoietic stem cell transplantation (HSCT)

IV. Transition of Care for Neuromuscular Patients

A successful, well-structured transition from pediatric to adult care is critical for maintaining function and continuity of care in complex neuromuscular patients.

- **Timeline:** transition discussions should begin by age 13, with formal legal competency assessment by age 14.

- **Documentation:** a structured Transfer Packet must be sent to the accepting adult provider, including a comprehensive medical summary and an individualized transition care plan.

EXAM TIP

Transition-of-care timelines (initiate discussion by age 13; competency assessment by age 14; formal transfer packet) are frequently tested in board and in-training examinations covering neuromuscular disease and general pediatric neurology practice management.

PART 5

Neuro-Infections, Autoimmune Syndromes & Neuro-Oncology

This chapter focuses on diagnostic gold standards, neuroimaging patterns, and precise therapeutic protocols for pediatric CNS infections, autoimmune/demyelinating disease, and neuro-oncologic emergencies.

I. Pediatric Infectious Meningitis and Encephalitis

Diagnosis of CNS infection in children relies on age-specific pathogen suspicion and rapid cerebrospinal fluid (CSF) analysis to differentiate bacterial, viral, and fungal etiologies.

A. Age-Specific Pathogens and Empiric Treatment

Empiric antimicrobial therapy must be initiated immediately after lumbar puncture — or before, if the procedure will be delayed — to cover the most likely age-specific organisms.

Age Group	Common Pathogens	Empiric Antibiotic Regimen
Neonates (< 28 days)	Group B Streptococcus, Escherichia coli, Listeria monocytogenes	Ampicillin + cefotaxime (or gentamicin)
Infants & children	Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae	Ceftriaxone + vancomycin

EMERGENCY

Suspected bacterial meningitis is a neurologic emergency. Do not delay empiric antibiotic administration to await lumbar puncture or neuroimaging if either will take significant time to arrange.

B. Viral Encephalitis: Herpes Simplex Virus (HSV)

HSV is a critical diagnostic consideration in any neonate or child presenting with fever, seizures, and altered mental status, given the high morbidity of delayed treatment.

- **Neonatal HSV dosing:** IV acyclovir 20 mg/kg every 8 hours is the standard empiric protocol, initiated promptly to prevent permanent neurological sequelae.
- **Neuroimaging:** classically shows temporal lobe involvement in older children, though neonatal HSV encephalitis may present with more diffuse cerebral injury.

⚠ WARNING

Empiric acyclovir should be started as soon as HSV encephalitis is a clinical consideration and should not be withheld pending confirmatory PCR results, given the time-sensitive nature of neurological injury.

C. CSF Profiles in Pediatric CNS Infection

Profile	White Blood Cell Count	Protein Level	Glucose Level
Bacterial	Markedly elevated (neutrophil/PMN predominance)	Significantly elevated	Markedly low
Viral	Mildly elevated (lymphocytic predominance)	Normal to mildly elevated	Normal
Fungal / Tuberculous	Moderately elevated	Elevated	Low

? MEMORY TIP / MNEMONIC

CSF pattern recall — Bacterial: PMNs up, protein way up, glucose way down. Viral: lymphocytes up, protein normal-ish, glucose normal. Fungal/TB: intermediate on every parameter, but with a subacute/chronic clinical course.

II. Autoimmune and Demyelinating Central Syndromes

Distinguishing monophasic events, such as acute disseminated encephalomyelitis (ADEM), from chronic conditions, such as pediatric-onset multiple sclerosis (POMS), is essential for guiding long-term management and prognosis.

A. Acute Disseminated Encephalomyelitis (ADEM)

- **Clinical hallmark:** encephalopathy — behavioral change or altered consciousness — is a mandatory diagnostic feature.
- **Neuroimaging:** MRI typically reveals large, asymmetric, poorly defined ('fuzzy') T2-hyperintense lesions involving both white matter and deep gray matter structures (e.g., the thalami).
- **First-line treatment:** IV methylprednisolone 20–30 mg/kg/day (maximum 1 g/day) for 3–5 days, followed by a slow oral steroid taper over 4–6 weeks.

B. Pediatric-Onset Multiple Sclerosis (POMS)

- **Diagnostic criteria (2017 McDonald revisions):** require Dissemination in Space (DIS) — lesions in ≥ 2 of 4 classic CNS regions — and Dissemination in Time (DIT).
- **CSF finding:** the presence of two or more CSF-restricted oligoclonal bands (OCBs), absent from serum, can now independently satisfy the Dissemination in Time criterion.
- **MOGAD:** MOG-antibody-associated disorders often present with a more ADEM-like phenotype and carry a high risk of recurrent optic neuritis.

🔍 CLINICAL PEARL

Two or more unique CSF-restricted oligoclonal bands is now, by itself, sufficient to fulfill Dissemination in Time under the 2017 McDonald criteria — a repeat MRI is no longer strictly required to establish DIT if this CSF finding is present.

C. Pediatric Anti-NMDA Receptor Encephalitis

- **Progression:** typically follows a psychiatric-to-motor staging pattern — beginning with behavioral outbursts and insomnia, then progressing to orofacial dyskinesias and autonomic instability.

Management

Line of Therapy	Agents
First-line	IV methylprednisolone and IVIg (or plasmapheresis)
Second-line (if no improvement in 10–14 days)	Rituximab or cyclophosphamide

- **Screening:** adolescent females require screening for an ovarian teratoma via pelvic ultrasound or MRI.

★ HIGH YIELD

Anti-NMDA receptor encephalitis is one of the most important 'psychiatric masquerader' diagnoses in pediatric neurology — a teenager with new-onset psychosis who develops orofacial dyskinesias, seizures, or autonomic instability should prompt urgent autoimmune encephalitis workup and teratoma screening.

D. Pediatric Steroid Escalation Tiers for Demyelinating Disease

Tier	Intervention	Dosing Parameter
Tier 1	IV methylprednisolone	20–30 mg/kg/day for 3–5 days
Tier 2	Plasmapheresis (PLEX)	5–7 exchanges, every other day, if Tier 1 fails
Tier 3	IVIg	2 g/kg total dose, given over 2–5 days

III. Pediatric Neuro-Oncology

Pediatric brain tumors are broadly categorized by location: supratentorial tumors are more common in infants, while infratentorial tumors predominate in children aged 4–10 years.

A. Common Pediatric Brain Tumors

Tumor Type	Typical Location	Key Features
Pilocytic astrocytoma	Infratentorial (cerebellum)	WHO Grade I; often associated with BRAF alterations
Medulloblastoma	Infratentorial (4th ventricle)	Highly malignant; molecular subgroups (WNT, SHH, Group 3, Group 4) dictate prognosis
Ependymoma	Infratentorial (floor of the 4th ventricle)	Frequently causes obstructive hydrocephalus
Diffuse intrinsic pontine glioma (DIPG)	Brainstem (pons)	Rapidly progressive course with poor prognosis
Subependymal giant cell astrocytoma (SEGA)	Supratentorial (foramen of Monro)	Histologically benign but causes obstructive hydrocephalus; associated with tuberous sclerosis complex

B. Management of Increased Intracranial Pressure

In the acute setting of a suspected tumor with midline shift or signs of impending herniation:

- **Emergency steroids:** IV dexamethasone, loading dose 0.5–1.0 mg/kg, to reduce peritumoral vasogenic edema.
- **Surgical intervention:** urgent neurosurgical consultation for tumor resection or CSF diversion (ventriculoperitoneal shunt or external ventricular drain).

📌 EMERGENCY

Signs of herniation (pupillary asymmetry, deteriorating consciousness, Cushing triad) in a child with a known or suspected mass lesion require immediate dexamethasone administration and emergent neurosurgical consultation — do not delay for advanced imaging if the clinical picture is unequivocal.

📌 MEMORY TIP / MNEMONIC

Posterior fossa tumor recall in children — 'PEM-D': Pilocytic astrocytoma, Ependymoma, Medulloblastoma, and DIPG account for the great majority of infratentorial pediatric CNS tumors, each with a distinct age, location, and molecular signature.

THE SPINAL CORD

Chapter 1

Clinical Neuroanatomy, Vascular Supply, Cross-Sectional Syndromes, and Compressive Myelopathies

I. Clinical Neuroanatomy & Vascular Supply

1. Major Functional Tracts and Somatotopic Organization

The spinal cord is organized into discrete white matter tracts and gray matter regions. Understanding their somatotopy is essential for accurate clinical localization.

Descending Corticospinal Tracts (Lateral)

- **Function:** Voluntary motor control.
- **Somatotopy:** Mesial-to-lateral organization — fibers for the upper extremities (arms) are located mesially (medially), while fibers for the lower extremities (legs) are lateral.

CLINICAL PEARL

The mesial-to-lateral somatotopy of the corticospinal tract explains the disproportionate arm weakness characteristic of central cord syndrome.

Ascending Dorsal Columns (Posterior)

- **Function:** Carry ipsilateral vibration and joint position sense (proprioception).
- **Organization:** Divided into the Fasciculus Gracilis (medial — carries information from the lower body/legs) and Fasciculus Cuneatus (lateral — carries information from the upper body/arms).

MEMORY TIP / MNEMONIC

"**Gracilis is medial and inferior; Cuneatus is lateral and superior.**" — Think alphabetically: G comes before C, and medial comes before lateral in the standard sagittal diagram; legs (Gracilis) travel the longest, most medial path; arms (Cuneatus) join more laterally at cervical levels.

Ascending Spinothalamic Tracts (Anterolateral)

- **Function:** Carry contralateral pain and temperature sensation.

CLINICAL PEARL

Spinothalamic fibers decussate at the anterior white commissure, usually 1 to 2 segments above their entry level. This accounts for the sensory level often being one to two segments below the true anatomic lesion in anterolateral pathology.

2. Vascular Architecture and Reinforcement

The spinal cord's blood supply is categorized into cranial-caudal (longitudinal) and axial (segmental/radicular) systems.

Anterior Spinal Artery (ASA)

- **Anatomy:** A single artery running along the anterior median fissure.
- **Territory:** Supplies the anterior two-thirds of the cord, including the corticospinal tracts, spinothalamic tracts, anterior horns, and central gray matter.

Posterior Spinal Arteries (PSAs)

- **Anatomy:** Paired arteries running along the posterolateral sulci.
- **Territory:** Supplies the posterior third of the cord, including the dorsal columns and dorsal horns.

Radiculomedullary Reinforcing Arteries

- **Artery of Lazorthes:** A prominent cervical radiculomedullary artery typically arising at the C3 or C6–C7 level.
- **Artery of Adamkiewicz (Arteria Radicularis Magna):** The principal reinforcing radiculomedullary artery for the lower thoracic and lumbar cord.
 - **Localization:** Typically arises from the left side, between T9 and T12, though it can originate anywhere from T5 to L3.
 - **Clinical relevance:** Makes a characteristic hairpin turn to anastomose with the ASA. Absence (noted in ~24% of patients) or surgical injury (e.g., during aortic or retroperitoneal surgery) leads to devastating lower cord infarction.
- **Artery of Desproges-Gotteron:** A singular branch of the internal iliac artery that provides specific supply to the conus medullaris.

⚠ WARNING

The variable origin of the artery of Adamkiewicz (T5–L3) makes preoperative spinal angiography or MR angiography valuable prior to thoracoabdominal aortic surgery to minimize the risk of iatrogenic spinal cord infarction.

Table 1.1. *Vascular Territories of the Spinal Cord*

Vessel	Course	Territory Supplied	Key Clinical Note
Anterior Spinal Artery (ASA)	Single vessel, anterior median fissure	Anterior 2/3 of cord: corticospinal tracts, spinothalamic tracts, anterior horns, central gray matter	Infarction → Anterior Cord Syndrome
Posterior Spinal Arteries (paired)	Posterolateral sulci	Posterior 1/3 of cord: dorsal columns, dorsal horns	Infarction → Posterior Cord Syndrome (rare, often collateralized)
Artery of Lazorthes	Cervical radiculomedullary branch (C3 or C6–C7)	Cervical cord reinforcement	Reinforces cervical ASA flow
Artery of Adamkiewicz	Radiculomedullary; left-sided, T9–T12 (range T5–L3); hairpin turn to ASA	Lower thoracic and lumbar cord	Absent in ~24%; at risk during aortic surgery
Artery of Desproges-Gotteron	Branch of internal iliac artery	Conus medullaris	Supplements conal blood supply

II. Cross-Sectional Spinal Cord Syndromes

The following tables differentiate spinal cord syndromes based on anatomic involvement and clinical markers.

Table 1.2. *Cross-Sectional Syndrome Matrix*

Syndrome	Primary Mechanism	Motor Deficit	Sensory Deficit	Autonomic / Bladder
Complete Cord Transection	Trauma; severe transverse myelitis	Total paralysis below the lesion (initially flaccid — spinal shock)	Complete loss of all sensory modalities below the level	Acute urinary retention; total loss of bowel/bladder control
Brown-Séquard (Hemicord)	Penetrating trauma (knife/bullet); lateral compression	Ipsilateral weakness/hemiparesis	Ipsilateral loss of vibration/proprioception; contralateral loss of	Generally mild or unilateral; rare significant

Syndrome	Primary Mechanism	Motor Deficit	Sensory Deficit	Autonomic / Bladder
			pain/temperature (1–2 levels below lesion)	sphincter involvement
Central Cord Syndrome	Hyperextension in a stenotic spine	Upper > lower extremity weakness (distal > proximal)	Variable; classically a "hanging" or "suspended" pain/temperature loss at the lesion level	Urinary retention possible; variable severity
Anterior Cord Syndrome	ASA infarction; bone/disk retropulsion	Bilateral paraparesis or quadriparesis	Bilateral loss of pain/temperature; proprioception and vibration spared	Early and severe bowel/bladder dysfunction
Posterior Cord Syndrome	PSA infarction; metabolic (B12 deficiency); tabes dorsalis (syphilis)	Generally spared or minimal	Bilateral loss of light touch, vibration, and proprioception (sensory ataxia)	Sphincters typically spared

🔍 CLINICAL PEARL

Anterior Cord Syndrome carries the worst prognosis among the incomplete cord syndromes, while Central Cord Syndrome typically carries the most favorable prognosis for ambulation.

🔍 MEMORY TIP / MNEMONIC

Anterior Cord = "Front Pain-Temp Falls, Back stays Fine."

Anterior (motor + pain/temperature loss) vs. Posterior (proprioception/vibration loss only, "posterior column, posterior sense").

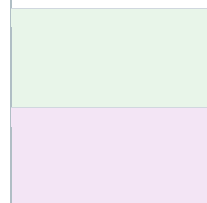


Table 1.3. *Conus Medullaris Syndrome vs. Cauda Equina Syndrome*

Metric	Conus Medullaris Syndrome	Cauda Equina Syndrome
Anatomic level	Terminal end of the cord (L1–L2)	Nerve roots (below L2)
Deficit symmetry	Typically symmetric	Typically asymmetric
Motor signs	Mixed UMN/LMN signs; spasticity possible	Pure LMN signs; flaccid weakness; atrophy

Metric	Conus Medullaris Syndrome	Cauda Equina Syndrome
Reflexes	Brisk patellar/Achilles (if UMN component); absent bulbocavernosus reflex	Hyporeflexia or areflexia
Bladder/bowel	Early onset; symmetric dysfunction	Late-occurring; urinary retention with overflow incontinence
Sensory loss	Perianal "saddle" anesthesia (symmetric)	Radicular or diffuse, asymmetric numbness
⚠ WARNING Cauda equina syndrome is a surgical emergency. New saddle anesthesia, bilateral leg weakness, or bowel/bladder dysfunction in the setting of a large disk herniation requires emergent MRI and neurosurgical evaluation.		

III. Compressive & Structural Myelopathies

1. Degenerative Cervical Myelopathy (DCM)

The leading cause of myelopathy worldwide in patients older than 55 years.

Pathophysiology

The pathologic cascade begins with disk degeneration, leading to canal narrowing, ligamentum flavum hypertrophy, and chronic ischemia/apoptosis of neurons and oligodendrocytes.

Clinical Presentation

- Insidious "clumsy hands" (difficulty with buttons/zippers) and subjective gait imbalance.
- **"Myelopathy Hand":** Characterized by hand muscle wasting (thenar/hypothenar) and medial forearm atrophy, often due to anterior horn cell dysfunction at C8–T1 levels, even when compression is at a higher cervical level.

MRI Signatures

- **"Pancake Sign":** A transverse band of gadolinium enhancement just below the site of maximal stenosis, sparing the gray matter on axial views.
- **STIR Sequence:** Essential within 48 hours of trauma to assess occult ligamentous instability.

i IMPORTANT NOTE

The "pancake-like" enhancement pattern may persist for years even after successful surgical decompression and should not be misinterpreted as idiopathic transverse myelitis.

2. Neoplastic Compression (MESCC)

EMERGENCY

Metastatic Epidural Spinal Cord Compression (MESCC) is a neurologic emergency. Pretreatment motor function is the strongest predictor of outcome — early recognition and treatment are critical to preserving ambulation.

Pathophysiology

Most commonly results from bony vertebral metastases (breast, lung, prostate) invading the epidural space.

Red Flags

- New-onset back pain in a patient with known cancer (especially thoracic pain)
- Night sweats
- Rapid symptom progression

Table 1.4. MESCC Emergent Corticosteroid Dosing Protocol

Phase	Medication	Dosing Strategy
Loading (bolus)	Dexamethasone	10 mg to 100 mg IV, depending on severity of neurologic deficit
Maintenance	Dexamethasone	Standing doses (e.g., 4 mg to 10 mg every 6 hours)
Taper	Dexamethasone	Gradual reduction over 7–14 days after definitive treatment (surgery or radiation)

3. Specialized Structural Disorders

Ossification of the Posterior Longitudinal Ligament (OPLL)

More common in Asian populations; involves bone formation within the ligament, leading to severe static spinal cord compression.

Atlantoaxial Subluxation

High risk in patients with rheumatoid arthritis, Down syndrome, or Klippel-Feil syndrome; requires careful screening for craniocervical stability, particularly prior to procedures requiring neck manipulation (e.g., intubation).

Hirayama Disease (Monomelic Amyotrophy)

Juvenile onset; neck flexion causes forward displacement of the posterior dural wall, leading to asymmetric hand wasting and the "snake eyes" sign (anterior horn ischemia) on MRI.

Epidural Lipomatosis

Accumulation of fat tissue (often from long-term steroid use) causing a "Y-sign" (polygonal deformation of the dural sac).

Table 1.5. Structural Myelopathy Signature Findings

Disorder	Population at Risk	Signature Sign	Key Point
OPLL	Asian populations (higher prevalence)	Ossified band along posterior vertebral bodies on CT/MRI	Causes severe, static canal compression
Atlantoaxial subluxation	Rheumatoid arthritis, Down syndrome, Klippel-Feil syndrome	Increased atlanto-dental interval on flexion-extension films	Screen before neck manipulation/intubation
Hirayama disease	Juvenile males, typically	"Snake eyes" sign on flexion MRI	Asymmetric hand/forearm wasting; neck-flexion-induced dural shift
Epidural lipomatosis	Chronic steroid use, obesity	"Y-sign" (polygonal dural sac deformation)	Reversible with steroid discontinuation/weight loss in many cases
★ HIGH YIELD Board exams frequently test signature MRI signs (pancake sign, snake eyes sign, Y-sign) paired with their associated disease. Learn the sign-disease pairing as a unit rather than in isolation.			

Chapter 2

Vascular Malformations, Ischemic Infarction, Traumatic Injury, and Metabolic Myelopathies

This chapter provides clinical pathways, biochemical thresholds, and management protocols for noninflammatory spinal cord disorders.

I. Vascular Disorders of the Spinal Cord

Vascular myelopathies represent approximately 22% of final diagnoses in patients initially suspected of having "transverse myelitis." Precise etiologic diagnosis is critical, as treatments for inflammation (e.g., corticosteroids) can be detrimental to vascular outcomes.

⚠ WARNING

Do not reflexively treat a presumed "transverse myelitis" with high-dose corticosteroids until vascular causes (particularly spinal dural arteriovenous fistula) have been reasonably excluded, since steroids can worsen venous congestion and precipitate clinical deterioration.

1. Spinal Cord Infarction (SCI)

Risk Factors

The most prominent risk factor is aortic surgery (especially thoracoabdominal repair), followed by aortic dissection, aortic atherosclerosis, and severe systemic hypotension (e.g., cardiac arrest).

Unique Mechanisms

- **Fibrocartilaginous Embolism (FCE):** Triggered by physical exertion, trauma, or the Valsalva maneuver; more common in younger patients.
- **Surfer's Myelopathy:** Associated with prolonged prone hyperextension.

Clinical Presentation

- Characterized by a hyperacute "apoplectic" temporal profile, with severe deficits reaching nadir in 12 hours or less.
- Abrupt, excruciating back or girdle-like pain occurs in 70% of cases at onset.

Management

Perfusion pressure must be optimized through hemodynamic augmentation and resistance reduction via lumbar CSF drainage.

CLINICAL PEARL

A hyperacute, "stroke-like" temporal profile with severe back/girdle pain at onset strongly favors spinal cord infarction over inflammatory myelitis, which typically evolves over hours to days (subacute).

2. Vascular Malformations

Spinal Dural Arteriovenous Fistulas (SDAVF)

- The most common spinal vascular malformation (approximately 70% of spinal vascular malformations).
- Typically affects men in their 60s.
- **Clinical clues:** Slowly progressive thoracic myelopathy that worsens with exertion (claudication), the Valsalva maneuver, or corticosteroid administration.

Intramedullary Arteriovenous Malformations (AVMs)

High-flow shunts common in younger patients (30s–40s); predominantly present with hematomyelia (intraparenchymal hemorrhage).

Foix-Alajouanine Syndrome

Subacute necrotic myelopathy resulting from chronic spinal venous hypertension, typically as a late consequence of untreated SDAVF.

Table 2.1. Vascular Diagnostic Signatures and Management Targets

Disorder	Diagnostic Signature	Hemodynamic / Target Thresholds	Management Protocol
Spinal Cord Infarct	"Owl Eyes" (axial T2) or "Pencil Sign" (sagittal T2)	MAP > 85–90 mmHg for 5–7 days	Hemodynamic augmentation; CSF drainage (target pressure 8–12 mmHg)
SDAVF	"Missing Piece Sign" (enhancement) and dorsal flow voids	No specific BP target; avoid steroids	Surgical ligation or endovascular embolization
Cavernous Malformation	"Popcorn Sign" (heterogeneous T1/T2 with hemosiderin rim)	Normotension	Observation if asymptomatic; resection if recurrent bleeds

Disorder	Diagnostic Signature	Hemodynamic / Target Thresholds	Management Protocol
Epidural Hematoma	Lentiform extradural mass	Correct coagulopathy	Emergent surgical evacuation (target < 12 hours)

II. Traumatic Spinal Cord Injury (SCI)

1. Pathophysiology: Shock States

Spinal Shock

A transient physiological state (hours to weeks) following acute injury, presenting with flaccid areflexia and anesthesia below the lesion.

Neurogenic Shock

A life-threatening distributive shock occurring with injuries at or above T6.

- **Triad:** Hypotension, bradycardia, and peripheral vasodilation (warm skin).

✗ PITFALL

Do not confuse spinal shock (a neurologic phenomenon of flaccid areflexia) with neurogenic shock (a hemodynamic phenomenon of hypotension and bradycardia). They can coexist but are physiologically distinct entities.

2. Autonomic Dysreflexia (AD)

🚨 EMERGENCY

Autonomic dysreflexia is a life-threatening hypertensive emergency in chronic spinal cord injury patients (injuries at or above T6), triggered by noxious stimuli below the level of injury. Untreated, it can cause seizure, intracranial hemorrhage, or death.

- **Threshold:** A rise in systolic BP greater than 20 mmHg above baseline may trigger symptoms.
- **Common triggers:** Full bladder (most common), bowel impaction, or pressure sores.

Table 2.2. Emergency Trauma Protocols

Condition	Mechanism	Emergency Target	Intervention Protocol
Neurogenic Shock	Loss of sympathetic tone	MAP 85–90 mmHg	IV fluids (restore euvoolemia), then vasopressors (norepinephrine)
Autonomic Dysreflexia	Unmodulated sympathetic surge below the lesion	SBP < 150 mmHg	1. Sit patient upright. 2. Empty bladder/bowel. 3. Captopril 25 mg or nitroglycerine
Acute SCI (Surgical)	Primary mechanical force	< 24 hours for surgery	Early decompression improves functional recovery

3. The Methylprednisolone (NASCIS) Controversy

Historical Protocol (NASCIS II/III)

- **Loading:** 30 mg/kg IV bolus over 1 hour.
- **Maintenance:** 5.4 mg/kg/hour infusion.
- **Windows:** 23-hour infusion if started within 3 hours of injury; 48-hour infusion if started within 3–8 hours of injury.

⚠ WARNING

Modern Update: High-dose methylprednisolone for acute traumatic SCI is now strongly discouraged (Level III recommendation) by major guidelines due to a lack of significant clinical efficacy and increased risks of sepsis, GI bleeding, and pneumonia.

III. Metabolic & Nutritional Myelopathies

1. Vitamin B12 and Nitrous Oxide

- **Subacute Combined Degeneration (SCD):** Selectively targets the posterior columns and lateral corticospinal tracts.
- **Nitrous Oxide:** Irreversibly oxidizes the cobalt atom of B12, creating a functional deficiency. May occur after a single exposure (e.g., dental procedure) in patients with low-normal B12 levels.

2. Copper and Zinc Interaction

- **Copper deficiency:** Clinically and radiographically indistinguishable from B12 deficiency.

- **Zinc mechanism:** Excess zinc (from supplements or denture cream) induces intestinal metallothionein, which traps copper and prevents its absorption.

🔍 CLINICAL PEARL

Always screen copper levels in a patient with a "B12 deficiency-like" myelopathy who has normal or borderline B12 levels — especially with a history of denture cream use or zinc supplementation.

Table 2.3. *Metabolic Thresholds and Repletion Protocols*

Nutrient	Biochemical Threshold	Deficiency	Classic MRI Pattern	Treatment Protocol
Vitamin B12	< 200 pg/mL (deficient); < 300 pg/mL (borderline)		"Inverted V" / "Rabbit Ears" sign (dorsal columns)	1000 µg IM/SC daily × 5 days, then monthly
Copper	< 0.75 µg/mL; ceruloplasmin < 21.5 mg/dL		"Inverted V" sign	Oral: 6 mg/day (week 1), 4 mg/day (week 2), then 2 mg/day maintenance
Vitamin E	< 5 µg/mL; ratio to lipids < 0.8 mg/g		Posterior hyperintensity column	200–300 mg/day; up to 3000 mg/day if malabsorption present
Folic Acid	< 3 ng/mL (serum); < 150 µg/L (red cell)		Posterior hyperintensity column	5 mg/day for 4 months, then 1 mg/day

3. Hepatic Myelopathy

- **Etiology:** Results from portosystemic shunting (e.g., following TIPS procedure).
- **Clinical:** Progressive spastic paraparesis, typically sparing sensory and sphincter function.
- **MRI:** Spinal cord is often normal; brain MRI shows T1 hyperintensity in the globus pallidus (manganese deposition).
- **Treatment:** Liver transplantation or shunt reduction.

★ HIGH YIELD

A patient with spastic paraparesis, a normal spine MRI, and known liver disease/portosystemic shunt should prompt consideration of hepatic myelopathy — look for globus pallidus T1 hyperintensity on brain MRI.

Chapter 3

Inflammatory, Demyelinating, and Autoimmune Myelopathies

This chapter integrates neuroimmunological and neuro-ophthalmologic board-level concepts for inflammatory spinal cord disorders, reflecting current expert consensus.

1. Acute Transverse Myelitis (ATM)

The diagnostic approach to ATM has undergone a paradigm shift, moving from a broad "wastebasket" term to a model of high-precision etiologic diagnosis.

Definition & Terminology

Myelitis refers specifically to inflammation of the spinal cord parenchyma. The term "transverse" is often misleading, as many inflammatory processes (e.g., multiple sclerosis) involve only a portion of the cord's cross-section.

Idiopathic ATM vs. Secondary Causes

- **Idiopathic ATM:** A diagnosis of exclusion requiring bilateral (though not necessarily symmetric) deficits, a clear sensory level, and objective evidence of inflammation (MRI enhancement or CSF pleocytosis/elevated IgG index) in the absence of a defined etiology.
- **Secondary causes:** Up to 70% of patients initially labeled with idiopathic ATM are later found to have a specific cause, such as NMOSD, MS, or noninflammatory mimics such as spinal cord infarction.

⚠ WARNING

Because up to 70% of "idiopathic" ATM diagnoses are later reclassified, a thorough etiologic work-up (serologic, MRI, and CSF) is mandatory before accepting an idiopathic label — particularly to exclude vascular mimics that would be harmed by immunosuppression.

Anatomic Stratification

- **Longitudinally Extensive Transverse Myelitis (LETM):** Lesions spanning ≥ 3 contiguous vertebral segments. Characteristically seen in NMOSD, MOGAD, and neurosarcoidosis.
- **Short-Segment Transverse Myelitis (SSTM):** Lesions extending < 3 vertebral segments. Prototypical for multiple sclerosis.

💡 MEMORY TIP / MNEMONIC

LETM = "Long lesion, Look for NMOSD/MOGAD/sarcoid." SSTM = "Short lesion, Suspect MS."

2. Autoimmune Demyelinating Phenotypes

Multiple Sclerosis (MS)

Clinical Presentation

Typically mild to moderate at nadir, following a subacute (2–21 day) course. A key clinical clue is the McArdle sign (rapidly reversible pyramidal weakness induced by neck flexion).

MRI Signatures

Lesions are typically short-segment, peripheral, and asymmetric. They are wedge-shaped on axial views, preferentially involving the dorsal or lateral white matter columns.

Primary Progressive MS (PPMS)

Frequently presents with exclusively spinal cord lesions and slow, insidious motor progression over years.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Biomarker Precision

The serum AQP4-IgG cell-based assay (CBA) is nearly 100% specific. Seropositivity confirms NMOSD even if a patient has coexisting systemic lupus erythematosus or Sjögren syndrome.

Classic MRI Features

- LETM lesions are usually central, involving both gray and white matter, and often expansile.
- "Bright spotty lesions" (T2 hyperintensities as bright as CSF) and ring enhancement are highly suggestive.

Acute Management

- **First-line:** High-dose IV methylprednisolone (1 g/day for 5 days).
- **Plasma exchange (PLEX):** Early initiation is the strongest predictor of a good outcome in severe attacks, especially when steroids are insufficient.

CLINICAL PEARL

In a severe NMOSD attack, do not delay plasma exchange while awaiting steroid response — early PLEX initiation is independently associated with better recovery.

MOG Antibody-Associated Disease (MOGAD)

Clinical Features

Often follows a viral prodrome or vaccination. Unlike NMOSD, recovery is typically excellent despite a severe presentation at nadir.

Radiographic Markers

Characterized by the "H-sign" (T2 hyperintensity restricted to the central gray matter on axial views).

Conus Predilection

MOGAD has a high frequency of conus medullaris involvement, manifesting as a flaccid bladder (urinary retention), neurogenic bowel, and sexual dysfunction.

Management

Acute attacks respond briskly to steroids, but patients are prone to steroid-withdrawal relapses. Prevention requires a prolonged oral steroid taper over 2 to 3 months.

✗ PITFALL

Tapering steroids too quickly in MOGAD is a common pitfall that precipitates relapse. Unlike typical post-inflammatory tapers, MOGAD requires an extended 2–3 month taper.

3. Rare Autoimmune & Paraneoplastic Myelopathies

Autoimmune GFAP Astrocytopathy

- Typically presents as meningoencephalomyelitis.
- A pathognomonic MRI finding is radial perivascular enhancement extending from the ventricles on brain imaging.
- CSF testing offers the highest sensitivity for GFAP-IgG.

Paraneoplastic Myelopathies

Often manifest as a "tractopathy," where longitudinally extensive T2 hyperintensity symmetrically tracks along specific white matter pathways (e.g., lateral columns).

Table 3.1. *Paraneoplastic Antibody–Cancer Associations*

Antibody	Associated Malignancy
Anti-Hu (ANNA-1)	Small cell lung cancer (SCLC)

Antibody	Associated Malignancy
Anti-CRMP5 (CV2)	SCLC and thymoma
Anti-Amphiphysin	Breast cancer and SCLC

Diagnostic and Therapeutic Reference Tables

Table 3.2. *Demyelinating Disease MRI Phenotypes*

Feature	Multiple Sclerosis	NMOSD (AQP4+)	MOGAD
Lesion length	Short (< 3 segments)	Long (≥ 3 segments)	Variable (often long)
Axial pattern	Peripheral / wedge-shaped	Central (gray + white matter)	Central / gray matter ("H-sign")
Enhancement	Solid or ring (up to 8 weeks)	Patchy or ring	Faint or none (< 50% of cases)
Predilection	Cervical > thoracic	Cervicomedullary junction	Conus medullaris

Table 3.3. *Antibody Biomarker Panel*

Antibody	Primary Target	Sensitivity / Specificity	Clinical Significance
AQP4-IgG	Astrocytic water channel	Specificity ≈ 100% (cell-based assay)	Predicts > 90% relapse risk; indicates need for lifelong treatment
MOG-IgG	Oligodendrocyte protein	High titer (> 1:100) is specific	Monophasic or relapsing course; tracking titer is useful
GFAP-IgG	Astrocyte protein	Optimal sensitivity in CSF	Meningoencephalomyelitis; 25% neoplastic association
CRMP-5	Neural antigen	Paraneoplastic marker	Screen for SCLC/thymoma

Table 3.4. *Acute Rescue Therapy Protocol*

Therapy	Indication	Dosing / Regimen
IV Methylprednisolone	First-line for all acute attacks	1 g IV daily for 5 days
Plasma Exchange (PLEX)	Steroid-refractory; severe NMOSD/LETM	Typically 5–7 exchanges; initiate early

Therapy	Indication	Dosing / Regimen
IVIG	Pediatric MOGAD; steroid-sparing strategy	2 g/kg total dose divided over 2–5 days
Oral Prednisone Taper	Specifically for MOGAD relapse prevention	Taper over 2 to 3 months

Table 3.5. NMOSD Maintenance Biologic Dosing (FDA-Approved Agents)

Medication	Target	Dosing Schedule
Eculizumab	C5 complement	IV every 2 weeks
Satralizumab	IL-6 receptor	Subcutaneous, once monthly
Inebilizumab	CD19 (B-cells/plasmablasts)	IV every 6 months
Rituximab	CD20 (B-cells)	Off-label: 1000 mg twice yearly
★ HIGH YIELD Know the MRI phenotype triad (lesion length, axial pattern, enhancement) for MS vs. NMOSD vs. MOGAD — this is one of the most frequently tested distinctions in neuroimmunology.		

Chapter 4

Infectious Myelopathies, Para-Infectious States, and Tropical Spinal Cord Disorders

This chapter reviews neuro-infectious spinal cord disorders, integrating clinical presentations, diagnostic parameters, and evidence-based therapeutic protocols.

1. Viral Infections of the Spinal Cord

Viruses cause spinal cord injury through direct neuroinvasion or by triggering secondary immune-mediated cascades.

A. Poliovirus and Non-Polio Enteroviruses (EV-D68, EV-A71)

Acute Flaccid Myelitis (AFM)

A clinical syndrome presenting with rapid-onset flaccid limb weakness, decreased reflexes, and hypotonicity.

- **Localization:** Preferentially targets the anterior horn cells (gray matter) of the spinal cord.

Diagnostic Markers

- **Clinical:** Preceding upper respiratory or gastrointestinal illness.
- **MRI:** Linear T2-hyperintense lesions localized to the gray matter ("owl eyes" or "snake eyes" sign).
- **CSF:** Pleocytosis (> 5 cells/mm³) is required for a "definite" diagnosis.

Therapies

- **Supportive:** Multidisciplinary rehabilitation is critical.
- **Experimental:** Early IV immunoglobulin (IVIG); steroids are used for cord edema but carry a theoretical risk of increasing viral titers.

B. Herpesviruses

Varicella-Zoster Virus (VZV) Myelitis

- **Presentation:** Progressive asymmetric paraparesis and sensory loss, often (but not always) preceded by a dermatomal zoster rash.
- **Diagnostic:** VZV PCR sensitivity decreases after 1 week; the CSF VZV antibody index (> 1.5) is more sensitive for detecting intrathecal antibody production.
- **Dosing:** IV acyclovir 10 mg/kg every 8 hours for 14–21 days.

Cytomegalovirus (CMV) Radiculomyelitis

- **Target population:** Primarily immunocompromised patients (e.g., AIDS with CD4 < 100 cells/mm³).
- **CSF parameters:** Characterized by severe polymorphonuclear (neutrophilic) pleocytosis and hypoglycorrhachia.
- **Dosing:** IV ganciclovir 5 mg/kg every 12 hours, or IV foscarnet 90 mg/kg every 12 hours.

C. Retroviruses

HIV-Associated Vacuolar Myelopathy

- **Pathophysiology:** White matter vacuolization in the posterior and lateral columns, mimicking vitamin B12 deficiency; direct viral infection and inflammation are notably absent.
- **Treatment:** Initiation of combination antiretroviral therapy (cART).

HTLV-1 Associated Myelopathy / Tropical Spastic Paraparesis (HAM/TSP)

- **Presentation:** Slowly progressive proximal spastic paraparesis, early urinary retention, and lumbar pain.
- **Diagnostic:** Positive HTLV-1 ELISA with confirmatory Western blot (p19, p24, rgp21, or rgp46env bands).
- **Biomarker:** HTLV-1 proviral load is significantly higher in CSF lymphocytes than in peripheral blood.
- **Dosing:** High-dose IV methylprednisolone 1 g daily for 3–5 days (induction), followed by low-dose oral maintenance (5–10 mg/day).

🔖 MEMORY TIP / MNEMONIC

AFM targets anterior horn cells (motor, gray matter); HIV vacuolar myelopathy targets posterior/lateral columns (mimics B12 deficiency); HAM/TSP produces a slow, progressive spastic gait — think of it as a "tropical" mimicker of primary progressive MS.

2. Bacterial, Fungal, and Parasitic Myelopathies

A. Spinal Epidural Abscess (SEA)

🔖 EMERGENCY

Spinal epidural abscess is a neurosurgical emergency. Emergent decompression/washout is required within 24 hours once weakness develops to prevent irreversible neurologic damage.

- **Classic triad:** Localized back pain, fever, and progressive neurologic deficits.
- **Risk factors:** IV drug use, diabetes, recent spinal surgery, and systemic infection (e.g., endocarditis).
- **Common pathogen:** *Staphylococcus aureus* (> 50% of cases).

Management

- **Imaging:** Emergent MRI with gadolinium (sensitivity > 90%).
- **Empiric antibiotics:** Directed by clinical suspicion; broad coverage required until culture results are available.

B. Bacterial and Mycobacterial Variants

Spinal Tuberculosis (Pott Disease)

- **Mechanics:** Vertebral osteomyelitis leading to kyphotic deformity (gibbus) and cord compression.
- **CSF:** Xpert MTB/RIF Ultra assay (100% specific, sensitivity ~89%).

- **RIPE regimen:** Isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by 7–10 months of isoniazid and rifampin.

Neuroborreliosis (Lyme Disease)

- **Presentation:** Bannwarth syndrome (radiculitis, facial nerve palsy, and pleocytosis).
- **Diagnostic:** Two-tiered serology; a positive CSF-to-serum antibody index (> 1.3 – 1.5) confirms intrathecal antibody production.
- **Dosing:** IV ceftriaxone 2 g daily for 10–28 days.

Neurosyphilis (Tabes Dorsalis)

- **Presentation:** Late-stage degeneration of the dorsal columns and dorsal root ganglia; features include lightning pains, sensory ataxia, and Argyll Robertson pupils.
- **Diagnostic:** Positive CSF VDRL ($> 99\%$ specific, low sensitivity).
- **Dosing:** IV penicillin G, 18–24 million units/day for 10–14 days.

C. Parasitic and Fungal Complications

- **Neuroschistosomiasis:** Lower thoracic/conus expansion with nodular enhancement; acquired through larval penetration in contaminated water. Treatment: praziquantel and steroids.
- **Neurocysticercosis:** The most common parasitic CNS infection; usually occurs in the subarachnoid space, causing compressive myelopathy. Treatment: albendazole and steroids.

Diagnostic and Treatment Reference Tables

Table 4.1. CSF Diagnostic Parameters by Etiology

Etiology	Pleocytosis Profile	Protein Level	Glucose Ratio	Key Specific Test
Viral	Lymphocytic	Normal to $\uparrow$	Normal	PCR (early); antibody index
CMV	Neutrophilic	$\uparrow\uparrow$	$\downarrow$	CSF CMV PCR
Bacterial (pyogenic)	Neutrophilic	$\uparrow\uparrow$	$\downarrow\downarrow$	Culture; 16S rRNA PCR
Tuberculosis	Lymphocytic	$\uparrow\uparrow\uparrow$	$\downarrow\downarrow$	Xpert MTB/RIF Ultra
Fungal	Lymphocytic	$\uparrow\uparrow$	$\downarrow$	(1,3)- β -D-Glucan; antigen testing
Parasitic	Eosinophilic	$\uparrow$	Normal	Microscopy (stool/urine)

Table 4.2. Targeted Antimicrobial/Antiviral Titration

Pathogen	Drug	Regimen / Dosing	Notes
VZV	Acyclovir	10 mg/kg IV q8h (14–21 days)	Add steroids if cord edema present
CMV	Ganciclovir	5 mg/kg IV q12h	Induction phase
Syphilis	Penicillin G	4 million units IV q4h (14 days)	Use steroids to cover Jarisch-Herxheimer reaction
Aspergillus	Voriconazole	6 mg/kg IV load × 2, then 4 mg/kg IV q12h	Angioinvasive; requires months of therapy
Spinal epidural abscess	Vancomycin + cephalosporin	Empiric broad coverage	Adjust based on bone biopsy/blood culture

Table 4.3. Para-Infectious Phenomena

Condition	Associated Trigger	Clinical Signature
Elsberg Syndrome	HSV-2 (most common), VZV	Subacute sacral myeloradiculitis; urinary retention
ADEM	EBV, MOG-IgG, vaccinations	Multifocal brain lesions plus myelitis; pediatric predominance
SARS-CoV-2 Myelitis	COVID-19	Longitudinally extensive lesions; neurotropism remains unconfirmed

★ **HIGH YIELD**

For CSF interpretation, remember: bacterial and tuberculous meningitis both cause low glucose ratios, but bacterial pleocytosis is neutrophilic with markedly elevated protein, while TB pleocytosis is lymphocytic with the highest protein elevation of the group.

Chapter 5

Hereditary, Degenerative, Neoplastic, and Toxic Myelopathies

This chapter distills the diagnostic algorithms, genetic foundations, and management protocols for hereditary, neoplastic, and toxic myelopathies.

I. Hereditary and Degenerative Spinal Disorders

Hereditary myelopathies are diverse genetic disorders in which clinical features reflect disturbance of elements within the spinal cord, often involving extraspinal structures such as the cerebellum or peripheral nerves.

Hereditary Spastic Paraplegias (HSPs)

HSPs are characterized by progressive degeneration of the corticospinal tracts and dorsal columns. They are classified as uncomplicated (spasticity and weakness isolated to the legs) or complicated (associated with cognitive impairment, ataxia, or neuropathy).

- **SPG4 (Spastin):** The most common autosomal dominant form, typically presenting as a pure phenotype of slowly progressive spastic paraparesis.
- **SPG3A (Atlastin):** The leading cause of childhood-onset autosomal dominant HSP, often resembling spastic diplegic cerebral palsy.
- **SPG11 (Spatacsin):** The most common autosomal recessive form; a complicated phenotype often presenting with the "ears of the lynx" sign (FLAIR hyperintensity in the forceps minor).

Friedreich Ataxia (FRDA)

FRDA is an autosomal recessive disorder caused by a GAA trinucleotide repeat expansion in the FXN gene on chromosome 9, which encodes the mitochondrial protein frataxin.

- **Expansion limits:** Normal alleles contain 8 to 30 repeats, while pathologic expansions range from 170 to 1700.
- **Systemic features:** Essential screening must include hypertrophic cardiomyopathy and diabetes mellitus.
- **Pathophysiology:** Involves primary degeneration of the dorsal root ganglia, spinocerebellar tracts, and corticospinal tracts.

i IMPORTANT NOTE

Friedreich ataxia is a multisystem disease. Cardiac and endocrine screening (echocardiography, glucose tolerance testing) is essential at diagnosis and during longitudinal follow-up, as cardiomyopathy is a leading cause of mortality.

Spinal Muscular Atrophy (SMA)

SMA is a lower motor neuron disorder caused by deletions or mutations in the SMN1 gene. The SMN2 gene acts as a disease modifier; higher SMN2 copy numbers correlate with milder clinical phenotypes.

Table 5.1. Key Genetic Mutation Screens and SMA Modifier Values

Disorder	Gene	Mutation Type	Clinical / Modifier Significance
HSP (SPG4)	SPAST	Autosomal dominant; missense/deletion	Most common AD HSP; pure phenotype
HSP (SPG11)	SPG11	Autosomal recessive; truncating	"Ears of the lynx" sign; complicated phenotype
Friedreich Ataxia	FXN	Autosomal recessive; GAA expansion	Pathologic range: 170–1700 repeats
SMA	SMN1	Autosomal recessive; deletion	Primary cause of anterior horn cell loss
SMA modifier	SMN2	Copy number variation	2 copies: severe (Type 1); 3+ copies: milder phenotype
Adrenomyeloneuropathy (AMN)	ABCD1	X-linked; varies	Elevated VLCFAs; progressive spasticity

MEMORY TIP / MNEMONIC

"SPG4 is Frequent (most common AD), SPG3A is the Small child (childhood onset AD), SPG11 is Recessive with a Lynx face" — anchoring each subtype to its most distinguishing feature aids rapid recall.

Table 5.2. Symptomatic Management: Spasticity Titration

Medication	Route	Titration / Parameters	Expert Notes
Baclofen	Oral	Start 5 mg TID; max 80 mg/day	Preferred first-line agent; safe in liver disease
Tizanidine	Oral	Start 2–4 mg QHS; max 36 mg/day	Alpha-2 agonist; risk of hypotension/sedation
Dantrolene	Oral	Start 25 mg QD; max 400 mg/day	Peripherally acting; risk of hepatotoxicity
Intrathecal Baclofen (ITB) Pump	Intrathecal	Basal flow or bolus dosing	Reserved for severe lower-extremity spasticity

II. Neoplastic and Infiltrative Tumors

Spinal neoplasms are organized by their anatomic compartment, which dictates both the surgical approach and the differential diagnosis.

1. Intramedullary (Parenchymal) Tumors

- **Ependymoma:** The most common primary intramedullary tumor in adults. Typically central, well-demarcated, and often presents with a "cap sign" (hemosiderin rim).
- **Astrocytoma:** Most common intramedullary tumor in children. Typically eccentric, infiltrative, and poorly marginated.
- **Hemangioblastoma:** Highly vascular nodules, often dorsal, associated with von Hippel-Lindau disease.

2. Intradural-Extramedullary Tumors

- **Meningioma:** The most common primary spinal tumor in adults overall, with a strong female predominance (9:1) in the thoracic region.
- **Schwannoma:** Benign nerve sheath tumors often presenting with a dumbbell morphology as they extend through the neural foramen.

3. Extradural Tumors

- **Metastases:** The most common spinal neoplasms overall, typically resulting from lung, breast, or prostate cancers spreading to the vertebrae.

Metastatic Epidural Spinal Cord Compression (MESCC) is a neurologic emergency (see Chapter 1, Section III.2 for management protocol).

Table 5.3. Tumor Localization and Neurosurgical Resection Criteria

Compartment	Prototypical Tumor	Imaging Hallmark	Resection Criteria / Goal
Intramedullary	Ependymoma	Central; "cap sign"	Gross total resection (GTR): high success due to encapsulation
Intramedullary	Astrocytoma	Eccentric; infiltrative	Subtotal resection/biopsy: infiltrative nature usually precludes GTR
Extramedullary (intradural)	Meningioma	Avid enhancement; dural tail	GTR: primary curative modality
Extramedullary (intradural)	Schwannoma	Dumbbell shape through the neural foramen	GTR: curative if symptomatic or compressing the cord
★ HIGH YIELD Differential diagnosis by compartment is the fastest route to a correct answer on imaging-based questions: intramedullary (ependymoma/astrocytoma) vs. intradural-extramedullary (meningioma/schwannoma) vs. extradural (metastases).			

III. Toxic and Radiation-Induced Myelopathies

Radiation-Induced Myelopathy

- **Early delayed:** Occurs 2 to 4 months post-treatment; presents as a transient Lhermitte sign that often resolves spontaneously.
- **Late delayed:** Occurs 6 to 24 months post-treatment; characterized by irreversible white matter necrosis, T2 hyperintensity, and fatty marrow replacement on T1 MRI.

Toxic Myelopathies

- **Clioquinol:** A metal chelator previously used for diarrhea; caused Subacute Myelo-Optico-Neuropathy (SMON).
- **Konzo:** Results from cyanide toxicity due to improperly processed bitter cassava; causes abrupt, permanent spastic paraparesis.
- **Lathyrism:** Results from the neurotoxin ODAP found in the grass pea; targets the longest corticospinal tract axons.

Table 5.4. Toxic and Iatrogenic Myelopathy Mechanisms

Toxic Agent	Mechanism of Injury	MRI / Diagnostic Hallmark	Clinical Profile
Radiation	Necrosis / vasculopathy	T2 hyperintensity; fatty marrow replacement	Late delayed (6–24 months); progressive
Nitrous Oxide	Oxidizes B12 cobalt atom	"Inverted V" sign (dorsal columns)	Functional B12 deficiency; sensory ataxia
Konzo	Cyanogen poisoning	Elevated thiocyanate (blood/urine)	Acute/subacute spasticity; drought-prone regions
Lathyrism	ODAP glutamate toxicity	Degeneration of corticospinal tracts	Subacute spastic paraparesis; male predominance
Methotrexate	Folate antagonism	Dorsal column T2 hyperintensity	Subacute combined degeneration mimic

CLINICAL PEARL

A transient Lhermitte sign appearing 2–4 months after cervical or mediastinal radiation is typically benign and self-limited (early delayed radiation myelopathy) — reassurance and observation are appropriate, distinguishing it from the irreversible late delayed form.

PERIPHERAL NEUROPATHIES AND MOTOR NEURON DISEASES

Chapter 1. Peripheral Nerve Disorders: Clinical Patterns and Electrodiagnosis

Peripheral nerve disorders are classified according to their anatomic distribution, the tempo of progression, and the underlying pathological process affecting the nerve fiber. A systematic approach to these three axes allows the clinician to generate a focused differential diagnosis before any investigation is ordered.

I. Pathological Process Differentiation

Pathological Pattern	Key Characteristics	Common Etiologies
Axonal degeneration	Primarily affects the axon; typically length-dependent (distal-to-proximal) because the distal axon is most metabolically vulnerable.	Diabetes mellitus Toxic (chemotherapy agents) Metabolic (vitamin B12 deficiency) HIV infection
Segmental demyelination	Damage to the myelin sheath or Schwann cells; may be focal (conduction block) or diffuse (velocity slowing).	Guillain-Barré syndrome (GBS) CIDP Paraproteinemic neuropathies
Wallerian degeneration	Degeneration of the axon and myelin sheath distal to a site of injury; seen in intense immune attacks such as AMSAN.	Trauma Vasculitis (nerve infarction) Severe axonal GBS variants
Nodopathy	Direct immune attack on the node of Ranvier / paranodal proteins; can cause “reversible conduction failure” rather than true structural damage.	AMAN Anti-neurofascin / anti-contactin antibody-mediated neuropathies

★ MEMORY TIP / MNEMONIC

“AWSN” – the four pathological patterns of peripheral nerve injury:

- Axonal degeneration
- Wallerian degeneration
- Segmental demyelination
- Nodopathy (Node of Ranvier attack)

II. Clinical Patterns of Localization

Pattern	Distribution	Clinical Clue
Symmetric polyneuropathy	distal “Stocking-glove” distribution	The longest, most metabolically active fibers are affected first.

Pattern	Distribution	Clinical Clue
Mononeuritis multiplex	Multifocal, patchy, asymmetric	Random segments of individual nerves are “picked off” one by one; often suggests vasculitis.
Radiculoplexopathy	Asymmetric, often monomelic (single limb)	Nerve roots and plexus involved; typically severe pain followed by focal weakness.
Focal entrapment	Restricted to a single nerve territory	Occurs at a common site of compression (e.g., median nerve at the wrist).

III. Rigorous Electrodiagnostic (EDX) Criteria

Nerve conduction studies (NCS) and needle electromyography (EMG) differentiate axonal loss from demyelinating processes using strict physiological thresholds. Correct application of these criteria is essential, since misclassification directly changes the differential diagnosis and treatment pathway.

A. Comparative EDX Thresholds: Axonal vs. Demyelinating Patterns

Parameter	Axonal Pattern	Demyelinating Pattern (EAN/PNS 2021)
Amplitudes (SNAP/CMAP)	Primary abnormality: significantly reduced or absent.	Usually relatively preserved early; may be low if secondary axonal loss develops.
Conduction velocity (CV)	Mild-to-moderate slowing; not below 70–75% of the lower limit of normal (LLN).	≥ 30% reduction below LLN in at least two nerves.
Distal motor latency (DML)	Normal or only slightly prolonged (usually < 130% of the upper limit of normal, ULN).	≥ 50% prolongation above ULN in at least two nerves (excluding carpal tunnel syndrome for the median nerve).
F-wave latency	Often normal; may be absent if amplitudes are very low.	≥ 20% prolongation above ULN (≥ 50% if distal CMAP < 80% LLN) in ≥ 2 nerves; or absent F-waves.
Conduction block (CB)	Not typical; “reversible conduction failure” can mimic it without true dispersion.	≥ 30% reduction of proximal vs. distal CMAP negative-peak amplitude (excluding the tibial nerve).
Temporal dispersion	Absent.	≥ 30% duration increase between proximal and distal negative-peak CMAP in ≥ 2 nerves.

B. Physiological Caveats and Technical Requirements

- **Temperature control:** Skin temperature must be ≥ 33°C (91°F) at the palm and ≥ 30°C (86°F) at the external malleolus to avoid artifactual slowing.
- **Proximally elicited conduction block:** Between Erb’s point and the wrist, a ≥ 50% CMAP amplitude reduction is required to define a conduction block in the ulnar and median nerves.
- **CMAP duration:** In AIDP/GBS, a distal CMAP duration > 8.5 ms is 98% specific for demyelination.

- **Needle EMG chronicity:** Fibrillation potentials appear only after 14–21 days of active axonal loss. Chronic reinnervation changes (high-amplitude, long-duration motor unit action potentials) take months to develop.

⚠ WARNING

Pitfall: Cool limbs are the single most common cause of a spuriously “demyelinating-looking” nerve conduction study — always verify and document limb temperature before interpreting slowed conduction velocities or prolonged latencies.

IV. Small Fiber Neuropathy (SFN): A Focused Approach

Small fiber neuropathy involves unmyelinated C-fibers and thinly myelinated A-delta fibers that mediate pain, temperature, and autonomic function. Because these fibers are not assessed by conventional nerve conduction studies, SFN is a common cause of a “normal NCS” in a patient with significant neuropathic symptoms.

A. Clinical Features of SFN

Domain	Features
Positive sensory symptoms	Burning pain “Electrical” or “shock-like” sensations Allodynia (pain from non-painful stimuli) Dysesthesia
Autonomic dysfunction	Orthostatic presyncope Sicca symptoms (dry eyes/mouth) Early satiety (gastroparesis) Anhidrosis (impaired sweating) Erectile dysfunction
Physical exam clues	Normal muscle stretch reflexes Normal vibration and proprioception (large-fiber functions are preserved) Impaired pinprick and thermal sensation

★ HIGH YIELD

A patient with severe burning pain, normal reflexes, normal vibration/proprioception, but impaired pinprick and temperature sensation has small fiber neuropathy until proven otherwise — order skin biopsy (IENFD), not repeat nerve conduction studies.

B. Diagnostic Gold Standards

Diagnostic Tool	Mechanism and Parameters
QSART (Quantitative Sudomotor Axon Reflex Test)	Evaluates postganglionic sympathetic sudomotor function by measuring the sweat response to acetylcholine iontophoresis; helps differentiate peripheral from central dysautonomia.
Autonomic reflex screening	Cardiovagal: heart rate variability with deep breathing and the Valsalva ratio. Cardiovascular adrenergic: tilt-table testing and blood pressure response to standing.
Skin biopsy (IENFD)	A 3-mm punch biopsy, typically from the distal leg, distal thigh, and proximal thigh, evaluating intraepidermal nerve fiber density.
Skin biopsy staining	Can additionally assess sudomotor innervation of sweat glands and detect amyloid deposition.

IMPORTANT NOTE

Key pathophysiological threshold: in patients with a 2–3% drop in hemoglobin A1c over 3 months, there is an approximately 20% absolute risk of developing acute “treatment-induced” small fiber neuropathy (insulin neuritis); this risk rises to > 80% if the A1c drop exceeds 4% over the same period. Rapid glycemic correction should therefore be undertaken cautiously in patients with long-standing poor glycemic control.

Chapter 2. Acute and Chronic Immune-Mediated Polyneuropathies

I. Guillain-Barré Syndrome (GBS) and Clinical Variants

Guillain-Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy characterized by a progressive phase reaching a nadir within 4 weeks, followed by a plateau and eventual recovery.

A. Pathophysiology and Molecular Mimicry

- **Molecular mimicry:** Humoral and T-cell-mediated responses are triggered by an antecedent infection (most commonly *Campylobacter jejuni*), in which microbial lipooligosaccharides mimic human nerve gangliosides.
- **Complement activation:** Binding of autoantibodies leads to membrane attack complex (MAC) formation, causing nodal lengthening, sodium channel disappearance, and subsequent segmental demyelination or axonal degeneration.

B. Diagnostic Tiers and CSF Profiles

- **Albuminocytologic dissociation:** The hallmark is elevated CSF protein with a normal cell count, reflecting increased blood-nerve barrier permeability.

- **Timing:** Protein levels may be normal in the first week (in up to 50% of patients) but are elevated in > 90% of patients by the end of week 2.
- **Pleocytosis rule:** Mild pleocytosis (10–20 cells/ μ L) occurs in about 5% of cases; however, a white blood cell count > 50 cells/ μ L should prompt evaluation for alternative causes (e.g., HIV, CMV, Lyme disease, sarcoidosis, or malignancy).

C. Clinical Profiles of GBS Variants

Variant	Key Clinical / Immunologic Features	Electrophysiologic Profile
AIDP	Most common variant in North America and Europe (85–90% of cases); symmetric proximal and distal weakness.	Demyelinating: prolonged distal latencies, conduction block, and slow velocities.
AMAN	Prevalent in Asia; often follows <i>C. jejuni</i> infection; IgG anti-GM1 or anti-GD1a antibodies.	Axonal (motor): low CMAP amplitudes with normal sensory responses.
AMSAN	Severe clinical course; involves both motor and sensory axons; poor prognosis.	Axonal (sensorimotor): reduced CMAP and SNAP amplitudes.
Miller Fisher syndrome (MFS)	Triad: ophthalmoplegia, ataxia, areflexia; strongly associated with IgG anti-GQ1b antibodies (85–90%).	Often shows reversible conduction failure in sensory nerves.

★ MEMORY TIP / MNEMONIC

MFS mnemonic — “OAR”:

- Ophthalmoplegia
- Ataxia
- aReflexia

...and remember “GQ1b for eyes” — anti-GQ1b antibodies target ocular motor nerves, explaining the ophthalmoplegia.

II. GBS Management and Critical Care

A. Disease-Specific Immunotherapy

Therapy	Regimen	Key Precautions
IVIG (total dose 2 g/kg)	Schedule 1: 0.4 g/kg/day for 5 consecutive days Schedule 2: 1 g/kg/day for 2 days (higher risk of clinical fluctuations in children with this regimen)	Renal injury (especially with sucrose-containing products) IgA deficiency (risk of anaphylaxis) Thromboembolism
Plasma exchange (PLEX) (total 200–250 mL/kg body weight)	4 to 5 exchanges over 7 to 10 days	Combining PLEX and IVIG provides no added benefit

Therapy	Regimen	Key Precautions
		Administering PLEX after IVIG is counterproductive, as it removes the therapeutic antibodies

⚠ WARNING

Sequential therapy warning: never sequence plasma exchange after IVIG. PLEX will simply remove the immunoglobulin just administered, negating its therapeutic benefit and wasting a limited, costly resource.

B. Respiratory and Triage Parameters

ICU admission should be considered for evolving respiratory distress, bulbar dysfunction, dysautonomia, or rapidly worsening weakness.

✖ EMERGENCY / RED FLAG

The “20-30-40 Rule” for impending respiratory failure in GBS — any one of the following should prompt urgent escalation:

- Forced vital capacity (FVC) < 20 mL/kg
- Negative inspiratory force (NIF/MIP) < -30 cmH₂O
- Maximum expiratory pressure (MEP) < 40 cmH₂O

◆ CLINICAL PEARL

The Erasmus GBS Respiratory Insufficiency Score (EGRIS) uses days from weakness onset to admission, facial/bulbar weakness, and MRC sum score to estimate risk. A score > 4 indicates a ≥ 65% risk of respiratory failure within 1 week, supporting early ICU triage and elective intubation planning.

III. CIDP and Atypical Variants

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is defined by symmetric proximal and distal weakness progressing for more than 8 weeks — the key temporal distinction from GBS.

A. EAN/PNS 2021 Electrodiagnostic Criteria (Strongly Supportive of Demyelination)

Criterion	Threshold
Motor distal latency prolongation	≥ 50% above ULN in ≥ 2 nerves
Motor conduction velocity reduction	≥ 30% below LLN in ≥ 2 nerves
F-wave latency prolongation	≥ 20% above ULN in ≥ 2 nerves (≥ 50% if distal CMAP < 80% LLN)

Criterion	Threshold
Motor conduction block	≥ 30% reduction of proximal vs. distal negative-peak CMAP (excluding the tibial nerve)

B. Atypical CIDP Phenotypes

Phenotype	Key Features
Lewis-Sumner syndrome (multifocal CIDP / MADSAM)	Asymmetric weakness and sensory loss; multifocal demyelination affecting motor and sensory nerves.
DADS (distal CIDP)	Symmetric sensory loss and distal weakness; approximately 66% associated with an IgM paraprotein (must test for anti-MAG antibodies).
Pure motor CIDP	Symmetric proximal/distal weakness without sensory loss; may worsen with corticosteroids.
Pure sensory CIDP	Proximal and distal sensory symptoms; normal motor conduction studies but potentially abnormal somatosensory evoked potentials (CISP protocol).

⚠ WARNING

Pure motor CIDP is a recognized exception to standard first-line therapy: corticosteroids can precipitate clinical worsening in this phenotype. IVIG is generally preferred as first-line therapy.

IV. Autoantibody Paranodopathies (IgG4-Mediated)

Approximately 10% of patients diagnosed with CIDP harbor antibodies against nodal or paranodal proteins, defining a biologically and therapeutically distinct group sometimes termed “autoimmune nodopathies.”

Target Antigens and Clinical Phenotype

Target Antigen	Distinguishing Clinical Feature
Anti-NF155 (neurofascin-155)	Rapidly progressive, severe symmetric distal weakness; action tremor and sensory ataxia.
Anti-CNTN1 (contactin-1)	Nephrotic syndrome is a specific association; rapidly progressive distal weakness.
Anti-Caspr1 (contactin-associated protein 1)	Severe neuropathic pain; rapidly progressive weakness; sensory ataxia.

📌 IMPORTANT NOTE

Common features across IgG4 nodopathies: rapidly progressive severe symmetric distal weakness, action tremor (high-amplitude, low-frequency), and sensory ataxia.

✗ EMERGENCY / RED FLAG

Therapeutic resistance is a diagnostic clue: IgG4-mediated nodopathies show a poor or absent response to IVIG and plasma exchange but respond significantly to B-cell depletion therapy (e.g., rituximab). Failure to respond to first-line CIDP therapy should prompt nodal/paranodal antibody testing.

V. CIDP and Nodopathy Medication Manual

A. Corticosteroids

Regimen	Dose	Notes
Oral prednisone	Starting dose 20–60 mg daily, or 0.5–1 mg/kg daily	Taper slowly after a plateau of improvement is achieved.
IV pulse methylprednisolone	1000 mg IV daily for 3 to 5 days	May be transitioned to 1000 mg IV monthly for maintenance.

B. Immunoglobulin Maintenance

Regimen	Details
IVIG maintenance	1 g/kg every 3 to 4 weeks. Once stable for 2–3 years, attempt tapering the interval or dose every 6 to 12 months.
SCIG (subcutaneous) transition	1:1 dosing conversion from IVIG (e.g., 20 g SCIG weekly for a patient previously on 80 g IVIG every 4 weeks).

C. Rituximab (Targeted for IgG4 Nodopathies / Refractory CIDP)

Protocol	Dosing
Standard oncology dosing	375 mg/m ² IV weekly for 4 weeks.
Neurology protocol	Two 1000-mg IV infusions separated by 2 weeks.
Low-dose / infection-sparing option	100 mg weekly for 4 weeks, then 100 mg monthly for 2 months.
Re-dosing	Redose upon clinical recurrence of symptoms.

Chapter 3. Paraproteinemic, Amyloid, and Vasculitic Neuropathies; Multifocal Motor Neuropathy

I. Paraproteinemic Neuropathies: IgM vs. IgG/IgA

A monoclonal gammopathy (paraproteinemia) is identified in approximately 10% of patients with otherwise idiopathic neuropathy. Causality is significantly higher with the IgM subtype (50–75% likelihood of a causal association) than with IgG or IgA.

A. IgM MGUS and Anti-MAG Neuropathy

- **Clinical phenotype:** A male-predominant, late-onset, slowly progressive sensory ataxia. Patients often present with gait impairment, a positive Romberg sign, and a distal action tremor.
- **Antibody association:** 50–65% of these patients harbor high titers of IgM anti-myelin-associated glycoprotein (MAG) antibodies, typically with kappa light chains.
- **Electrodiagnostic hallmark:** A pattern of distal acquired demyelinating symmetric neuropathy (DADS), with severely prolonged distal motor latencies and uniform slowing of conduction velocities without prominent conduction block or temporal dispersion.

✦ CLINICAL PEARL

Terminal Latency Index (TLI) = (distal distance) ÷ (proximal conduction velocity × distal motor latency). A low TLI (< 0.25–0.30) indicates disproportionate slowing in the distal nerve segments — a signature finding in anti-MAG neuropathy that helps distinguish it from CIDP, where slowing is more uniform along the nerve.

B. Differentiating IgG/IgA MGUS from IgM MGUS

Feature	IgM MGUS (Anti-MAG)	IgG / IgA MGUS
Causal relationship to neuropathy	Often causative	Often coincidental rather than causative
Typical phenotype	DADS with sensory ataxia and tremor	Usually presents as classic CIDP
Response to standard therapy	Poor response to standard CIDP immunotherapy	Responds to standard first-line CIDP immunotherapies (steroids, IVIG)
Key exclusion	N/A	Must rigorously exclude POEMS syndrome or AL amyloidosis before labeling the paraprotein as coincidental

II. POEMS Syndrome: Definitive Diagnostic Checklist

POEMS syndrome is a multiorgan paraneoplastic disorder driven by an underlying plasma cell dyscrasia. Diagnosis requires both mandatory criteria, at least one major criterion, and at least one minor criterion.

Category	Diagnostic Feature	Required Markers / Notes
Mandatory	Polyneuropathy	Typically demyelinating with prominent axonal loss.
Mandatory	Monoclonal protein	Almost always lambda light chain (IgA > IgG).
Major	VEGF elevation	Plasma VEGF > 200 pg/mL is 95% specific.
Major	Bone lesions	Osteosclerotic bone lesions (not lytic).
Major	Castleman disease	Underlying lymphoproliferative disorder.
Minor	Organomegaly	Splenomegaly, hepatomegaly, or lymphadenopathy.
Minor	Endocrinopathy	Adrenal, thyroid, pituitary, gonadal (low testosterone), parathyroid, or pancreatic.
Minor	Skin changes	Hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, or white nails.
Minor	Volume overload	Edema, pleural effusion, or ascites.
Minor	Papilledema	Optic disc swelling.

★ MEMORY TIP / MNEMONIC

POEMS mnemonic:

- Polyneuropathy
- Organomegaly
- Endocrinopathy
- Monoclonal protein (M-protein)
- Skin changes

III. Amyloid Polyneuropathy (ATTR and AL)

A. AL (Light Chain) Amyloidosis

- **Presentation:** Rapidly progressive, painful, length-dependent sensory-predominant neuropathy with severe autonomic failure (orthostatic hypotension, early satiety).
- **Markers:** Associated with lambda MGUS. Diagnosis is confirmed by Congo red staining (apple-green birefringence under polarized light) on fat pad aspirate or nerve biopsy.

B. ATTR (Transthyretin) Amyloidosis

Caused by TTR gene variations (hereditary, ATTRv) or age-related misfolding of wild-type protein (wild-type, wtATTR), leading to multisystem amyloid deposition.

System	Manifestations
Neuropathy	Initially small-fiber (pain and temperature loss), progressing to large-fiber involvement.
Autonomic	Orthostatic hypotension, gastrointestinal dysmotility (diarrhea or constipation).
Focal / musculoskeletal	Bilateral carpal tunnel syndrome and lumbar spinal stenosis are frequent early (“herald”) signs, often preceding neuropathy diagnosis by years.
Cardiac	Restrictive cardiomyopathy with heart failure with preserved ejection fraction.

★ HIGH YIELD

Bilateral carpal tunnel syndrome in an older adult, especially when combined with unexplained heart failure with preserved ejection fraction or lumbar stenosis, should prompt screening for ATTR amyloidosis.

C. Targeted ATTR Pharmacotherapy

Drug Class	Example Agent(s)	Mechanism	Monitoring
TTR stabilizer	Tafamidis	Oral agent that binds the TTR tetramer to prevent misfolding.	—
RNA interference (siRNA)	Patisiran, Vutrisiran	siRNA agents that target and degrade TTR mRNA to reduce protein production.	—
Antisense oligonucleotide	Inotersen	Single-stranded DNA that binds TTR mRNA to inhibit translation.	Mandatory monitoring for thrombocytopenia (platelet count) and renal toxicity.

⚠ WARNING

Inotersen carries a boxed-warning-level risk of severe thrombocytopenia and glomerulonephritis; platelet counts and renal function must be monitored on a strict schedule throughout treatment.

IV. Vasculitic Neuropathies

A. Classification and Biopsy Features

Category	Examples / Features
Systemic vasculitis	EGPA (asthma, eosinophilia, MPO-ANCA); MPA (renal involvement, MPO-ANCA); PAN (hepatitis B association, ANCA-negative).
Non-systemic vasculitic neuropathy (NSVN)	Vasculitis limited strictly to the peripheral nerves; often presents as a painful mononeuritis multiplex.

Nerve Biopsy Finding	Significance
Active lesions	Inflammatory cell infiltration of the vessel wall plus fibrinoid necrosis, endothelial disruption, or fragmentation of the internal elastic lamina.
Ischemic patterns	Asymmetric or multifocal nerve fiber loss and hemosiderin deposits (demonstrated with Perls stain), reflecting prior microvascular hemorrhage/infarction.

B. Therapeutic Regimens: Induction and Maintenance

Phase	Regimen
Induction (severe / organ-threatening disease)	Glucocorticoids: pulse IV methylprednisolone (1000 mg daily for 3–5 days), followed by oral prednisone (0.5–1 mg/kg) Cyclophosphamide: traditional induction agent Rituximab: demonstrated non-inferiority to cyclophosphamide for ANCA-associated vasculitis induction
Maintenance	Rituximab: preferred agent for ANCA-associated vasculitis maintenance Azathioprine or methotrexate: used if rituximab is contraindicated or unavailable Note: mycophenolate mofetil has a higher relapse rate for maintenance compared to azathioprine

V. Multifocal Motor Neuropathy (MMN)

MMN is a purely motor, immune-mediated neuropathy that mimics amyotrophic lateral sclerosis but, critically, is treatable — making its early recognition essential.

Feature	Clinical / Diagnostic Parameter
Clinical traits	Asymmetric, distal upper-limb-predominant weakness. Purely lower motor neuron (LMN) — no upper motor neuron signs and no sensory loss.
EDX hallmark	Multifocal, persistent motor conduction blocks at sites not prone to compression.
Serology	High titers of IgM anti-GM1 antibodies (present in 30–80% of cases).
First-line therapy	IVIg (2 g/kg loading dose), followed by maintenance (e.g., 1 g/kg every 3–4 weeks).
Absolute contraindication	Corticosteroids typically provide no benefit and can worsen MMN symptoms.

✗ EMERGENCY / RED FLAG

MMN vs. ALS: the presence of any upper motor neuron sign (spasticity, hyperreflexia, extensor plantar response) argues strongly against MMN. When LMN-only weakness is asymmetric and distal-predominant, especially in the arms, obtain nerve conduction studies specifically looking for conduction block before committing to a diagnosis of ALS — misdiagnosis denies the patient a highly effective treatment.

VI. Drug Tracking and Monitoring: Side Effects Summary

Medication	Primary Use	Critical Side Effects / Monitoring
IVIG	MMN, CIDP, GBS	Thromboembolism (including pulmonary embolism), renal injury (sucrose-containing products), aseptic meningitis.
Rituximab	Anti-MAG neuropathy, vasculitis	Infection risk, infusion reactions.
Cyclophosphamide	Refractory vasculitis	Malignancy risk, infertility, cytopenias.
Inotersen	ATTR amyloidosis	Platelet count (thrombocytopenia), renal function monitoring.
Bortezomib	Myeloma syndrome / POEMS	Neurotoxicity (can cause or worsen axonal neuropathy); second-generation proteasome inhibitors (e.g., carfilzomib) are preferred in patients with pre-existing neuropathy.
Dapsone	Leprosy	Hemolytic anemia, methemoglobinemia.

Chapter 4. Hereditary, Metabolic, Toxic, and Focal Peripheral Nerve Disorders

I. Charcot-Marie-Tooth (CMT) Disease: A Comprehensive Compass

Hereditary neuropathies are characterized by chronic, slowly progressive motor and sensory deficits, often accompanied by distinctive foot morphology such as pes cavus (high arches), hammer toes, and “stork legs” (tapered calves due to distal muscle atrophy).

A. Neurogenetic and Electrodiagnostic Classification

CMT Type	Genetic Gene	Locus /	EDX Feature (Upper Extremity Motor)	Clinical Pearls
CMT1 (demyelinating)	Varies by subtype		Conduction velocity < 38 m/s	Uniform slowing; usually presents in the first two decades of life.
CMT1A	PMP22 duplication (17p11.2)		Uniform, severe slowing (often ~20 m/s)	The prototypical form; accounts for 55% of genetically confirmed CMT cases.
CMT2 (axonal)	Varies (e.g., MFN2, SORD)		Conduction velocity > 38 m/s; reduced amplitudes	Onset can range from childhood to late adulthood.
CMTX1	GJB1 (connexin 32)		Intermediate slowing; conduction block possible	X-linked dominant; associated with transient stroke-like CNS episodes with white matter lesions.
HNPP	PMP22 deletion (17p11.2)		Prolonged distal motor latencies; focal slowing at entrapment sites	Hereditary liability to painless pressure palsies; pathology shows tomacula (sausage-shaped myelin swellings).
SORD-CMT	Biallelic SORD variants		Low-amplitude axonal pattern	Autosomal recessive; plantar flexion is more affected than dorsiflexion.

B. Therapeutic Limits and Absolute Contraindications

Patients with CMT, particularly CMT1A, have an increased susceptibility to medication-induced neurotoxicity.

✗ EMERGENCY / RED FLAG

Absolute contraindication: vincristine is strictly avoided in all CMT patients, as it can trigger fulminant, irreversible weakness. Always screen for a personal or family history of CMT before prescribing vincristine-containing chemotherapy regimens.

⚠ WARNING

Relative caution: other neurotoxic chemotherapeutic agents, including platinum compounds and taxanes, require extreme vigilance in patients with underlying CMT.

II. Metabolic and Toxic Neuropathies

A. Diabetic and Uremic Neuropathies

- **Distal symmetric polyneuropathy (DSPN):** The prototypical length-dependent, axonal process, and the most common cause of neuropathy in the United States.

- **Diabetic amyotrophy (lumbosacral radiculoplexus neuropathy):** Characterized by sudden-onset, severe hip/thigh pain followed by asymmetric weakness, weight loss (> 10 lb), and muscle wasting. Thought to be caused by focal microvasculitis.
- **Uremic neuropathy:** Occurs when GFR < 12 mL/min; presents as an axonal neuropathy with mild-to-moderate conduction velocity slowing, without conduction block.

B. Nutritional Deficiencies and Toxicities

Nutrient	Deficiency Manifestation	Toxicity Profile
Vitamin B12	Subacute combined degeneration (dorsal columns and corticospinal tracts) plus axonal neuropathy.	Functional B12 deficiency can be caused by nitrous oxide ("whippets") exposure.
Vitamin (thiamine)	B1 Dry beriberi (axonal neuropathy); Wernicke-Korsakoff syndrome; can mimic GBS.	Not applicable.
Vitamin (pyridoxine)	B6 Mild axonal neuropathy.	Toxicity causes a sensory ganglionopathy with sensory ataxia and pseudoathetosis.
Copper	A myeloneuropathy identical to B12 deficiency.	Often secondary to zinc toxicity (zinc induces copper deficiency).

★ MEMORY TIP / MNEMONIC

Both B12 deficiency and copper deficiency cause an identical myeloneuropathy (combined dorsal column and corticospinal tract dysfunction with peripheral neuropathy) — always check copper and ceruloplasmin in a patient with a "B12-like" syndrome but normal B12 levels, especially after bariatric surgery or with zinc overuse (e.g., denture cream).

C. Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Agent	Primary Mechanism	Phenotypic Hallmark
Cisplatin / Oxaliplatin	DNA cross-linking; dorsal root ganglion (DRG) toxicity.	Sensory neuronopathy; oxaliplatin characteristically causes acute cold-induced allodynia.
Paclitaxel	Microtubule disruption affecting axonal transport.	Paclitaxel-associated acute pain syndrome (myalgias/arthralgias) occurring 1–7 days post-infusion.
Vincristine	Microtubule destabilization.	Sensorimotor axonal neuropathy; high rate of autonomic dysfunction (constipation).
Bortezomib	Proteasome inhibition.	Painful, length-dependent, small-fiber-predominant neuropathy.

III. Focal Mononeuropathies and Plexopathies

Absolute anatomical precision is required to differentiate focal nerve entrapments from more proximal radiculopathies or plexopathies.

A. Diagnostic Localization and EDX/Clinical Tricks

Nerve	Entrapment Site	EDX / Clinical Localization Trick
Median	Carpal tunnel (wrist)	Prolonged distal motor latency. Ultrasound: cross-sectional area > 10 mm ² at the wrist.
Ulnar	Cubital tunnel (elbow)	Localize by stimulating above versus below the elbow; check for focal slowing across the segment.
Radial	Spiral groove (humerus)	Presents with wrist and finger drop; classically “Saturday night palsy”; also seen in vasculitis.
Peroneal	Fibular head	Weakness in dorsiflexion/eversion; inversion (tibialis posterior) is spared, as it is L5-innervated but travels via the tibial nerve.
Lateral femoral cutaneous	Inguinal ligament	Meralgia paresthetica: purely sensory burning/numbness of the lateral thigh, with no motor or reflex loss.

★ HIGH YIELD

Peroneal palsy localization pearl: preserved inversion strength despite foot drop localizes the lesion to the common peroneal nerve at the fibular head rather than to the L5 root, because inversion is L5-innervated but carried by the tibial (not peroneal) nerve.

B. Plexopathies

Entity	Key Features
Neuralgic amyotrophy (Parsonage-Turner syndrome)	Triggers: viral illness, vaccination, or surgery Stage 1: acute, severe unilateral shoulder pain lasting weeks Stage 2: focal weakness/atrophy (suprascapular, long thoracic, or axillary nerve distributions)
Malignant infiltrative plexopathy	Characteristically painful Rapid progression of neurological deficits
Radiation plexopathy	Often painless Myokymic discharges on needle EMG are a highly specific hallmark distinguishing this from tumor recurrence
Postsurgical inflammatory neuropathy	Delayed onset (median 2 days, up to 30 days) of focal/multifocal deficits, often involving the lumbosacral plexus, after a surgical procedure Represents a form of microvasculitis

◆ CLINICAL PEARL

Painful vs. painless plexopathy is a key discriminator in oncology patients: malignant infiltration is typically painful with rapid progression, whereas radiation-induced plexopathy is typically painless, develops after a latency of months to years, and shows myokymic discharges on EMG.

Chapter 5. Paraneoplastic Neuropathies, Immune Checkpoint Inhibitor Toxicity, and Rare Motor Neuron Disease Mimics

I. Paraneoplastic Neuropathies and Onconeural Antibodies

Paraneoplastic neuropathies are immune-mediated disorders triggered by an underlying malignancy. They typically present with an acute-to-subacute onset and are often asymmetric or non-length-dependent — features that should raise suspicion when encountered in an otherwise atypical neuropathy.

A. Key Paraneoplastic Syndromes and Antibodies

Antibody	Primary Association	Cancer	Neurologic Presentation and Phenotype
ANNA-1 (anti-Hu)	Small cell lung cancer (81% of cases)		Subacute sensory neuronopathy (ganglionitis): severe loss of large-fiber modalities, sensory ataxia, and pseudoathetosis. Approximately 70% are purely sensory; 25% are sensorimotor.
CRMP-5 (anti-CV2)	Small cell lung cancer (75%), thymoma (15%)		Painful polyradiculoneuropathy, usually an asymmetric axonal process; often associated with gastroparesis and autonomic dysfunction.
Amphiphysin	Small cell lung cancer (73%), breast adenocarcinoma (25%)		Polyradiculoneuropathy or sensory neuronopathy, often associated with CNS disease including encephalopathy and stiff-person syndrome.
MAP1B	Lung cancer		Painless polyradiculoneuropathy; symmetric sensory neuronopathy.
LUZP4	Seminoma		Motor neuronopathy and polyradiculopathy; often improves with both immunotherapy and cancer treatment.

B. Diagnostic and Screening Protocols

- **Temporal relationship:** In 97% of ANNA-1 cases and 96% of CRMP-5 cases, neurologic symptoms precede the cancer diagnosis — underscoring the importance of aggressive cancer screening even when initial imaging is negative.
- **Screening high yield:** PET-CT and MRI have a diagnostic yield of 84% and 77%, respectively, for identifying underlying malignancy, including neurolymphomatosis.
- **Panel testing:** Because paraneoplastic antibodies are often linked to multiple neurologic syndromes, antibody panel testing (rather than single-antibody testing) is recommended to better formulate a cancer screening plan.
- **CSF markers:** Lymphocytic pleocytosis and elevated protein are common in CSF, even when only peripheral nerve involvement is clinically apparent.

II. Immune Checkpoint Inhibitor (ICI) Neurologic Complications

Immune checkpoint inhibitors are monoclonal antibodies that enhance the immune system's anti-tumor response by blocking inhibitory checkpoints. Their growing use across oncology means neurologists will increasingly encounter their neurologic adverse effects.

A. Targeted Therapeutics and Mechanism

Target	Example Agents
Anti-PD-1	Nivolumab, pembrolizumab, cemiplimab
Anti-PD-L1	Atezolizumab, durvalumab, avelumab
Anti-CTLA-4	Ipilimumab, tremelimumab

IMPORTANT NOTE

Toxicity mechanism: blockade of inhibitory checkpoint receptors increases the risk of the immune system misrecognizing self-antigens as foreign, producing immune-related adverse events (irAEs), including neurologic irAEs.

B. Presentation and Overlap Syndromes

- **Incidence:** Neurologic irAEs occur in 1% to 12% of patients treated with ICIs.
- **Distribution:** 75% involve the peripheral nervous system; toxic neuropathies represent 29% of all neurologic irAEs.
- **GBS-like phenotype (AIDP):** Accounts for 25% of cases; unlike classic GBS, these often show CSF pleocytosis and respond to corticosteroids.
- **Cranial neuropathies:** Account for 25% of cases.
- **Overlap syndromes:** High frequency of co-occurrence with myositis (elevated creatine kinase) and myasthenia gravis (fatigable weakness); these combinations are associated with high mortality and risk of myocarditis.

✗ EMERGENCY / RED FLAG

The myositis-myasthenia gravis-myocarditis overlap triad is a life-threatening ICI complication. Any patient on checkpoint inhibitor therapy presenting with new ptosis, dysphagia, or fatigable weakness should have an urgent troponin, ECG, and creatine kinase evaluation for concurrent cardiac and muscle involvement.

C. Management by CTCAE Severity Grade

Management follows the Common Terminology Criteria for Adverse Events (CTCAE) grading system.

Grade	Clinical Features	Management
Grade 1 (mild)	Mild sensory symptoms only.	Hold ICI; initiate neurologic workup.
Grade 2 (moderate)	Any weakness; neuropathic pain; cranial neuropathy.	Hold ICI; consider oral prednisone 0.5–1 mg/kg.
Grade 3 (severe)	Impaired ambulation or proprioception; limitation of activities of daily living.	Permanently discontinue ICI; admit to hospital; IV methylprednisolone 2–4 mg/kg/day.
Grade 4 (fulminant)	Respiratory failure; dysphagia requiring feeding tube.	Same as Grade 3; add plasma exchange or IVIG if no response to steroids.

III. Rare Motor Neuron Disease Mimics and Variants

Distinguishing motor neuron disease from its mimics is critical for accurate prognosis and treatment, since several mimics are treatable while ALS currently is not curative.

A. Monomelic Amyotrophy (Hirayama Disease)

- **Pathophysiology:** Caused by a discordance between spinal cord length and spinal canal length during growth. During neck flexion, the posterior dural wall undergoes an anterior shift, compressing the anterior cord and causing focal cervical cord ischemia.
- **Clinical presentation:** Asymmetric juvenile upper limb distal atrophy (hands and forearms) in males aged 15–25 years. Symptoms progress for 1–5 years and then plateau.
- **MRI criteria:** Flexion cervical MRI is the diagnostic hallmark, showing anterior displacement of the dural sac, further cord compression, and a prominent epidural venous plexus.

◆ CLINICAL PEARL

A young man with slowly progressive, asymmetric, distal-hand-predominant weakness that has plateaued should prompt flexion-view cervical spine MRI to evaluate for Hirayama disease before an ALS workup is pursued — this diagnosis carries a fundamentally different (favorable, self-limited) prognosis.

B. Additional MND Mimics

Mimic	Distinguishing Features
Kennedy disease (spinobulbar muscular atrophy, SBMA)	X-linked CAG repeat expansion in the androgen receptor gene. Distinguished from ALS by gynecomastia, increased creatine kinase (> 1000 U/L), perioral fasciculations, and a concurrent sensory neuropathy (decreased SNAP amplitudes).
Multifocal motor neuropathy (MMN)	Pure lower motor neuron weakness in peripheral nerve distributions (distal upper limb predominant) with conduction block on nerve conduction studies. Responds to IVIG but worsens with corticosteroids.

🔍 IMPORTANT NOTE

Additional recognized board-level ALS mimics not detailed with specific parameters in the source material include adult-onset hexosaminidase A deficiency (GM2 gangliosidosis) and Madras motor neuron disease. These should remain on the differential for atypical, especially young-onset, motor neuron syndromes, though comprehensive diagnostic criteria for them are outside the scope of this section.

Chapter 6. Autonomic Neuropathies, Hereditary Sensory and Autonomic Neuropathies, and Neuropathic Pain Management

I. Acute and Chronic Autonomic Neuropathies

Autonomic dysfunction is a critical component of many peripheral nerve disorders, ranging from primary immune-mediated attacks to secondary metabolic complications.

A. Diabetic Autonomic Neuropathy (DAN)

Diabetes commonly causes a length-dependent autonomic neuropathy, initially affecting the longest fibers (the vagus nerve) and progressing to systemic involvement.

- **Cardiovascular autonomic neuropathy (CAN):** One of the earliest signs is a reduction in heart rate variability with an elevated resting heart rate (parasympathetic failure). Later, sympathetic failure leads to neurogenic orthostatic hypotension.
- **Gastrointestinal / genitourinary:** Symptoms include gastroparesis (early satiety), constipation, diarrhea, and erectile dysfunction.
- **Pupillary dysregulation:** Tonic pupils may be a clinical clue to underlying dysautonomia.

B. Immune-Mediated Autonomic Neuropathies

- **Acute pandysautonomia:** A rare variant of GBS characterized by rapid-onset failure of both sympathetic and parasympathetic systems.

- **Amyloid neuropathy:** Dysautonomia is a hallmark feature, often presenting with severe orthostatic hypotension and gastrointestinal dysmotility.

⚠ WARNING

In idiopathic neuropathy, prominent dysautonomia out of proportion to sensorimotor findings should prompt immediate evaluation for amyloidosis.

II. Hereditary Sensory and Autonomic Neuropathies (HSAN)

HSAN constitutes a spectrum of disorders characterized by degeneration of sensory and autonomic neurons, often leading to significant morbidity such as skin ulcerations and acral amputations.

Genetic Classification of HSAN Subtypes

Type	Gene(s)	Inheritance	Key Clinical Traits
HSAN I	SPTLC1, SPTLC2, ATL1, DNMT1, RAB7	AD	Onset in adolescence/early adulthood. Lancing pain, painless ulcerations, Charcot joints, and osteolysis.
HSAN II	WNK1 (2A), RETREG1 (2B), KIF1A (2C), SCN9A (2D)	AR	Early-onset sensory loss; the WNK1 variant involves prominent autonomic features.
HSAN III	ELP1 (formerly IKBKAP)	AR	Familial dysautonomia (Riley-Day syndrome). Onset at birth; strong association with Ashkenazi Jewish ancestry. Severe autonomic crises.
HSAN IV	NTRK1	AR	Congenital insensitivity to pain, anhidrosis, and variable intellectual disability; risk of hyperthermia.
HSAN V	NGF	AR	Similar to Type IV but without intellectual disability; isolated pain insensitivity.
HSAN VI	DST	AR	Severe neonatal hypotonia, respiratory failure, and dysautonomia.
HSAN VII	SCN11A	AD	Congenital pain insensitivity, gastrointestinal dysmotility, and extreme itching.
HSAN VIII	PRDM12	AR	Congenital insensitivity to pain.

★ MEMORY TIP / MNEMONIC

HSAN III (familial dysautonomia) pearl: think “three things” — the ELP1 gene, Ashkenazi Jewish ancestry, and onset at birth with severe autonomic crises. This is the HSAN subtype most likely to be tested.

✗ EMERGENCY / RED FLAG

HSAN IV (NTRK1) carries a risk of unexplained hyperthermia due to congenital anhidrosis — affected children can develop dangerously high fevers without an infectious source because they cannot sweat.

III. Advanced Quantitative Biomarkers for Small Fiber Nerves

Small fiber nerves — unmyelinated C-fibers and thinly myelinated A-delta fibers — are not captured by routine nerve conduction studies, necessitating specialized quantitative testing.

A. Skin Biopsy Calibration and Parameters

- **Procedure:** A 3-mm punch biopsy is typically performed on a single limb.
- **Standard sites:** Distal leg (typically 10 cm above the lateral malleolus), distal thigh, and proximal thigh.
- **Marker assessed:** Intraepidermal nerve fiber density (IENFD).
- **Clinical significance:** A reduced IENFD at the distal site indicates a length-dependent process; non-length-dependent loss suggests a sensory neuronopathy or ganglionitis instead.

B. Quantitative Sensory Testing (QST)

- **Vibration thresholds:** Best quantified using a 64-Hz Rydel-Seiffer tuning fork, which provides objective measurements that correlate with sensory nerve action potential (SNAP) amplitudes.
- **Thermal thresholds:** Quantifiable stimulus devices assess the function of small fibers mediating cold and heat sensation.

IV. Neuropathic Pain Pharmacotherapy Manual

Effective management of neuropathic pain requires selecting agents based on patient comorbidities, adverse effect profiles, and organ function.

A. Neuropathic Pain Medication Dosing and Titration

Drug Class	Medication	Typical Starting & Target Dose	Max Dose / Key Adjustments
Gabapentinoids	Gabapentin	Start: 100–300 mg TID. Target: 1800–3600 mg/day.	Max 3600 mg/day. Mandatory dose reduction in renal impairment.
Gabapentinoids	Pregabalin	Start: 50 mg TID. Target: 300–600 mg/day.	Max 600 mg/day. Mandatory dose reduction in renal impairment.
SNRIs	Duloxetine	30–60 mg once daily.	Max 60 mg/day. Contraindicated with tamoxifen; caution with other serotonergic agents.

Drug Class	Medication	Typical Starting & Target Dose	Max Dose / Key Adjustments
SNRIs	Venlafaxine	75–225 mg daily.	Off-label use for painful polyneuropathy; requires gradual titration.
TCAs	Amitriptyline	25–100 mg at bedtime.	Contraindicated if corrected QT interval is prolonged.
TCAs	Nortriptyline	25–100 mg at bedtime.	Often better tolerated than amitriptyline in older adults.
Topical agents	Lidocaine 5%	Patch or gel.	Apply 1–4 times daily to intact skin only.
Topical agents	Capsaicin 8%	High-concentration patch.	Applied by healthcare professionals for localized postherpetic neuralgia.

⚠ WARNING

Duloxetine and tamoxifen must never be co-prescribed: duloxetine's CYP2D6 inhibition blocks conversion of tamoxifen to its active metabolite, potentially compromising breast cancer treatment efficacy.

B. Orthostatic Hypotension (OH) Management

Agent	Dosing
Fludrocortisone	Start 0.05 mg daily; target 0.1–0.2 mg/day.
Midodrine	2.5–10 mg three times daily (every 3–4 hours); avoid dosing within 4 hours of bedtime.
Droxidopa	100–600 mg three times daily.
Pyridostigmine	Test dose 30 mg; target 60 mg up to three times daily.

? IMPORTANT NOTE

Midodrine's supine hypertension risk is the rationale for avoiding bedtime dosing — patients should remain upright or semi-upright for several hours after each dose.

Chapter 7. Motor Neuron Diseases: ALS, Genetic Variants, and Spinal Muscular Atrophy

This reference section for motor neuron diseases (MND) covers diagnostic frameworks, genetic parameters, and therapeutic protocols for amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA).

I. Amyotrophic Lateral Sclerosis (ALS) Diagnostics

ALS is a progressive neurodegenerative disorder characterized by the coexistence of upper motor neuron (UMN) and lower motor neuron (LMN) signs. Diagnosis requires clinical and electrophysiological evidence across four body regions: bulbar, cervical, thoracic, and lumbosacral.

A. Comparison of Diagnostic Criteria Frameworks

Feature	El Escorial (Revised 2000)	Awaji Criteria (2008)	Gold Coast Criteria (2020)
Structure	5 categories of diagnostic certainty (Definite to Possible).	Retained categories; increased sensitivity by including fasciculations.	Simplified: eliminates categories of diagnostic certainty.
Requirements	UMN and LMN signs in multiple regions.	Fasciculation potentials accepted as electrophysiological evidence of LMN involvement.	Progressive motor impairment plus UMN and LMN signs in ≥ 1 region, OR LMN signs alone in ≥ 2 regions.
Utility	Viewed as overly complex for routine clinical practice.	Improved sensitivity for early diagnosis.	Increased sensitivity for detecting patients at earlier disease stages.

★ HIGH YIELD

The Gold Coast criteria (2020) are the current standard for ALS diagnosis in both clinical trials and routine practice, chosen for their simplicity and superior sensitivity compared to El Escorial and Awaji.

II. ALS Genetics and Clinical Variants

A. Genetic Pathogenic Mechanisms

Gene	Mechanism	Key Associations
C9orf72	Hexanucleotide (G4C2) repeat expansion.	The most common monogenic cause of ALS (40% of familial cases); strongly associated with frontotemporal dementia (FTD), with 40–50% of carriers showing cognitive impairment.
SOD1 (superoxide dismutase 1)	Toxic gain-of-function point mutations.	The second most common genetic cause; more than 200 variants identified; typically 90% penetrant by age 70.
TARDBP (TDP-43)	Mutations link to the hallmark pathological aggregate.	Cytoplasmic TDP-43 inclusions are found in > 90% of sporadic ALS cases.
FUS (Fused in Sarcoma)	Disruption of RNA processing and protein homeostasis.	Associated with younger-onset, often more aggressive familial ALS.

★ MEMORY TIP / MNEMONIC

C9orf72 pearl: “C9 = Cognitive” — the C9orf72 repeat expansion is the single most important gene to remember for the ALS-FTD spectrum, given its high prevalence and strong association with frontotemporal dementia.

B. Distinct Motor Neuron Phenotypes

Variant	Key Clinical Profile	Diagnostic / Tracking Rules
Primary lateral sclerosis (PLS)	Isolated UMN signs (spasticity, stiffness, spastic dysarthria).	Probable PLS: 2–4 years from symptom onset without LMN signs. Definite PLS: > 4 years without LMN signs.
Progressive muscular atrophy (PMA)	Isolated LMN signs (atrophy, weakness, fasciculations).	Portends a more favorable prognosis than classic ALS.
Progressive bulbar palsy (PBP)	Isolated bulbar-onset disease (dysphagia, dysarthria).	High risk of rapid progression to respiratory insufficiency.
Kennedy disease (SBMA)	X-linked trinucleotide (CAG) repeat expansion in the androgen receptor gene.	Signs: gynecomastia, perioral fasciculations, increased creatine kinase (> 1000 U/L), and a concurrent sensory neuropathy.

III. Disease-Modifying and Symptomatic Medication Manual

A. Disease-Modifying Therapeutics

Agent	Dosing / Schedule	Monitoring / Biomarker
Riluzole	50 mg twice daily, orally.	Mandatory liver function tests (LFTs) monthly for the first 3 months, then every 3 months thereafter.
Edaravone — IV	Cycle 1: 60 mg daily for 14 days, then 14 days off. Subsequent cycles: 60 mg daily for 10 days within a 14-day period, then 14 days off.	—
Edaravone — oral	105 mg (5 mL) daily, following the same cycle-based schedule as the IV formulation.	—
Tofersen (for SOD1 mutations)	Loading dose: 100 mg intrathecally on Days 1, 15, and 29. Maintenance: 100 mg intrathecally every 28 days thereafter.	Reduction in neurofilament light chain (NfL) is tracked as a biomarker of treatment effect.

B. Symptomatic and Supportive Care

Symptom	Management
Pseudobulbar affect	Dextromethorphan-quinidine, or SSRIs.
Sialorrhea	Sublingual atropine drops, oral glycopyrrolate, or botulinum toxin injections to the salivary glands.
Respiratory decline (NIV thresholds)	Start non-invasive ventilation if FVC < 50%, sniff nasal pressure worse than -40 cmH ₂ O, or orthopnea is present.
Nutritional decline (PEG indicators)	Gastrostomy tube recommended for significant weight loss, severe dysphagia, or when FVC approaches 50%.

◆ CLINICAL PEARL

Timing of respiratory and nutritional interventions in ALS matters: proactively discussing non-invasive ventilation and gastrostomy tube placement while FVC is still near 50% — rather than waiting for crisis — allows safer procedural risk and better patient acceptance.

IV. Spinal Muscular Atrophy (SMA) and Gene Therapy

SMA is caused by homozygous deletions of SMN1 (specifically exon 7). Disease severity is modified by SMN2 copy number, with higher copy numbers correlating with milder phenotypes.

A. Phenotypic Classification

SMA Type	Onset Age	Highest Milestone (Untreated)	Typical SMN2 Copy Number
Type 1	< 6 months	Never sits independently.	Typically 2 copies.
Type 2	6–18 months	Sits independently; never walks.	Typically 3 copies.
Type 3	> 18 months	Walks independently; may lose ability later in life.	Typically 3–4 copies.
Type 4	> 21 years	Walks independently throughout adulthood.	Typically 4–5 copies.

☆ MEMORY TIP / MNEMONIC

SMN2 copy number and SMA severity are inversely related to disease severity — more copies of the “backup” SMN2 gene produce more functional SMN protein, resulting in a milder phenotype and later onset.

V. SMA Therapeutic Dosing Protocols

A. Nusinersen (Antisense Oligonucleotide)

- **Loading protocol:** 12 mg intrathecally on Days 0, 14, 28, and 60.
- **Maintenance:** 12 mg intrathecally every 4 months, for life.
- **Safety benchmarks:** Complete blood count (platelets), coagulation parameters, and quantitative spot urine protein must be checked before every injection.

B. Risdiplam (Small-Molecule Splicing Modifier)

- **Administration:** A liquid oral daily dose given after a meal.

Age / Weight Group	Weight-Based Dose
< 2 months old	0.15 mg/kg daily
2 months to < 2 years old	0.20 mg/kg daily
≥ 2 years old, < 20 kg	0.25 mg/kg daily
≥ 2 years old, ≥ 20 kg	5 mg fixed daily cap

C. Onasemnogene Apeparvovec (Gene Replacement Therapy)

- **Dosing:** A one-time intravenous infusion of 1.1×10^{14} vector genomes (vg) per kg.
- **Age limit:** Approved for children younger than 2 years old.
- **Corticosteroid safety protocol:** 1 mg/kg/day of prednisolone (or equivalent), starting the day before infusion and continued for 28 days, to mitigate hepatic injury.
- **Exclusion benchmark:** AAV9 antibody titers > 1:50 exclude patients from treatment due to the risk of immune reaction.

WARNING

Onasemnogene abeparvovec carries risks of acute liver injury and thrombotic microangiopathy; strict adherence to the corticosteroid prophylaxis protocol and pre-infusion AAV9 antibody screening is mandatory for safe administration.

DISEASES OF MUSCLE and NMJ

CHAPTER I — CLINICAL PHENOTYPING OF MUSCLE DISEASE

A systematic clinical approach to weakness — using temporal pattern, distribution, and specific physical signs — narrows the differential diagnosis before a single test is ordered. This chapter organizes the bedside reasoning that underlies all subsequent diagnostic testing.

A. Temporal and Progression Patterns

Temporal Pattern	Diagnostic Implication
Early symptom onset (infancy/childhood)	Suggests an inherited myopathy, particularly with skeletal abnormalities such as rigid spine, joint contractures, or high-arched palate
Static or slowly progressive course (early-onset)	Favors congenital myopathies over the clearly progressive course of muscular dystrophies
Subacute onset	Typically points to acquired etiologies such as immune-mediated myopathies
Acute onset with rhabdomyolysis	Suggests toxic, infectious, or inherited metabolic myopathy (e.g., CPT II deficiency, myophosphorylase deficiency)
Episodic weakness without rhabdomyolysis	Suggests periodic paralysis, though NMJ defects must be excluded

B. Distribution of Weakness (Phenotypes)

- **Proximal Symmetry:** characteristic of most acquired myopathies, involving neck flexors, shoulder girdle, and hip girdle.
- **Distal Pattern:** refers specifically to a subset of inherited muscle diseases, though weakness starting distally may later extend proximally.
- **Ocular Involvement:** binocular diplopia suggests extraocular muscle (EOM) involvement — common in mitochondrial myopathy, thyroid ophthalmopathy, and certain myositis forms.

Bulbar and Facial Weakness

- **Facial weakness** occurs in inherited diseases (myotonic dystrophy, FSHD) and in 20–30% of patients with Inclusion Body Myositis (IBM).
- **Bulbar symptoms** include chewing fatigue, dysphagia, and nasal (flaccid) dysarthria.

Axial and Neck Weakness

- **Neck extensor weakness** results in head drop.
- **Axial weakness** manifests as camptocormia (inability to stand erect) or difficulty rising from supine.

- **Scapular winging** is caused by weakness of scapular stabilizers (trapezius, serratus anterior); common in FSHD and certain LGMDs.

C. Physical Signs and Maneuvers

Sign	Description	Clinical Association
Gowers Sign	Patient 'marches' hands up the legs to stand	Proximal pelvic girdle weakness
Beevor Sign	Upward movement of the umbilicus during neck flexion	FSHD
Poly-hill Sign	Elevations on the upper back from selective trapezius wasting with displaced joints	FSHD
Waddling Gait	Pelvic drop / lurching gait	Gluteus medius weakness

Muscle tone and reflexes: tone is typically normal or reduced; reflexes are often normal, hypoactive, or absent unless coexisting CNS involvement is present.

D. Differentiating Fatigue from Fixed Weakness

- **Fixed weakness** is objectively measured by Manual Muscle Testing (MMT).
- **Fatigue and exercise intolerance** are more difficult to assess; exertional pain specifically suggests a compromised energy supply, as in metabolic myopathies.

MEMORY TIP / MNEMONIC

Warm-Up vs. Paradoxical Myotonia:

- **Warm-Up Phenomenon:** myotonia that IMPROVES with repetitive activity → typical of chloride channelopathies (myotonia congenita).
- **Paradoxical Myotonia:** stiffness that WORSENS with repetition → characteristic of paramyotonia congenita (SCN4A).

CHAPTER II — ELECTRODIAGNOSTIC (EDX) TESTING

A. NMJ Disorders — Repetitive Nerve Stimulation (RNS)

RNS Protocol	Target Disorder	Diagnostic Finding
Low-Frequency RNS (2–3 Hz)	Distinguishes myopathy from autoimmune/congenital NMJ defects; Myasthenia Gravis	Decrement $\geq 10\%$ in CMAP amplitude between 1st and 4th potentials = positive for MG

RNS Protocol	Target Disorder	Diagnostic Finding
High-Frequency RNS (20–50 Hz) or Post-Exercise Facilitation	Presynaptic defects: Lambert-Eaton Myasthenic Syndrome (LEMS), Botulism	LEMS: low-amplitude baseline CMAPs + increment (facilitation) >60% (often >100%) after maximal voluntary contraction or high-frequency stimulation

B. Single-Fiber EMG (SFEMG)

- **Sensitivity:** SFEMG is the most sensitive test for NMJ disorders, reaching 99% sensitivity when multiple muscles (e.g., extensor digitorum communis and frontalis) are tested.
- **Jitter:** temporal variability in endplate potentials reaching threshold; proportional to the number of abnormal endplates and disease severity.
- **Blocking:** complete failure of neuromuscular transmission.

⚠ WARNING

Specificity Caution: increased jitter is NONSPECIFIC and can occur in LEMS, botulism, and during immature reinnervation in neurogenic disorders.

C. Needle EMG for Muscle Disorders

Quantitative MUAP Features

- **Myopathic MUAPs:** short duration, small amplitude, polyphasic morphology.
- **Recruitment:** myopathies typically show rapid (early) recruitment — a large number of MUAPs fire with minimal effort.

Spontaneous Activity

Finding	Significance
Fibrillation Potentials / Positive Sharp Waves	Muscle membrane irritability; hallmark of inflammatory or necrotizing myopathies and some dystrophies
Myotonic Discharges	Spontaneous, rhythmic firing (40–100 Hz) with waxing/waning 'dive bomber' sound. Occur in myotonic disorders, but also inflammatory myopathy (IBM, IMNM), Pompe disease, and certain toxic myopathies

Long Exercise Test

Used to evaluate for periodic paralysis: a concordant decrement in CMAP amplitude (>40%) or area (>50%) is diagnostic.

CHAPTER III — MUSCLE BIOPSY AND IMAGING

A. Muscle MRI Patterns

- **T1-Weighted Sequences:** detect fatty replacement and chronic atrophy.
- **STIR (Short Tau Inversion Recovery):** sensitive for muscle edema, a marker for active inflammation or acute muscle damage.

Specific MRI Patterns

Pattern	Description	Association
Outside-In	Fatty replacement moving from periphery inward	Collagen VI–related myopathies
Tigroid Appearance	Preferential involvement of the muscle periphery	Collagen VI–related myopathies
IBM Pattern	Prominent distal vastus medialis/lateralis and medial gastrocnemius involvement, with relative sparing of rectus femoris	Inclusion Body Myositis

B. Histopathological Hallmarks

Finding	Definition	Key Association
Perifascicular Atrophy	Small regenerating/degenerating fibers at fascicle periphery	Dermatomyositis (specific hallmark)
Rimmed Vacuoles	Autophagic vacuoles reflecting disrupted protein homeostasis	IBM, multisystem proteinopathy (MSP), some distal myopathies
Necrotic Fibers	Fiber breakdown and phagocytosis; if scattered with minimal inflammation	Immune-Mediated Necrotizing Myopathy (IMNM)
Protein Aggregates	p62, TDP-43, or amyloid (Congo red positive)	IBM (degenerative process)
Mitochondrial Abnormalities	COX-negative fibers	Present in nearly all IBM samples and mitochondrial disorders

Inflammatory Infiltrate Patterns

Infiltrate Location	Cell Type	Classic For
Endomysial	CD8+ T cells invading non-necrotic fibers	Polymyositis, IBM
Perimysial / Perivascular	Infiltrates around vessels or connective tissue	Dermatomyositis, Antisynthetase Syndrome

Immunohistochemical Markers

- **MHC-I / MHC-II Upregulation:** found on sarcolemma of non-necrotic fibers in many inflammatory and some inherited myopathies.
- **MxA (Myxovirus Resistance Protein A):** robust sarcoplasmic marker for the type I interferon pathway in Dermatomyositis, present even before atrophy appears.
- **Complement (C5b-9) Deposition:** membrane attack complex (MAC) deposition on small vessels — relatively specific for the microangiopathy of Dermatomyositis.

★ **HIGH YIELD — EXAM TIP**

Perifascicular atrophy + MxA positivity + C5b-9 on capillaries = the histologic triad that clinches Dermatomyositis on biopsy, even before overt atrophy is visible.

CHAPTER IV — NEUROMUSCULAR JUNCTION PHYSIOLOGY AND MYASTHENIA GRAVIS

I. Pathophysiology: Mechanisms of Transmission Failure

A. Normal Neuromuscular Transmission

1. **ACh Release:** motor nerve action potentials trigger acetylcholine (ACh) release into the synaptic space.
2. **AChR Binding:** ACh diffuses across the cleft and binds alpha subunits of acetylcholine receptors (AChRs) on the postsynaptic muscle endplate.
3. **Depolarization:** binding opens cation channels, generating an endplate potential.
4. **Amplification:** the potential is amplified by voltage-gated sodium channels in the junctional folds; if threshold is reached, muscle contraction occurs.
5. **AChR Clustering:** regulated by the agrin–LRP4–MuSK–Dok-7–rapsyn pathway. Agrin binds LRP4, initiating MuSK phosphorylation, which interacts with Dok-7 and rapsyn to aggregate AChRs.
6. **Inactivation:** acetylcholinesterase (anchored by collagen Q) inactivates ACh to prevent prolonged depolarization.

📌 **MEMORY TIP / MNEMONIC**

NMJ Signal Cascade Mnemonic — 'A Big Dog Runs, Making Clusters':

- Agrin → binds LRP4 → activates MuSK → Dok-7 → Rapsyn → AChR Clustering

B. Mechanisms of Autoimmune Attack

- **Complement-Mediated Destruction:** in AChR-MG, IgG1 and IgG3 antibodies activate the complement cascade, forming the membrane attack complex (MAC). This causes structural damage, simplification of the postsynaptic membrane, and loss of voltage-gated sodium channels.

- **AChR Cross-linking:** bivalent antibodies cross-link receptors, increasing internalization and degradation (antigenic modulation).
- **Functional Blockade:** some antibodies directly block the ACh binding sites on the receptor.
- **Clustering Disruption:** antibodies against MuSK or LRP4 impair maintenance and aggregation of AChRs, reducing receptor density.

II. Serological Subtypes and Antibody Profiles

A. Anti-AChR Antibodies (80% of Generalized MG)

Antibody Class	Function	Clinical Utility
Binding Antibodies	Primary diagnostic marker	Found in 70–85% of all MG (85–90% generalized; 50–70% ocular)
Modulating Antibodies	Measure rate of AChR internalization	Increase diagnostic sensitivity by ~10%; sent when binding titers are low/negative
Blocking Antibodies	Directly interfere with ACh binding	Generally do not add diagnostic sensitivity
📌 IMPORTANT NOTE Clinical Nuance: antibody titers do NOT correlate with clinical disease severity or predict remission		

B. Anti-MuSK (Muscle-Specific Tyrosine Kinase) Antibodies

- **Detection:** found in 40–50% of AChR-negative generalized MG patients (~7% of MG overall).
- **IgG4 Subclass:** most MuSK antibodies are IgG4, functionally monovalent due to Fab-arm exchange.
- **Pathogenic Mechanism:** do NOT activate complement or cause antigenic modulation/cross-linking — instead, directly inhibit MuSK activation and disrupt clustering.

Clinical Profile of Anti-MuSK MG

- Predilection for bulbar, respiratory, and neck extensor weakness.
- **Muscle Atrophy:** can produce focal atrophy (e.g., triple furrowing of the tongue) due to functional denervation.
- **Pyridostigmine Resistance:** often poor response or cholinergic hypersensitivity (profuse fasciculations at low doses) because MuSK antibodies disrupt collagen Q-anchored acetylcholinesterase.
- **Treatment Response:** highly responsive to rituximab. IVIg is notably LESS effective than plasma exchange for rescue therapy.

C. Anti-LRP4 and Seronegative MG

- **Anti-LRP4:** seen in ~2% of MG patients; typically IgG1 and may activate complement. Often associated with mild generalized or purely ocular disease.

⚠ WARNING

Specificity Caution: LRP4 antibodies have low specificity and are found in 23% of ALS patients and some healthy controls.

- **Seronegative MG:** defined by absence of measurable antibodies (AChR, MuSK, LRP4) via standard radioimmunoassay (RIA).
- **Cell-Based Assays (CBA):** highly sensitive assays detect low-level AChR antibodies in nearly one-fifth (20%) of patients previously labeled seronegative by RIA.

III. Clinical Phenotypes and Classification

A. Ocular MG (OMG) vs. Generalized MG (GMG)

- **OMG:** weakness restricted to the extraocular and orbicularis oculi muscles.
- **Conversion Rates:** approximately 85% of patients presenting with ocular symptoms develop generalized weakness (bulbar, neck, limb) within 2 years.
- **Predictors of Generalization:** AChR seropositivity, comorbid autoimmune disease, or thymic hyperplasia.

B. MGFA Clinical Classification and Severity

MGFA Grade	Description
I	Ocular weakness only
II	Mild generalized weakness
III	Moderate generalized weakness
IV	Severe generalized weakness
V	Myasthenic crisis — respiratory failure requiring intubation or noninvasive support

The goal of modern therapy is reaching Minimal Manifestation Status (MMS) — subtle findings on exam but no symptoms. Impending crisis refers to a rapid increase in weakness signaling potential failure within days to weeks.

C. Demographic and Thymic Profiles

Subtype	Onset Age	Sex Predominance	Thymic/Genetic Association
Early-Onset MG (EOMG)	≤50 years	Female (3:1)	Thymic hyperplasia; HLA-B8-DR3-DQ2
Late-Onset MG (LOMG)	>50 years	Male predominance	Thymic atrophy; HLA-DRB1*15:01

Subtype	Onset Age	Sex Predominance	Thymic/Genetic Association
Thymoma-Associated MG (TAMG)	Any	—	Occurs in 10–20% of MG; thymectomy required regardless of severity to prevent tumor spread
Checkpoint Inhibitor-Associated MG	Any (drug-related)	—	Fulminant, often seronegative, monophasic; frequently overlaps with myositis and myocarditis — high mortality

CHAPTER V — MYASTHENIA GRAVIS PHARMACOTHERAPY MANUAL

The primary goal of MG therapy is reaching Minimal Manifestation Status (MMS) — subtle findings on examination but no symptoms — while minimizing adverse effects.

1. Symptomatic Treatment: Cholinesterase Inhibitors

Parameter	Detail
Drug	Pyridostigmine bromide
Mechanism	Inhibits hydrolysis of ACh at the NMJ, increasing availability of ACh to bind postsynaptic receptors
Starting Dose	30–60 mg, 3–4 times daily
Maximum Threshold	Dose-dependent muscarinic and nicotinic side effects typically limit maximum dose
Extended-Release (ER)	180 mg tablets exist but seldom used due to irregular absorption and unpredictable clinical response

Side Effect Management

Effect Type	Symptoms	Adjunctive Management
Muscarinic	Nausea, abdominal cramping, diarrhea, sweating, increased secretions	Glycopyrrolate, hyoscyamine, or loperamide
Nicotinic	Muscle fasciculations and cramping	—
⚠ WARNING Pyridostigmine is purely symptomatic and does not affect the natural history of disease. Use cautiously in MuSK MG due to cholinergic hypersensitivity.		

2. Traditional Immunosuppression

A. Corticosteroids (Prednisone/Prednisolone)

- **Mechanism:** broad immunosuppressive effects.
- **High-dose initiation:** 0.75 mg/kg/day or 60 mg/day for moderate-to-severe disease.
- **Low-dose escalation:** gradual increase to avoid transient worsening, which occurs in up to 15% of patients within the first 10 days of treatment.
- **Titration and taper:** taper to <7.5 mg/day within 1 year. If stable, reduce by ~25% every 4–8 weeks.
- **Monitoring:** blood pressure, weight, serum glucose (HbA1c), bone density (DEXA), tonometry (for glaucoma).

B–D. Steroid-Sparing Agents

Agent	Mechanism	Dosing	Key Monitoring
Azathioprine	Inhibits purine synthesis; suppresses T- and B-cell proliferation	2–3 mg/kg/day; start 50 mg/day, advance weekly by 50 mg/day	TPMT genotype/activity mandatory before starting; CBC + LFTs weekly ×1 month, then monthly ×1 year, then every 3–6 months
Mycophenolate Mofetil	Selective inhibition of T- and B-lymphocyte proliferation	1000–1500 mg BID; start 500 mg BID ×1 week, then advance to 1000 mg BID	CBC monthly ×3 months then every 6 months; REMS program mandatory for patients of childbearing potential (teratogenic)
Cyclosporine	Inhibits IL-2 production and T-cell activation	3–5 mg/kg/day; trough target 100–150 ng/mL	Monitor BP and serum creatinine
Tacrolimus	Inhibits IL-2 production and T-cell activation	1–2 mg BID; trough target 2–9 ng/mL	Monitor glucose, BUN, creatinine

3. Targeted Modern Biologics and Complement Inhibitors

A. Neonatal Fc Receptor (FcRn) Antagonists

Mechanism: interrupts cellular recycling of IgG, leading to increased lysosomal degradation of pathogenic antibodies.

Drug	Dosing	Cycle Interval
Efgartigimod alfa	10 mg/kg IV weekly for 4-week cycles	Repeat no sooner than 50 days from start of previous cycle

Drug	Dosing	Cycle Interval
Rozanolixizumab	Weight-tiered SC dosing (up to 100 kg); 6 weekly infusions per cycle	Repeat no sooner than 63 days from start of previous cycle

B. Complement C5 Inhibitors

Mechanism: blocks C5 cleavage to C5a/C5b, preventing membrane attack complex (MAC) formation.

Drug	Dosing Regimen
Eculizumab	900 mg IV weekly ×4 weeks, 1200 mg on week 5, then 1200 mg every 2 weeks
Ravulizumab	Weight-based IV loading dose, followed by weight-based maintenance every 8 weeks
Zilucoplan	Weight-based SC daily self-administration

⚠ WARNING

Mandatory Safety Protocol for Complement Inhibitors:

- **Vaccination:** Quadrivalent (MenACWY) and Serogroup B (MenB) series required ≥2 weeks before first dose.
- **Antibiotics:** prophylactic Penicillin V (500 mg BID) if treatment starts before the primary vaccine series is complete

C. Anti-CD20: Rituximab

- **Mechanism:** B-cell depletion (>95% reduction in circulating CD20+ B cells).
- **Protocols:** 375 mg/m² IV weekly ×4 weeks OR 1000 mg IV twice (2 weeks apart). Repeat every 6 months as needed.
- **Target Population:** standard of care for MuSK MG (often achieving durable remission).
- **Monitoring:** hepatitis B screening and CBC with differential before each cycle.

4. Acute Crisis Management

🚨 EMERGENCY

Myasthenic Crisis — Rescue Therapy:

- **IVIG:** 2 g/kg total dose divided over 2–5 days. Preferred for children and those with poor vascular access.
- **Plasma Exchange (PLEX):** 5–6 exchanges (2–3 L each) on alternate days. Typically more effective than IVIG for MuSK MG.

Differentiating Crises

Crisis Type	Mechanism	Key Features
Myasthenic Crisis	Respiratory failure from MG weakness itself	Progressive weakness, bulbar/respiratory failure
Cholinergic Crisis	Excessive cholinesterase inhibitor dosing causing depolarization block	Increased secretions, aspiration risk, muscarinic excess
EMERGENCY Intubation Thresholds (standard neuro-critical care practice): - Forced Vital Capacity (FVC) < 15 mL/kg - Negative Inspiratory Force (NIF) < -20 cmH₂O Preoperative note: proactive rescue therapy (IVIg/PLEX) is recommended if FVC is <70% predicted before surgery/thymectomy.		

CHAPTER VI — PRESYNAPTIC AND NON-IMMUNE JUNCTIONAL DISORDERS

I. Lambert-Eaton Myasthenic Syndrome (LEMS)

A. Pathophysiology

- Antibody Target:** presynaptic P/Q-type Voltage-Gated Calcium Channels (VGCCs), in approximately 90% of patients.
- Mechanism:** antibody binding leads to internalization of the channels, reducing calcium influx after a nerve action potential — preventing synaptic vesicle docking and ACh release.
- Triggers:** often triggered by small cell lung carcinoma (SCLC) cells expressing VGCCs on their surface. May also occur as an immune-related adverse event following immune checkpoint inhibitor cancer treatment.

B. Clinical Triad and Physical Signs

- Proximal Weakness:** usually starts in the lower limbs, progressing in an ascending pattern to the upper limbs; oculobulbar involvement occurs later.
- Autonomic Dysfunction:** present in most patients — dry mouth, constipation, erectile dysfunction.
- Hyporeflexia/Areflexia:** decreased or absent muscle stretch reflexes.

CLINICAL PEARL

Post-Exercise Facilitation: a hallmark sign where reflexes and muscle strength improve transiently following a brief (~10-second) muscle contraction — a bedside clue that immediately raises suspicion for LEMS.

C. Electrodiagnostic (EDX) Features

Test	Finding in LEMS
Baseline CMAP	Typically low-amplitude
Low-Frequency RNS (1–5 Hz)	Decrement >10% in CMAP amplitude
High-Frequency RNS (50 Hz) or Post-Exercise	Marked increment (facilitation) >60% (often >100%) in amplitude
SFEMG	Increased jitter and blocking — nonspecific, does not distinguish LEMS from MG

D. Paraneoplastic Association and Screening

- **SCLC Association:** found in 50–60% of patients; usually undiagnosed at the time of LEMS presentation.
- **Screening Protocol:** the Dutch-English LEMS Tumour Association (DELTA) Prediction score helps differentiate paraneoplastic from nontumor LEMS. Screening involves chest CT or MRI.

E. Pharmacotherapy

Agent	Role	Key Details
Amifampridine (3,4-DAP)	First-line treatment	Blocks presynaptic potassium channels, prolonging motor nerve action potential and increasing ACh release. Side effects: distal/perioral paresthesia, mild GI disturbance. Seizures and cardiac arrhythmia rare at standard doses but risk increases >100 mg/day
Prednisone/Azathioprine or Rituximab	Immunosuppression	For moderate-to-severe symptoms
PLEX or IVIg	Acute rescue	—

II. Botulism

A. Pathophysiology

- **Etiology:** botulinum neurotoxin from *Clostridium botulinum* (and rarely *C. baratii*, *butyricum*, *sporogenes*).
- **Mechanism:** the toxin's light chain blocks SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex assembly, preventing ACh release from the presynaptic motor neuron.
- **Serotypes:** humans are primarily affected by serotypes A, B, E, and rarely F. Type A causes the most severe symptoms and respiratory failure.

B. Clinical Presentation

EMERGENCY

Acute descending flaccid paralysis.

- **Autonomic/Oculobulbar:** blurred vision, fixed dilated pupils, dry mouth, slurred speech, dysphagia.
- **Respiratory Failure:** occurs rapidly — 46% of adults require intubation (87% of these within the first 2 days).
- **Cognition/Sensation:** patients remain cognitively unaffected with normal sensation.

C. Workup and Antitoxin Protocols

- **Diagnostic Gold Standard:** mouse bioassay (detects toxin in serum, stool, or food over 96 hours).
- **Other Tests:** mass spectrometry (fast serotype differentiation) and PCR (detects Clostridium DNA).
- **EDX Findings:** facilitation (incremental CMAP) after exercise or 30–50 Hz RNS; needle EMG shows fibrillation potentials and small/short MUAPs.

Antitoxin Type	Population	Composition
Non-infantile	Older children and adults	Heptavalent antitoxin (covers serotypes A–G)
Infantile (2–8 months)	Infants	Human-origin anti-A, anti-B antitoxin

⚠ WARNING

Botulinum antitoxin prevents progression but does NOT reverse existing paralysis. Maximal benefit within 7 days of onset, but can be given later if there is clinical progression.

III. Congenital Myasthenic Syndromes (CMS)

A. General Features

- **Nature:** genetic (non-immune) defects affecting NMJ transmission proteins.
- **Inheritance:** mostly autosomal recessive; exceptions with dominant inheritance include slow-channel syndrome (CHRNA1/E), SNAP25, PURA, and some SYT2 cases.

B. Classification and Genetic Variants

Category	Genes / Mechanism	Key Feature
Presynaptic Synthesis/Recycling —	CHAT, SLC18A3, SLC5A7, PREPL	—
Presynaptic — Vesicle Docking/Exocytosis	SYT2, SNAP25B, VAMP1, UNC13A, RPH3A	May show incremental responses on high-frequency RNS
Synaptic Space — AChE Deficiency	COLQ	Endplate acetylcholinesterase deficiency
Synaptic Space — Structural	COL13A1, LAMA5, LAMB2	—
Postsynaptic — AChR Deficiency	CHRNE (most common)	Substitution of adult ϵ for fetal γ subunit
Postsynaptic — Fast-Channel Syndrome	Kinetic abnormality	Short channel opening → failure of muscle action potential
Postsynaptic — Slow-Channel Syndrome	Kinetic abnormality	Prolonged channel opening → depolarization block and secondary myopathy
Clustering Defects	AGRN, LRP4, MUSK, DOK7, RAPSN	—

C. Treatment Protocols and Critical Warnings

CMS Subtype	Recommended Therapy	Notes
CHAT, SLC5A7, RAPSN, primary AChR deficiency	Pyridostigmine (first-line)	Standard approach for most CMS subtypes
COLQ	β -adrenergic agonists (albuterol/salbutamol or ephedrine)	Stabilize synaptic structure over months
DOK7	β -adrenergic agonists (albuterol/salbutamol or ephedrine)	Stabilize synaptic structure over months
Slow-Channel Syndrome	Fluoxetine or quinidine (AChR ion channel blockers)	Requires ECG monitoring for QT prolongation and conduction defects
⚠ WARNING Critical Prescribing Warning — Avoid Pyridostigmine and 3,4-DAP in: • COLQ Congenital Myasthenia — worsens symptoms		

CMS Subtype	Recommended Therapy	Notes
- DOK7 Congenital Myasthenia — worsens symptoms - Slow-Channel Syndrome — worsens depolarization block		

CHAPTER VII — IMMUNE-MEDIATED AND INFLAMMATORY MYOPATHIES

I. Dermatomyositis (DM) and Antisynthetase Syndrome

A. Dermatomyositis: Pathophysiology and Histopathology

- Mechanism:** driven by activation of the type I interferon (IFN-I) pathway, with upregulation of IFN-I-associated genes and proteins.
- Perifascicular Atrophy:** a specific hallmark of DM — small regenerating and degenerating muscle fibers at fascicle periphery.
- MxA:** robust sarcoplasmic marker for the IFN-I pathway, expressed in the perifascicular region even before atrophy onset.
- Microangiopathy:** complement (C5b-9) MAC deposition on small vessels, leading to reduced capillary density and endothelial abnormalities (e.g., tubuloreticular inclusions).
- MHC-I/MHC-II Upregulation:** increased sarcolemmal expression, particularly perifascicular.

B. DM: Clinical Cutaneous Signs

Sign	Description
Gottron's Papules	Raised, erythematous rash over the knuckles and interphalangeal joints
Heliotrope Rash	Purplish discoloration of the eyelids, often with periorbital edema
V Sign / Shawl Sign / Holster Sign	Erythematous rashes over anterior chest/neck, shoulders/upper back, and hips respectively
Periungual Telangiectasia	Dilated nailfold capillary loops with possible thrombi
Poikiloderma / Calcinosis Cutis	Chronic pigmentary change and subcutaneous calcifications; calcinosis is common in juvenile DM and linked to NXP-2/SAE antibodies in adults

C. Myositis-Specific Antibody (MSA) Chart for DM

Antibody	Clinical Phenotype	Malignancy Risk
Anti-Mi-2	'Classic DM' — rapid onset, prominent rash, severe weakness	Good treatment response

Antibody	Clinical Phenotype	Malignancy Risk
Anti-TIF1-γ	Severe skin involvement, milder myositis	Highest malignancy association in adults
Anti-NXP2	Moderate-to-severe weakness, dysphagia, subcutaneous edema, calcinosis	Increased cancer risk
Anti-MDA5	Amyopathic DM, rapidly progressive ILD, palmar rashes, ischemic skin ulcers	—
Anti-SAE	Amyopathic/mild myositis, severe skin changes, ILD	Responds well to therapy

D. Antisynthetase Syndrome (AS)

A subacute or chronic syndrome defined by anti-aminoacyl tRNA synthetase antibodies. Features include myositis (proximal weakness), interstitial lung disease (ILD), nonerosive arthritis, Raynaud phenomenon, fever, and mechanic's hands.

- **Histopathology:** shares perivascular inflammation with DM, but is specifically characterized by perimysial fragmentation and intense alkaline phosphatase staining in the perimysial connective tissue.

MSA	Key Feature
Anti-Jo-1 (Histidyl)	Most common; highest frequency of muscle involvement
Others (PL-7, PL-12, EJ, OJ, KS, Zo, Ha/YRS)	PL-7 and PL-12 often have severe ILD with minimal muscle involvement

E. Malignancy Screening in DM

★ HIGH YIELD — EXAM TIP

Risk ranking (highest → lowest): TIF1-γ > NXP-2 > SAE > Mi-2.

Most cancers are identified within 2–3 years of DM onset.

Screening: Chest/Abdomen/Pelvis CT, mammogram, colonoscopy, gynecologic imaging, and whole-body PET scan; initial and repeat screening within 3 years for high-risk patients.

II. Immune-Mediated Necrotizing Myopathy (IMNM)

A. Histopathology

- **Hallmarks:** abundant scattered necrotic muscle fibers and regenerating fibers in the ABSENCE of prominent inflammatory infiltrates.
- **MHC-I:** expression is variable and often faint on the sarcolemmal surface.

B. Serological Markers

Antibody	Frequency	Clinical Features	Malignancy Risk
Anti-HMGCR	70% of IMNM	Often statin-associated (33% statin-naive); persistent/slowly progressive myopathy not resolving after statin cessation	Increased
Anti-SRP	10% of cases	Severe, rapidly progressive proximal weakness; potential cardiac involvement; resistant to standard immunosuppression	Not clearly increased
Antibody-Negative	~1/3 of IMNM	—	Increased

III. Inclusion Body Myositis (IBM)

A. Clinical Phenotype

- **Demographics:** the most common myopathy in adults >45 years old, affecting males twice as often as females.
- **Weakness Pattern:** slowly progressive and asymmetric.

Hallmark Feature	Manifestation
Deep Finger Flexors	Flexor pollicis longus and flexor digitorum profundus (DIP joint flexion) weakness → weak grip
Quadriceps	Knees 'giving out'; difficulty standing from a kneel
Bulbar/Axial	Dysphagia highly prominent — can be the initial or sole manifestation. Facial weakness and neck flexor weakness are common
⚠ WARNING Most patients require a wheelchair within a decade of onset; death is often due to aspiration pneumonia or respiratory failure.	

B. Histopathology: The Canonical Features

- **Inflammation:** endomysial infiltrates where cytotoxic CD8+ T cells surround and invade non-necrotic muscle fibers ('autoaggressive inflammation').
- **Degenerative Signs:** rimmed vacuoles (autophagic) and protein aggregates including p62, TDP-43, and amyloid.
- **Mitochondrial Dysfunction:** increased COX-negative fibers, present in nearly all IBM samples.

C. Serology and Imaging

- **Anti-cN1A:** antibodies against cytosolic 5'-nucleotidase 1A present in nearly 50% of patients; specificity is lower than originally reported as they also occur in other connective tissue diseases.
- **Muscle MRI:** fatty replacement in distal vastus medialis/lateralis and medial gastrocnemius, with relative sparing of the rectus femoris.
- **T-Cell Large Granular Lymphocytes:** a benign clone can often be detected in the serum of IBM patients.

D. Diagnostic Framework (ENMC 2024)

Diagnosis requires integrating clinical patterns (Typical: both finger flexor and quad weakness; Atypical: axial, isolated dysphagia, or limb-girdle) with biopsy findings. Mandatory criterion: muscle histopathology showing endomysial inflammation.

CHAPTER VIII — TREATMENT OF INFLAMMATORY MYOPATHIES

I. Corticosteroid Protocols

A. Initial Dosing and Escalation

Regimen	Indication	Dosing
Oral Prednisone	First-line for most inflammatory myopathies	0.75–1 mg/kg/day (generally totaling 60 mg daily)
Pulse IV Methylprednisolone	Severe cases: significant proximal weakness, dysphagia, dyspnea, or rhabdomyolysis-level CK	1 g daily for 3–5 days, followed by oral prednisone taper

Clinical improvement usually begins within 2–4 months and typically plateaus between 4–6 months.

B. Strict Taper Schedules

Tapering should only begin after the plateau phase with close monitoring of strength and side effects.

Taper Step	Rate	Target Dose
Step 1	Reduce by 10 mg every 4 weeks	Until daily dose of 20 mg
Step 2	Reduce by 2.5–5 mg every 4 weeks	Until daily dose of 10 mg
Step 3	Reduce by 1–2 mg every 4 weeks thereafter	—

IMPORTANT NOTE

Alternative regimens: monthly IV pulse methylprednisolone, or switching to every-other-day dosing after the first 4 weeks, may minimize cumulative toxicity.

C. Prophylaxis and Side Effect Management

Issue	Prophylaxis / Management
PJP Prophylaxis	Mandatory for long-term high-dose steroids or combination therapy. First-line: TMP/SMX (160/80 mg daily or double-strength 3×/week). Sulfa allergy alternatives: atovaquone, dapsone, pentamidine
Osteoporosis	Baseline and periodic DEXA every 1–2 years
Supplements	Calcium 1000–1200 mg/day; Vitamin D 600–800 IU/day (target serum 30–50 ng/mL)
Bisphosphonates	Advised for high-risk patients (men >50, postmenopausal women) on steroids >3 months (e.g., alendronate)
Metabolic/Ophthalmologic	Low-sodium, low-carbohydrate, low-sugar, high-protein diet; periodic eye exams for cataracts and glaucoma

II. Steroid-Sparing and Second-Line Immunosuppression

Agent	Dosing	Key Points
Methotrexate	7.5 mg once weekly; increase by 2.5 mg/week every 2–3 weeks, max 25 mg weekly	Oral folic acid 1 mg daily mandatory. Often avoided if ILD present/at risk (e.g., antisynthetase syndrome)
Azathioprine	Start 50 mg daily, increase weekly by 50 mg to target 2–3 mg/kg/day	Onset slow — response may be delayed 4–8 months. TPMT testing mandatory before initiation
Mycophenolate Mofetil	Start 1 g daily, titrate to 3 g daily (divided BID)	CBC required for leukopenia; lacks the hepatotoxicity of azathioprine/methotrexate

III. Advanced Therapies for Refractory Cases

A. IV Immunoglobulin (IVIg)

- **Indications:** first-line for Dermatomyositis; first-line or add-on for HMGCR-positive IMNM; add-on for other refractory myositides.
- **Dosing Protocol:** 2 g/kg total dose (calculated by ideal body weight), divided over 2–5 days.
- **Maintenance:** monthly infusions for at least 3 months before considering taper in dose or frequency.

B. Rituximab (B-Cell Depletor)

- **Indications:** refractory IMNM, antisynthetase syndrome, or cases with ILD.

Regimen	Schedule
Cycle 1	750 mg/m ² (up to 1 g) IV, repeated 14 days later

Regimen	Schedule
Alternative Cycle	375 mg/m ² weekly for 4 weeks
Retreatment	Repeated every 6–18 months based on clinical response

IV. IBM Management Compass

⚠ WARNING

IBM is characteristically **NONRESPONSIVE** to standard immunosuppressive or immunomodulatory agents. Corticosteroids and other immunosuppressants may even be associated with **WORSE** clinical outcomes in IBM.

Dysphagia Management and Safety

- **Swallowing Assessment:** regular safety tracking via structured questionnaires such as the ten-item Eating Assessment Tool (EAT-10).
- **Obstructive Components:** for a prominent cricopharyngeal bar, treatment options include dilation or cricopharyngeal myotomy.
- **Swallowing Support:** referral to a speech pathologist to manage oropharyngeal weakness and prevent aspiration pneumonia.
- **Respiratory Surveillance:** typically occurs at advanced stages, or earlier with severe craniobulbar involvement — requires overnight oximetry and pulmonary function tests.

CHAPTER IX — MUSCULAR DYSTROPHIES

I. Dystrophinopathies: DMD and BMD

A. Genetic Basis and Molecular Pathology

- **Genetic Locus:** pathogenic variants in the DMD gene on chromosome Xp21 (79 exons), encoding the protein dystrophin.

The Reading-Frame Rule

Disease	Mutation Type	Molecular Consequence
Duchenne MD (DMD)	Out-of-frame (frameshift) mutations	Unstable mRNA transcript; total or near-total absence of dystrophin (>95% reduction)
Becker MD (BMD)	In-frame mutations	Truncated, partially functional dystrophin in reduced amounts
 IMPORTANT NOTE		

Disease	Mutation Type	Molecular Consequence
Exceptions: roughly 10% of cases do not obey the reading-frame rule — e.g., nonsense mutations bypassed by spontaneous exon skipping, or in-frame deletions in crucial binding domains that behave like DMD. Large deletions/duplications account for ~75% of cases; the remaining 25% are point mutations and splicing variants.		

B. Clinical Markers and Phenotypes

- **Classic Signs:** motor delay (walking after 18 months), neck flexion weakness, Gowers sign.
- **Physical Features:** calf pseudohypertrophy and progressive proximal/axial weakness.
- **Laboratory:** CK markedly elevated, typically >1000 U/L, often reaching tens of thousands.
- **Multi-system Involvement:** dilated cardiomyopathy and respiratory failure are major causes of mortality. Neurodevelopmental disorders (autism spectrum disorder, ADHD) are significantly more prevalent.

C. Advanced Therapeutics

Corticosteroid Regimens

Agent	Dosing	Notes
Prednisone/Prednisolone	0.75 mg/kg/day	Standard dose
Deflazacort	0.9 mg/kg/day	Less weight gain, higher risk of asymptomatic cataracts
Vamorolone	6 mg/kg/day	Dissociative steroid analog for patients ≥2 years old; reduces bone-related side effects

Exon-Skipping Therapies (weekly IV infusions)

Drug	Exon Skipped	Eligible Patients
Eteplirsen	Exon 51	~13% of DMD patients
Golodirsen / Viltolarsen	Exon 53	~10% of DMD patients
Casimersen	Exon 45	~8% of DMD patients

- **Histone Deacetylase Inhibitors:** givinostat is approved for DMD patients ≥6 years old to reduce fibrosis and increase muscle tissue.
- **Gene Therapy:** delandistrogene moxeparvovec (AAVrh74 vector, MHCK7 promoter) is approved for ambulatory boys ≥4 years old.

⚠ WARNING

Absolute contraindication for delandistrogene moxeparvovec: deletions in exons 8 and/or 9 (risk of immune-mediated myositis).

Safety hold: dosing in nonambulatory patients was paused in 2025 following reports of fatal acute liver failure.

II. Other Muscular Dystrophies: LGMD, FSHD, and OPMD

A. Limb-Girdle Muscular Dystrophy (LGMD)

Reclassified into LGMD-D (Dominant) and LGMD-R (Recessive), followed by a number indicating order of gene discovery.

Subtype	Gene/Mechanism	Distinguishing Feature
LGMD-R3 to R6 (Sarcoglycanopathies)	α , β , γ , δ sarcoglycans	Often mimic the severe DMD phenotype
LGMD-R1 (Calpainopathy)	Calpain-3	Most common subtype in the US; scapular winging, hip/knee flexor weakness
LGMD-R2 (Dysferlinopathy)	Dysferlin	Prominent calf atrophy, difficulty toe walking
LGMD-R12 (Anoctaminopathy-5)	Anoctamin-5	Marked asymmetric atrophy of biceps and quadriceps
LGMD-D5 / R22 (Collagen VI-related)	Collagen VI	Muscle MRI: characteristic 'outside-in' fatty replacement pattern

B. Facioscapulohumeral Dystrophy (FSHD)

- **Genetic Basis:** derepression of the DUX4 gene on chromosome 4q35, toxic to skeletal muscle.

Type	Frequency	Mechanism
FSHD1	95%	Contraction of D4Z4 repeat array to 1–10 units on a permissive 4qA haplotype
FSHD2	5%	Digenic inheritance involving chromatin modifiers (SMCHD1, DNMT3B, or LRIF1)

- **Clinical Features:** asymmetric weakness of facial, scapular stabilizer, and upper arm muscles ('Popeye arms').
- **Physical Signs:** poly-hill sign (scapular displacement), Beevor sign (upward umbilicus movement on neck flexion), horizontal axillary folds.

📌 IMPORTANT NOTE

Screening: baseline PFTs for all patients. Those with large contractions (1–3 repeats) require audiology (high-frequency hearing loss) and ophthalmology screening (retinal vascular disease/Coats syndrome).

C. Oculopharyngeal Muscular Dystrophy (OPMD)

- **Genetics:** (GCG) repeat expansion in the PABPN1 gene.
- **Clinical Phenotype:** progressive ptosis and dysphagia starting in the fifth or sixth decade.

III. Myotonic Dystrophies: DM1 and DM2

A. Myotonic Dystrophy Type 1 (DM1 — Steinert Disease)

Genetic basis: CTG repeat expansion in DMPK (19q13.32).

Category	Repeat Number	Phenotype
Normal	<35 repeats	—
Premutation	35–49 repeats	Asymptomatic but risk for offspring
Late-onset	50–100 repeats	Mild, late presentation
Classic Adult	100–1000 repeats	Typical adult DM1
Congenital	>1000 repeats	Severe neonatal presentation

- **Clinical Features:** distal predominant weakness, facial wasting, ptosis, frontal balding, executive dysfunction.
- **Systemic Involvement:** 'Christmas tree' cataracts, cardiac conduction blocks (PR/QRS prolongation), central sleep apnea.

B. Myotonic Dystrophy Type 2 (DM2)

- **Genetics:** CCTG tetranucleotide expansion in CNBP (3q21.3); diagnosis requires >75 repeats.
- **Clinical Features:** proximal predominant weakness (hip and neck flexors) and prominent muscle pain/stiffness, often misdiagnosed as fibromyalgia.
- **Asymmetry:** unlike DM1, weakness can be notably asymmetric.

MEMORY TIP / MNEMONIC

DM1 vs. DM2 — 'PROXimal 2, DISTal 1':

- DM1 → DISTal weakness predominant
- DM2 → PROXimal weakness predominant (hip/neck flexors)

C. Clinical Myotonia Management

Parameter	Detail
First-line	Mexiletine
Starting Dose	150 mg 2×/day, titrated up to 200–300 mg 3×/day

Parameter	Detail
Safety Monitoring	ECG mandatory at baseline, 1 month, and annually to screen for arrhythmias. Monitor LFTs
Symptomatic Support	Modafinil for excessive daytime sleepiness

D. Multi-system Screening Protocols (DM1 and DM2)

System	Screening
Cardiovascular	Annual 12-lead ECG (or 24-hour Holter) for all patients
Respiratory	PFTs and overnight oximetry to detect nocturnal hypoventilation/sleep apnea
Endocrine	Baseline and repeat screening (every 3 years) for diabetes (HbA1c), thyroid dysfunction, hyperlipidemia
Neoplastic	Increased malignancy risk (thyroid, skin, sex organs); age-appropriate cancer screening essential
Anesthesia	High risk of delayed awakening and respiratory failure; formal anesthesia management plan required

CHAPTER X — METABOLIC, MITOCHONDRIAL, AND CONGENITAL MYOPATHIES

I. Metabolic Myopathies

A. Glycogen Storage Diseases (GSD)

Pompe Disease (Acid Maltase Deficiency)

- **Pathophysiology:** variations in the GAA gene leading to deficiency of the lysosomal enzyme acid α -glucosidase.

Phenotype	Presentation
Infantile-onset	Fulminant presentation: severe generalized hypotonia, cardiomyopathy, respiratory failure
Adult-onset	Slowly progressive proximal weakness with early respiratory insufficiency due to diaphragmatic involvement

- **Diagnosis:** screening via acid α -glucosidase activity in a dried blood spot; confirmation via GAA gene testing.
- **Electrodiagnosis:** may show myotonic discharges (electrical myotonia) in the absence of clinical myotonia, especially in the paraspinal muscles.
- **Therapeutics:** FDA-approved Enzyme Replacement Therapy (ERT) — alglucosidase alfa and avalglucosidase alfa.

McArdle Disease (GSD Type V)

- **Pathophysiology:** deficiency of the enzyme myophosphorylase (encoded by PYGM).
- **Clinical Hallmark:** exercise-induced muscle cramps and myalgia, often at the start of activity.

CLINICAL PEARL

Second-Wind Phenomenon: a pathognomonic feature of McArdle disease where exercise becomes easier after ~10 minutes of moderate activity, as bloodborne substrates (glucose and free fatty acids) become available for aerobic metabolism.

- **Risks:** high risk of exertional rhabdomyolysis and 'cola'-colored urine (myoglobinuria).
- **Diagnosis:** forearm exercise testing shows a rise in ammonia WITHOUT a corresponding rise in lactate.

B. Lipid Storage Myopathies and Others

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

- **Genetics:** autosomal recessive variants in ETFDH, ETFA, or ETFB.
- **Clinical Presentation:** subacute progressive proximal weakness, severe dysphagia, respiratory insufficiency.
- **Diagnosis:** elevation of short-, medium-, and long-chain acylcarnitines in plasma and increased organic acids in urine. Muscle biopsy shows lipid-filled nonrimmed vacuoles (Oil Red O positive).

★ HIGH YIELD — EXAM TIP

MADD is highly responsive to riboflavin (Vitamin B2) and coenzyme Q10 supplementation — one of the few treatable metabolic myopathies.

- **CPT II Deficiency:** a common cause of inherited recurrent rhabdomyolysis triggered by prolonged exercise, fasting, or infection.

II. Mitochondrial Myopathies

- **Diagnostic Hallmarks:** persistent or intermittent elevated blood lactate (though normal levels do not exclude it). Serum GDF-15 and FGF21 serve as screening biomarkers for mitochondrial translation and mtDNA maintenance disorders.
- **Pathology:** muscle biopsy features ragged red fibers (Gomori trichrome), ragged blue fibers (SDH), and COX-negative fibers.

Clinical Phenotypes

Syndrome	Key Features
CPEO	Slowly progressive, often asymmetric ptosis and ophthalmoparesis; frequently caused by single mtDNA deletions

Syndrome	Key Features
Kearns-Sayre Syndrome (KSS)	CPEO onset before age 20 + pigmentary retinopathy + cardiac conduction blocks (often requiring urgent pacemaker placement)
MELAS	May manifest with early respiratory insufficiency and stroke-like episodes
📌 IMPORTANT NOTE Due to heteroplasmy, mitochondrial DNA testing is most reliable when performed directly on muscle tissue	

III. Congenital Myopathies

Disease	Genetics	Key Features
Central Core Disease	RYR1 mutations (most common)	Hypotonia and proximal weakness from infancy; high arched palate; thin face
Nemaline Myopathy	NEB, ACTA1, MYH2	Nemaline rods (rod-like inclusions) on modified Gomori trichrome stain
Centronuclear / Myotubular Myopathy	X-linked: MTM1 (myotubularin); Autosomal: DNM2, BIN1, TTN	Abundance of internally/centrally located nuclei on biopsy
📌 EMERGENCY Malignant Hyperthermia (MH) Protocol: RYR1 variants confer high susceptibility to MH triggered by volatile anesthetics or succinylcholine. Patients and surgical teams must be alerted to this risk before any general anesthesia.		

CHAPTER XI — SKELETAL MUSCLE CHANNELOPATHIES

A. Periodic Paralysis (Autosomal Dominant)

General management: avoidance of triggers is primary. Acute therapy for all forms includes mild exercise at the onset of an attack.

Hypokalemic Periodic Paralysis (HypoPP)

Parameter	Detail
Genetics	CACNA1S (Type 1) or SCN4A (Type 2)
Clinical Triggers	High-carbohydrate meals, salt, and rest after exercise

Parameter	Detail
Acute Treatment	Oral potassium 0.2–0.4 mEq/kg every 30 minutes, max 200–250 mEq/day

Hyperkalemic Periodic Paralysis (HyperPP)

Parameter	Detail
Genetics	SCN4A
Clinical Triggers	Potassium-rich foods (bananas, potatoes), fasting, cold. Paramyotonia (paradoxical myotonia) often coexists
Acute Treatment	Oral carbohydrates (up to 2 g/kg) or inhaled β -agonists (e.g., salbutamol)

Andersen-Tawil Syndrome (ATS)

- **Genetics:** KCNJ2 gene variations (inward rectifier potassium channel Kir2.1).

CLINICAL PEARL

Clinical Triad: periodic paralysis + cardiac arrhythmias (Long QT, enlarged U-waves) + dysmorphic features (low-set ears, micrognathia, clinodactyly).

WARNING

Holter monitoring is mandatory in ATS, as standard ECGs may be normal despite significant arrhythmia risk.

Chronic Preventative Dosing — Carbonic Anhydrase Inhibitors

Drug	Dosing
Acetazolamide	125 mg to 1000 mg daily, divided into two doses. Avoid in ATP1A2 variants — may worsen symptoms
Dichlorphenamide	50 mg to 200 mg daily, divided into two doses

B. Myotonia Congenita

- **Pathophysiology:** CLCN1 mutations affecting chloride channels.

Subtype	Inheritance	Severity
Thomsen Disease	Autosomal dominant	Milder
Becker Disease	Autosomal recessive	More severe, with proximal weakness

- **Clinical Features:** warm-up phenomenon (stiffness improves with repetition) and 'athletic' muscle hypertrophy.

Therapeutic Dosing

Parameter	Detail
Mexiletine (First-line)	Start 150 mg 2×/day; titrate to 200–300 mg 3×/day
Safety	Mandatory ECG at baseline, 1 month, and annually to monitor for arrhythmias

CHAPTER XII — TOXIC, ENDOCRINE, AND CRITICAL ILLNESS MYOPATHIES

I. Toxic Myopathies

A. Statin-Induced Toxic Myopathy

Feature	Self-Limiting Myotoxicity	Immune-Mediated (HMGR Myositis)
CK / Course	Elevated CK; resolves or decreases significantly within 2 weeks of stopping the statin	Persistent or increasing weakness and CK elevation (often >10,000 U/L) despite statin cessation
Diagnosis	Clinical resolution after cessation	Confirmed by HMGR antibodies
Management	Physical therapy only	Highly responsive to IVIg, often as monotherapy at 2 g/kg/month

CLINICAL PEARL

Diagnostic monitoring pearl: use the CK lifetime (~36 hours) to differentiate etiologies. A CK of 12,000 U/L that declines at the expected rate after stopping the drug favors toxic rhabdomyolysis over an active immune-mediated process.

B. Corticosteroid-Induced Myopathy

Differentiation from active myositis:

Test	Active Myositis	Steroid Myopathy
Muscle MRI	STIR hyperintensity (muscle edema/inflammation)	Absent
Needle EMG	Abnormal spontaneous activity (fibrillations/positive sharp waves)	Normal EMG

IMPORTANT NOTE

Steroid myopathy is characterized by selective Type II muscle fiber atrophy; serum CK is usually normal.

C. Hydroxychloroquine, Colchicine, and Alcohol

- **Hydroxychloroquine/Colchicine:** these acquired diseases frequently require a muscle biopsy for definitive diagnosis. Hydroxychloroquine-induced myopathy can manifest as severe dysphagia. Both can produce myotonic discharges (electrical myotonia) on needle EMG.
- **Alcohol:** a common acquired cause of acute necrotizing rhabdomyolysis.

II. Endocrine Myopathies

A. Hypothyroid Myopathy

- **Clinical Presentation:** muscle mounding (myoedema) and rippling on percussion. 'Hoffmann Syndrome' refers to this presentation when accompanied by muscle pseudohypertrophy.
- **Electrodiagnosis:** commonly associated with myotonic discharges on needle EMG, even in the absence of clinical myotonia.

★ HIGH YIELD — EXAM TIP

TSH screening is mandatory in the workup of any unexplained myopathy or episodic weakness.

B. Hyperthyroid Myopathy

Hyperthyroidism must be ruled out in cases of episodic weakness, as it is a known cause of periodic paralysis.

III. Critical Illness Myopathy (CIM)

A. Pathophysiology and Risk Factors

- **Patient Profile:** typically occurs in patients recently hospitalized in an ICU.
- **Triggers:** primary risk factors are administration of high-dose corticosteroids or paralytic (neuromuscular blocking) drugs during the ICU stay.

📌 IMPORTANT NOTE

Also known as 'acute quadriplegic myopathy,' involving thick filament/myosin loss.

B. Electrodiagnostic Strategies

- **Needle EMG:** a hallmark feature is the presence of electrical myotonia (myotonic discharges).

Differentiation from Critical Illness Polyneuropathy (CIP)

Feature	CIM	CIP
Sensory Fibers	Preserved sensory nerve action potentials (SNAPs)	Sensorimotor process with reduced SNAPs

Feature	CIM	CIP
Muscle Excitability	Inexcitable muscle membranes on direct muscle stimulation	Neurogenic failure pattern
MUAP Morphology	Short-duration, low-amplitude, polyphasic MUAPs with rapid recruitment	Neurogenic MUAP changes

DIAGNOSTIC ALGORITHM: UNPROVOKED RHABDOMYOLYSIS

10. **Exclude Acquired Causes:** screen for statins, alcohol, trauma, and infection.
11. **Evaluate CK Trend:** monitor decline against a 36-hour half-life.
12. **Metabolic/Mitochondrial Screening:** if history suggests multisystem disease or unprovoked episodes, check lactate, GDF-15, and FGF-21.
13. **Genetic Testing:** proceed to next-generation sequencing (NGS) for metabolic myopathies, channelopathies, and muscular dystrophies if interictal CK remains elevated.

★ HIGH YIELD — EXAM TIP

Rhabdomyolysis work-up flow, in one line:

Acquired causes ruled out → CK kinetics tracked → metabolic/mitochondrial markers checked → NGS panel if still unexplained.

Autonomic Disorders

Chapter 1. Anatomical and Physiological Foundations

This chapter details the anatomy, physiology, and central control mechanisms of the autonomic nervous system (ANS), forming the essential foundation for interpreting autonomic testing and disease patterns discussed in later chapters.

1.1 The Central Autonomic Network (CAN)

The CAN consists of interconnected forebrain and brainstem regions that modulate preganglionic autonomic activity to maintain homeostasis. Damage to any node of this network can produce distinct autonomic phenotypes.

Key Components of the Central Autonomic Network

Structure	Subregion	Function
Insular Cortex	Posterior insula	Primary viscerosensory (interoceptive) cortex; represents bodily sensations
Insular Cortex	Anterior insula	Integrates visceral input with emotional/cognitive signals for conscious bodily awareness
Anterior & Midcingulate Cortex	"Salience network"	Generates autonomic responses to behaviorally relevant stimuli; correlates with sympathetic muscle activity
Amygdala	Central nucleus	Initiates autonomic, neuroendocrine, and motor responses to emotionally salient stimuli (e.g., fear)
Hypothalamus	Paraventricular nucleus	Triggers responses to internal stressors (pain, hypoglycemia, hypovolemia)
Hypothalamus	Dorsomedial nucleus	Mediates responses to social stress and cold
Hypothalamus	Perifornical area	Contains orexin neurons for behavioral arousal
Nucleus Tractus Solitarius (NTS)	Medulla	First relay station for visceral afferents; triggers cardiovascular, respiratory, and GI medullary reflexes
Rostral Ventrolateral Medulla (RVLM)	Medulla	Premotor sympathoexcitatory neurons; critical for the baroreflex

Structure	Subregion	Function
Caudal Ventrolateral Medulla (CVLM)	Medulla	Mediates the sympathoinhibitory limb of the baroreflex

🔍 MNEMONIC / MEMORY TIP

"Hypothalamus = the pattern generator." Remember it as a three-part homeostatic dispatcher: PVN → internal stress, DMN → social stress/cold, Perifornical → arousal (orexin).

1.2 Peripheral Autonomic Outflow and Neurotransmission

All preganglionic neurons are myelinated and release acetylcholine (ACh) acting on nicotinic receptors ($\alpha 3/\beta 4$ subtype) at the ganglion.

Sympathetic System

- Preganglionic neurons reside in the intermediolateral (IML) column of the spinal cord, spanning T1–L2.
- Axons terminate in paravertebral (sympathetic chain) or prevertebral ganglia.
- Postganglionic neurotransmitter: primarily norepinephrine (NE).
- Major exception: sudomotor (sweat gland) postganglionic neurons are cholinergic, despite being part of the sympathetic system.

Parasympathetic System

- Preganglionic neurons originate in the brainstem (cranial nerves III, VII, IX, and X) or the sacral spinal segments (S2–S4).
- CN III (Oculomotor): synapses in the ciliary ganglion, controlling pupillary constriction and accommodation.
- CN X (Vagus): innervates thoracic and abdominal viscera; critical for beat-to-beat heart rate control.
- Sacral outflow (S2–S4): controls micturition, defecation, and erectile function.

★ HIGH YIELD — EXAM TIP

Sudomotor neurons are the classic exam trap: anatomically sympathetic, but pharmacologically cholinergic (using ACh on M3 receptors at the sweat gland), not adrenergic.

Autonomic Receptor Subtypes and Functional Impact

Receptor	Primary Locations	Functional Impact
α_1	Blood vessels, iris dilator, bladder neck	Vasoconstriction, mydriasis, bladder storage
α_2	Presynaptic terminals	Inhibition of NE or ACh release (autoreceptor)
β_1	Heart (sinus node, myocardium)	Increased heart rate (chronotropy) and contractility (inotropy)
β_2	Bronchi, skeletal muscle vessels, bladder	Bronchodilation, vasodilation, detrusor relaxation
β_3	Bladder detrusor	Detrusor relaxation (urine storage)
M2	Heart (sinus node, AV node)	Decreased heart rate and AV conduction (inhibitory)
M3	Sweat glands, pupils, bladder detrusor	Sweating, miosis, detrusor contraction (voiding)

1.3 Cardiovascular Autonomic Testing Protocols

Heart Rate Variability to Deep Breathing (HRV-DB)

HRV-DB is the most reliable index of cardiovagal (parasympathetic) integrity.

- Protocol: patient supine and relaxed, performing deep inspiration/expiration at a frequency of 6 breaths/min.
- Metric: mean of the differences between maximum and minimum heart rate (respiratory sinus arrhythmia).
- Reference standards: magnitude declines significantly with advancing age. Subnormal responses for age indicate cardiovagal failure.

Valsalva Maneuver Mechanics

The Valsalva maneuver assesses baroreflex-sympathoneural (noradrenergic) function via beat-to-beat finger plethysmography.

- Protocol: exhalation against resistance (30–40 mm Hg) for 15 seconds.
- Valsalva Ratio: maximum heart rate divided by the lowest heart rate within 30 seconds of peak heart rate.

Valsalva Phases — Normal vs. Adrenergic Failure

Phase	Mechanical/Physiological Event	Normal Phenotype	Adrenergic Failure Phenotype
I	Onset of straining	Brief mechanical rise in BP	Preserved (mechanical)

Phase	Mechanical/Physiological Event	Normal Phenotype	Adrenergic Failure Phenotype
II (Early)	Reduced cardiac filling	Decline in stroke volume and BP	Exaggerated/prolonged BP fall
II (Late)	Baroreflex activation	BP recovers toward baseline; HR rises	Absence of BP recovery
III	Release of strain	Brief mechanical fall in BP	Preserved (mechanical)
IV	Venous return/vasoconstriction	BP overshoot above baseline; bradycardia	Absent/delayed overshoot; slow BP recovery

CLINICAL PEARL

The absence of a Phase IV BP overshoot, combined with failure of BP recovery in late Phase II, is the hallmark signature of neurogenic (adrenergic) autonomic failure on Valsalva testing.

Head-Up Tilt Table (HUTT) Testing

HUTT assesses autonomic responses to orthostatic stress independently of skeletal muscle activation (unlike active standing).

- Patient preparation: supine rest for at least 2–5 minutes to obtain baseline measurements.
- Monitoring: continuous non-invasive beat-to-beat BP and HR tracking.
- Tilt parameters:
 - Angle: 60–70 degrees
 - Duration: 30–45 minutes for unexplained syncope workup
 - Duration: 5 minutes to diagnose neurogenic orthostatic hypotension (nOH)
- Pharmacological provocation (e.g., sublingual nitroglycerin or IV isoproterenol) may be used to increase sensitivity in syncope workups, though this reduces specificity.

Chapter 2. Sudomotor and Thermoregulatory Testing

Sweating is exclusively under sympathetic cholinergic control, making sudomotor testing uniquely valuable for localizing lesions along the sympathetic pathway.

2.1 Quantitative Sudomotor Axon Reflex Test (QSART)

QSART evaluates the postganglionic sympathetic cholinergic sudomotor axon.

- Mechanism: iontophoresis of acetylcholine activates an axon reflex; impulses travel antidromically to a branch point, then orthodromically to adjacent eccrine glands.
- Capsule locations: standardized at four sites — forearm, proximal leg, distal leg, and foot.
- Abnormalities: reduced or absent sweat volumes indicate postganglionic sudomotor failure or small fiber neuropathy.

2.2 Thermoregulatory Sweat Test (TST)

TST evaluates the entire thermoregulatory pathway, from the hypothalamus to the eccrine gland — making it complementary to QSART for localization.

- Mechanism: an indicator dye (e.g., alizarin red) is applied to the skin; it changes color from yellow to purple when wet.
- Heating protocol: the patient's body is heated in a controlled chamber (elevated temperature/humidity) until core temperature rises by approximately 1°C.

Distribution Patterns and Localization

Test Result Combination	Localization	Typical Disease Association
Abnormal TST + Normal QSART	Preganglionic / Central	Multiple System Atrophy (MSA)
Abnormal TST + Abnormal QSART	Postganglionic / Peripheral	Parkinson Disease (PD), Pure Autonomic Failure (PAF)
Distal Anhidrosis	Length-dependent	Diabetic Neuropathy, Small Fiber Neuropathy
Global Anhidrosis	Widespread / Central	Multiple System Atrophy (MSA)

Summary of QSART Abnormality Patterns

Phenotype	Pattern	Diagnostic Significance
Length-dependent	Reduced volumes at foot/distal leg	Typical of diabetic/amyloid polyneuropathy

Phenotype	Pattern	Diagnostic Significance
Patchy / Non-segmental	Asymmetric reduction	Suggests immune-mediated ganglionopathy (AAG)
Global anhidrosis	Absent volumes at all 4 sites	Severe pandysautonomia (AAG or advanced PAF)
Preserved volumes	Normal output despite anhidrosis on TST	Localizes lesion to central/preganglionic pathways (MSA)

CLINICAL PEARL

The single most important localizing concept in this chapter: QSART tests the postganglionic sudomotor axon only, while TST tests the entire pathway from hypothalamus to gland. A lesion that is preganglionic (as in MSA) spares the QSART response but impairs the TST — this TST/QSART dissociation is a classic board question.

MNEMONIC / MEMORY TIP

"Q for Quiet nerve ending" — QSART only sees the last (postganglionic) leg of the journey. TST sees the whole road, from hypothalamus to gland.

Chapter 3. Orthostatic Intolerance Syndromes, Syncope Phenotypes, and Peripheral Autonomic Neuropathies

3.1 Neurogenic Orthostatic Hypotension (nOH)

nOH is a physical sign defined by a failure of the autonomic nervous system to adequately increase peripheral vascular resistance upon standing, due to deficient norepinephrine release.

Diagnostic Criteria

Criterion	Definition
Standard diagnostic threshold	A sustained reduction in systolic BP (SBP) ≥ 20 mmHg or diastolic BP (DBP) ≥ 10 mmHg within 3 minutes of standing or head-up tilt
"Gold standard" bedside ratio	$\Delta HR / \Delta SBP$ ratio < 0.5 bpm/mmHg is highly specific for nOH, distinguishing it from non-neurogenic OH (e.g., dehydration)
Neurogenic Supine Hypertension (nSH)	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg after 5 minutes of supine rest

⚠ WARNING

Neurogenic supine hypertension (nSH) affects approximately 50% of nOH patients and significantly complicates treatment, since pressor agents used for nOH (e.g., midodrine, droxidopa) often worsen nSH. Always screen for and manage nSH before escalating pressor therapy.

3.2 Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is a heterogeneous syndrome characterized by symptoms of orthostatic intolerance associated with an excessive heart rate increase in the absence of orthostatic hypotension.

Diagnostic Criteria by Age

Parameter	Adult Criteria (Age ≥ 20)	Adolescent Criteria (Age 12–19)
HR increment	≥ 30 beats/min within 10 min of standing/tilt	≥ 40 beats/min within 10 min of standing/tilt
Hemodynamics	No drop in BP > 20/10 mmHg	No drop in BP > 20/10 mmHg
Standing HR	Often ≥ 120 beats/min	Often ≥ 120 beats/min

POTS Pathophysiologic Phenotypes

Phenotype	Key Features
Neuropathic POTS	Limited autonomic (small-fiber) neuropathy in the lower limbs, causing venous pooling
Hyperadrenergic POTS	Standing plasma norepinephrine often > 600 pg/mL (primary hyperadrenergic POTS may exceed 1000–2000 pg/mL)
Hypovolemic POTS	Low plasma and total blood volume, with low renin/aldosterone activity

★ HIGH YIELD — EXAM TIP

A standing plasma norepinephrine > 600 pg/mL is the key laboratory cut-off for hyperadrenergic POTS — a frequently tested number.

3.3 Neurally Mediated Syncope (NMS) and Baroreflex Disorders

NMS involves a transient loss of consciousness due to global cerebral hypoperfusion triggered by reflex dysfunction.

Vasovagal Syncope (VVS) — the most common NMS

- Prodromal phase: usually < 1 minute; involves pallor, diaphoresis, and nausea.
- Two hemodynamic subtypes:
 - Cardioinhibitory type — bradycardia < 40 bpm or asystole > 3 seconds
 - Vasodepressor type — abrupt fall in BP without a significant fall in HR

Carotid Sinus Hypersensitivity (CSH)

Triggered by mechanical stimulation of the neck. Diagnosis requires asystole > 3 seconds or a fall in SBP > 50 mmHg during carotid sinus massage.

Baroreflex Failure

Characterized by volatile BP — episodic hypertensive crises alternating with hypotension — often resulting from neck surgery or radiation therapy affecting the carotid baroreceptors.

3.4 Comprehensive Pharmacotherapy for Orthostatic Hypotension

Pharmacologic intervention is considered only after non-pharmacologic strategies (water bolus, increased salt intake, compression garments) have been implemented.

Drug	Starting Dose	Maintenance/Ma x Dose	Titration/Monitoring	Key Notes
Fludrocortisone	0.05 mg daily	0.1–0.2 mg daily	Monitor for hypokalemia, edema, and fluid retention	No added benefit > 0.2 mg/day
Midodrine	2.5 mg TID	10–15 mg TID	Avoid dosing within 4 hours of bedtime to prevent supine hypertension	Direct α_1 agonist
Droxidopa	100 mg TID	600 mg TID	Supervised titration is recommended	Norepinephrine precursor; decarboxylated by AADC
Pyridostigmine	30 mg TID	60 mg TID	Monitor for abdominal cramps/diarrhea	Enhances ganglionic ACh transmission; works best combined with midodrine

? MNEMONIC / MEMORY TIP

For pressor drugs, remember "FMDP": Fludrocortisone (volume expander), Midodrine (α_1 agonist), Droxidopa (NE precursor), Pyridostigmine (ganglionic booster) — a stepwise ladder from volume to neurotransmission.

3.5 Peripheral Autonomic Neuropathies

Autonomic fibers (small, unmyelinated C-fibers) are often the target of immune, metabolic, or protein-misfolding disorders.

Diabetic Autonomic Neuropathy

Affects up to 70% of long-term diabetics.

- Clinical signs: resting tachycardia, orthostatic hypotension, gastroparesis, and gustatory sweating.
- Treatment-induced neuropathy of diabetes (TIND): acute pain and autonomic failure following a rapid drop in HbA1c.

Amyloid Neuropathy

Characterized by "apple-green birefringence" on Congo red staining under polarized light.

Subtype	Key Feature
AL Amyloid	Associated with monoclonal plasma cell disorders
ATTR (Hereditary)	Val30Met is the most common mutation; genetic testing is definitive

Autoimmune Autonomic Ganglionopathy (AAG)

- Antibody target: ganglionic α_3 -nicotinic acetylcholine receptor antibodies.
- High-yield cut-off: antibody levels > 1.0 nmol/L are highly specific for AAG.
- Clinical triad: subacute onset of severe pan-autonomic failure, sicca symptoms, and tonic pupils.

Acute Panautonomic Neuropathy

A rare form of Guillain-Barré syndrome variant, presenting with acute sympathetic and parasympathetic failure.

? CLINICAL PEARL

Think of AAG as the "autonomic myasthenia gravis" — it targets nicotinic ACh receptors, but at the autonomic ganglion rather than the neuromuscular junction, producing pan-autonomic failure rather than muscle weakness.

Chapter 4. Central Autonomic Degenerative States, Synucleinopathies, and Focal Syndromes

4.1 Autonomic Failure in Synucleinopathies

The synucleinopathies are neurodegenerative disorders characterized by abnormal accumulation of misfolded α -synuclein. A critical diagnostic pivot is distinguishing central/preganglionic failure (Multiple System Atrophy) from peripheral/postganglionic failure (Parkinson Disease, Dementia with Lewy Bodies, Pure Autonomic Failure).

Multiple System Atrophy (MSA)

MSA is characterized by glial cytoplasmic inclusions (GCIs) — aggregated α -synuclein within oligodendrocytes.

Phenotype	Predominant Feature
MSA-P	Predominant parkinsonism: bradykinesia, rigidity, postural instability
MSA-C	Predominant cerebellar ataxia: wide-based gait, dysarthria, oculomotor dysfunction

Neuroimaging Indicators

Sign	Description	Association
Putaminal Rim Sign	T2-hyperintense border of the lateral putamen	Common in MSA-P
Hot Cross Bun Sign	Cruciform T2-hyperintensity in the pons	Classic in MSA-C
Atrophy	Pons, cerebellum, or middle cerebellar peduncles	Both subtypes

Synucleinopathy Differentiation Matrix

Feature	Multiple System Atrophy (MSA)	Parkinson Disease (PD) / DLB
Primary pathology	Central (preganglionic)	Peripheral (postganglionic)
Pathological marker	Glial cytoplasmic inclusions	Lewy bodies / Lewy neurites
Cardiac ¹²³ I-MIBG scintigraphy	Normal sympathetic innervation	Decreased heart/mediastinum (H/M) ratio (denervation)
Plasma norepinephrine	Normal or high (decentralization)	Low (denervation)
Sweat pattern (TST)	Global/regional anhidrosis	Distal/length-dependent anhidrosis
QSART volumes	Preserved (intact postganglionic fiber)	Reduced (distal fiber loss)

★ HIGH YIELD — EXAM TIP

A normal cardiac ¹²³I-MIBG scan in a parkinsonian patient argues strongly against Parkinson Disease and favors MSA, since MIBG uptake reflects postganglionic sympathetic cardiac innervation, which is preserved in MSA but lost in PD/DLB.

Second Consensus Diagnostic Criteria for MSA

- Probable MSA — requires sporadic, adult-onset disease with autonomic failure (urinary incontinence with erectile dysfunction, OR an orthostatic drop $\geq 30/15$ mmHg) PLUS poorly levodopa-responsive parkinsonism OR a cerebellar syndrome.
- Possible MSA — requires parkinsonism or cerebellar syndrome PLUS at least one autonomic feature (urinary urgency/frequency, or orthostatic hypotension not meeting probable thresholds) PLUS at least one additional feature (e.g., Babinski sign, stridor, or specific MRI atrophy).

4.2 Spinal Cord Autonomic Disruption

Autonomic Dysreflexia (AD)

🚨 EMERGENCY

Autonomic dysreflexia is a medical emergency occurring in patients with spinal cord injuries at or above T6. It requires prompt recognition and treatment to prevent stroke, seizure, or death.

Pathophysiology: noxious stimuli below the level of the lesion (e.g., bladder distension, fecal impaction) trigger a massive, uninhibited sympathetic surge via spinal reflexes disconnected from supraspinal inhibition.

Clinical presentation: severe hypertension, headache, and sweating/flushing above the lesion; cold skin and piloerection below the lesion. The hypertension triggers baroreflex-mediated bradycardia.

Autonomic Dysreflexia — Stepwise Rescue Guide

Step	Intervention	Technical Details
1. Positioning	Upright seating	Minimize intracranial pressure and utilize orthostatic pooling to lower BP
2. Trigger identification	Check bladder/bowel	Catheterize bladder; check for fecal impaction (use lidocaine jelly to avoid further stimulus)
3. Non-pharmacologic	Skin/garment check	Remove tight clothing; check for pressure sores or ingrown toenails
4. Pharmacological	Fast-acting agents	Nitropaste (topical) or sublingual nitrates; nifedipine (short-acting oral)
Avoid	Beta-blockers	Risk of exacerbating compensatory bradycardia into heart block

IMPORTANT NOTE

In spinal shock (the acute phase immediately after spinal cord injury), the clinical priority is the opposite: managing neurogenic hypotension with Trendelenburg positioning and IV fluids. Vasopressors are used only with extreme caution due to denervation supersensitivity.

4.3 Focal Autonomic Syndromes

Sweating Syndromes

Syndrome	Key Features
Ross Syndrome	Triad of segmental anhidrosis, areflexia, and tonic (Adie) pupil. Skin biopsy reveals severely reduced cholinergic innervation of sweat glands.
Harlequin Syndrome	Asymmetric facial flushing and sweating on one side (the "normal" side) induced by heat/stress, while the other side remains pale and dry due to a sympathetic deficit.

Pupillary Syndromes: Pharmacological Testing Algorithms

Syndrome	Localization/Pathophysiology	Diagnostic Agent	Expected Result
Adie's Tonic Pupil	Postganglionic (ciliary ganglion/short ciliary nerves)	Dilute pilocarpine (0.125%)	Supersensitivity: affected pupil constricts briskly; normal pupil does not

Syndrome	Localization/Pathophysiology	Diagnostic Agent	Expected Result
Horner Syndrome	Three-neuron oculosympathetic pathway (hypothalamus to eye)	Apraclonidine (0.5%)	Reversal of anisocoria: affected pupil dilates (α_1 supersensitivity) and ptosis improves
Horner (localizing)	Differentiates pre- vs. postganglionic lesion	Hydroxyamphetamine	Postganglionic (3rd neuron) lesion: affected pupil fails to dilate (NE stores depleted)
Horner (classic)	Confirmatory test	Cocaine (4%)	Confirmation: affected pupil fails to dilate (lack of NE release into synaptic cleft)

🔍 MNEMONIC / MEMORY TIP

Horner testing order: Cocaine confirms Horner (fails to dilate = NE not released); Hydroxyamphetamine localizes it (fails to dilate = postganglionic lesion, since it depends on stored NE release); Apraclonidine reveals denervation supersensitivity and reverses the anisocoria.

4.4 Advanced Biomarkers: Skin Biopsy

A major evidence-based advance is the use of skin biopsy as a diagnostic biomarker for synucleinopathies.

- Phosphorylated α -synuclein is detected in cutaneous autonomic nerve fibers (blood vessels, sweat glands, and pilomotor muscles).
- Sensitivity: positive in > 90% of patients with clinical synucleinopathies and > 50% of those with prodromal REM sleep behavior disorder.
- Localizing value: reduced fiber density in PD/PAF (postganglionic) vs. relatively preserved fiber density in MSA (preganglionic).

Chapter 5. Gastrointestinal, Urogenital, and Sudomotor Autonomic Dysfunction

This chapter addresses clinical management of autonomic dysfunction affecting the gastrointestinal, urogenital, and sudomotor systems, along with secondary autonomic enhancement states that represent neurological emergencies.

5.1 Gastrointestinal Motility Disorders

Autonomic GI dysfunction results from damage to the enteric nervous system (ENS), extrinsic parasympathetic/sympathetic inputs, or visceral afferents.

Gastroparesis and Upper GI Motility

- Definition: symptomatic delayed gastric emptying in the absence of mechanical obstruction.
- Clinical presentation: nausea, postprandial vomiting, bloating, early satiety, and abdominal pain.
- Pathophysiology: impaired gastric accommodation and visceral hypersensitivity. Hyperglycemia (> 140 mg/dL) can acutely slow emptying.
- Diagnostic standard: scintigraphic transit studies are used to confirm delayed emptying.

Chronic Constipation and Lower GI Dysfunction

- Lewy body constipation: severe constipation often precedes motor signs in Parkinson Disease by over 20 years.
- Mechanisms:
 - Slow transit — loss of peristalsis
 - Anorectal dysfunction — weak strain or anismus (paradoxical sphincter contraction during defecation)

WARNING

Severe constipation in autonomic failure can progress to gastrointestinal emergencies: intestinal pseudo-obstruction (paralytic ileus), volvulus, or stercoral ulcers (colonic ulcers caused by pressure from impacted stool). Maintain a low threshold to image the abdomen in severely constipated autonomic-failure patients with new abdominal pain.

GI Pharmacotherapy and Management

Drug Class	Agent	Mechanism/Indication	Notes

α -Glucosidase inhibitor	Acarbose (50–100 mg)	Postprandial hypotension (PPH)	Delays glucose absorption; reduces insulin-mediated vasodilation
Somatostatin analogue	Octreotide (0.2–0.4 μ g/kg)	Refractory PPH	Induces splanchnic vasoconstriction; subcutaneous administration
Prokinetic (serotonergic)	Mosapride, tegaserod	Slow-transit constipation	5-HT ₄ agonists; stimulate the peristaltic reflex
Chloride channel activator	Lubiprostone	Softening agent	Used when bulking agents fail
Acetylcholinesterase inhibitor	Pyridostigmine	Dysmotility/nOH	Enhances ganglionic transmission; improves transit

5.2 Neurogenic Bladder and Sexual Dysfunction

The pattern of bladder dysfunction depends on the site of the neurologic lesion.

Bladder Localization

Lesion Level	Resulting Dysfunction
Suprapontine lesions	Detrusor overactivity (storage failure/incontinence)
Spinal (suprasacral) lesions	Detrusor overactivity PLUS detrusor sphincter dyssynergia (DSD) — high-pressure storage and voiding failure
Sacral/infrasacral lesions	Hypo- or acontractile detrusor (voiding failure/retention)

★ HIGH YIELD — EXAM TIP

Post-void residual (PVR) > 100 mL is considered abnormal and warrants intervention, such as intermittent catheterization, to prevent recurrent urinary tract infections.

Urogenital Pharmacotherapy Profile

Medication Category	Agents & Dosing	Clinical Considerations
Antimuscarinics	Oxybutynin (5–20 mg daily); Solifenacin (5–10 mg daily); Tolterodine (2–4 mg BID)	First-line for urge incontinence. Caution: high anticholinergic burden is linked to cognitive decline and brain atrophy
CNS-sparing anticholinergics	Trospium, Darifenacin	Preferred in elderly/cognitively impaired patients; lower blood-brain barrier penetration

Medication Category	Agents & Dosing	Clinical Considerations
β3-adrenergic agonists	Mirabegron (25–50 mg daily)	Relaxes the detrusor; lacks anticholinergic side effects. May mildly increase BP
Antidiuretic analogue	Desmopressin (10 mcg)	Specifically for nocturia; promotes renal fluid reabsorption. Monitor for hyponatremia
Intradetrusor injection	OnabotulinumtoxinA (200 units)	Second-line for refractory overactivity. Risk of transient retention (may require catheterization)

Sexual Dysfunction in Autonomic Failure

Erectile dysfunction (ED) affects up to 75% of diabetic men and 79% of men with Parkinson Disease.

EMERGENCY

PDE5 inhibitors (sildenafil, tadalafil) are effective for ED but carry a strict warning: co-administration with nitrates or α1-blockers (e.g., tamsulosin) can cause catastrophic drops in blood pressure due to synergistic vasodilation. Always screen medication lists before prescribing.

5.3 Disorders of Sweating and Temperature Regulation

Anhidrosis and Hypothermia

Condition	Key Features
Primary Generalized Anhidrosis	Heat intolerance, flushing, and risk of heatstroke
Ross Syndrome	Triad of segmental anhidrosis, areflexia, and tonic pupil
Shapiro Syndrome	Rare disorder with episodic hypothermia and hyperhidrosis; associated with agenesis of the corpus callosum

Hyperhidrosis Syndromes and Management

- Primary focal hyperhidrosis: typically involves palms, soles, and axillae; independent of thermoregulation.
- Harlequin Syndrome: striking asymmetric facial flushing/sweating induced by heat/stress; the pale/dry side is the side with the sympathetic deficit.

Management Ladder for Hyperhidrosis

Modality	Details
Topical	Aluminum chloride (6%–25%)
Iontophoresis	Tap water with low-intensity current (15–30 mA)
Botulinum toxin	Intradermal injections; effect lasts approximately 6 months
Surgical	Endoscopic transthoracic sympathectomy (level T2) for refractory palmar hyperhidrosis

5.4 Secondary Autonomic Enhancement States

These states involve potentially life-threatening autonomic instability triggered by medications and represent critical neurological emergencies.

Serotonin Syndrome vs. Neuroleptic Malignant Syndrome (NMS)

Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome (NMS)
Primary triggers	SSRIs, SNRIs, opioids	Dopamine antagonists (haloperidol, chlorpromazine)
Autonomic signs	Heavy sweating, tachycardia, hypertension, diarrhea	Hyperthermia, hyperhidrosis, labile BP, tachycardia
Neuromuscular signs	Confusion, agitation, muscle twitching (myoclonus, hyperreflexia)	Severe muscle rigidity ("lead-pipe"), dystonic posturing

Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome (NMS)
Antidote/rescue	Cyproheptadine (antihistamine with 5-HT antagonism)	Dantrolene (for rigidity); Bromocriptine (dopamine agonist)

🚨 EMERGENCY

For patients with NMS or paroxysmal sympathetic hyperactivity, morphine is the most effective agent to abort acute paroxysms, while gabapentin and propranolol are preferred agents for longer-term prevention.

💡 CLINICAL PEARL

Distinguish the two syndromes by tempo and exam: serotonin syndrome develops rapidly (hours) and produces hyperreflexia/clonus, especially in the lower limbs; NMS develops slowly (days) and produces uniform "lead-pipe" rigidity with hyporeflexia. This distinction guides antidote choice — cyproheptadine vs. dantrolene/bromocriptine.

CSF Dynamics, Hydrocephalus & Intracranial Pressure Disorders

PART I

CSF Physiology, Hydrocephalus & Idiopathic Normal Pressure Hydrocephalus

I. CSF Production & Dynamics

1. Secretion and Anatomy

- **Choroid Plexus:** CSF is produced continuously by the choroid plexus located in the lateral, third, and fourth ventricles. Beyond volume production, it secretes trophic factors (e.g., orthodenticle homeobox 2, OTX2) essential for maintaining perineuronal nets and brain health.
- **Parenchymal Secretion:** CSF is also secreted by the brain parenchyma, though the specific mechanisms are less well defined.
- **Production Rate:** CSF is produced at a rate of approximately 0.3–0.5 mL/min (standard total CSF volume $\approx$ 150 mL, turning over roughly 3–4 times per day).

❗ **IMPORTANT NOTE:** The original source material listed the CSF production rate as 0.3–0.5 mL/h. Standard physiological references cite this rate in mL/min, not mL/h. This has been corrected here to reflect accepted physiological values.

2. Propulsion and Circulation

- **Convection:** Flow is traditionally viewed as convective, moving from the lateral ventricles through the foramen of Monro to the third ventricle, then through the cerebral aqueduct to the fourth ventricle, and finally into the subarachnoid space.
- **Ependymal Motile Cilia:** The ependymal lining of the ventricles features motile cilia that develop during the third trimester and the first six months of life. These cilia propel CSF in a directed manner (e.g., toward the foramen of Monro) and regulate ventricular development.
- **Pulsatility:** CSF flow is significantly influenced by the mechanical pulsations of the heartbeat and respiration.

3. Clearance and Reabsorption Pathways

- **Traditional Pathway:** Reabsorption occurs primarily via arachnoid granulations into the venous sinuses (superior sagittal sinus).
- **The Glymphatic System:** A reconceptualization of CSF clearance in which solutes and waste products enter perivascular channels and are ultimately reabsorbed through lymphatic channels at the skull base. Perivascular astrocytes (via aquaporin-4 channels) regulate this fluid flow.
- **Alternative Routes:** Clearance also occurs via periarterial/perivenular channels and the perineural sheaths of cranial nerves (e.g., olfactory) and spinal nerves.

📌 **CLINICAL PEARL:** The glymphatic system is most active during sleep, particularly slow-wave sleep, providing a physiological link between sleep disruption and impaired clearance of metabolic waste (including amyloid-beta).

4. Compliance and Biomechanics

- **Monro-Kellie Doctrine:** The total volume of the cranium (brain, blood, and CSF) is constant; a decrease in one compartment must be compensated by an increase in another.
- **iNPH Biomechanics:** A postulated increase in brain compliance occurs in parallel with a decrease in inertance (resistance to changes in flow rate). Stiffer arteries (arteriosclerosis) transmit more pulsatile energy to the brain parenchyma, which a system with reduced inertance cannot adequately buffer, leading to chronic tissue injury.

📌 **EXAM / HIGH-YIELD TIP:** The Monro-Kellie doctrine is frequently tested in the context of raised ICP: an expanding mass lesion is initially compensated by displacement of CSF and venous blood before ICP rises sharply (the exhausted-compliance phase of the pressure-volume curve).

II. Hydrocephalus Classification

Hydrocephalus is classified by mechanism of CSF flow disruption, etiological onset, and special morphological variants.

Classification Type	Subtypes & Features
Communicating Obstructive vs.	• Communicating: CSF flows freely through the ventricular system into the subarachnoid space; typically due to reabsorption failure. • Obstructive (Non-communicating): Physical blockage of CSF flow, most commonly at the cerebral aqueduct or the fourth ventricle outlets.
Etiological Onset	• Congenital: Includes aqueductal stenosis, Dandy-Walker malformation, and Chiari malformations. • Acquired (Secondary): Results from intraventricular hemorrhage (IVH), meningitis, trauma, or tumors.
Special Variants	• Hydrocephalus ex vacuo: Enlarged ventricles due to deficient parenchymal development/atrophy; typically associated with normal or small cranial size. • Transient: Temporary impairment (e.g., post-trauma or in preterm infants) that may not require permanent shunting.
Congenital NPH Subtypes	• LOVA (Long-standing Overt Ventriculomegaly in Adults): Marked triventriculomegaly, macrocephaly, and often aqueductal stenosis/web. • PaVM (Panventriculomegaly): Wide foramen of Magendie with a large cisterna magna.

Table 1.1 — Classification schema for hydrocephalus by mechanism, onset, and morphology.

📌 MNEMONIC — Causes of Obstructive Hydrocephalus — "CATS"

- C** Congenital aqueductal stenosis
- A** Arnold-Chiari malformation
- T** Tumors (posterior fossa, pineal region)
- S** Subarachnoid/intraventricular hemorrhage with clot obstruction

III. Idiopathic Normal Pressure Hydrocephalus (iNPH)

1. The Hakim-Adams Triad (Clinical Semiology)

Idiopathic normal pressure hydrocephalus classically presents with the Hakim-Adams triad, though not all components need be present simultaneously, and gait dysfunction typically predominates and appears earliest.

Gait Dysfunction (Cardinal Symptom)

Typically the presenting and most severe domain.

- **Semantics:** "Magnetic" gait — broad-based, with feet externally rotated, shuffling with short steps, and en bloc turning (requiring more than 2 steps for a 180-degree turn).

Cognitive Decline

Characterized by subcortical dysfunction.

- **Semantics:** Psychomotor slowing, impaired attention, and executive dysfunction. Aphasia or early cortical signs argue against a diagnosis of pure iNPH and should prompt consideration of a coexisting neurodegenerative process.

Bladder Dysfunction

Ranges from mild urgency to frank incontinence.

- **Semantics:** Increased frequency, nocturia, and detrusor overactivity on urodynamic testing. Bladder symptoms often affect quality of life more than cognitive symptoms.

📌 CLINICAL PEARL — Differentiating iNPH from Neurodegenerative Mimics

- Gait impairment preceding cognitive decline favors iNPH over Alzheimer disease, in which memory impairment typically dominates early.
- Early prominent aphasia, apraxia, or cortical visual symptoms should raise suspicion for an alternative or coexisting diagnosis.
- Parkinsonian rigidity/tremor with poor levodopa response and early falls may suggest progressive supranuclear palsy rather than iNPH.

⚠ WARNING: Response to CSF drainage testing (tap test) does not have perfect sensitivity — a negative test does not exclude iNPH, and patients may still benefit from shunting after a carefully considered multidisciplinary evaluation.

IV. Diagnostic Imaging & Testing Biomarkers

1. Structural Neuroimaging Thresholds

Radiographic Feature	Measurement Cut-off / Threshold	Clinical Significance
Evans Index	> 0.3	Screening threshold for ventriculomegaly; sensitive but not specific.
Callosal Angle	< 90° (typical iNPH); < 63° (predictive)	Measured in the coronal plane at the posterior commissure. A threshold of < 63° predicts shunt responsiveness.
z-Evans Index	≥ 0.42	Coronal height of frontal horns / vertical skull diameter; predicts a positive tap test.
Temporal Horns	≥ 6 mm (Score 2); 4.0–5.9 mm (Score 1)	Component of the iNPH Radscale.
DESH Sign	Ventriculomegaly + high-convexity tight sulci + enlarged Sylvian fissures	Strong predictor of shunt-responsive hydrocephalus.
Periventricular Lucency	Fazekas Grade 2–3 (confluent)	Suggests transependymal edema/CSF flow; negatively associated with outcomes if extensive.

Table 1.2 — Structural neuroimaging thresholds used in the diagnostic evaluation of iNPH.

⚠ MNEMONIC — DESH — Disproportionately Enlarged Subarachnoid-space Hydrocephalus

D Disproportionately

E Enlarged

S Subarachnoid-space

H Hydrocephalus (ventriculomegaly + tight high-convexity sulci + enlarged Sylvian fissures)

2. Supplemental Diagnostic Testing Protocols

Large-Volume Lumbar Puncture (Tap Test)

- **Protocol:** Drainage of 30–50 mL of CSF.
- **Assessment:** Pre- and post-gait quantitative measures (see Table 1.4). Positive predictive value is high, but a negative result does not exclude iNPH.

External Lumbar Drainage (ELD)

- **Protocol:** Continuous drainage of 300–600 mL over 48–72 hours.
- **Performance:** Higher sensitivity/specificity (~90%) than the tap test, but carries higher procedural risks (hemorrhage, infection).

Infusion Testing (R_{out})

- Measures the resistance to CSF outflow via lumbar saline infusion. Elevated R_{out} supports the reabsorption-failure hypothesis and the decision to shunt, though a normal value does not rule out a treatment response.

Test	Volume / Duration	Performance Characteristics
Tap Test	30–50 mL, single session	High positive predictive value; negative result does not exclude iNPH
External Lumbar Drainage	300–600 mL over 48–72 h	~90% sensitivity/specificity; higher risk of hemorrhage/infection
Infusion Test (R_{out})	Continuous saline infusion	Elevated R_{out} supports shunt-responsive reabsorption failure

Table 1.3 — Comparison of supplemental CSF dynamic testing protocols.

3. Pre- and Post-Tap Test Assessment Parameters

Assessment Category	Timed / Quantitative Test	Normal Reference / Metrics
Gait Speed & Balance	Timed Up and Go (TUG)	Time to walk 3 m and back. Normal: ≤ 12 seconds.
Gait & Executive Function	Dual Timed Up and Go	TUG performed while simultaneously completing serial subtractions.
Gait Speed	10-Meter Walk Test	Time to walk 10 m. Normal: ≤ 10 seconds.
Static Balance	Four-Stage Balance Test	Ability to stand for 10 s in 4 progressively challenging positions (feet together to one-foot stance).
Composite NPH Score	NPH Scale	0–100 point scale (gait, balance, cognition, urinary function); gait is weighted double.

Table 1.4 — Standardized pre- and post-tap test gait and balance assessment battery.

📌 **EXAM / HIGH-YIELD TIP:** A drop of $\geq 10\%$ in TUG time, or $\geq 20\%$ improvement in gait speed after a tap test, is commonly used clinically to define a 'positive' tap test, supporting the decision to proceed to shunting.

V. Surgical Shunting Strategies

1. Shunt Types and Configurations

Shunt Type	Drainage Route	Key Features / Risks
Ventriculoperitoneal (VP)	Lateral ventricle → peritoneum	Most common configuration.
Ventriculoatrial (VA)	Lateral ventricle → right atrium	Used if the peritoneum is unsuitable; risks include arrhythmias and clot formation.
Lumboperitoneal (LP)	Lumbar subarachnoid space → peritoneum	Higher risk of overdrainage due to gravitational column effects.
Ventriculopleural	Lateral ventricle → pleural space	Risk of hydrothorax or siphoning with inspiration.

Table 1.5 — Shunt configurations, routes, and characteristic risks.

2. Valve Mechanics and Technology

- **Programmable Valves:** Allow non-invasive adjustment of drainage settings using external magnets. Typically set initially just above the patient's opening pressure.
- **Anti-Siphon / Gravitational Devices:** Prevent the "siphoning effect" (excessive drainage when the patient stands upright).
- **Fixed Valves:** Simple, with no risk of unexpected setting changes, but require surgery if drainage needs adjustment.

⚠ **MRI SAFETY WARNING:** Programmable shunt valves can be inadvertently reprogrammed by strong magnetic fields (including some consumer devices and MRI in older valve models). Always verify and, if necessary, reset the valve setting after any MRI scan.

3. Complications and Failure Criteria

Complication	Presentation	Approximate Incidence
Over-drainage	Orthostatic headaches (mimicking SIH); subdural hematomas or hygromas; slit ventricle syndrome	Subdural hematoma/hygroma in ~9%
Under-drainage / Obstruction	Recurrence of original symptoms (gait decline, etc.); may be proximal (choroid plexus, debris) or distal catheter obstruction	Common cause of shunt failure
Infection	Typically requires removal of the entire shunt system	~2%
Mechanical Failure	Requires surgical revision	~16%

Table 1.6 — Shunt complications, clinical presentation, and approximate incidence.

🚨 EMERGENCY — Recognizing Shunt Malfunction

- New or worsening headache, vomiting, altered mental status, or recurrence of gait/cognitive decline in a shunted patient should prompt urgent shunt series imaging and cross-sectional neuroimaging.
- Rapid neurological deterioration with signs of raised ICP (Cushing's triad, papilledema, reduced consciousness) constitutes a neurosurgical emergency.
- Fever with shunt malfunction symptoms raises concern for shunt infection/ventriculitis and requires urgent CSF sampling and empiric antibiotics per local protocol.

⚡ **PITFALL:** Do not attribute new headache or cognitive decline in a shunted iNPH patient to disease progression without first excluding shunt malfunction or overdrainage — both are common and correctable.

✓KEY POINTS — Part I Summary

- CSF is produced at ~0.3–0.5 mL/min by the choroid plexus and reabsorbed via arachnoid granulations and the glymphatic-lymphatic pathway.
- Hydrocephalus is classified as communicating vs. obstructive, and congenital vs. acquired.
- iNPH presents with the Hakim-Adams triad: gait dysfunction (cardinal and earliest), subcortical cognitive decline, and urinary dysfunction.
- DESH, a callosal angle $< 63^\circ$, and z-Evans index ≥ 0.42 support a diagnosis of shunt-responsive iNPH.
- Tap test, ELD, and infusion testing (Rout) are complementary tools to predict shunt responsiveness.
- VP shunting is the most common surgical treatment; overdrainage, obstruction, infection, and mechanical failure are the principal complications.

PART II

Idiopathic Intracranial Hypertension & Pseudotumor Cerebri Syndromes

I. Diagnostic Criteria and Pathophysiology

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by unexplained elevated intracranial pressure (ICP) in an alert and awake patient. It is a diagnosis of exclusion, necessitating rule-out of secondary causes such as venous sinus thrombosis or infection.

Modified Dandy Criteria for Diagnosis

- Signs and symptoms of increased ICP (e.g., headaches, transient visual obscurations, papilledema, pulse-synchronous tinnitus, visual loss).
- No altered level of consciousness nor localizing neurologic signs, except unilateral or bilateral sixth (abducens) nerve palsy.
- Increased ICP with normal CSF composition.
- Neuroimaging without any structural lesion or venous sinus thrombosis.
- No other etiology explaining intracranial hypertension.

Lumbar Puncture (LP) Target Parameters

Parameter	Detail
Positioning	Opening pressure is ideally measured in the left lateral decubitus position, with the patient relaxed, legs extended, and head in a neutral position.
Adult Threshold	ICP is considered elevated at values greater than 25 cm H ₂ O.
Pediatric Threshold	ICP is considered elevated at greater than 28 cm H ₂ O.

Table 2.1 — Lumbar puncture technique and diagnostic opening-pressure thresholds.

Proposed Pathophysiology

Proposed mechanisms include dural venous sinus congestion leading to activation of the calcitonin gene-related peptide (CGRP) pathway, which sensitizes migraine processing pathways. Additionally, central adiposity in obese patients is thought to actively secrete mineralocorticoid-releasing factors, which may contribute to increased ICP.

IMPORTANT NOTE: Pathophysiologic mechanisms in IIH remain incompletely understood and are the subject of ongoing research; the mechanisms above represent proposed, not definitively established, pathways.

II. Risk Factors and Syndromic Associations

IIH is strongly associated with specific demographics and secondary systemic triggers.

Demographics

- **Primary Risk Group:** Women of reproductive age (15–44 years) with a body mass index (BMI) greater than 30 kg/m².
- **Gender Nuance:** Being assigned female at birth is the dominant risk factor; transgender men remain at risk regardless of gender-affirming hormone therapy.

Secondary Causes of Increased ICP

Category	Systemic Triggers and Associations
Medications	Tetracyclines (minocycline, doxycycline), vitamin A and retinoids, growth hormone, levonorgestrel, anabolic steroids, lithium, corticosteroid withdrawal, methotrexate.
Medical Conditions	Obesity, obstructive sleep apnea (OSA), polycystic ovarian syndrome (PCOS), anemia, Addison disease, renal failure, systemic lupus erythematosus.
Intracranial	Cerebral venous sinus thrombosis (CVST), jugular vein thrombosis, hydrocephalus, Chiari malformation.

Table 2.2 — Secondary causes and risk associations for intracranial hypertension (pseudotumor cerebri syndrome).

🔍 **MNEMONIC — Secondary Causes of Pseudotumor Cerebri — "TOO MUCH PRESSURE"**

- T** Tetracyclines
- O** OSA (obstructive sleep apnea)
- O** Obesity
- M** Medications (retinoids, growth hormone, lithium)
- P** PCOS
- R** Renal failure
- S** Sinus thrombosis (CVST)

🔍 **WARNING:** Always screen for and exclude cerebral venous sinus thrombosis with MR/CT venography before establishing a diagnosis of IIH — this is a secondary cause that requires distinct (anticoagulation-based) management.

III. Clinical Manifestations and Visual Threats

Symptom Profile

Symptom	Approx. Prevalence	Description
Headache	84%	Most common symptom; often mimics migraine (52%) or tension-type (22%) phenotypes.
Pulsatile Tinnitus	52%	A "whooshing" sound synchronous with the heartbeat.
Transient Visual Obscurations (TVOs)	Variable	Brief (seconds to minutes) episodes of painless blurred or graying vision, often induced by sudden head movement or orthostatic changes.
Diplopia	Variable	Horizontal binocular diplopia, typically caused by sixth nerve palsy — a false localizing sign.

Table 2.3 — Prevalence and description of the principal clinical manifestations of IIH.

Papilledema Grading (Frisén Scale)

Frisén Grade	Key Diagnostic Feature
Grade 0	Normal optic disc.
Grade 1 (Minimal)	Subtle, gray C-shaped halo obscuring underlying retinal details; temporal area is spared.
Grade 2 (Low)	Complete circumferential halo; elevated nasal border; no major vessel obscuration.
Grade 3 (Moderate)	One or more major blood vessels obscured as they leave the disc; halo has an irregular outer fringe.
Grade 4 (Marked)	A major blood vessel is obscured on the disc; the entire optic nerve head is elevated, including the cup.
Grade 5 (Severe)	All vessels are obscured, both on the disc and as they leave the disc.

Table 2.4 — Frisén scale for grading papilledema severity.

Monitoring with Optical Coherence Tomography (OCT)

- **RNFL:** Quantifies peripapillary retinal nerve fiber layer thickness; the magnitude of change correlates with treatment response.
- **Ganglion Cell Layer (GCL):** Macular GCL thickness helps determine whether RNFL thinning is due to resolving edema (stable GCL) or permanent axonal loss/atrophy (thinning GCL).

CLINICAL PEARL: A falling RNFL thickness on OCT with a stable GCL suggests resolving papilledema (a favorable sign), whereas concurrent GCL thinning suggests true axonal loss and irreversible visual damage.

IV. Medical Pharmacotherapy Manual

Medical management aims to preserve vision and reduce headache burden.

Medication	Starting Dose	Titration / Max Dose	Side-Effect Profile / Notes
Acetazolamide	250–500 mg BID	Rapid titration up to 4000 mg/day	Paresthesias, dysgeusia (metallic taste), nausea, metabolic acidosis, fatigue
Topiramate	25 mg daily	Increase by 25 mg every 2 weeks to 100 mg BID	Carbonic anhydrase inhibition plus weight loss; dual benefit for comorbid migraine
Furosemide	20 mg BID	Up to 40 mg BID	Loop diuretic; inhibits CSF secretion by 20–50% in animal studies
Corticosteroids	High-dose IV	Short-course methylprednisolone	Reserved for fulminant presentations as a temporizing measure

Table 2.5 — Drug summary table for medical management of IIH.

PITFALL: Corticosteroids are a temporizing measure only in fulminant IIH — they are not appropriate for chronic maintenance therapy and can themselves precipitate intracranial hypertension on withdrawal.

V. Surgical and Interventional Options

Surgery is indicated for fulminant cases (rapid vision loss) or when medical therapy is exhausted.

FULMINANT IIH: Fulminant IIH is characterized by Frisén grade 4–5 papilledema with rapid visual field loss over a few days. Management requires immediate high-dose acetazolamide and urgent surgical intervention (ONSF, shunt, or stenting); a lumbar drain may be used as a temporizing measure if surgery is delayed.

Surgical Parameters

Procedure	Functional Objective	Target Parameters and Success Rates
Optic Nerve Sheath Fenestration (ONSF)	Creates a slit/window in the dural sheath to filter CSF	Papilledema improvement in 90.5%; headache improvement in only 49.3%
CSF Shunting (VP favored over LP)	Diverts CSF to another cavity (e.g., peritoneum)	Regresses papilledema in 90.9%; failure/revision rate is high (43.4%)
Transverse Venous Sinus Stenting (TVSS)	Resolves venous outflow resistance	Requires a pressure gradient ≥ 8 mmHg across the stenosis (some centers accept ≥ 4 mmHg)

Table 2.6 — Surgical and endovascular treatment options, objectives, and outcomes in IIH.

Venous Sinus Stenting Postoperative Protocol

Patients are typically placed on dual antiplatelet therapy (e.g., clopidogrel and aspirin) for 3 months, followed by aspirin monotherapy for at least 1 year, to prevent in-stent thrombosis.

✓KEY POINTS — Part II Summary

- IIH is a diagnosis of exclusion requiring the Modified Dandy Criteria, with opening pressure > 25 cm H₂O in adults (> 28 cm H₂O in children).
- Classic demographic: women of reproductive age with BMI > 30 kg/m².
- Papilledema is graded using the Frisén scale (0–5); OCT (RNFL/GCL) helps monitor treatment response and detect irreversible axonal loss.
- First-line medical therapy is acetazolamide; topiramate offers dual benefit if migraine coexists.
- Fulminant IIH (Frisén grade 4–5 with rapid visual loss) is a neuro-ophthalmic emergency requiring urgent surgical intervention.
- ONSF, CSF shunting, and venous sinus stenting are the principal surgical/endovascular options, each with distinct risk-benefit profiles.

PART III

Spontaneous Intracranial Hypotension & Spinal CSF Leaks

I. Clinical Syndrome & Phenotypes

- **Classic Presentation:** Orthostatic headache is the hallmark symptom, defined as head pain that worsens when upright and improves when lying flat. Symptoms often worsen immediately upon standing (42%) or within minutes (43%), while improvement when recumbent may take up to 15 minutes.
- **Phenotypic Evolution:** The orthostatic nature of the headache can be lost over time, or it may present initially as a new daily persistent headache (NDPH) that worsens with Valsalva maneuvers or increases in intensity throughout the afternoon. A small percentage of patients experience no headache at all.
- **Associated Cranial Nerve and Brainstem Symptoms:** Downward traction on pain-sensitive structures and nerves leads to diplopia (CN VI traction), facial numbness/pain, and vestibulo-auditory distortions such as pulsatile tinnitus, hyperacusis, or vertigo.
- **Encephalopathy — Brain Sagging Dementia:** Mimics behavioral variant frontotemporal dementia (bvFTD), presenting with disinhibition, dysexecutive features, and personality change. Unlike true bvFTD, these patients often exhibit hypersomnolence and cerebellar signs such as ataxia.

🚫 **PITFALL: SIH MASQUERADING AS DEMENTIA:** Brain sagging dementia is a frequently missed mimic of bvFTD. Consider SIH in any patient with a behavioral-variant dementia picture accompanied by hypersomnolence, ataxia, or a postural headache history — misdiagnosis leads to inappropriate dementia work-up while a treatable cause is overlooked.

II. Diagnostic Neuroimaging Hallmarks

- **Pathognomonic Finding:** Smooth, non-nodular, diffuse pachymeningeal enhancement is essentially pathognomonic for SIH. It must be distinguished from leptomeningeal enhancement, which follows gyral surfaces and suggests infectious or neoplastic processes.

The "SEEPS" Mnemonic

📌 MNEMONIC — SEEPS — Brain MRI Findings in SIH

- S** Subdural fluid collections (hematomas or hygromas)
- E** Enhancement of the pachymeninges (diffuse and smooth)
- E** Engorgement of venous structures (venous sinus bowing)
- P** Pituitary hyperemia (enlargement and upward bowing)
- S** Sagging of the brain (low cerebellar tonsils, effaced prepontine/suprasellar cisterns)

Brain MRI Metrics (Bern Score)

Category	Criteria	Points
Major Criteria	Pachymeningeal enhancement	2
	Engorgement of dural venous sinuses	2
	Suprasellar cistern ≤ 4 mm	2
Minor Criteria	Subdural fluid collections	1
	Prepontine cistern ≤ 5 mm	1
	Mamillopontine distance ≤ 6.5 mm	1
Probability Scale	High likelihood of spinal leak	5–9 points

Table 3.1 — Bern Score: brain MRI scoring system predicting likelihood of a spinal CSF leak.

III. Advanced Spine Imaging & Leak Localization

Screening Modalities

Spine MRI is the preferred initial screening tool to search for spinal longitudinal extradural fluid collections (SLEC), which indicate a fast leak.

Myelographic Techniques

Modality	Strength	Notes
Digital Subtraction Myelography (DSM)	Highest temporal resolution (1–2 frames/sec); visualizes leaks in real time	Preferred for fast/high-flow leaks
Dynamic CT Myelography (CTM)	Cross-sectional detail; identifies bone spicules or osteophytes causing dural tears	Useful for Type 1a leaks
Photon-Counting CT	Next-generation resolution rivaling DSM; can detect subtle CSF-venous fistulas missed by other modalities	Emerging technology
MR Myelogram (Intrathecal Gadolinium)	Can detect slow or intermittently draining fistulas	Unlabeled use; lower temporal resolution

Table 3.2 — Comparison of advanced spinal imaging modalities for CSF leak localization.

Spinal CSF Leak Classification

Leak Type	Mechanism	Characteristic Finding
Type 1a	Ventral dural tear	Often caused by a calcified bone spicule; SLEC present
Type 1b	Posterolateral dural tear	Associated with connective tissue disorders; SLEC present
Type 2	Leaking meningeal diverticula	"Slow" leaks; often best seen on delayed (30-minute) CT
Type 3	CSF-venous fistula (CVF)	Direct egress into veins; no SLEC on imaging; a common cause of SIH

Table 3.3 — Classification of spinal CSF leaks by mechanism and imaging characteristics.

EXAM / HIGH-YIELD TIP: Type 3 CSF-venous fistulas are a common but easily missed cause of SIH because there is no extradural fluid collection (no SLEC) — this leak type direct-drains into paraspinal veins and requires targeted imaging (DSM or dynamic CTM) for detection.

IV. Conservative & Interventional Management

Supportive Care

- Hydration (2.0–2.5 L daily).
- Abdominal binders to increase spinal canal pressure.
- Short-term bed rest.
- **Caffeine:** Provides transient symptomatic relief but may lower ICP in animal models.

Epidural Blood Patch (EBP) Mechanics

EBP works via a tamponade effect that reduces the pressure gradient, allowing the dural rent to repair itself spontaneously; it is not a direct sealant.

Patch Strategy	Injectate Volume	Clinical Application
Nontargeted (Empiric)	20–40 mL	Used when the leak site is unidentified; typically lumbar or low thoracic
Targeted (Directed)	Variable (often higher)	Applied directly to a localized leak site to improve clinical outcomes
Fibrin Glue Patch	Low volume	Reserved for refractory cases or distal nerve root sleeve tears (Type 2)
Saturation Point	Patient-dependent	Injection is paused if the patient develops pressure paresthesia or new back pain

Table 3.4 — Epidural blood patch strategies, injectate volumes, and clinical applications.

V. Advanced & Surgical Treatments

- **Transvenous Embolization:** The preferred minimally invasive treatment for Type 3 CSF-venous fistulas. A permanent embolic agent (e.g., ethylene-vinyl alcohol copolymer) is used to occlude the foraminal venous plexus.

Surgical Options

- **Direct Dural Repair:** For ventral tears (Type 1a), often requiring discectomy to remove the offending bone spicule.
- **Ligation/Stripping:** For CVFs (Type 3) at non-appendicular levels, with care taken to avoid injury to the artery of Adamkiewicz.

Rebound Intracranial Hypertension (RIH)

⚠ WARNING — Rebound Intracranial Hypertension

- Clinical presentation: A new headache phenotype (often frontal/periorbital) that is worse when lying flat or in the morning; typically occurs within 1–3 days of successful leak treatment.
- Diagnosed by opening pressure verification (if severe) and managed with acetazolamide.

💡 CLINICAL PEARL: A change in headache character from orthostatic (worse upright) to the opposite pattern (worse recumbent) shortly after EBP or surgical repair should raise suspicion for rebound intracranial hypertension rather than treatment failure — the management approach is entirely different.

✓KEY POINTS — Part III Summary

- Orthostatic headache is the hallmark of SIH, but the pattern can evolve or be absent entirely.
- Brain sagging dementia is an important, often-missed mimic of behavioral-variant frontotemporal dementia.
- The SEEPS mnemonic and Bern Score summarize the key brain MRI findings and their diagnostic weight.
- Spinal CSF leaks are classified into Type 1a/1b (dural tear), Type 2 (diverticulum), and Type 3 (CSF-venous fistula).
- Epidural blood patch works via tamponade, not sealant action; targeted patches are used when a leak site is localized.
- Type 3 fistulas are best treated with transvenous embolization.
- Rebound intracranial hypertension is a recognized complication after successful leak repair and is managed with acetazolamide.

PART IV

Congenital CSF Anomalies, Arachnoid Cysts, Syringomyelia & Complex Hydrocephalus Variants

I. Syringomyelia and Hydromyelia

1. Definitions and Pathophysiological Differentiation

Term	Definition
Syringomyelia	Formation of a fluid-filled cavity (syrinx) within the spinal cord parenchyma.
Hydromyelia	Dilatation of the central canal of the spinal cord (often used interchangeably with syringomyelia in clinical practice).

Table 4.1 — Definitions of syringomyelia and hydromyelia.

- **Pathophysiology:** These cavities often result from disrupted CSF flow patterns at the craniocervical junction. In Chiari Malformation Type I, the crowded posterior fossa forces the cerebellar tonsils through the foramen magnum, creating a "piston-like" effect that drives CSF into the cord.
- **Secondary Etiologies:** Syrinxes are also observed in Spontaneous Intracranial Hypotension due to severe brain sagging, and in cases of post-traumatic spinal arachnoiditis.

2. Clinical Localization Patterns

- **Dissociated Sensory Loss:** A classic "cape-like" distribution of pain and temperature loss across the shoulders and arms, with preserved light touch (due to central cord involvement sparing the dorsal columns).
- **Motor Signs:** Progressive upper motor neuron (UMN) signs in the lower extremities (spasticity, hyperreflexia) and lower motor neuron (LMN) signs in the upper extremities (atrophy, fasciculations).

📌 MNEMONIC — Classic Syrinx Presentation

C Cape-like distribution of sensory loss

A Analgesia and thermoanesthesia (pain/temperature loss)

P Preserved light touch/proprioception (dorsal columns spared)

E Extremity weakness — LMN signs in arms, UMN signs in legs

3. Management: Posterior Fossa Decompression (PFD)

- **Objective:** To restore normal CSF dynamics at the foramen magnum.
- **Parameters:** PFD is indicated for symptomatic Chiari I with an associated syrinx.

📌 **CRITICAL DIAGNOSTIC PITFALL:** If tonsillar ectopia is due to SIH (acquired brain sagging) rather than true Chiari malformation (congenital), posterior fossa decompression will exacerbate brain sagging and worsen clinical symptoms. Always exclude SIH before proceeding with PFD in a patient with low-lying tonsils.

II. Intracranial Arachnoid Cysts

1. Pathophysiology and Localization

- **Mechanism:** Arise from splitting or duplication of the arachnoid membrane.
- **Common Localizations:** Middle cranial fossa (most common), posterior fossa, and suprasellar regions.
- **Diagnostic Differentiation:** In adults, focally enlarged sulci (seen in DESH) can be misinterpreted as arachnoid cysts; however, sulci will normalize after shunting, whereas true cysts will not.

Galassi Classification of Middle Fossa Arachnoid Cysts

Type	Radiographic Description	Clinical Significance
Type I	Small, spindle-shaped; limited to the anterior pole of the temporal fossa	Usually asymptomatic; rarely requires intervention
Type II	Medium-sized; occupies the anterior and middle portions of the fossa; opens into the Sylvian fissure	May cause mass effect/bone thinning; requires longitudinal tracking
Type III	Large; occupies the entire temporal fossa with significant displacement of the temporal lobe and midline shift	Highest risk for symptoms or rupture (subdural hematoma); often requires surgery

Table 4.2 — Galassi classification of middle cranial fossa arachnoid cysts.

CLINICAL PEARL: A key bedside/imaging clue: true arachnoid cysts do not change in size after CSF diversion, whereas the focally enlarged sulci of DESH will normalize following successful shunting — this distinction is useful when a suspected cyst is found incidentally in an INPH work-up.

III. Secondary Ventriculomegaly and Aqueductal Stenosis

1. Late-Onset Idiopathic Aqueductal Stenosis (LIAS)

LIAS presents similarly to idiopathic Normal Pressure Hydrocephalus (iNPH), with gait instability and cognitive decline, making imaging differentiation essential.

Imaging Differentiation

Feature	LIAS	iNPH / DESH
Ventriculomegaly Pattern	Marked triventriculomegaly (lateral and 3rd ventricles)	Ventriculomegaly disproportionate with subarachnoid spaces
Aqueduct Flow Void	Absence of flow void, or a web at the aqueduct	Hyperdynamic flow void
Sylvian Fissures	Not characteristically enlarged	Enlarged (extraventricular hydrocephalus)

Table 4.3 — Imaging features distinguishing late-onset idiopathic aqueductal stenosis (LIAS) from iNPH/DESH.

2. Specialized Treatment: ETV vs. Shunting

- **Endoscopic Third Ventriculostomy (ETV):** The preferred treatment for obstructive hydrocephalus (aqueductal stenosis), as it bypasses the block without permanent hardware.
- **Success Predictors:** Success depends on the ETV Success Score (ETVSS), which evaluates age, etiology, and prior shunting.

ETV Success Score (ETVSS) Components

Points	Age	Etiology	Previous Shunt
0	< 1 month	Post-infectious	Yes
10	1 month to 1 year	Post-hemorrhagic Myelomeningocele	—
20	> 1 year to 10 years	Other (e.g., trauma)	No
30	> 10 years	Aqueductal stenosis / tectal tumor	—

Table 4.4 — ETV Success Score (ETVSS) components. The total score (summed across age, etiology, and prior shunt category, up to ~90 points) predicts approximate percentage success at 6 months (e.g., a score of 80 corresponds to an ~80% success rate).

EXAM / HIGH-YIELD TIP: The ETVSS is calculated by summing points across three domains (age, etiology, prior shunt history). Aqueductal stenosis in an older child/adult without a prior shunt carries the highest predicted success rate for ETV.

IV. Neuro-Endoscopic Advancements

1. Mechanics and Intraventricular Visualization

Neuro-endoscopy involves navigating through a frontal burr hole into the lateral ventricle and through the foramen of Monro to access the third ventricle.

2. Specialized Indications

- **Multi-loculated Hydrocephalus:** Endoscopic fenestration of septations/membranes is used to convert multiple isolated compartments into a single communicating system for easier shunting.
- **Choroid Plexus Cauterization (CPC):** Often combined with ETV (ETV+CPC) to reduce CSF secretion volume.
- **Success in Neonates:** CPC is particularly useful in post-infectious hydrocephalus (common in Africa) but has a lower success rate (~22%) in post-hemorrhagic hydrocephalus of prematurity.

Chiari I vs. SIH Brain Sagging — Diagnostic Measurements

Metric	Chiari Malformation Type I	Spontaneous Intracranial Hypotension
Etiology	Congenital structural defect (small posterior fossa)	Acquired (CSF volume loss)
Tonsillar Position	> 5 mm below the foramen magnum	Variable; often associated with brain sag

Metric	Chiari Malformation Type I	Spontaneous Intracranial Hypotension
Mamilllopontine Distance	Usually normal (> 6.5 mm)	Decreased ($\leq$ 6.5 mm)
Pontomesencephalic Angle	Usually normal	Acute / decreased
Syrinx	Frequently present (cervical)	Rare, but possible

Table 4.5 — Differentiating Chiari Malformation Type I from SIH-related brain sagging on imaging.

⚡ **PITFALL:** Low-lying cerebellar tonsils are a shared finding in both Chiari I and SIH. Relying on tonsillar position alone risks misdiagnosis; the mamillopontine distance and pontomesencephalic angle are more discriminating, and a full SIH work-up (including brain MRI for the SEEPS findings) should precede any posterior fossa decompression.

✓KEY POINTS — Part IV Summary

- Syringomyelia/hydromyelia most often arises from disrupted CSF dynamics at the craniocervical junction (classically Chiari I).
- PFD is the treatment for symptomatic Chiari I with syrinx — but is contraindicated (and harmful) if tonsillar ectopia is due to SIH rather than true Chiari malformation.
- Arachnoid cysts are graded by the Galassi classification (Types I–III) based on size and mass effect.
- LIAS mimics iNPH but shows an absent aqueductal flow void and triventriculomegaly without Sylvian fissure enlargement.
- ETV is preferred for obstructive hydrocephalus; the ETVSS predicts success based on age, etiology, and shunt history.
- Distinguishing Chiari I from SIH-related brain sagging requires assessment of the mamillopontine distance and pontomesencephalic angle, not tonsillar position alone.

Neurology of Systemic Disease

CHAPTER 1

Neurology of Rheumatologic & Connective Tissue Disease

Systemic Lupus Erythematosus, Sjögren Syndrome, Systemic Vasculitides, and Neurosarcoidosis

1.1 Systemic Lupus Erythematosus (SLE) & Neuropsychiatric SLE (NPSLE)

Pathophysiology

Primary NPSLE injury arises from a heterogeneous combination of inflammatory and vascular mechanisms. This includes microvascular injury, loss of white-matter integrity secondary to vasculopathy, and immune-mediated tissue damage.

- **Disease-activity dissociation:** Headache and mood disorders are the most common neuropsychiatric manifestations, but they frequently do not track with systemic disease activity.
- **Psychosis mechanism:** Primary lupus psychosis is thought to be driven by hypercytokinemia (particularly IL-6 and interferon- α pathways) rather than direct antibody-mediated neuronal injury.

The ACR Neuropsychiatric Lupus Syndromes

The American College of Rheumatology (ACR) 1999 nomenclature identifies 19 neuropsychiatric syndromes in SLE — 12 affecting the central nervous system (CNS) and 7 affecting the peripheral nervous system (PNS).

CNS Syndromes (12)	PNS Syndromes (7)
1. Acute confusional state	1. Axonal polyneuropathy
2. Aseptic meningitis	2. Cranial neuropathy
3. Cognitive dysfunction	3. Demyelinating neuropathy (AIDP-like)
4. Headache	4. Mononeuritis multiplex
5. Mood disorders	5. Myasthenia gravis
6. Movement disorder (chorea)	6. Plexopathy
7. Myelitis	7. Small-fiber neuropathy
8. Optic neuritis	
9. Psychosis	
10. Seizures / seizure disorders	
11. Cerebrovascular disease (stroke)	
12. Demyelinating syndrome (MS/NMOSD overlap)	

Diagnostic Biomarkers and Clinical Patterns

Biomarker / Finding	Clinical Significance
Antiphospholipid antibodies (aPL)	Present in ~65% of SLE patients with ischemic stroke; the strongest predictors of stroke and objective cognitive impairment.
Anti-dsDNA & Anti-Smith	High specificity for SLE; titers often correlate with systemic disease activity.
CSF findings	May show mild pleocytosis, elevated IgG index, or CSF-restricted oligoclonal bands in primary inflammatory NPSLE.
Demyelinating mimics	Optic neuritis and myelitis in SLE often reflect comorbid NMOSD (check anti-AQP4) rather than SLE itself.

📌 IMPORTANT NOTE

Optic neuritis or myelitis occurring in a patient with SLE should always prompt anti-AQP4 (aquaporin-4) antibody testing to exclude a comorbid NMOSD, since management and prognosis differ substantially from primary NPSLE demyelination.

Step-Wise Immunosuppressive Protocol for Severe NPSLE

The following protocol is standard for severe, immune-mediated NPSLE (e.g., psychosis, myelitis, refractory seizures):

Phase	Protocol	Details
Acute induction	IV methylprednisolone pulse	Typically 1 g/day for 3–5 days.
Oral transition	Prednisone taper	Begun after the IV pulse; tapered according to clinical response.
Steroid-sparing	Cyclophosphamide	Favored for severe or refractory CNS disease.
Maintenance	Mycophenolate azathioprine) mofetil (or	Used to sustain remission.
Alternative	Rituximab	Considered for refractory cases or when NMOSD overlap is present.

In one illustrative severe case, IV pulse therapy was given for 3 days with early transition to rituximab, reflecting the flexibility of protocols in refractory disease.

📌 CLINICAL PEARL

A patient with SLE and a demyelinating CNS event (optic neuritis or myelitis) should be tested for anti-AQP4 before attributing the event to "lupus cerebritis" — NMOSD overlap changes both treatment intensity and long-term secondary-prevention strategy.

1.2 Sjögren Syndrome

Clinical Manifestations

- **Central nervous system:** MS-mimics and NMOSD are common central overlaps. Anti-AQP4 antibodies often define the demyelinating syndrome rather than reflecting a primary Sjögren mechanism.
- **Peripheral nervous system:** Pathognomonic patterns include sensory ganglionopathy (dorsal root ganglionitis), producing non-length-dependent sensory loss and sensory ataxia, and painful small-fiber neuropathy.

Diagnostic Gold Standards (2016 ACR/EULAR Criteria)

Current classification criteria prioritize objective exocrine dysfunction together with specific serology.

Test	Finding / Significance
Anti-SSA (Ro) / Anti-SSB (La)	Present in 60–80% of patients; anti-SSB carries higher specificity.
Minor salivary gland biopsy	Gold standard; must demonstrate focal lymphocytic sialadenitis.
Skin biopsy	Confirms small-fiber neuropathy via epidermal nerve fiber density.
Schirmer test	Objective measure of reduced tear production.

Management Protocols

- **Neuropathies:** Small-fiber neuropathy (SFN) is managed symptomatically, though IVIg has reported benefit. Sensory ganglionopathy is often refractory to immunotherapy.
- **Vasculitis:** Mononeuritis multiplex in Sjögren syndrome requires high-dose corticosteroids plus rituximab or cyclophosphamide.

⚠ PITFALL

Sensory ganglionopathy is frequently mistaken for a length-dependent axonal polyneuropathy. Its non-length-dependent, asymmetric distribution and prominent sensory ataxia should trigger consideration of dorsal root ganglionitis and Sjögren serology.

1.3 Systemic Vasculitides

ANCA-Associated & Large-Vessel Patterns

Vasculitides are categorized by predominant vessel size and are characterized neurologically by mononeuritis multiplex — sequential, painful, asymmetric mononeuropathies that may become confluent over time.

Disorder	Clinical Pearl	Primary Neuro-Ocular Manifestation
Giant Cell Arteritis (GCA)	Large-vessel vasculitis; peak incidence in the 7th decade of life.	Arteritic anterior ischemic optic neuropathy (AION); jaw claudication.
GPA / MPA	Small-vessel vasculitis; frequently causes meningitis.	Pachymeningeal enhancement; cranial nerve palsies.
EGPA	Adult-onset asthma + eosinophilia + neuropathy.	Severe mononeuritis multiplex.
Behçet Disease	Variable-vessel vasculitis; more common in men from the Middle East and Far East.	Brainstem syndromes (parenchymal-neuro-Behçet) or venous sinus thrombosis (vascular-neuro-Behçet).

MEMORY TIP / MNEMONIC

"MOVE" for mononeuritis multiplex red flags — Multiple nerves, Often asymmetric, Vasculitic pain, Evolving stepwise. Any patient with sequential, painful, asymmetric mononeuropathies should be screened for an underlying systemic vasculitis.

Pharmacological Dosing Manual for Vasculitis

Management follows sequential induction and maintenance phases.

Drug	Indication	Protocol Details
Prednisone	GCA	1 mg/kg (max 60 mg/day). Taper to 20 mg over 6 weeks, then to 10 mg over the following 6 weeks.
Tocilizumab	GCA	Adjunctive therapy to facilitate a more rapid prednisone taper.
Cyclophosphamide	ANCA-associated vasculitis / PAN	High-dose induction for severe multi-organ involvement.
Rituximab	ANCA-associated vasculitis	Induction therapy with efficacy comparable to cyclophosphamide.
Azathioprine	Behçet disease / ANCA maintenance	First-line for Behçet parenchymal disease and for ANCA maintenance therapy.
Mycophenolate mofetil	ANCA maintenance	Standard transition agent after cyclophosphamide induction.

WARNING

Jaw claudication and new headache in a patient over 50 years old warrants urgent evaluation for GCA and empiric high-dose corticosteroids while awaiting temporal artery biopsy — delay risks irreversible monocular or binocular vision loss from AION.

1.4 Neurosarcoidosis

Neurosarcoidosis is a granulomatous disorder of the nervous system that complicates approximately 5–10% of systemic sarcoidosis cases and, less commonly, may present in isolation without evident systemic disease.

Clinical Manifestations

Pathophysiology involves non-caseating granulomatous inflammation infiltrating the central nervous system.

1. **Cranial neuropathies:** Cranial nerve VII palsy is the most common presentation and is often bilateral.
2. **Basilar meningitis:** Preferential involvement of the base of the brain, often producing pachymeningeal or leptomeningeal enhancement.

3. **Hypothalamic-pituitary involvement:** Granulomatous infiltration may cause diabetes insipidus or panhypopituitarism.
4. **Spinal cord disease:** Intramedullary lesions with patchy, often longitudinally extensive enhancement.

Diagnostic Criteria (Definite, Probable, Possible)

The widely used consensus framework (Neurosarcoidosis Consortium Consensus Group, 2018) stratifies diagnostic certainty as follows:

Category	Criteria
Definite	Compatible CNS clinical syndrome plus a positive CNS biopsy demonstrating non-caseating granulomas.
Probable	Compatible CNS clinical syndrome plus supportive MRI/CSF findings plus histologic confirmation of systemic sarcoidosis (extraneural biopsy).
Possible	Compatible CNS clinical syndrome plus supportive MRI/CSF findings, without tissue confirmation.

Pharmacological Escalation Manual

Step	Therapy	Target Dosing
First-line	Prednisone	Starting at 1 mg/kg/day, followed by a long, gradual taper.
Second-line (steroid-sparing)	Mycophenolate mofetil / azathioprine / methotrexate	Selected based on comorbidities and tolerability.
Refractory	Infliximab (anti-TNF- α)	Loading dose 5 mg/kg at weeks 0, 2, and 6; maintenance every 6–8 weeks.

IMPORTANT NOTE

The specific 2018 consensus diagnostic criteria and infliximab dosing protocol reflect widely accepted expert consensus data rather than a single primary source; clinicians should verify current institutional or society guidance when making treatment decisions.

Differential Diagnosis of Basilar/Pachymeningeal Enhancement

Diagnosis	Distinguishing Feature
Neurosarcoidosis	Non-caseating granulomas; ACE and CSF findings; systemic sarcoid on chest imaging.
Tuberculous meningitis	Basal exudates, hydrocephalus, stroke from vasculitis; positive AFB/PCR.
GPA / MPA	ANCA-positive; associated sinonasal or renal disease.
IgG4-related disease	Elevated serum IgG4; hypertrophic pachymeningitis; may mimic sarcoid.
Lymphomatous/carcinomatous meningitis	Malignant cells on CSF cytology; known primary malignancy.

CHAPTER 2

Neurology of Endocrine, Metabolic, Gastrointestinal & Renal Disease

Thyroid & Parathyroid Disorders, Diabetic Neuropathies, Uremic & Hepatic Encephalopathy, Nutritional Deficiencies, and Correction Thresholds

2.1 Thyroid and Parathyroid Disorders

Thyroid Homeostasis and Encephalopathy

Disruptions of the hypothalamic-pituitary-thyroid axis produce a broad range of central and peripheral neurological manifestations. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), also known as Hashimoto encephalopathy, is a critical diagnosis because it is reversible with immunotherapy.

Disorder	Neurological Manifestations	Diagnostic Biomarkers / Clues
Hypothyroidism	Cerebellar ataxia, proximal limb-girdle weakness, entrapment neuropathies (carpal tunnel syndrome), and length-dependent sensory neuropathy.	Elevated TSH; low free T4.
Myxedema coma	Medical emergency: acute encephalopathy, psychosis (“myxedema madness”), seizures, and hypothermia.	Delayed relaxation phase of muscle stretch reflexes.
Hyperthyroidism	Fine postural tremor, chorea, myoclonus, emotional lability, and anxiety.	Suppressed TSH; high free T4.
Thyrotoxic periodic paralysis	Acute flaccid quadriplegia from intracellular potassium shifts; often precipitated by high-carbohydrate meals.	Exaggerated insulin response; mimics hereditary hypokalemic periodic paralysis.
SREAT (Hashimoto encephalopathy)	Subacute fluctuating encephalopathy, stroke-like episodes, and myoclonus.	High titers of anti-thyroglobulin or anti-thyroid peroxidase (anti-TPO) antibodies.

🚨 EMERGENCY

Myxedema coma is a life-threatening emergency with high mortality. Treatment requires IV levothyroxine ($\pm$ liothyronine), stress-dose corticosteroids (to cover concomitant adrenal insufficiency), passive rewarming, and supportive ICU care.

💡 CLINICAL PEARL

SREAT should be considered in any patient with subacute, fluctuating encephalopathy of unclear etiology — even in the absence of overt thyroid dysfunction — because thyroid function tests may be normal. The diagnosis is supported by dramatic clinical response to corticosteroids.

Calcium and Parathyroid Homeostasis

Calcium derangements directly alter neuronal excitability and cerebrovascular dynamics.

State	Central Nervous System Effects	Peripheral / Systemic Effects
Hypocalcemia	Seizures, encephalopathy, and increased intracranial pressure.	Tetany, carpopedal spasm, Chvostek and Trousseau signs, and prolonged QT interval.
Hypercalcemia	Encephalopathy progressing to stupor or coma; psychiatric disturbance (classically described as “moans” in the “stones, bones, groans, moans” mnemonic).	Severe muscle weakness, shortened QT interval, and risk of pancreatitis.

🔍 MEMORY TIP / MNEMONIC

Hypercalcemia — “Stones, Bones, Groans, Moans, and Psychiatric Overtones”: renal stones, bone pain, abdominal groans, psychiatric moans (depression, confusion), and neuropsychiatric disturbance.

2.2 Diabetic Neurological Complications

Diabetes-related neurological injury results from combined metabolic cascades — oxidative stress and advanced glycation end-product formation — together with microangiopathy.

Syndrome	Pathophysiology & Pattern	Key Clinical Clues
Distal symmetric polyneuropathy (DSPN)	Length-dependent, axonal loss of large and small fibers.	Begins with toe paresthesia; progresses to “anesthesia dolorosa” and gait ataxia.
Diabetic amyotrophy (lumbosacral radiculoplexus neuropathy)	Ischemic/inflammatory injury to the lumbosacral plexus; motor-predominant.	Acute, severe, asymmetric proximal leg pain followed by atrophic weakness.
Treatment-induced neuropathy of diabetes (TIND)	Iatrogenic: relative hypoglycemia and axonal energy failure.	Occurs when HbA1c drops more than 2% over 3 months; features hyperacute pain and autonomic dysfunction.
Diabetic striatopathy	Hyperglycemia-induced movement disorder.	MRI shows unilateral T1 hyperintensity in the putamen/caudate; presents with hemichorea.
Cranial mononeuropathies	Ischemic injury to CN III, IV, or VI.	CN III palsy is classically pupil-sparing due to sparing of peripherally-located pupillomotor fibers by central nerve-core ischemia.

🔍 PITFALL

A pupil-involving CN III palsy should never be attributed to diabetic microvascular disease until a compressive lesion (e.g., posterior communicating artery aneurysm) has been excluded. Diabetic CN III palsy is classically pupil-sparing.

⚠ WARNING

TIND (treatment-induced neuropathy of diabetes) is a recognized risk whenever HbA1c is lowered too rapidly (>2% in 3 months). Clinicians should counsel patients undergoing rapid glycemic control about this risk, particularly before bariatric surgery or intensive insulin initiation.

2.3 Renal & Hepatic Encephalopathies

Uremia and hepatic failure induce toxic shifts in neurotransmission, particularly involving GABA and NMDA receptor systems.

Feature	Uremic Encephalopathy	Hepatic Encephalopathy
Pathophysiology	Retained urea and guanidine compounds; inhibition of GABA and stimulation of NMDA receptors.	Portosystemic shunting; accumulation of ammonia and manganese.
Classic MRI sign	“Lentiform fork sign” — T2 hyperintensity in the bilateral basal ganglia.	T1 hyperintensity in the globi pallidi (manganese deposition).
Dialysis-related risk	Dialysis disequilibrium syndrome: cerebral edema from the “reverse urea effect.”	Post-transplant hyperammonemia (associated with Ureaplasma infection risk).
Movement disorder clues	Myoclonus, asterixis, and restless legs.	Asterixis (a form of negative myoclonus); acquired hepatocerebral degeneration (parkinsonism).

Management Protocols

- **Hepatic clearing:** Titrate lactulose to 2–3 soft stools per day; rifaximin is used for prophylaxis and to reduce recurrence.
- **Hyperammonemic emergency:** Ammonia levels greater than 150 $\mu\text{mol/L}$ carry a high risk of cerebral edema; prioritize osmotic therapy and consider dialysis.

⚠ EMERGENCY

Serum ammonia > 150 $\mu\text{mol/L}$ signals a high risk of cerebral edema and warrants urgent osmotic therapy and consideration of renal replacement therapy (CRRT), particularly in the post-transplant setting.

2.4 Gastrointestinal & Nutritional Deficiencies

Chronic malabsorption states (e.g., celiac disease, post-bariatric surgery) produce predictable neurological deficiency syndromes.

Nutrient	Deficiency Syndrome	Management Protocol
Vitamin B1 (Thiamine)	Wernicke-Korsakoff syndrome: ataxia, oculomotor palsy, and confusion.	Emergency: 500 mg IV three times daily for 2 days, then 250 mg IV/IM daily for 5 days. Always administer thiamine before glucose.
Vitamin B12 (Cobalamin)	Subacute combined degeneration: “inverted V” sign on cord MRI; axonal DSPN.	1000 µg IM daily for 1 week, then 1000 µg PO daily (indefinitely if absorption is impaired).
Vitamin E	Spinocerebellar syndrome mimicking Friedreich ataxia.	Diagnosis by serum α-tocopherol level.
Celiac disease (gluten sensitivity)	Gluten ataxia: Purkinje cell loss; sensory ganglionopathy.	Diagnosis via IgA anti-tissue transglutaminase (tTG) antibody and duodenal biopsy.

📌 MEMORY TIP / MNEMONIC

“Thiamine before glucose” — administering dextrose to a thiamine-deficient patient can precipitate fulminant Wernicke encephalopathy by accelerating depletion of remaining thiamine stores.

2.5 Critical Metabolic Correction & Safety Thresholds

The speed of metabolic correction is often as clinically important as the treatment itself in preventing iatrogenic neurological injury.

Metric	Threshold / Limit	Rationale
Hyponatremia correction	Avoid correcting > 8–10 mmol/L in 24 hours.	Prevents central pontine myelinolysis (osmotic demyelination syndrome).
Hypernatremia correction	Avoid correcting > 8–10 mmol/L in 24 hours.	Prevents cerebral edema.
TIND risk	HbA1c drop > 2% within 3 months.	Identifies patients at risk for acute treatment-induced neuropathy.
Cefepime neurotoxicity	Renal impairment (low GFR) without dose adjustment.	GABA-antagonism leads to encephalopathy and myoclonus.
SREAT treatment	High-dose IV methylprednisolone.	1 g/day for 3–5 days for severe inflammatory CNS syndromes.

📌 EXAM TIP

Any question describing rapid correction of sodium followed by delayed-onset quadriparesis, dysarthria, or a “locked-in” presentation is describing osmotic demyelination syndrome (central pontine myelinolysis) — always check the rate of sodium correction first.

CHAPTER 3

Neurology of Hematologic & Oncologic Disease

Paraneoplastic Syndromes, Paraproteinemic Neuropathies, Hematologic Emergencies, and Neurotoxicities of Modern Cancer Therapy

3.1 Paraneoplastic Neurological Syndromes (PNS)

Primary paraneoplastic injury results from immune-mediated responses triggered by an underlying malignancy. A common mimic is Sjögren-associated sensory ganglionopathy (associated with anti-Hu/ANNA-1); the key distinguishing feature is the specific antibody target and associated tumor.

Table 3.1 — Paraneoplastic Antibody Classification & Primary Malignancies

Antibody Category	Specific Antibody	Associated Malignancy	Primary	Clinical Syndrome
Intracellular / Onconeural	Anti-Hu (ANNA-1)	Small cell lung cancer (SCLC)		Sensory neuronopathy; limbic encephalitis.
	Anti-Yo (PCA-1)	Ovarian, breast		Cerebellar degeneration.
	Anti-Ri (ANNA-2)	Lung, breast		Opsoclonus-myoclonus, ataxia.
	Anti-Ma2	Testicular, lung		Limbic/brainstem encephalitis.
	Anti-CV2 (CRMP5)	SCLC, thymoma		Chorea, uveitis, neuropathy.
Surface / Synaptic	Anti-NMDAR	Ovarian teratoma		Psychosis, orofacial dyskinesia.
	Anti-LGI1	Thymoma, SCLC		Faciobrachial dystonic seizures.
	Anti-CASPR2	Thymoma, SCLC		Morvan syndrome, neuromyotonia.
	Anti-AMPA	Thymoma, lung, breast		Limbic encephalitis.

CLINICAL PEARL

Intracellular (onconeural) antibodies are markers of a T-cell-mediated cytotoxic process and respond poorly to immunotherapy; surface/synaptic antibody syndromes are directly pathogenic and typically respond well to immunotherapy and tumor removal — this distinction should guide prognosis discussions.

PNS-Care Diagnostic Probability Criteria

Probability	Criteria
High probability	Classic syndrome with a high-risk antibody, or a classic syndrome with cancer (regardless of antibody status).
Intermediate probability	Non-classic syndrome with a high-risk antibody, or a classic syndrome without cancer or antibody.

Probability	Criteria
Low probability	Non-classic syndrome without cancer or a high-risk antibody.

First-Line Immunotherapy Dosing

Therapy	Dosing
IVIg	2 g/kg total dose, typically fractionated over 2–5 days.
Plasma exchange (PLEX)	5–7 exchanges over 10–14 days.
Rituximab	Often used second-line or for surface-antibody syndromes (e.g., 375 mg/m ² weekly for 4 weeks).

3.2 Paraproteinemic Neuropathies

Neurological complications are defining features of plasma cell dyscrasias, occurring in up to 20% of multiple myeloma (MM) cases and in nearly 100% of POEMS syndrome cases.

Table 3.2 — Diagnostic Biomarkers & Neuropathy Phenotypes

Disorder	Monoclonal Protein	Neuropathy Pattern	Key Diagnostic Biomarker
MGUS	IgG, IgA, or IgM	Distal sensory neuropathy	Clonal plasma cells < 10%.
POEMS syndrome	Lambda (IgG/IgA)	Demyelinating (CIDP-mimic)	VEGF: plasma > 200 pg/mL; serum > 1920 pg/mL.
Anti-MAG neuropathy	IgM kappa	DADS (distal acquired demyelinating symmetric)	Strongly positive anti-MAG antibody, > 70,000 BTU (Buhlmann titer units).
AL amyloidosis	Lambda light chain	Painful, axonal neuropathy	Apple-green birefringence on Congo red staining.
CANOMAD	IgM	Chronic ataxic neuropathy	Anti-disialosyl antibodies (GD1b, GQ1b).

MEMORY TIP / MNEMONIC

CANOMAD — Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM paraprotein, cold Agglutinins, Disialosyl antibodies.

Management Parameters

- **POEMS syndrome:** Treatment targets the underlying plasma cell clone via chemotherapy or autologous stem cell transplantation.
- **Anti-MAG neuropathy:** IVIg may provide short-term benefit; rituximab is used off-label for progressive disease.

- **AL amyloidosis:** Requires autonomic screening (orthostatic vitals, gastric motility studies), as autonomic dysfunction occurs in up to 50% of cases.

3.3 Hematologic & Coagulation Emergencies

Thrombotic Thrombocytopenic Purpura (TTP)

- **Pathophysiology:** Autoimmune inhibition of ADAMTS13, leading to accumulation of uncleaved von Willebrand factor multimers and diffuse microthrombi.
- **Classic pentad:** Hemolytic anemia (with schistocytes), thrombocytopenia, neurologic symptoms, fever, and renal insufficiency.
- **Diagnostic threshold:** ADAMTS13 activity < 10% confirms the diagnosis.
- **Emergent management:** Immediate plasma exchange plus high-dose corticosteroids.

🚨 EMERGENCY

TTP is a hematologic emergency. Platelet transfusion should generally be avoided unless there is life-threatening hemorrhage, as it may worsen microthrombosis. Plasma exchange should be initiated as soon as the diagnosis is suspected, without waiting for ADAMTS13 results.

Sickle Cell Disease (SCD)

- **Pediatric screening:** Annual transcranial Doppler (TCD) screening for children ages 2–16 to identify elevated velocities (> 200 cm/s) requiring prophylactic transfusion.
- **Silent infarcts:** Occur in up to 30% of children, cumulatively contributing to cognitive decline.
- **Emergency exchange transfusion:** Recommended for acute stroke; aim to maintain hemoglobin S < 30% and total hemoglobin > 9.0 g/dL.
- **Contraindication:** Avoid vasoconstrictors (triptans, ergots) for migraine, as they exacerbate underlying vasculopathy.

Hyperviscosity & Leukostasis

- **Symptoms:** Headache, visual loss (from retinal vein occlusion), and encephalopathy.
- **Threshold:** Symptomatic at IgM > 4000 mg/dL or serum viscosity of 4–5 centipoise.
- **Management:** Urgent plasma exchange.

3.4 Neurological Toxicities of Modern Oncology Therapy

Immune Checkpoint Inhibitor (ICI) Toxicities

Immune checkpoint inhibitors (anti-PD-1/PD-L1 and anti-CTLA-4 agents) trigger immune-related adverse events (irAEs) by breaking peripheral immunologic tolerance.

- **Peripheral manifestations:** AIDP/Guillain-Barré syndrome (often with atypical CSF pleocytosis), myasthenia-like syndrome, and severe myositis.
- **Central manifestations:** Encephalitis, hypophysitis, and aseptic meningitis.
- **Mitigation:** Grade 2 or higher toxicities require holding the offending agent and starting high-dose corticosteroids (1–2 mg/kg prednisone equivalent).

⚠ WARNING

ICI-related myasthenia-like syndrome carries a higher risk of concurrent myocarditis and myositis than idiopathic myasthenia gravis (the “triple-M overlap”) and has a higher fatality rate — screen for cardiac and muscle involvement (troponin, CK) in any ICI patient with new bulbar or limb weakness.

CAR T-Cell Therapy: ICANS

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) follows cytokine release from CAR T-cell activation.

Table 3.3 — ICANS Severity & Grading (ICE Score)

Grade	Clinical Features	Monitoring (ICE Score)	Targeted Management
1 (Mild)	Awake; mild aphasia.	ICE 7–9: orientation, naming, writing intact.	Supportive care; consider dexamethasone.
2 (Moderate)	Somnolent; moderate aphasia.	ICE 3–6: impaired handwriting/naming.	Dexamethasone 10 mg IV every 6 hours.
3 (Severe)	Stuporous; seizures.	ICE 0–2: global aphasia, depressed arousal.	Dexamethasone escalation; tocilizumab if concurrent CRS.
4 (Critical)	Coma; cerebral edema.	ICE 0: non-responsive to pain.	Methylprednisolone pulse (1 g/day); ICU-level care.

💡 CLINICAL PEARL

A subtle change in handwriting is often the earliest detectable sign of ICANS and should be actively screened for during structured neurologic checks after CAR T-cell infusion.

⚠ WARNING

Tocilizumab is used for the associated cytokine release syndrome (CRS) but may not improve — and could potentially worsen — ICANS by increasing CNS cytokine concentrations through impaired peripheral IL-6 clearance.

CHAPTER 4

Critical Care, Cardiopulmonary, and Transplant Neurology

Cardiac-Neurological Interfaces, Post-Hypoxic Encephalopathy, Organ Transplantation Neurology, and Critical Illness Emergencies

4.1 Cardiac-Neurological Interfaces

Infective Endocarditis (IE)

Neurological sequelae occur in 25% to 70% of patients with sepsis from infective endocarditis. The primary mechanism is embolic seeding from infected valvular vegetations, most commonly involving the mitral valve, which tends to embolize during the acute period.

Complication	Pathophysiology	Clinical Localization / Sign
Embolic stroke	Fragments of vegetation are showered into the cerebral circulation.	Multiple arterial territories; mitral valve carries high embolic risk.
Mycotic aneurysm	Infective vasculitis/endotheliitis weakens the vessel wall.	Typically distal vessel involvement; may abut associated hematomas.
Brain abscess	Septic emboli seed parenchymal infection.	Ring-enhancing lesions on MRI.
Hemorrhage	Rupture of infectious (mycotic) aneurysms or hemorrhagic transformation of infarct.	May occur even without a demonstrable aneurysm on initial digital subtraction angiography (DSA).

Surgical Timing Guidelines After Stroke

A multidisciplinary approach is required to balance the risk of recurrent embolization against the risk of hemorrhagic conversion during cardiopulmonary bypass anticoagulation.

Stroke Type	Recommended Delay Before Cardiac Surgery
Nonhemorrhagic (ischemic) stroke	1 to 2 weeks.
Hemorrhagic stroke	At least 3 to 4 weeks.

IMPORTANT NOTE

Surgical timing after endocarditis-related stroke must be individualized by a multidisciplinary heart-valve team; these intervals reflect general guidance and may be adjusted for hemodynamic instability, uncontrolled infection, or recurrent embolic events.

Atrial Fibrillation (AFib) & Stroke Prevention

- **Prevalence:** AFib is twice as prevalent in patients with chronic kidney disease (CKD) compared with age-matched controls.
- **Secondary prevention:** Warfarin is recommended for secondary stroke prevention in patients with SLE and antiphospholipid syndrome (APS).
- **DOAC vs. warfarin:** Direct oral anticoagulants (DOACs) are noninferior for venous thromboembolism, but carry a relatively increased risk of recurrent arterial thromboembolism in APS patients with a history of arterial thrombosis.
- **Postoperative AFib:** Occurs in up to 50% of patients after coronary artery bypass grafting, peaking on postoperative day 2.

⚠ WARNING

In patients with APS and a history of arterial thrombosis, DOACs should generally be avoided in favor of warfarin for secondary stroke prevention, given demonstrated increased rates of recurrent arterial events.

4.2 Pulmonary-Neurological Pathologies

Post-Hypoxic Encephalopathy

It is essential to distinguish purely hypoxic events (e.g., airway obstruction) from hypoxic-ischemic injury (e.g., cardiac arrest).

- **Pure hypoxia:** Systemic circulation is preserved, so glucose and nutrients remain available; irreversible damage is less likely. Neuronal dysfunction occurs at the synaptic level due to selective GABA deficiency.
- **Recovery window:** The time course for recovery in purely hypoxic events mirrors synaptic regeneration (approximately 2 weeks).
- **Prognostication delay:** Prognosis should be delayed for at least 72 hours after injury.

Localization Patterns in Hypoxic-Ischemic Injury

Damage is most notable in regions with the highest metabolic demand:

Vulnerable Region	Clinical Consequence
CA1 pyramidal neurons (hippocampus)	Memory impairment.
Cerebellar Purkinje cells	Ataxia.
Thalamic reticular neurons	Impaired arousal and attention.
Striatal neurons	Postanoxic myoclonus.
Neocortex (layers 3, 5, 6)	Impaired processing speed and executive function.

💡 MEMORY TIP / MNEMONIC

Selective vulnerability follows metabolic demand: hippocampal CA1, cerebellar Purkinje cells, and neocortical layers 3/5/6 are the classic “watershed for oxygen” regions in hypoxic-ischemic injury.

Chronic Hypercapnic Encephalopathy

Hypercapnia (elevated PaCO₂) causes potent vasodilation of cerebral arterioles, particularly affecting small vessels.

- **Threshold:** Manifests acutely when PaCO₂ exceeds 50 mmHg in normocapnic patients, or greater than 60 mmHg in chronic CO₂ retainers (e.g., COPD).
- **Symptoms:** The “hypercapnic encephalopathy syndrome” includes headache, psychomotor agitation, and coma.

4.3 Organ Transplantation Neurology

A. Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is driven by endothelial dysfunction and failed cerebral autoregulation.

- **Neuroimaging hallmark:** Symmetric parieto-occipital vasogenic edema involving subcortical white matter and overlying cortex.
- **Triggers in transplant recipients:** Calcineurin inhibitors (cyclosporine, tacrolimus) cause drug-related endothelial activation and increased vascular permeability.
- **Management:** Rapid blood pressure titration is a mainstay of treatment, alongside removal or dose optimization of the precipitating immunosuppressant.

B. Calcineurin Inhibitor Toxicity (Cyclosporine and Tacrolimus)

Commonly used for maintenance immunosuppression in solid organ transplant recipients.

- **Neuro-toxicities:** Tremor, polyneuropathy, seizures, and severe encephalopathy (including PRES).
- **Monitoring pearl:** PRES may develop after months of otherwise stable therapy; the severity of neurologic symptoms may not correlate with serum drug levels.

PITFALL

Do not rely on a “normal” calcineurin-inhibitor trough level to exclude PRES or drug-related neurotoxicity — clinical severity frequently does not correlate with measured serum drug concentration.

C. Opportunistic CNS Infections in Transplant Recipients

The type of infection varies by the organ transplanted and by the time elapsed since transplantation.

Pathogen	Context / Sign	Management
Cytomegalovirus (CMV)	Most common in kidney recipients; may be donor-derived.	Prophylaxis and donor screening are key preventive measures.
Listeria monocytogenes	Risk in T-cell suppressed patients.	Ampicillin is the standard treatment.
Cryptococcus	Common fungal opportunistic infection.	Liposomal amphotericin B.
Ureaplasma / Mycoplasma	Associated with idiopathic hyperammonemia after lung transplantation.	High mortality; requires urgent ammonia clearance.

Pathogen	Context / Sign	Management
JC virus (PML)	Seen with anti-integrin agents (e.g., natalizumab) or severe immunosuppression.	Progressive multifocal leukoencephalopathy; reduce/reverse immunosuppression.

Hyperammonemia Clearing Protocol (Post-Lung Transplant)

- **Threshold:** Ammonia greater than 150 $\mu\text{mol/L}$ carries a high risk for cerebral edema.
- **Management:** Continuous renal replacement therapy (CRRT) or a molecular adsorbent recirculating system (MARS) is used to clear ammonia.

EMERGENCY

Idiopathic hyperammonemia after lung transplantation, typically due to Ureaplasma/Mycoplasma infection, is a high-mortality emergency requiring urgent ammonia clearance (CRRT or MARS) and targeted antimicrobial therapy.

Wernicke Encephalopathy Dosing (Critical Illness Emergency)

Required for patients at nutritional risk in the ICU, including those with a history of bariatric surgery or hyperemesis gravidarum.

Phase	Dose
Induction	500 mg IV three times daily for 2 days.
Transition	250 mg IV/IM daily for 5 days, followed by 100 mg PO daily.

EMERGENCY

Always administer thiamine before glucose in any at-risk patient to avoid precipitating fulminant Wernicke encephalopathy.

CHAPTER 5

Neurology of Systemic Infections, Toxicology, and Inborn Errors of Metabolism

Neurotropic Infections, Heavy Metal & Alcohol-Related Neurotoxicity, Wilson Disease, and Metabolic Crisis Protocols

5.1 Systemic Infectious Diseases with Neuro-Tropism

Specialized serologic tests such as syphilis serology are often low-yield when ordered indiscriminately in an undifferentiated critically ill population; nonetheless, specific diagnostic and treatment algorithms remain essential for targeted management once clinical suspicion is raised.

Table 5.1 — Diagnostic and Treatment Parameters for Systemic Infections

Disease	Clinical Stages / Syndromes	Diagnostic Biomarkers & CSF Criteria	Treatment Protocol
Neurosyphilis	Meningovascular: stroke-like presentations. General paresis: dementia, psychiatric change. Tabes dorsalis: sensory ataxia, lightning pains.	CSF: reactive VDRL (highly specific); elevated protein (>45 mg/dL); WBC pleocytosis (>5 cells/ μ L). Serum: FTA-ABS or TP-PA.	IV penicillin G: 18–24 million units daily (3–4 million units every 4 hours) for 10–14 days.
Lyme neuroborreliosis	Bannwarth syndrome: triad of lymphocytic meningitis, cranial neuritis (often facial nerve), and painful radiculopathy.	Two-tier serologic testing: ELISA followed by Western blot confirmation (IgM/IgG).	IV ceftriaxone 2 g daily for 14–21 days.
HIV-associated neurological disease	HAND: subcortical dementia. Opportunistic: toxoplasmosis (ring-enhancing lesions), cryptococcal meningitis, primary CNS lymphoma.	Cryptococcus: CSF CrAg titers. Toxoplasmosis: serum IgG. JC virus: CSF PCR for PML.	Combination antiretroviral therapy (ART) for HAND. Toxoplasmosis: pyrimethamine/sulfadiazine. Cryptococcus: amphotericin B.

MEMORY TIP / MNEMONIC

Bannwarth syndrome (Lyme neuroborreliosis) triad: lymphocytic meningitis + facial nerve palsy (often bilateral) + painful radiculopathy.

Differential Diagnosis — Ring-Enhancing Brain Lesions in HIV

Diagnosis	Distinguishing Feature
Toxoplasmosis	Multiple lesions, basal ganglia predilection; responds to empiric pyrimethamine/sulfadiazine within 2 weeks.

Diagnosis	Distinguishing Feature
Primary CNS lymphoma	Often single, periventricular; positive EBV PCR in CSF; does not improve with empiric anti-toxoplasma therapy.
Progressive multifocal leukoencephalopathy (PML)	Non-enhancing (or minimally enhancing) white matter lesions; positive CSF JC virus PCR.
Tuberculoma	Associated basilar meningitis; may show central caseation on MRI; positive AFB/PCR.

5.2 Clinical Neurotoxicology

Bilateral, symmetric abnormalities on MRI should immediately prompt the clinician to consider a toxic or metabolic pathology rather than a focal structural process.

Table 5.2 — Heavy Metal and Alcohol-Related Neurotoxicity

Agent / Syndrome	Clinical Features	Diagnostic Clues / MRI Patterns	Management / Chelation
Lead (Pb)	Encephalopathy, wrist drop, abdominal colic.	Whole blood lead level.	Succimer or EDTA (calcium disodium).
Mercury (Hg)	Tremor, erethism (irritability/emotional lability), constricted visual fields.	24-hour urine mercury.	Dimercaprol (BAL) or succimer.
Arsenic (As)	Mees lines, painful polyneuropathy.	Spot or 24-hour urine arsenic.	Dimercaprol (BAL).
Marchiafava-Bignami disease	Associated with chronic alcohol use and malnutrition.	MRI: selective necrosis of the corpus callosum.	Aggressive IV thiamine (B1) supplementation.
Central pontine myelinolysis	Result of rapid electrolyte shift (typically overcorrection of hyponatremia).	MRI: central pontine T2 hyperintensity sparing the periphery (“trident” sign).	Preventive: limit sodium correction to < 8–10 mmol/L per 24 hours.

📌 IMPORTANT NOTE

Specific heavy-metal chelation regimens (agent selection and mg/kg dosing) reflect general toxicology consensus rather than a single verified primary source in this material; confirm current dosing against a regional poison control center or toxicology reference before clinical use.

5.3 Systemic Metabolic & Storage Diseases

Wilson disease remains a critical, treatable cause of hepatocerebral degeneration that can present as late as age 70.

Table 5.3 — Wilson Disease Diagnostic (Leipzig) Scoring System

Criterion	Finding / Threshold	Points
Kayser-Fleischer rings	Present on slit-lamp examination.	2
Neurologic signs	Severe (2) or mild (1) — e.g., wing-beating tremor, risus sardonicus.	1–2
Serum ceruloplasmin	< 0.1 g/L (2 pts); 0.1–0.2 g/L (1 pt); normal (0 pts).	0–2
Urinary copper (24-hour)	> 2 × upper limit of normal (ULN) (2 pts); 1–2 × ULN (1 pt).	0–2
Genetic testing	ATP7B mutation on both chromosomes (4 pts) or one chromosome (1 pt).	1–4
Liver copper (quantitative)	> 4 µmol/g dry weight.	2

Score	Interpretation
≥ 4	Diagnosis established.
2–3	Diagnosis possible; further testing indicated.
0–1	Diagnosis unlikely.

CLINICAL PEARL

The “face of the giant panda” sign on midbrain MRI — T2 hyperintensity in the midbrain tegmentum with sparing of the red nuclei and substantia nigra — is highly specific for Wilson disease.

Table 5.4 — Metabolic Crisis & Maintenance Dosing Protocols

Condition	Emergent / Induction Dose	Maintenance / Chronic Target
Wilson disease	Chelation: D-penicillamine or trientine.	Zinc salts: competitive inhibition of intestinal copper absorption.
Acute intermittent porphyria	Hemin/hematin: 3–4 mg/kg IV daily for 4 days.	Avoid porphyrinogenic medications (e.g., certain barbiturates).
Wernicke encephalopathy	High-dose B1: 500 mg IV three times daily for 2 days.	Transition: 250 mg IV/IM daily for 5 days.

WARNING

Acute intermittent porphyria attacks can be precipitated by numerous common medications (including many barbiturates, some anticonvulsants, and certain antibiotics). Always cross-check new prescriptions against a porphyria-safe drug list in known or suspected porphyria patients.

Differential Diagnosis — Bilateral Basal Ganglia / Midbrain MRI Signal Change

Diagnosis	Distinguishing Pattern
Wilson disease	“Face of the giant panda” sign in midbrain; Kayser-Fleischer rings; low ceruloplasmin.
Uremic encephalopathy	“Lentiform fork sign” in bilateral basal ganglia; elevated BUN/creatinine.
Hepatic encephalopathy (manganese deposition)	T1 hyperintensity in globi pallidi; elevated ammonia; liver disease.
Diabetic striatopathy	Unilateral T1 hyperintensity in putamen/caudate; hemichorea; marked hyperglycemia.
Central pontine myelinolysis	T2 hyperintensity confined to central pons; history of rapid sodium correction.

Abbreviations

Abbreviation	Full Term
ACR	American College of Rheumatology
AFib	Atrial Fibrillation
AION	Arteritic Anterior Ischemic Optic Neuropathy
AL	Amyloid Light-chain
ANCA	Antineutrophil Cytoplasmic Antibody
aPL	Antiphospholipid Antibody
APS	Antiphospholipid Syndrome
ART	Antiretroviral Therapy
BAL	British Anti-Lewisite (Dimercaprol)
CANOMAD	Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM paraprotein, cold Agglutinins, Disialosyl antibodies
CAR T	Chimeric Antigen Receptor T-cell
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CRRT	Continuous Renal Replacement Therapy
CRS	Cytokine Release Syndrome
CSF	Cerebrospinal Fluid
DADS	Distal Acquired Demyelinating Symmetric neuropathy
DOAC	Direct Oral Anticoagulant
DSA	Digital Subtraction Angiography
DSPN	Distal Symmetric Polyneuropathy
EGPA	Eosinophilic Granulomatosis with Polyangiitis
GCA	Giant Cell Arteritis
GPA	Granulomatosis with Polyangiitis
HAND	HIV-Associated Neurocognitive Disorder
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICI	Immune Checkpoint Inhibitor
IE	Infective Endocarditis
irAE	Immune-Related Adverse Event

Abbreviation	Full Term
IVIg	Intravenous Immunoglobulin
MARS	Molecular Adsorbent Recirculating System
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
MPA	Microscopic Polyangiitis
NMOSD	Neuromyelitis Optica Spectrum Disorder
NPSLE	Neuropsychiatric Systemic Lupus Erythematosus
PAN	Polyarteritis Nodosa
PLEX	Plasma Exchange
PML	Progressive Multifocal Leukoencephalopathy
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes
PRES	Posterior Reversible Encephalopathy Syndrome
SCD	Sickle Cell Disease
SCLC	Small Cell Lung Cancer
SFN	Small Fiber Neuropathy
SLE	Systemic Lupus Erythematosus
SREAT	Steroid-Responsive Encephalopathy associated with Autoimmune Thyroiditis
TCD	Transcranial Doppler
TIND	Treatment-Induced Neuropathy of Diabetes
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor



NEURO NOTES

RASHAD ALGHURABI

*May these notes
guide your learning,
sharpen your thinking,
and support your journey
to becoming an excellent
neurologist.*

KEEP LEARNING.
KEEP GROWING.

THANK YOU FOR TRUSTING
NEURO NOTES.



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