NEUROLOGY & NEUROIMMUNOLOGY REFERENCE

Multiple Sclerosis (MS)

Pathophysiology, Clinical Phenotypes, McDonald Diagnostic Criteria, and Disease-Modifying Therapies

Multiple Sclerosis (MS) is a chronic, immune-mediated inflammatory, demyelinating, and neurodegenerative disorder of the central nervous system (CNS)—affecting the brain, optic nerves, and spinal cord. Primarily diagnosed in young adults (typically ages 20–40) with a roughly 3:1 female-to-male predominance, MS is the leading cause of non-traumatic neurological disability in young adults.

> **Therapeutic Paradigm Shift:** Contemporary MS care emphasizes early initiation of high-efficacy Disease-Modifying Therapies (DMTs) rather than gradual escalation, aiming to achieve "No Evidence of Disease Activity" (NEDA)—absence of clinical relapses, MRI lesion progression, and disability worsening—before irreversible axonal loss occurs.

1. Pathophysiology & Etiology

MS arises from complex interactions between genetic susceptibility (notably the *HLA-DRB1*15:01* allele) and environmental triggers—most strongly prior Epstein-Barr Virus (EBV) seroconversion, alongside low vitamin D levels, limited sunlight exposure, smoking, and adolescent obesity.

- **Blood-Brain Barrier (BBB) Breakdown & Focal Inflammation:** Autoreactive peripheral T-lymphocytes (Th1, Th17, and CD8+ T-cells) and B-lymphocytes cross a compromised BBB into the CNS parenchyma, initiating perivenular inflammatory plaques.
- **Demyelination & Conduction Block:** Macrophages, activated microglia, and complement-fixing antibodies strip myelin sheaths from axons and destroy oligodendrocytes. Loss of saltatory conduction slows or blocks action potentials, producing acute neurological deficits.
- **Neurodegeneration & Progression Independent of Relapse (PIRA):** Over time, chronic compartmentalized CNS inflammation, mitochondrial dysfunction, and lack of trophic myelin support drive diffuse axonal transection and gray/white matter brain atrophy, causing gradual neurological progression.

2. Clinical Disease Phenotypes

MS is classified into clinical phenotypes based on disease activity (clinical relapses or new MRI lesions) and disability progression over time.

Phenotype	Proportion at Onset	Clinical Trajectory & Key Characteristics
Clinically Isolated Syndrome (CIS)	First clinical presentation	A first monophasic neurological episode lasting ≥24 hours suggestive of CNS demyelination (e.g., optic neuritis, transverse myelitis, brainstem syndrome) that does not yet fulfill full dissemination in time criteria.
Relapsing-Remitting MS (RRMS)	~85% of patients	Characterized by clearly defined acute attacks (relapses) of new or worsening neurological symptoms followed by periods of partial or complete recovery (remission) without baseline progression between relapses.
Secondary Progressive MS (SPMS)	Evolves from RRMS	Gradual, steady accumulation of neurological disability independent of relapses following an initial relapsing-remitting course, with or without superimposed occasional relapses or MRI activity.
Primary Progressive MS (PPMS)	~10–15% of patients	Steady, progressive accumulation of neurological disability from symptom onset without distinct relapses or remissions. Typically presents later (ages 40–50) with equal sex distribution and prominent spinal cord involvement (progressive spastic paraparesis).

3. Clinical Manifestations & Diagnostic Criteria

Symptoms reflect the anatomical location of demyelinating plaques throughout the CNS and frequently exhibit transient worsening with elevated core body temperature (**Uhthoff's phenomenon**).

- **Classic Presenting Syndromes:** Unilateral optic neuritis (painful subacute monocular vision loss with afferent pupillary defect), partial transverse myelitis (asymmetric sensory levels, limb weakness, bladder/bowel urgency), brainstem/cerebellar syndromes (internuclear ophthalmoplegia [INO], diplopia, trigeminal neuralgia, ataxia), and Lhermitte's sign (electric-shock sensation down the spine upon neck flexion).
- **McDonald Diagnostic Principles:** Diagnosis requires objective clinical or paraclinical evidence of CNS lesions demonstrating **Dissemination in Space (DIS)** and **Dissemination in Time (DIT)**, after excluding alternative mimics (e.g., NMOSD, MOGAD, neurosarcoidosis, CNS vasculitis, B12 deficiency).
- **MRI & CSF Biomarkers:** Brain and spinal cord MRI reveals ovoid T2/FLAIR hyperintense lesions perpendicular to the lateral ventricles (*Dawson's fingers*), juxtacortical/cortical, infratentorial, and short-segment spinal lesions. DIS requires ≥1 T2 lesion in ≥2 of 4 typical CNS regions; DIT is shown by simultaneous gadolinium-enhancing and non-enhancing lesions, new T2 lesions on follow-up MRI, or **CSF-specific oligoclonal bands (OCBs)** substituting for DIT in CIS/RRMS.

4. Management: Relapses, DMTs & Symptom Care

Comprehensive MS treatment combines acute relapse shortening, long-term immunomodulation to prevent future CNS injury, and targeted multidisciplinary symptom management.

Acute Relapse Treatment

- **High-Dose Corticosteroids:** Intravenous methylprednisolone (500–1,000 mg daily for 3–5 days) or bioequivalent high-dose oral prednisone (1,250 mg daily) accelerates functional recovery from disabling relapses by restoring BBB integrity and resolving acute edema, though it does not alter long-term disability outcomes.
- **Plasmapheresis (PLEX):** Reserved as rescue therapy for severe, steroid-refractory relapses (e.g., severe optic neuritis or transverse myelitis).

Disease-Modifying Therapies (DMTs)

- **High-Efficacy Monoclonal Antibodies:** Anti-CD20 B-cell-depleting agents (**ocrelizumab**—also approved for PPMS—**ofatumumab**, **ublituximab**, rituximab), anti-α4-integrin leukocyte trafficking blocker (**natalizumab**—requires JC virus antibody monitoring for PML risk), and anti-CD52 immune reconstitution therapy (**alemtuzumab**).
- **Oral Agents:** Sphingosine-1-phosphate (S1P) receptor modulators sequestering lymphocytes in lymph nodes (**fingolimod**, **siponimod**, **ozanimod**, **ponesimod**), Nrf2 activators (**dimethyl fumarate**, diroximel fumarate), pyrimidine synthesis inhibitor (**teriflunomide**), and purine analog (**cladribine**).
- **Platform Injectable Therapies:** Interferon-beta formulations and glatiramer acetate, offering favorable long-term safety profiles for milder disease or pregnancy planning.

Symptom Management & Neurorehabilitation

- **Targeted Symptomatic Relief:** Baclofen or tizanidine for spasticity; dalfampridine (4-aminopyridine) to improve walking speed; amantadine, modafinil, or structured aerobic exercise for MS-related fatigue; anticholinergics, mirabegron, or intermittent catheterization for neurogenic bladder; and physical, occupational, and cognitive rehabilitation.