Annals of Internal Medicine®

In the Clinic®

Multiple Sclerosis

Many groundbreaking advances have occurred in the field of multiple sclerosis since this series last reviewed the disorder in 2014. The U.S. Food and Drug Administration has approved 7 new medications for relapsing–remitting multiple sclerosis and approved the first medication for primary progressive multiple sclerosis. The McDonald criteria for diagnosing multiple sclerosis were updated in 2017. New blood tests can now differentiate patients with multiple sclerosis from those with neuromyelitis optica spectrum disorder, and 3 new medications have been approved specifically for the latter disorder. Also, new medications for treating the symptoms of multiple sclerosis have been introduced.

CME/MOC activity available at Annals.org.

Physician Writer
Michael J. Olek, DO
Touro University Nevada, Henderson, Nevada

doi:10.7326/AITC202106150

This article was published at Annals.org on 8 June 2021.

CME Objective: To review current evidence for diagnosis and treatment of multiple sclerosis.

Funding Source: American College of Physicians.

Acknowledgment: The author thanks Daniel M. Harrison, MD, author of the previous version of this In the Clinic.

Disclosures: Dr. Olek, ACP Contributing Author, reports that he is the first author of the chapter on multiple sclerosis in UpToDate. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-0830.

With the assistance of additional physician writers, the editors of **Annals of Internal Medicine** develop **In the Clinic** using **MKSAP** and other resources of the American College of Physicians. The patient information page was written by Monica Lizarraga from the Patient and Interprofessional Partnership Initiative at the American College of Physicians.

1. Wallin MT, Culpepper WJ, Campbell JD, et al; US Multiple Sclerosis Prevalence Workgroup. The prevalence of MS in the United States: a population-based estimate using health claims data. Neurology. 2019;92: e1029-e1040. [PMID: 30770430]
2. Islam T, Gauderman WJ, Cozen W, et al. Differential twin concordance for multiple sclerosis by latitude of birthplace. Ann Neurol. 2006;60:56-64. [PMID: 16685699]
3. Patsopoulos NA, Barcellos LF, Hintzen RQ, et al; IMSGC. Fine-mapping the genetic association of the major histocompatibility complex in multiple sclerosis: HLA and non-HLA effects. PLoS Genet. 2013;9:e1003926. [PMID: 24278027]
4. Beecham AH, Patsopoulos NA, Xifara DK, et al; International Multiple Sclerosis Genetics Consortium (IMSGC). Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. Nat Genet. 2013;45:1353-60. [PMID: 24076602]
5. Sintzel MB, Rametta M, Reder AT. Vitamin D and multiple sclerosis: a comprehensive review. Neurol Ther. 2018;7:59-85. [PMID: 29243029]
6. Lassmann H, Niedobitek G, Aloisi F, et al; NeuroproMiSe EBV Working Group. Epstein–Barr virus in the multiple sclerosis brain: a controversial issue–report on a focused workshop held in the Centre for Brain Research of the Medical University of Vienna, Austria. Brain. 2011;134:2772-86. [PMID: 21846731]
7. de la Cruz J, Kupersmith MJ.. Clinical profile of simultaneous bilateral optic neuritis in adults. Br J Ophthalmol. 2006;90:551-4. [PMID: 16622084]
8. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162-73. [PMID: 29275977]
9. O'Riordan JI, Thompson AJ, Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain. 1998;121:495-503. [PMID: 9549525]
10. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain. 1989;112:133-46. [PMID: 2917275]

Multiple sclerosis is an autoimmune condition that results in inflammatory damage to the central nervous system (CNS). The pathologic hallmarks are diffuse and focal areas of inflammation, demyelination, gliosis, and neuronal injury in the optic nerves, brain, and spinal cord. In addition to affecting white matter tracts, multiple sclerosis results in injury to the cortical and deep gray matter. The neurologic symptoms and disability that patients experience are a direct consequence of these pathologic processes, resulting in acute and chronic disruption of white matter tracts and gray matter structures.

Multiple sclerosis is the most common nontraumatic cause of neurologic disability in persons younger than 40 years. In 2010, the estimated prevalence in the United States was 309.2 per 100 000 persons, or 727 433 adults (1). It occurs in a female–male ratio of 2.8 to 1 (1).

The cause of multiple sclerosis is multifactorial and is probably the cumulative result of multiple genetic and environmental risk factors. Studies have shown concordance rates between 20% and 30% in monozygotic twins and between 2% and 3% in dizygotic twins (2). Genome-wide assays have identified risk alleles in the genes for major histocompatibility complex, interleukin-2 receptor, and interleukin-7 receptor, among others (3,4). Geographic location of residence before adolescence also predicts risk, with increased rates in northern and southern latitudes compared with equatorial areas. This may be related to the observation that persons with vitamin D deficiency seem to have increased risk for multiple sclerosis. Because ultraviolet radiation to the skin is the major source of vitamin D synthesis, vitamin D deficiency is more common among persons living in regions with low levels of seasonal sunlight (5). Risk may also be influenced by exposure or lack of exposure to infectious agents because antibodies against certain viruses, such as Epstein–Barr virus, are more frequently seen in patients with multiple sclerosis than in those without it (6).

Diagnosis

What characteristic symptoms or physical findings should alert clinicians to the diagnosis of multiple sclerosis?

Symptoms typically occur as a consequence of focal inflammatory plaques that cause functional areas of neuronal loss or interruption of critical axonal tracts. In most patients, focal lesions occur intermittently and acutely, leading to a "relapse" or "flare" in which symptoms evolve over the course of days and may last for weeks or months before improving, if they do improve.

Because multiple sclerosis can affect nearly any part of the CNS, clinical presentations vary widely. The most common initial clinical manifestations are the result of inflammation of the optic nerve (optic neuritis), focal inflammation within the spinal cord (myelitis), and brainstem or cerebellar lesions. Each of these is termed a clinically isolated syndrome (CIS). Optic neuritis often presents with subacute vision changes that vary from blindness to a central scotoma or a horizontal oval scotoma embracing both the fixation point and the blind spot (centrocecal scotoma)—predominantly in 1 eye (90%) and rarely in both eyes (10%)—along with pain during eye

movement (7). Ocular examination usually reveals a reduction in visual acuity, a visual field deficit, and a decreased ability to differentiate colors. Examination of the pupil in patients with unilateral optic neuritis reveals paradoxical dilation of the pupil in the affected eye when light is rapidly and repeatedly shifted from one eye to the other (afferent pupillary defect). If the anterior portion of the optic nerve is involved, funduscopic examination may also reveal inflammatory changes of the optic disc (papillitis).

Myelitis usually manifests as sensory or motor symptoms below the affected spinal level, and examination often reveals focal muscle weakness and reduced sensation in the same distribution. Muscles can be flaccid in the acute setting, but spasticity develops over time in patients who do not recover completely from the attack. Unlike other spinal cord processes, multiple sclerosis tends to cause a partial myelitis, so symptoms similar to a full-cord transection are exceedingly rare. Some patients may also have a tight, band-like sensation around the chest or abdomen during the acute inflammatory process; shock-like sensations radiating down the spine or limbs induced by neck movements (Lhermitte sign); and urinary frequency, urinary urgency, or urine retention.

Disruption of vestibular or cerebellar pathways can lead to ataxia and vertigo. Examination can also find impaired ability to perform smoothly coordinated voluntary movements of the limbs or trunk (appendicular or truncal ataxia), dysmetria on finger-to-nose testing, and dysfunction during tandem gait. Brainstem involvement can lead to eye movement abnormalities that cause symptoms of diplopia or a sensation of jerking of the visual field (oscillopsia). Oculomotor examination can also find disconjugate eye movements, nystagmus, or an inability to adduct 1 eye with nystagmus in the abducting eye (internuclear ophthalmoplegia).

In addition to the development of acute or subacute focal symptoms, patients with multiple sclerosis may have chronic symptoms due to widespread cortical demyelination and global brain atrophy. Common manifestations include cognitive dysfunction and mental and physical fatigue.

Many patients with multiple sclerosis also have transient worsening of baseline neurologic symptoms when body temperature is elevated (Uhthoff phenomenon) because electrical messages travel more slowly over areas with demyelination-related injury when temperature is increased. These events are sometimes termed "pseudorelapses." They must be differentiated from true relapses because they do not represent new inflammatory events; do not require direct treatment; and typically resolve in cooler temperatures or after resolution of fever and infection, which usually indicates an asymptomatic urinary tract infection. If the elevated temperature is due to an infection, it is even more important to distinguish a pseudorelapse from a true relapse because antibiotics are indicated and steroids may make the infection worse.

What are the characteristics of each subtype of multiple sclerosis?

The time course of symptom onset and the evolution of symptoms determine the clinical subtype of multiple sclerosis, and this is important for choosing the correct disease-modifying therapy (DMT). For example, it is important to differentiate relapsing–remitting multiple sclerosis (RRMS) from primary

11. Kremenchutzky M, Rice GP, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. Brain. 2006;129:584-94. [PMID: 16401620]
12. Filippi M, Rocca MA, Ciccarelli O, et al; MAGNIMS Study Group. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016;15:292-303. [PMID: 26822746]
13. Bakshi R, Thompson AJ, Rocca MA, et al. MRI in multiple sclerosis: current status and future prospects. Lancet Neurol. 2008;7:615-25. [PMID: 18565455]
14. Stangel M, Fredrikson S, Meinl E, et al. The utility of cerebrospinal fluid analysis in patients with multiple sclerosis. Nat Rev Neurol. 2013;9:267-76. [PMID: 23528543]
15. Gronseth GS, Ashman EJ. Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;54:1720-5. [PMID: 10802774]
16. Costello F, Burton JM. Retinal imaging with optical coherence tomography: a biomarker in multiple sclerosis. Eye Brain. 2018;10:47-63. [PMID: 30104912]
17. Garcia-Martin E, Pablo LE, Herrero R, et al. Diagnostic ability of a linear discriminant function for spectral-domain optical coherence tomography in patients with multiple sclerosis. Ophthalmology. 2012;119:1705-11. [PMID: 22480742]
18. Solomon AJ, Naismith RT, Cross AH. Misdiagnosis of multiple sclerosis: impact of the 2017 McDonald criteria on clinical practice. Neurology. 2019;92:26-33. [PMID: 30381369]
19. Jarius S, Wildemann B. The history of neuromyelitis optica. J Neuroinflammation. 2013;10:8. [PMID: 23320783]
20. Wallach AI, Tremblay M, Kister I. Advances in the treatment of neuromyelitis optica spectrum disorder. Neurol Clin. 2021;39:35-49. [PMID: 33223088]

21. Goldschmidt C, McGinley MP. Advances in the treatment of multiple sclerosis. Neurol Clin. 2021;39:21-33. [PMID: 33223085]
22. Amato MP, Fonderico M, Portaccio E, et al. Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis. Brain. 2020;143:3013-24. [PMID: 32935843]
23. Buron MD, Chalmer TA, Sellebjerg F, et al. Initial high-efficacy disease-modifying therapy in multiple sclerosis: a nationwide cohort study. Neurology. 2020;95:e1041-e1051. [PMID: 32636328]
24. Polman CH, O'Connor PW, Havrdova E, et al; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899-910. [PMID: 16510744]
25. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870-80. [PMID: 22591293]
26. Reuwer AQ, Heron M, van der Dussen D, et al. The clinical utility of JC virus antibody index measurements in the context of progressive multifocal leukoencephalopathy. Acta Neurol Scand. 2017;136 Suppl 201:37-44. [PMID: 29068484]
27. Kolcava J, Hulova M, Benesova Y, et al. The value of anti-JCV antibody index assessment in multiple sclerosis patients treated with natalizumab with respect to demographic, clinical and radiological findings. Mult Scler Relat Disord. 2019;30:187-91. [PMID: 30785075]
28. Lee P, Plavina T, Castro A, et al. A second-generation ELISA (STRATIFY JCV™ DxSelect™) for detection of JC virus antibodies in human serum and plasma to support progressive multifocal leukoencephalopathy risk stratification. J Clin Virol. 2013;57:141-6. [PMID: 23465394]
29. Gold R, Kappos L, Arnold DL, et al; DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012;367:1098-107. [PMID: 22992073]
30. Freeman L, Kee A, Tian M, et al. Evaluating treatment patterns, relapses, healthcare resource utilization, and costs associated with disease-modifying treatments for multiple sclerosis in DMT-naïve patients. Clinicoecon Outcomes Res. 2021;13:65-75. [PMID: 33519217]

progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS).

Approximately 85% of patients with multiple sclerosis initially have RRMS, in which neurologic symptoms appear as repeated episodes of relapse followed by recovery. Patients who do not meet the full criteria for multiple sclerosis when they have their first event are said to have had a CIS. Because DMTs can extend the time from the first clinical event to the second event, it is important to correctly identify patients who have RRMS or have a high likelihood of having the diagnosis confirmed at a later date, which is why specific diagnostic criteria are so important (8). For example, people who have an acute demyelinating attack, such as optic neuritis or partial myelitis with brain lesions on magnetic resonance imaging (MRI) scans, have a 10-year risk of approximately 90% for eventually meeting criteria for multiple sclerosis. In contrast, those who have a similar event without brain lesions have a risk of approximately 10% to 20% (9).

The symptoms of an individual relapse tend to peak after a few days or weeks. A period of recovery follows that may last weeks or months. During the first few years, many patients experience significant recovery of previous functioning. However, as time passes and more relapses occur, the amount of recovery from each relapse diminishes and permanent disability can occur. In approximately 50% to 60% of patients with RRMS, relapses become infrequent or cease completely after a median of 10 to 15 years, but neurologic deficits continue to accrue in a slowly progressive manner (10). This stage of multiple sclerosis is termed *secondary progressive multiple sclerosis*.

Approximately 15% of patients with multiple sclerosis have steady accumulation of progressive disability from the time of disease onset, with only a rare relapse. This subtype is termed *primary progressive multiple sclerosis*, and it often presents later in life, with the first symptoms typically occurring in the fifth or sixth decade. The accumulation of disability can occur rapidly. Early studies of the natural history of this subtype implicated sex and age at onset as predictors of rapid progression, but recent studies support only accrual of early disability as a predictor of long-term progression rates (11).

What are the McDonald criteria, and how can they help clinicians diagnose multiple sclerosis?

Confirming the diagnosis of multiple sclerosis requires a full assessment of clinical symptoms, physical examination, testing, and consideration of other conditions in the differential diagnosis because diagnostic biomarkers for this condition do not exist. The 2017 McDonald criteria are widely accepted as the best way to integrate the different types of evidence (8). For example, to establish a diagnosis of multiple sclerosis, the McDonald criteria may require 2 relapses plus 2 objective signs over time or 1 relapse (as a CIS) plus 2 clinical signs plus specific MRI findings (12). There also must be no better explanation for the patient's symptoms, clinical findings, and MRI findings. The McDonald criteria are readily available online (for example, at www.aan.com). Although clinical research studies usually adhere strictly to the McDonald criteria, many specialists use them in individual patients more as a guideline than as strict criteria. For example, a clinician may diagnose possible multiple sclerosis and start a DMT even though the patient does not meet criteria because the tradeoff between risk and benefit favors early treatment.

The McDonald criteria can also be used to diagnose PPMS. These criteria require at least 1 year of progressive neurologic disability plus at least 2 of the following: dissemination in space on a brain MRI scan, dissemination in space on a spinal cord MRI scan, or cerebrospinal fluid (CSF) findings consistent with multiple sclerosis.

Proper application of the McDonald criteria can also help differentiate multiple sclerosis from other conditions and thus prevent unnecessary neurologic testing and referrals. This is especially true for common conditions, such as migraine, microvascular ischemic disease, and head trauma, which can cause white matter lesions on MRI scans but do not cause lesions that meet the McDonald criteria for location.

What is the role of MRI in diagnosis?

MRI is the primary diagnostic and prognostic tool for the evaluation of patients with multiple sclerosis. For most patients, the McDonald criteria require confirmation with MRI findings. Typical MRI findings are lesions in white matter regions that appear hyperintense on T2-weighted and fluid-attenuated inversion recovery images and hypointense on T1-weighted images. These lesions are areas of demyelination and gliosis. In addition, administration of gadolinium contrast will enhance lesions that are undergoing an active inflammatory process with breakdown of the blood–brain barrier. The **Figure** shows examples of lesions in each of the 4 locations emphasized by the McDonald criteria: periventricular, juxtacortical, brainstem and cerebellum (infratentorial), and spinal cord. Dissemination in space can be demonstrated by characteristic T2-hyperintense lesions that are in 2 or more of the 4 locations. Dissemination in time can be demonstrated by the simultaneous presence of a gadolinium-enhancing lesion and a nonenhancing lesion or by a new T2-hyperintense or gadolinium-enhancing lesion not present on a baseline scan, regardless of the timing of the baseline scan.

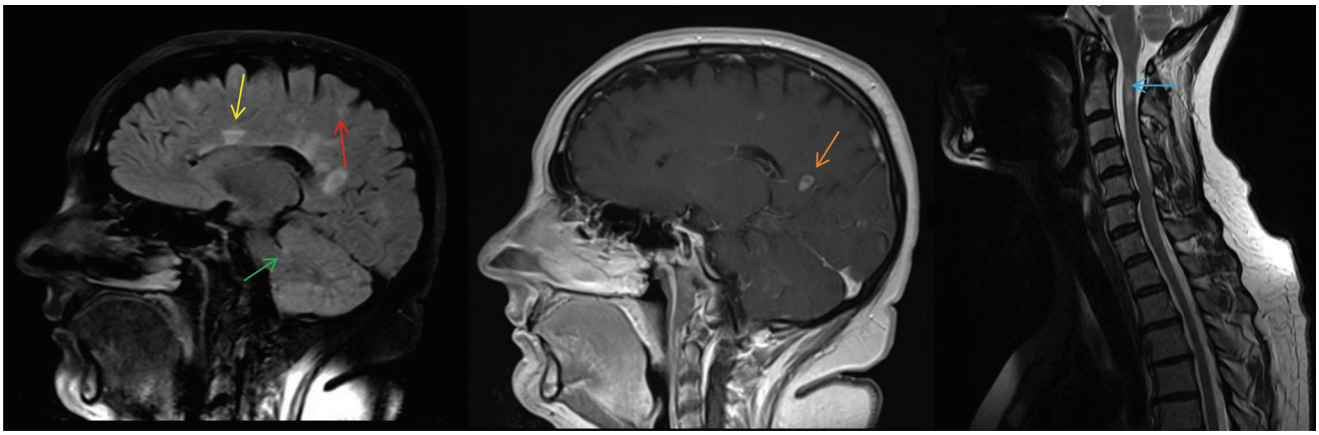
Although diagnostic criteria focus specifically on the presence of lesions in white matter, other MRI changes can be seen, including demyelinating lesions in the cortex; atrophy of cortical and deep gray matter; atrophy of white matter structure; and alterations in lesions and normal-appearing white matter indicated by magnetization transfer, diffusion tensor imaging, and other quantitative MRI measures (13).

What role does lumbar puncture play in diagnosis?

The McDonald criteria do not require testing of CSF to confirm the diagnosis of RRMS. For the diagnosis of PPMS, CSF testing is necessary only if MRI findings do not meet criteria for dissemination in space. However, CSF testing can be a useful diagnostic tool in cases where the diagnosis is not clear. CSF testing with isoelectric focusing finds unique oligoclonal bands in 90% to 95% of patients with multiple sclerosis (14). An elevation of the IgG index is seen in 50% to 75% of patients, and mild pleocytosis is seen in about half of patients. Given the sensitivity and specificity of these tests, negative CSF test results by themselves cannot rule out the diagnosis of multiple sclerosis. However, when negative CSF test results occur in patients with a low suspicion for multiple sclerosis based on clinical and radiologic findings, clinicians should consider other possible diagnoses and advise patients that they probably do not have multiple sclerosis.

31. Boffa G, Massacesi L, Inglese M, et al; Italian BMT-MS study group. Long-term clinical outcomes of hematopoietic stem cell transplantation in multiple sclerosis. Neurology. 2021. [PMID: 33472915]
32. Correale J, Ysrraelit MC, Gaitán MI. Gender differences in 1,25 dihydroxyvitamin D3 immunomodulatory effects in multiple sclerosis patients and healthy subjects. J Immunol. 2010;185:4948-58. [PMID: 20855882]
33. Mowry EM, Waubant E, McCulloch CE, et al. Vitamin D status predicts new brain magnetic resonance imaging activity in multiple sclerosis. Ann Neurol. 2012;72:234-40. [PMID: 22926855]
34. Simpson S Jr, Taylor B, Blizzard L, et al.. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. Ann Neurol. 2010;68:193-203. [PMID: 20695012]
35. Soilu-Hänninen M, Aivo J, Lindström BM, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012;83:565-71. [PMID: 22362918]
36. Miclea A, Bagnoud M, Chan A, et al. A brief review of the effects of vitamin D on multiple sclerosis. Front Immunol. 2020;11:781. [PMID: 32435244]
37. Runia TF, Hop WC, de Rijke YB, et al. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. Neurology. 2012;79:261-6. [PMID: 22700811]
38. Ramo-Tello C, Grau-López L, Tintoré M, et al. A randomized clinical trial of oral versus intravenous methylprednisolone for relapse of MS. Mult Scler. 2014;20:717-25. [PMID: 24144876]
39. Morrow SA, Stoian CA, Dmitrovic J, et al. The bioavailability of IV methylprednisolone and oral prednisone in multiple sclerosis. Neurology. 2004;63:1079-80. [PMID: 15452302]
40. Trebst C, Reising A, Kielstein JT, et al. Plasma exchange therapy in steroid-unresponsive relapses in patients with multiple sclerosis. Blood Purif. 2009;28:108-15. [PMID: 19521072]

Figure. **Examples of lesion locations emphasized by the McDonald criteria.**



Left. Sagittal, fluid-attenuated, inversion recovery brain sequence showing periventricular (*top arrow*), juxtacortical (*right-hand arrow*), and infratentorial (*bottom arrow*) lesions. **Middle.** Sagittal T1 image after administration of intravenous contrast. Lesions are typically either silent or dark on T1 imaging, but lesions that enhance with contrast (*arrow*) do so because of active inflammation in the lesion. **Right.** Sagittal T2 scan of the cervical spine showing a lesion at approximately the C2 level (*arrow*).

41. Simsarian JP, Saunders C, Smith DM. Five-day regimen of intramuscular or subcutaneous self-administered adrenocorticotropic hormone gel for acute exacerbations of multiple sclerosis: a prospective, randomized, open-label pilot trial. Drug Des Devel Ther. 2011;5:381-9. [PMID: 21792296]
42. Gómez-Figueroa E, Gutierrez-Lanz E, Alvarado-Bolaños A, et al. Cyclophosphamide treatment in active multiple sclerosis. Neurol Sci. 2021. [PMID: 33452657]
43. Rutschmann OT, McCrory DC, Matchar DB; Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines. Immunization and MS: a summary of published evidence and recommendations. Neurology. 2002;59:1837-43. [PMID: 12499473]
44. Farez MF, Correale J. Immunizations and risk of multiple sclerosis: systematic review and meta-analysis. J Neurol. 2011;258:1197-206. [PMID: 21431896]
45. Costa-Frossard L, Moreno-Torres I, Meca-Lallana V, et al. [EMCAM (Multiple Sclerosis Autonomous Community of Madrid) document for the management of patients with multiple sclerosis during the SARS-CoV-2 pandemic]. Rev Neurol. 2020;70:329-40. [PMID: 32329046]

When should clinicians consider obtaining evoked potentials?

Evoked potentials can be useful when the clinical examination and MRI are unable to provide evidence of dissemination in space because they can provide evidence of subclinical demyelinating lesions. Evoked potential tests measure the time it takes for the brain to respond to sensory stimulation, and the results are reported as conduction velocities. For example, reduced conduction velocity after visual stimuli can detect prior demyelination in an optic nerve even in patients who cannot recall an episode of optic neuritis (15). Reduced conduction velocity measured in the brainstem after auditory stimuli can detect a lesion along the acoustic and brainstem pathways, and reduced conduction velocity after somatosensory stimuli can detect lesions in spinal sensory pathways. Care should be taken in interpreting all of these results but especially the results of tests involving the brainstem and spinal cord because in patients with multiple sclerosis, these results are less likely to be abnormal than the results of visual-evoked potentials (15).

When should clinicians consider obtaining optical coherence tomography?

Optical coherence tomography uses near-infrared light to measure the thickness of the different layers that make up the retina. Patients with multiple sclerosis have reductions in the thickness of the retinal nerve fiber layer after optic neuritis (16), and this also can be seen in patients with multiple sclerosis who have not had optic neuritis (17). However, thinning of this layer also occurs after isolated optic neuritis without other manifestations of multiple sclerosis, in patients with neuromyelitis optica, and in patients with compressive lesions of the optic nerve. Thus, optical coherence tomography is not a definitive test for multiple sclerosis, but it can be useful for documenting dissemination in space for patients having a first attack that does not include optic neuritis.

Table 1. **Differential Diagnosis of Multiple Sclerosis**

Other Demyelinating Diseases	*Notes*
Acute disseminated encephalomyelitis	Monophasic, often postinfectious syndrome causing large, diffuse areas of inflammatory CNS demyelination, fever, and encephalopathy More common in children; rare in adults
NMO-SD	Antibody-mediated inflammation directed at aquaporin-4 channels in the CNS, resulting in inflammatory demyelination in the optic nerves and spinal cord Can be differentiated from MS by NMO IgG antibody testing; lack of significant brain involvement; large, longitudinally extensive spinal cord lesions; and profound cerebrospinal fluid leukocytosis
Idiopathic transverse myelitis	Monophasic, often postinfectious syndrome causing spinal cord inflammation
Systemic inflammatory disease	Differentiated from MS by the presence of symptoms and findings unique to the underlying systemic disorder in addition to neurologic symptoms
Systemic lupus erythematosus	Can present with encephalopathy and white matter changes on MRI
Sjögren syndrome	Can cause an NMO-SD–like disorder with optic neuritis and myelitis Also can cause multiple cranial neuropathies and small-fiber neuropathy
Sarcoidosis	Results in granulomatous inflammation in the parenchyma and meninges of the brain and spinal cord
Behçet syndrome	Can cause brainstem abnormalities and encephalopathy and is occasionally associated with myelopathy
Metabolic disorders	
Adult-onset leukodystrophy	Rare, adult-onset forms of leukodystrophy, such as adrenoleukodystrophy or metachromatic leukodystrophy, may cause white matter changes and progressive neurologic symptoms Family history typically present
Vitamin B_{12} deficiency	Can cause optic neuropathy, cognitive changes, and subacute combined degeneration of the spinal cord (spasticity, weakness, and vibratory and proprioceptive sensory loss)
Copper deficiency	Can cause a myelopathy identical to B_{12} deficiency
Zinc toxicity	Can cause an acquired copper deficiency
Vitamin E deficiency	Can cause cerebellar ataxia
Infections: HIV, Lyme disease, syphilis, HTLV	These disorders (except HTLV) can cause encephalopathy and myelopathy and can be diagnosed with appropriate serologic testing and spinal fluid analysis HTLV-1 causes a slowly progressive myelopathy with thoracic cord atrophy; it is sometimes termed *tropical spastic paraparesis* because it is more common in patients in equatorial latitudes
Vascular disorders	
Sporadic and genetic stroke syndromes (hypercoagulability disorders)	Microvascular ischemic disease can cause nonspecific white matter changes on MRI Age, other vascular risk factors, and neurologic examination findings help to distinguish it from MS
CNS vasculitis	Primary CNS vasculitis, which can be diagnosed by catheter angiography or tissue biopsy, can present with both stroke-like changes on MRI and meningeal contrast enhancement
Susac syndrome	Causes a small-vessel arteriopathy, which leads to dysfunction of the retina and cochlea and to corpus callosum lesions on MRI
Dural arteriovenous fistula	Can result in spinal cord infarction or vascular congestion with cord lesions that can be confused with MS lesions Subacute clinical progression without remission or relapse
Migraine	Subcortical white matter lesions can occur in patients with migraine and can often be confused with MS lesions Cerebral autosomal dominant arteriopathy with subcortical infarction and leukoencephalopathy (CADASIL) should be considered in patients with a familial syndrome of migraine, subcortical strokes, mood disorders, and early dementia
Neoplasia (i.e., primary CNS neoplasm [glioma or lymphoma] or metastatic disease)	Neoplasms have progressively worsening symptoms and neuroimaging findings When imaging cannot differentiate neoplasms from demyelinating disease, brain biopsy is indicated
Paraneoplastic syndromes	May cause progressive cerebellar ataxia or myeloneuropathy (neuropathy affecting the spinal cord and peripheral nerves) Paraneoplastic limbic encephalitis can cause personality and mental status changes in addition to seizures and movement disorders Metastatic evaluation and antibody testing may lead to diagnosis
Somatoform disorders	Psychiatric disorders can sometimes present with neurologic-like symptoms that are due to somatization, conversion, and similar conditions Neurologic work-up will be normal

CNS = central nervous system; HTLV = human T-lymphotropic virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; NMO-SD = neuromyelitis optica spectrum disorder.

What is the differential diagnosis?

Whenever the diagnosis of multiple sclerosis is being considered, conditions that mimic it (**Table 1**) should be part of the differential diagnosis. These include disorders that can cause neurologic symptoms and changes in MRI scans that are sometimes incorrectly diagnosed as multiple sclerosis. For example, a recent study found that approximately 30% of patients referred to a tertiary multiple sclerosis center had an incorrect diagnosis (18). The best way to distinguish patients with multiple sclerosis from those with other diagnoses is to conduct a comprehensive review of the patient's medical history, review of systems, and physical examination. Knowledge about other potential diagnoses that might be confused with multiple sclerosis is also useful.

One condition that may be confused with multiple sclerosis is neuromyelitis optica spectrum disorder (**Table 1**). Since 2004, it has been possible to diagnose this disorder by testing for a novel serum autoantibody termed neuromyelitis optica IgG or AQP4-Ab (19). An important reason to diagnose this disorder is that the U.S. Food and Drug Administration (FDA) has approved 3 medications to treat it in the past 2 years (eculizumab, inebilizumab, and satralizumab-mwge) (20).

When should clinicians consider consulting with a neurologist or another specialist for diagnosis?

Given the complexity of the diagnosis, if initial findings suggest multiple sclerosis, the clinician should refer the patient to a neurologist for further evaluation and testing. For cases in which the diagnosis is unclear or if initial treatment has failed, clinicians should consider obtaining a second opinion from 1 or more multiple sclerosis specialty clinics.

Diagnosis... Patients presenting with symptoms of a demyelinating disorder should have a thorough review of their medical history and physical examination, with special attention to the possibility of optic neuritis, myelitis, and brainstem or cerebellar lesions, and they should have an MRI scan of their brain and spinal cord. The diagnosis of multiple sclerosis is made by applying the revised 2017 McDonald criteria, which use a combination of findings to show dissemination of disease activity over space and time. Early referral to a neurologist is encouraged. Additional testing, such as lumbar puncture, evoked potentials, optical coherence tomography, and serum markers for other diseases, is not required but can be helpful in some patients for separating multiple sclerosis from other disorders.

CLINICAL BOTTOM LINE

Treatment

What is the overall approach to treating patients with multiple sclerosis?

The care of patients with multiple sclerosis requires a multidisciplinary approach and a comprehensive strategy with medication and nonmedical approaches for relapse management; prevention of relapses and delay of disease progression; and management of fatigue, cognitive function, spasticity, bladder dysfunction, and other symptoms. An increasing number of effective medications are available for these purposes. Treatment should also include assisting patients in maximizing daily function. Use of all of these tools has led to significant improvements in quality of life for many patients with multiple sclerosis. Although reducing disease progression currently focuses on controlling inflammatory disease activity early in RRMS, ongoing research provides hope for alleviating tissue injury through enhanced repair and the prevention of neurodegeneration.

What role does clinical subtype play in guiding treatment decisions?

Assigning a clinical subtype is a critical first step before starting any drug therapy. Most of the FDA's approvals for DMTs have been for CISs, RRMS, and active SPMS, but 1 new medication has been approved for PPMS (21).

Immunotherapy is indicated as soon as the diagnosis is established for most patients with CISs, RRMS, or PPMS. If patients with SPMS are having relapses, a DMT should be considered; if the patient is declining slowly, general immunosuppressive agents may be used.

What medications are typically used, and what are their benefits, potential harms, and costs?

First-line DMTs include immunomodulatory and immunosuppressive medications that have been shown on MRI scans to reduce risk for relapse, disease progression, and new lesion formation (22). In addition, recent evidence supports the idea that some DMTs provide real-world clinical benefits.

A Danish registry compared 194 patients started on high-efficacy DMTs (natalizumab, fingolimod,

alemtuzumab, cladribine, and ocrelizumab) with 194 patients receiving medium-efficacy DMTs. The high-efficacy patients had lower rates of clinical worsening and fewer on-treatment relapses. In addition, an Italian registry concluded that starting patients within 2 years of diagnosis on a high-efficacy DMT (rituximab, ocrelizumab, mitoxantrone, alemtuzumab, or natalizumab) was associated with less disability 6 to 10 years after disease onset (23).

Before 1993, there were no FDA-approved medications for multiple sclerosis. Since then, the FDA has approved 23 DMTs (**Table 2**) with different routes of administration, mechanisms of action, and potential adverse effects. A comprehensive review of all DMTs by nonpartisan groups may be found at https://ms-coalition.org/wp-content/uploads/2019/06/MSC_DMTPaper_062019.pdf. This document provides the route of administration, mechanism of action, adverse effects, warnings, and clinical and MRI data for all DMTs and is updated on a regular basis. The **Appendix Figure** (available at Annals.org) shows the current understanding of the pathophysiology of multiple sclerosis as well as the mechanisms of action of the major medications. The following sections provide information on 2 frequently used medications.

Natalizumab

Natalizumab is a monoclonal antibody that is administered by monthly intravenous infusion. It reduces entry of activated T cells through the blood–brain barrier into the CNS by inhibiting the α4-integrin cellular adhesion molecule on these immune cells and thus interfering with binding to the vascular endothelium. Natalizumab is highly effective; it reduces relapse rates by 68% compared with placebo and slows disability progression by approximately 40% (24). Another advantage is adherence, given that the medication is administered once monthly by infusion in a clinical setting rather than by the patient as an oral or injectable medication. Despite its efficacy, natalizumab is limited by its risk for progressive multifocal leukoencephalopathy (PML), a potentially fatal demyelinating infection caused by reactivation of the John Cunningham (JC) virus in the CNS. This is more likely to occur in patients with low CD4 T-cell counts, such as those treated with natalizumab, those on long-term immunosuppressive regimens, or those with AIDS. The estimated initial risk for PML in patients beginning treatment with natalizumab is approximately 1 in 1000 but is significantly higher in those with previous exposure to immunosuppressants or chemotherapy and those with elevated serum titers of antibodies against the JC virus (25). The results of tests for antibodies against JC virus may be reported as direct antibody levels or as an index (the STRATIFY or JC antibody index), which is a ratio of direct antibody levels to levels in a calibrator sample (26). An index value below 0.2 is regarded as evidence of seronegativity, between 0.2 and 0.4 as indeterminate, and above 0.4 as evidence of seropositivity. A serum test for JC virus antibodies is an effective risk stratification tool before starting use of natalizumab and for monitoring risk during use. For example, a positive baseline anti–JC virus antibody index above 0.90 predicts stable positive JC virus serostatus (27) and is a reason to use a DMT other than natalizumab.

An assessment of the sera of more than 1300 patients with multiple sclerosis receiving natalizumab showed a seroprevalence of 50% to 60% positivity. In an assessment of the sera of 63 patients who developed PML while receiving natalizumab, antibodies to the JC virus were present before PML diagnosis in all cases. The risk for PML increased to approximately 3 cases per 1000 patients in those with a positive antibody result at screening or during treatment and to 13 cases per 1000 patients if there was a history of immunosuppression (28).

Dimethyl fumarate

Oral dimethyl fumarate exerts its immunomodulatory effects by modulating the nuclear factor–like 2 transcriptional pathway.

In the pivotal clinical trial of dimethyl fumarate, the annualized relapse rate in patients receiving 240 mg twice daily was 0.17 compared with 0.36 for placebo ($P < 0.001$*). The relative risk reduction for disability progression was 38% compared with placebo (*$P = 0.005$*), and new lesions on MRI scans were reduced compared with placebo.*

These data led to FDA approval for use of this medication in patients with RRMS (29). The package insert has been updated to include CISs, RRMS, and SPMS with relapses.

The cost of multiple sclerosis treatment has skyrocketed in the past decade, and this is being increasingly questioned by patients and analysts. A 2021 article that examined cost data from 5906 patients with multiple sclerosis reported that the yearly range for DMTs was $70 000 to $82 000 (30).

Current treatment varies greatly, with different specialists using different medications for different stages of the disease. One approach is as follows:

- For patients with a newly diagnosed CIS or RRMS, start intravenous natalizumab and perform tests for JC virus antibodies and their index. If the results are positive, continue natalizumab for 1 year and then switch to oral dimethyl fumarate.

Table 2. **Disease-Modifying Therapies for Multiple Sclerosis**

Medication	*Route of Administration*	*Warnings, Contraindications, and Potential AEs*	*Recommended Monitoring*	*Pregnancy Category**
Interferon-β1a and interferon-β1b	Intramuscular or subcutaneous injection	AEs: Flu-like symptoms, fatigue, depression, increased spasticity, transaminitis, injection site reactions, seizures, congestive heart failure, leukopenia, autoimmune disorders	CBC and liver function testing every 6 mo	C
Glatiramer acetate	Subcutaneous injection	AEs: Injection site reactions, lipoatrophy of skin at injection sites, rare systemic panic attack–like syndrome	None	B
Daclizumab	Subcutaneous injection	Black box warning: Hepatic injury, including autoimmune hepatitis and other immune-mediated disorders Contraindications: Preexisting hepatic disease or hepatic impairment, including alanine aminotransferase or aspartate aminotransferase level ≥2 times the upper limit of normal and history of autoimmune hepatitis or other autoimmune condition involving the liver AEs: Injection site reactions, upper respiratory infections, depression, transaminitis	Liver function testing every 3–6 mo	No adequate data; see full prescribing information
Ofatumumab	Subcutaneous injection	Contraindication: Active HBV infection AEs: Upper respiratory tract infections, headache, injection-related reactions, reduction in immunoglobulins, local injection site reactions	Must have HBV screening and serum immunoglobulins before use	No adequate data; see full prescribing information
Fingolimod	Oral	Contraindications: • Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or class III/IV heart failure • History of Mobitz type II second- or third-degree AV block or sick sinus syndrome, unless patient has pacemaker • Baseline QTc interval ≥500 ms • Treatment with class Ia or class III antiarrhythmic drugs AEs: Transaminitis, lymphopenia, increased risk for serious herpesvirus infection, hypertension, PML, posterior reversible encephalopathy syndrome, cutaneous tumors, bradycardia (usually only with the first dose), macular edema	Cardiac monitoring for administration of first dose; ophthalmologic screening; liver function testing and CBC; yearly skin examinations	C
Dimethyl fumarate	Oral	AEs: Diarrhea, nausea, abdominal cramping, flushing, lymphopenia	Monitor CBC frequently in the first 6 mo, every 6 mo thereafter as well as for infections	C
Diroximel fumarate	Oral	Same as dimethyl fumarate, plus PML and transaminitis	Same as dimethyl fumarate plus liver function tests before start	C
Monomethyl fumarate	Oral	Same as diroximel fumarate	Same as diroximel fumarate	C
Teriflunomide	Oral	Black box warnings: Hepatotoxicity and risk for teratogenicity Contraindications: Severe hepatic impairment, pregnancy, hypersensitivity, current leflunomide treatment AEs: Alopecia, respiratory infections (including tuberculosis), pancreatitis, transaminitis, lymphopenia, hypertension, peripheral neuropathy	Monitor CBC, hepatic panel, amylase, lipase, and blood pressure frequently in the first 6 mo, every 6 mo thereafter	X

Continued on following page

Table 2–**Continued**

Medication	*Route of Administration*	*Warnings, Contraindications, and Potential AEs*	*Recommended Monitoring*	*Pregnancy Category**
Cladribine	Oral	Black box warnings: Cancer and risk for teratogenicity Contraindications: • Patients with current cancer • Pregnant women and adults of reproductive potential who do not plan to use effective contraception during cladribine dosing and for 6 mo after the last dose in each treatment course • HIV infection • Active chronic infections (e.g., hepatitis or tuberculosis) • History of hypersensitivity to cladribine • Women intending to breastfeed on a cladribine treatment day and for 10 d after the last dose AEs: Upper respiratory infection, headache, lymphopenia, liver injury	CBC every 3–6 mo; screen for TB, hepatitis, shingles, or other infections as appropriate	D
Siponimod	Oral	Contraindications: • Patients with a CYP2C9*3/*3 genotype • Patients with myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or class III/IV heart failure in the past 6 mo • Presence of Mobitz type II second- or third-degree AV block or sick sinus syndrome, unless patient has functioning pacemaker AEs: Headache, hypertension, transaminitis, infection	Obtain CBC, liver function tests, electrocardiogram, and ophthalmologic assessment before initiating treatment Monitor for infection during treatment Do not start in patients with active infection Other warnings include macular edema, bradyarrhythmia, respiratory effects, liver injury, increased blood pressure, and fetal risk	No adequate data; see full prescribing information
Ozanimod	Oral	Same as siponimod, plus contraindication for severe untreated sleep apnea	Same as siponimod	Same as siponimod
Alemtuzumab	Intravenous	Black box warnings: Autoimmunity, infusion reactions, tumors Contraindication: HIV infection AEs: >90% of patients in clinical trials experienced infusion reactions (rash; fever; headache; muscle aches; temporary recurrence of previous neurologic symptoms; and, rarely, anaphylaxis and heart rhythm abnormalities) Serious AEs: Autoimmunity, infusion reactions, tumors, immune thrombocytopenia, glomerular nephropathies, thyroid disorder, other autoimmune cytopenias, infections, pneumonitis, immediate and significant depletion of lymphocytes; herpes simplex and zoster infections more common in patients who received alemtuzumab in clinical trials, especially soon after infusions; prophylaxis with antiviral agent is recommended for ≥2 mo or until CD4 count is >0.200 × 10^9 cells/L	Available only through restricted distribution under a Risk Evaluation Mitigation Strategy program	C
Natalizumab	Intravenous	Black box warning: Increased risk for PML AEs: headache, chest discomfort (common); hepatotoxicity, infusion reactions, anaphylaxis (rare)	Rigorous, regimented, industry-sponsored monitoring (TOUCH program) JC virus antibody and index testing	C

Continued on following page

Table 2–**Continued**

Medication	*Route of Administration*	*Warnings, Contraindications, and Potential AEs*	*Recommended Monitoring*	*Pregnancy Category**
Ocrelizumab	Intravenous	Contraindication: Active HBV infection AEs: Infusion reactions (possibly life-threatening), infections, possible increase in tumors	Prescreen for hepatitis B	No adequate data; see full prescribing information
Mitoxantrone	Intravenous	Black box warnings: Cardiotoxicity and acute myeloid leukemia AEs: Infection, nausea, oral sores, alopecia, menstrual irregularities, blue discoloration of urine	Required monitoring of cardiac function by echocardiography or multigated radio-nucleotide angiography before each infusion and regular CBC	D

AE = adverse effect; AV = atrioventricular; CBC = complete blood count; HBV = hepatitis B virus; JC = John Cunningham; PML = progressive multifocal leukoencephalopathy.
** B = fetal risk in animal studies but no adequate human studies or fetal risk in animal studies but adequate human studies with no risk; C = fetal risk in animal studies and no adequate human studies, but potential benefit to pregnant women may outweigh risk; D = fetal risk in human studies, but potential benefit to pregnant women may outweigh risk; X = studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.*

- For patients with RRMS who already are receiving a DMT and are doing well—meaning that they can tolerate the medication, have had no relapses in 1 to 2 years, and have had no changes on their MRI scans for 1 year—maintain them on that therapy. For those who are not doing well, switch to a different DMT.
- For patients with newly diagnosed PPMS, start ocrelizumab.
- For patients with SPMS who are stable with no medication, maximize physical therapy and symptomatic medications. Do not start a DMT because of the risk for infection.
- For patients with SPMS who are using a DMT but continue to have relapses, add an immunosuppressant agent or consider switching to a different DMT.
- For patients with SPMS who continue to have attacks despite having used multiple different DMTs, start intravenous cyclophosphamide.

Bone marrow transplant, a more aggressive approach that is not FDA approved for multiple sclerosis, has been used as a rescue therapy for patients who do not respond to therapy and those with SPMS.

In a recent study of autologous hematopoietic stem cell transplant patients, 210 with RRMS or SPMS underwent this procedure. For patients with RRMS, 85% had no worsening of disability at 5 years and 71.3% had no worsening at 10 years. For patients with SPMS, 71% showed no worsening of disability at 5 years and 57.2% showed no worsening at 10 years (31).

When should clinicians consider immunomodulatory therapy?

Immunomodulatory drugs should be initiated at the time of diagnosis. In the past, clinicians were encouraged to wait until a clinically definite diagnosis of multiple sclerosis could be established. Guidelines now recommend initiating immunomodulatory treatment at the time of first clinical symptoms for those with RRMS and for those with a CIS and risk factors for later conversion to a diagnosis of multiple sclerosis.

What is the role of vitamin D?

Researchers have established clear links between vitamin D deficiency and the pathophysiology of multiple sclerosis. Immunoregulatory vitamin D receptors are present on T cells, and vitamin D interacts with the immunomodulatory effects of estrogen and testosterone (32). Reduced serum vitamin D levels have been shown to predict accumulation of new lesions on MRI scans, and high levels are associated with decreased risk for relapse (33, 34).

A randomized, double-blind, placebo-controlled trial of the addition of vitamin D supplements (14 007 IU/d) to interferon-β treatment found that vitamin D supplementation reduced lesion accumulation on MRI scans compared with placebo (35). *Another trial found that the number of new gadolinium-enhancing lesions or T2 lesions that were new or enlarging was reduced by 32% in patients supplemented with cholecalciferol compared with placebo* (36).

Although the ideal serum 25-hydroxyvitamin D levels are still unknown, most studies have shown benefit for levels of 50 nmol/L or greater (37), so some multiple sclerosis specialists measure vitamin D levels in all of their patients and prescribe supplements if the values are less than 50 nmol/L.

How should clinicians choose therapy for patients having an acute relapse?

Relapses are defined by the development of new or worsening neurologic symptoms lasting 24 hours or more without an increase in body temperature, identifiable infection, or another trigger for a pseudo-relapse. When a relapse has been confirmed, the standard treatment is high-dose corticosteroids, which are typically administered as an intravenous infusion of methylprednisolone, 1 g/d for 3 to 5 days, with no oral taper. Recent trials have shown that oral methylprednisolone, 1 g/d for 5 days (38), and oral prednisone, 1250 mg/d for 5 days (39), have equivalent efficacy. For relapses that do not respond to steroids, plasma exchange (40), 5 days of intramuscular or subcutaneous adrenocorticotrophic hormone gel (41), and pulse-dose intravenous cyclophosphamide (42) are available rescue treatments.

When should a patient with multiple sclerosis be hospitalized?

Most relapses do not require hospitalization. Oral steroid treatment does not require observation in the hospital, and most insurance plans cover home nursing services for intravenous infusions of corticosteroids because this is more cost-effective than hospitalization and decreases the chance of infection.

Hospitalization may be beneficial for severe relapses causing complete loss of mobility or impaired bladder or bowel control, which can lead to serious infection risks. Patients who have marked worsening during relapse require nursing and rehabilitation services, which are often beyond the capacity of their family. Hospitalization may also be beneficial for patients who require special monitoring while receiving relapse treatment, such as blood glucose monitoring for steroid administration in a patient with diabetes. Rescue treatment for steroid-refractory relapses with adrenocorticotrophic hormone gel does not require hospitalization, but plasma exchange or pulse-dose cyclophosphamide therapy should be done in the hospital.

What treatments are used to alleviate chronic symptoms?

To adequately treat a patient with multiple sclerosis, it is important

Table 3. **Symptom Management in Multiple Sclerosis**

Symptom	*Nonpharmacologic Management*	*Pharmacologic Management*
Spasticity	Physical therapy, stretching, massage therapy	Baclofen (oral or intrathecal pump), tizanidine, cyclobenzaprine, dantrolene, gabapentin, benzodiazepines, carisoprodol, botulinum toxin
Neuropathic pain	Not applicable	Gabapentin, pregabalin, duloxetine, tricyclic antidepressants, tramadol, carbamazepine, topiramate, capsaicin patch
Fatigue	Proper sleep hygiene, regular exercise	Modafinil, armodafinil, amantadine, fluoxetine or amphetamine stimulants
Depression	Individual or group counseling	Antidepressants (such as SSRIs, SNRIs, tricyclic antidepressants, antipsychotics)
Cognitive dysfunction	Cognitive rehabilitation and accommodation strategies	No proven therapy
Mobility	Physical and occupational therapy; use of braces, canes, rolling walkers, electrostimulatory walk-assist devices	Dalfampridine
Urinary urgency/frequency	Timed voids, avoidance of caffeine	Oxybutynin, tolterodine, desmopressin, darifenacin, tamsulosin, mirabegron, imipramine, solifenacin, botulinum toxin, implantable bladder stimulators
Urine retention	Manual pelvic pressure, intermittent catheterization	Antibiotics for urinary tract infection Consider BPH, which can be treated with α-blocker and/or 5-α reductase inhibitor
Bowel dysfunction	None	Metamucil, docusate, bisacodyl, milk of magnesia, mineral oil, enemas or suppositories
Erectile dysfunction	Vacuum pump	Sildenafil, tadalafil, vardenafil, alprostadil, avanafil
Heat intolerance	Avoidance of hot weather and hot tubs Cooling equipment (fans, cooling vests)	None
Pseudobulbar affect	None	Dextromethorphan/quinidine
Limb tremor	Occupational therapy	Isoniazid, clonazepam, botulinum toxin, thalamic stimulation via deep-brain stimulator

BPH = benign prostatic hypertrophy; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

to use DMTs and to address symptoms that remain chronic after a previous relapse or progression. **Table 3** provides a comprehensive review of symptom management. It is important to recognize the usefulness of these interventions for increasing quality of life in patients with multiple sclerosis.

How should clinicians monitor patients being treated for multiple sclerosis?

Monitoring should involve regular assessments of the efficacy and safety of DMTs. There are no clinical guidelines for monitoring treatment efficacy, but the practices developed for clinical trials can provide indirect guidance. In these trials, DMTs have been shown to decrease the frequencies of relapse and new MRI lesions and to reduce the accumulation of disability. Therefore, clinical assessment of efficacy should include documentation of relapses, periodic neurologic examinations, and regular MRI scans. Clinicians should consider changing immunomodulatory treatment for patients with recurrent relapses, new lesion formation on MRI, or progressive accumulation of disability. Safety assessments are targeted toward the known adverse effects of the immunomodulatory treatment being used. Recommended monitoring tests are listed in **Table 2**.

Should patients with multiple sclerosis receive immunizations?

The American Academy of Neurology clinical practice guidelines recommend the same immunizations for patients with multiple sclerosis that are recommended for others (43). One reason is that the risk for relapses increases during the weeks surrounding infectious episodes. In addition, there is no evidence that multiple sclerosis worsens as a consequence of immunization with any vaccines, including those against influenza, hepatitis B, varicella, tetanus, and tuberculosis (bacille Calmette–Guérin vaccine) (44). However, fingolimod decreases a patient's ability to recover from viral infections, and the manufacturer recommends that patients avoid live viral vaccines while receiving the drug.

Treatment... Treatment includes medications to prevent relapses, additional medications during acute relapses, and other medications and nonmedication treatments for symptom management. DMTs are approved to prevent relapses in patients with CISs, RRMS, and PPMS and in those with SPMS who have recurrent relapses. Less disability over time has been associated with high-efficacy DMTs (natalizumab, fingolimod, alemtuzumab, cladribine, ocrelizumab, rituximab, and mitoxantrone). Vitamin D supplementation may also be helpful when serum levels are low. High-dose corticosteroids are the standard treatment for acute relapses, although plasma exchange, adrenocorticotrophic hormone gel, and cyclophosphamide can be used. Symptoms are managed on an individual basis through combined use of pharmacologic and nonpharmacologic means.

CLINICAL BOTTOM LINE

COVID-19 and Multiple Sclerosis

The COVID-19 Neurology Resource Center (www.aan.com/tools-and-resources/covid-19-neurology-resource-center) keeps practitioners updated on the latest developments regarding the interaction between SARS-CoV-2 and neurologic conditions, including multiple sclerosis. Current practice is to continue DMTs in patients with multiple sclerosis because these therapies and COVID-19 do not seem to affect each other (45).

In the Clinic
Tool Kit

Multiple Sclerosis

Patient Information

https://medlineplus.gov/multiplesclerosis.html
https://medlineplus.gov/spanish/multiplesclerosis.html
Information and handouts in English and Spanish from the National Institutes of Health's MedlinePlus.

www.ninds.nih.gov/disorders/all-disorders/multiple-sclerosis-information-page
https://espanol.ninds.nih.gov/trastornos/esclerosis_multiple.htm
Information in English and Spanish from the National Institute of Neurological Disorders and Stroke.

www.nationalmssociety.org/What-is-MS
www.nationalmssociety.org/Resources-Support/Library-Education-Programs/Informacion-en-Espanol
Resources in English and Spanish from the National Multiple Sclerosis Society.

Information for Health Professionals

www.thelancet.com/journals/laneur/article/PIIS1474-4422(17)30470-2/fulltext
2017 revisions of the McDonald criteria for diagnosis of multiple sclerosis.

www.aan.com/Guidelines/home/GuidelineDetail/899
2018 practice guideline systematic review summary on disease-modifying therapies for adults with multiple sclerosis from the American Academy of Neurology.

www.aan.com/Guidelines/home/GuidelineDetail/974
2019 practice guideline update summary on vaccine-preventable infections and immunization in multiple sclerosis from the American Academy of Neurology.

www.nationalmssociety.org/For-Professionals/Clinical-Care
Resources from the National Multiple Sclerosis Society.

WHAT YOU SHOULD KNOW ABOUT MULTIPLE SCLEROSIS

What Is Multiple Sclerosis?

Multiple sclerosis is a progressive, chronic disease that affects the central nervous system. It causes the immune system to attack cells in the brain, spinal cord, and optic nerves. It is important to diagnose and treat multiple sclerosis early to prevent relapse, delay disease progression, and maximize quality of life.

Doctors don't know for sure what causes multiple sclerosis, but it is most likely a combination of environmental and genetic factors. It affects women more than men.

What Are the Symptoms?

Symptoms differ depending on where the nerve cells are damaged. Symptoms may come and go, or they may be permanent. They can include:

- Changes in vision (1 eye more common than both eyes)
- Muscle weakness
- Fatigue
- Loss of balance or trouble with coordination
- Tremors, numbness, or slurred speech
- Partial or total paralysis
- Thinking or memory problems
- Frequent urge to urinate

Many patients with multiple sclerosis experience "flares" or "relapses" when symptoms suddenly get worse or new ones appear and last more than 24 hours.

How Is It Diagnosed?

- No single test is available to diagnose multiple sclerosis. Your doctor will ask about your medical history, do a physical examination, and run a combination of other tests.
- Blood tests may show signs of other illnesses that cause symptoms similar to those of multiple sclerosis.
- Magnetic resonance imaging is essential for diagnosis. It takes a detailed picture of your brain and spinal cord, where lesions that suggest multiple sclerosis may be present.
- More specialized testing may be needed if the diagnosis is unclear.

How Is It Treated?

- You and your neurologist will come up with a treatment plan that is best for you based on the type of multiple sclerosis you have.
- Early treatment with immunotherapy is very important and has been shown to lower risk for relapse, disease progression, and development of new lesions in many patients.
- A multidisciplinary approach to care that includes nondrug therapies (physical, occupational, and speech therapy) and symptom management (pain, muscle stiffness and spasms, fatigue, and bladder problems) may help preserve function and quality of life.
- Steroids, such as prednisone, can reduce nerve inflammation during a relapse or flare.
- Low levels of vitamin D are common in patients with multiple sclerosis and are associated with increased risk for relapse. You may be instructed to take a vitamin D supplement.
- Lifestyle changes, including a healthy diet, being physically active, and getting enough sleep, may also help symptoms.

Questions for My Doctor

- What kind of multiple sclerosis do I have?
- What can I do to manage my symptoms?
- Will my symptoms get worse over time?
- What treatments are available to me?
- What are the risks and side effects of the treatment?
- How often should I have follow-up visits?

For More Information

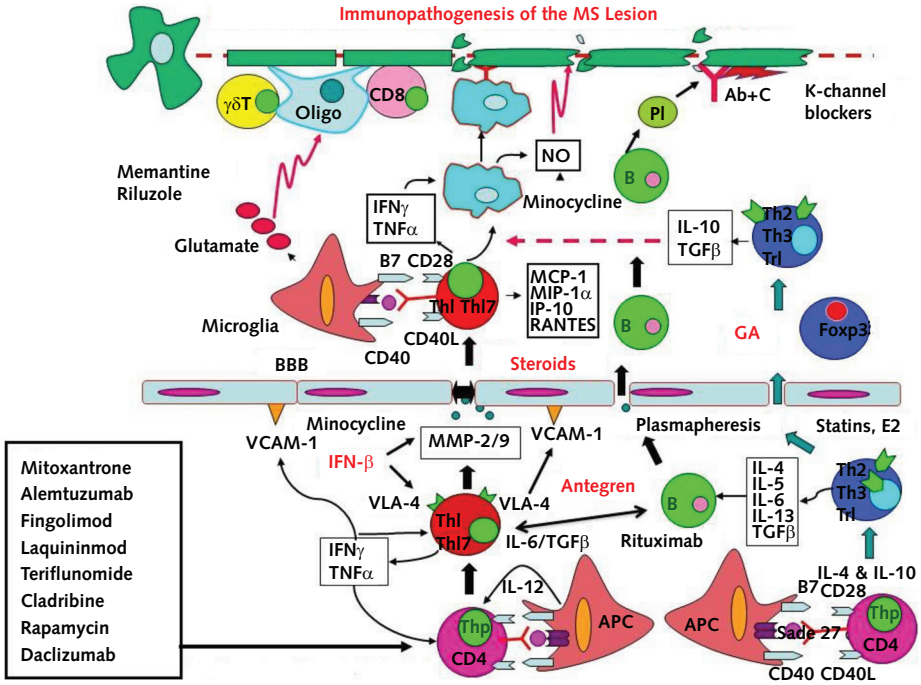
ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

MedlinePlus
https://medlineplus.gov/multiplesclerosis.html

National Multiple Sclerosis Society
www.nationalmssociety.org/What-is-MS

Patient Information

Appendix Figure. **Overview of the components of the immune system that are involved in pathogenesis of MS and where various medications exert their actions.**



5-HT = 5-hydroxytryptamine; Ab+C = antibody plus complement; APC = antigen-presenting cell; APRIL = a proliferation-inducing ligand; ATP = adenosine triphosphate; B = B cell; BAFF = B-cell–activating factor; CTL = cytotoxic T lymphocytes; FcR = Fc receptor; GA = glatiramer acetate; ICAM-1 = intercellular adhesion molecule 1; IFN = interferon; IL = interleukin; IP-10 = interferon γ-inducible protein-10; LFA-1 = lymphocyte function–associated antigen 1; MCP = monocyte chemotactic protein; MIP = macrophage inflammatory protein; MMP = matrix metalloproteinase; MS = multiple sclerosis; NAA = *N*-acetyl aspartate; NO = nitric oxide; Oi = free oxygen radicals; Pl = plasma cell; RANTES = regulated on activation, normal T cell expressed and secreted; TACI = transmembrane activator and calcium-modulating cyclophilin ligand; TGFβ = transforming growth factor β; Th = T helper; Thp = T-helper precursor; TNFα = tumor necrosis factor α; VCAM-1 = vascular cell adhesion molecule 1; VLA-4 = very late antigen 4. Reprinted from *Journal of Neuroimmunology*, vol. 176, Dhib-Jalbut S, Arnold DL, Cleveland DW, et al, "Neurodegeneration and Neuroprotection in MS and Other Neurodegenerative Diseases," pp. 198-215, copyright 2006, with permission from Elsevier.

