EMERGENCY MEDICINE REPORTS

Practical, Evidence-Based Reviews in Emergency Care

SEPTEMBER 15, 2021 VOL. 42, NO. 18

AUTHORS

**Jay Bernstein, MD, MPH, MS, FACEP,** Assistant Professor, Department of Emergency Medicine, Wright State University, Dayton, OH

**Shannon Lyon, MD,** Emergency Medicine Resident, Wright State University, Dayton, OH

**Rachel Tabbouche,** University of Maryland, College Park

PEER REVIEWER

**Frank LoVecchio, DO, FACEP,** Vice-Chair for Research, Medical Director, Samaritan Regional Poison Control Center, Emergency Medicine Department, Maricopa Medical Center, Phoenix, AZ

STATEMENT OF FINANCIAL DISCLOSURE

None of the authors or planners for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients

Relias Media

From Relias

# Multiple Sclerosis in the Emergency Department

## Introduction

Multiple sclerosis (MS) is an immune-mediated process causing impairment to the neurons of the optic nerve, brain, and spinal cord. This leads to central nervous system (CNS) demyelination, chronic inflammation, axonal transections, and scarring, manifesting by clinical signs and symptoms and an abnormal magnetic resonance imaging (MRI).

The signs and symptoms of MS can be nonspecific or can mimic other neurologic entities. One study showed that 26.6% of MS diagnoses were missed on presentation to the ED and took up to a year to diagnose in 18.4%.[1] Prompt and accurate diagnosis of MS is important for early treatment, since early treatment of MS improves neurologic outcomes.[2]

There are five subgroups of MS presentations:[3]

- **clinically isolated syndrome (CIS):** A self-limited episode that most often is monophasic, lasting at least 24 hours, and most commonly involving the optic nerve or a single area of the brain or the spinal cord;[4]
- **relapsing-remitting MS (RRMS):** Progressive MS symptoms with periods of improvement or resolution;
- **primary progressive MS (PPMS):** A continuous decline in MS from the time of an initial diagnosis of MS without relapses;
- **secondary progressive MS (SPMS):** This occurs only after the RRMS has been present > 10 years, manifested by a chronic decline with fewer relapses;
- **progressive (or primary) relapsing MS (PRMS):** A rare variant that is a continual decline in MS from the time of an initial diagnosis of MS.

Although these five subgroups are not always clinically useful, especially in the ED, the utility of citing them is to be aware of the variability of MS presentations. The forms of MS that are associated with acute episodes of disability are due to inflammation vs. degeneration in the progressive subtypes. The rate and degree to which patients develop and remain with disability are highly variable. As symptoms decline over time, age is the only predictor for disease progression.[5] Therapies appear to be less beneficial in the older population.[6]

## Epidemiology

Approximately 23 million people are diagnosed with MS worldwide.[7] The prevalence of MS in North America is more than 140/100,000, and it is the most common demyelinating disease.[8,9] MS is more prevalent in women than men, with a 3:1 ratio, and it is most common among Caucasians.[9,10] A majority of MS cases are found in North America and Europe and are less common closer to the equator.[11,12] CIS typically occurs between the ages of 20 and 45

## EXECUTIVE SUMMARY

- Multiple sclerosis (MS) is an inflammatory and demyelination disease of the central nervous system. Early diagnosis and treatment are important.
- Optic neuritis and bilateral internuclear ophthalmoplegia are important eye findings that are highly correlated with a diagnosis of MS. Therefore, it is important to do a visual field and visual acuity assessment as well as test extraocular movements.
- Patients with an acute relapse are treated with very high doses of steroids and should be seen by a neurologist early in their course.
- Magnetic resonance imaging is the imaging test of choice.

years, and 2.5:1 in females to males.[13] Optic neuritis CIS progresses to MS with an incidence of 10% to 85%. The incidence of a CIS progressing to MS in the brainstem is 53% to 60%, and to the spinal cord is 41% to 61%.[4] RRMS is the most common form of MS, involving 85% of MS cases, and is more prevalent among females.[8] RRMS typically presents at 30 years of age, younger than PPMS, and occurs after the onset of RRMS 20% to 50% of the time.[3,10,14] PPMS occurs in 10% to 15% of MS patients.[15]

## Etiology

The primary etiology of MS has not been established and it is thought to be multifactorial.[16] Risk factors include infections, immunity, genetics, demographics, and environmental influences.[17] The Epstein-Barr virus (EBV) is a strong risk factor for MS. Recurrent episodes of RRMS are caused by recurrent EBV infections.[18,19] Roseola infantum (human herpesvirus 6) has been associated with an increased risk of MS later in life.[17] A previous history of herpes simplex virus and human endogenous retroviruses has been shown to be associated with MS as well.[17] Many nonviral environmental exposures have been linked to the development of MS. In adults, onset, relapse, and progression are positively affected by sun exposure and vitamin D levels and negatively by smoking.[17] Genetic factors and their relationship to the patient's environment affect MS risk. Autoimmune diseases share many genetic markers with those of MS, suggesting an overlap between autoimmune diseases and MS.[20]

## Pathophysiology

MS can involve the brain, sphincter, visual, pyramidal, brainstem, cerebellar, or sensory pathways. MS occurs in two stages.[21] The first phase is caused by acute inflammatory demyelination, which leads to interruptions within axonal conduction, expressed as flares of symptoms. Six months of persistent demyelination leads to the second phase, which is disability. Disability is a manifestation of a complete loss of axons and mitochondrial dysfunction, which increases the likelihood that these changes are irreversible. This is independent of focal inflammation and can be visualized by MRI. MS signs and symptoms typically present over hours to days and gradually resolve within weeks to months. It can manifest as a lesion of the optic nerve, the brain (including the brainstem, cerebellum, or, less commonly, the cerebrum), and the spinal cord.

## Clinical Features

New neurologic complaints consistent with MS develop over hours to days. The typical patient is between 15 and 50 years of age and female.[6] The most common presentations of new-onset MS are numbness or weakness of the extremities, followed closely by visual deficits.[1]

The differential diagnosis for numbness and weakness is broad (*see Table 1*), but the most specific presentation is an ophthalmologic complaint that presents as unilateral optic neuritis.[22] Patients typically will have acute onset of ocular pain with eye movements (92% of cases), usually followed by decreased vision in the same eye, and absence of visible external eye abnormalities. Most often, symptoms will spontaneously improve over several weeks, and the patient typically will have normal vision in six to 12 months. Optic neuritis presents as diminished visual acuity and pain with extraocular movements from the loss of axonal conduction. This pain typically is unilateral and associated with loss of central vision. Flashing lights represent a hyperexcitable symptom of optic neuritis. Optic neuritis can be seen on MRI approximately six months after the onset of symptoms.[23] When the brainstem or cerebellum is involved, MS will present most often as bilateral internuclear ophthalmoplegia (INO). MS-induced bilateral INO is caused by inflammation and plaques that cause demyelination present at the site of the medial longitudinal fasciculus (MLF) between the third and sixth cranial nerve (CN) nuclei. This leads to a diminished conjugate gaze when looking to either side. The patient senses it as double vision when looking to the right or left.[24] When a lesion of the INO is unilateral, one should consider other diagnoses, such as a stroke. When bilateral INO is present, this is considered to be pathognomonic for MS. [24]

Less common presentations involve the cerebrum, which manifest as deficits of language, spatial orientation, memory, and mood.[25,26] Spinal cord involvement leads to gait impairment, partial myopathy, Lhermitte sign or phenomenon (electric shocks), paresthesias, erectile dysfunction or urinary urgency or incontinence, and pain of the bladder or bowel.[27]

Although early recognition and diagnosis of a new onset of MS are important, the emergency physician will encounter and manage those with a known diagnosis of MS more often. The patient with known MS who presents with increasing or additional neurologic symptoms could represent a relapse or a pseudorelapse. Clinically, these can be indistinguishable. The difference is the underlying pathophysiology and treatments.[28] An MS relapse, also referred

**Table 1. Differential Diagnosis**

| | |
|---|---|
| Vascular | Ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA), cerebral aneurysm, vertebral/carotid dissection, central venous thrombosis, amaurosis fugax, anemia |
| Infectious/inflammatory | Severe infection (sepsis), viral encephalitis (including herpes simplex virus [HSV]), bacterial meningitis, Lemierre syndrome, human immunodeficiency virus (HIV), neurosyphilis, systemic lupus erythematosus, polyarteritis nodosa, Lyme disease |
| Toxicologic/traumatic | Concussion/traumatic brain injury (TBI), neuropraxia, spinal injury, rhabdomyolysis, ciguatera poisoning, coral snake bite, bark scorpion sting, tick paralysis, botulism, organophosphates, methanol poisoning |
| Autoimmune | Guillain-Barré syndrome, myasthenia gravis, Lambert-Eaton syndrome, autoimmune encephalitis |
| Metabolic | Hypoglycemia, hypokalemia, hypocalcemia, vitamin B12 deficiency |
| Neoplastic | Intracranial tumors, spinal cord tumors, Schwannoma, metastatic lesions |
| Congenital | Arnold-Chiari malformation |
| Degenerative | Diabetic neuropathy, amyotrophic lateral sclerosis (ALS), Huntington's disease |
| Endocrine | Hypothyroidism, hyperthyroidism |
| (In particular, the close mimickers that have a relapsing and remitting course are: neuromyelitis optica, neurosarcoidosis, central nervous system vasculitis, Susac's syndrome, CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy], systemic lupus erythematosus, Sjögren's syndrome, antiphospholipid syndrome, Behçet's disease, CLIPPERS [chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids], and Leber's hereditary optic neuropathy.) | |

to as a flare, an exacerbation, or an attack, occurs at least one month after a previous MS relapse, and the signs and symptoms will be continuous for at least 12-24 hours or longer. MS relapses are common and unpredictable. They may involve a similar presentation as prior MS episodes or different areas of the nervous system and involve a single symptom 71% of the time.[29] An MS relapse affects an additional area in the CNS, and new lesions appear on MRI. New deficits identified that represent a true relapse should be managed by mitigation of new inflammation.

In contrast, a pseudorelapse is when the signs and symptoms result from an exacerbation of an existing area of MS axonal lesions and are intermittent and/or waxing and waning for a duration less than 24 hours. A pseudorelapse will not reveal MRI findings, and it is triggered by a form of stress. The types of stress include fatigue, exertion, infection and/or increased body temperature, exposure to elevated external (air) temperature or humidity, and distended bowel or bladder. Treating a pseudorelapse involves treating the underlying stress. A urinary tract infection (UTI) and an upper respiratory infection (URI) are the most common causes.[30] Spinal cord lesions often lead to urinary retention, which increases the risk of a UTI.[31] Up to 30% of patients with MS have oropharyngeal dysphagia as well, placing them at risk for aspiration pneumonia and pneumonitis.[32] Uhthoff's phenomenon or Uhthoff's sign is an exacerbation of MS signs or symptoms from exercise or exposure to heat that occurs in 60% to 80% of patients with MS.[33] MS causes a decline in respiration as a result of weak respiratory muscles, bulbar dysfunction, impaired cough, abnormalities of the control of breathing, neurogenic pulmonary edema, and leading to hypercarbia and, less commonly, hypoxia or respiratory arrest.[34,35]

If the patient has altered mental status or one of the common pain syndromes (chest pain, low back pain, etc.), it is unlikely to represent a pseudorelapse (or a relapse as well), and other non-MS conditions should be considered.[36] If neurologic symptoms are hyperacute (seconds to minutes), non-MS conditions, such as hypoglycemia, toxins, seizures, or stroke, need to be considered. Acute onset of symptoms (hours to days) could be caused by meningitis and cerebral venous thrombosis, which is a similar time course onset as MS. A subacute onset (weeks to months) is not consistent with an MS presentation or relapse, and other causes need to be considered, such as malignancies, autoimmune disorders, fungal meningitis, human immunodeficiency virus (HIV)/human T-cell leukemia virus type 1 (HTLV-1), and other metabolic syndromes.[36]

In addition to the medications listed in Table 2, adjunct medications also can be used. These may include antimuscarinics for bladder dysfunction, antidepressants/anxiolytics, amantadine for fatigue, muscle relaxants, and stimulant medications to aid with cognitive dysfunction.[31,37-39]

## Cognitive Effects

MS patients may have an underlying psychiatric condition that may exacerbate or cloud the clinical picture of an MS flare or pseudorelapse. This includes less emotional expression, depression, or involvement in control issues, including abuse or manipulation by family or friends. Cognitive deficits caused by MS influence the expression of disease or ability to cope. Cognition can affect multitasking, performing activities of daily living (ADLs), concentration,

## Table 2. Medication Side Effects

| Name | Types of MS Treated | Frequency | Most Common Side Effects | Possible Clinical Syndromes | Possible Lab Abnormalities | Rare Life-Threatening Conditions |
|---|---|---|---|---|---|---|
| **Injectable Medications** | | | | | | |
| Interferon beta-1a (Avonex, Rebif) | CIS, RRMS, SPMS | Avonex: weekly; Rebif: 3 times/week | Headache, flu-like symptoms, injection site symptoms, depression | Psychosis, CHF, TMA, seizures | Transaminitis, decreased cell counts, UTIs | Suicidality, liver failure, anaphylaxis |
| Interferon beta-1b (Betaseron, Extavia) | CIS, RRMS, SPMS | Every other day | Flu-like symptoms, headache, injection site reactions (including necrosis), hypertonia | Drug-induced SLE, CHF, TMA | Lymphopenia, transaminitis | Anaphylaxis, fatal capillary leak syndrome |
| Glatiramer acetate (Copaxone, Glatopa) | CIS, RRMS, SPMS | Daily (20 mg) or 3 times/ week (40 mg) | Injection site reactions (including lipoatrophy), infection, flushing | | Transaminitis | Liver failure |
| Ofatumumab (Kesimpta) | CIS, RRMS, SPMS | Monthly | URIs, flu-like symptoms, injection site reactions, UTIs | Immunosuppression | Reduction in immunoglobulins | PML, hepatic failure (due to hepatitis B) |
| Peginterferon beta-1a (Plegridy) | CIS, RRMS, SPMS | Every 2 weeks | Injection site symptoms, flu-like symptoms, headache, pyrexia | CHF, TMA, autoimmune disorders, seizures | Transaminitis, decreased cell counts | Liver failure, anaphylaxis |
| **Oral Medications** | | | | | | |
| Teriflunomide (Aubagio) | CIS, RRMS, SPMS | Daily | Headache, diarrhea, alopecia | Immunosuppression, DRESS, interstitial lung disease | Transaminitis, decreased cell counts | Liver failure |
| Monomethyl fumarate (Bafiertam) | CIS, RRMS, SPMS | Twice daily | Flushing, abdominal pain, nausea | Immunosuppression | Transaminitis, lymphopenia | Anaphylaxis, angioedema, PML, opportunistic infections (PJP, disseminated HSV, etc.) |
| Dimethyl fumarate (Tecfidera) | CIS, RRMS, SPMS | Twice daily | Flushing, abdominal pain, diarrhea | Immunosuppression | Transaminitis, lymphopenia, eosinophilia | Anaphylaxis, angioedema, PML, fatal opportunistic infections (PJP, disseminated HSV, etc.) |
| Fingolimod (Gilenya) | CIS, RRMS, SPMS | Daily | Infections, hypertension | Immunosuppression, bradycardia, AV blocks, QT prolongation, Kaposi's sarcoma, macular edema, cutaneous malignancies, lymphoma | Lymphopenia, transaminitis | Opportunistic viral, bacteria, and fungal infections, PRES |
| Cladribine (Mavenclad) | CIS, RRMS, SPMS | Two separate treatment cycles | URIs, headache, nausea | Immunosuppression, malignancy, TB, GVHD with blood transfusion, cardiac failure | Lymphopenia, transaminitis, pancytopenia | Opportunistic viral, bacteria, and fungal infections, liver failure (due to direct liver injury or hepatitis), PML (*continued*) |

## Table 2. Medication Side Effects (*continued*)

| Name | Types of MS Treated | Frequency | Most Common Side Effects | Possible Clinical Syndromes | Possible Lab Abnormalities | Rare Life-Threatening Conditions |
|---|---|---|---|---|---|---|
| **Oral Medications** | | | | | | |
| Siponimod (Mayzent) | CIS, RRMS, SPMS | Daily | Headache, hypertension | Immunosuppression, bradycardia, AV blocks, QT prolongation, macular edema, cutaneous malignancies, PRES | Lymphopenia, transaminitis | Opportunistic viral, bacteria, and fungal infections, PML |
| Ponesimod (Ponvory) | CIS, RRMS, SPMS | Daily | Headache, hypertension | Immunosuppression, bradycardia, AV blocks, QT prolongation, macular edema, cutaneous malignancies, PRES | Lymphopenia, transaminitis | Opportunistic viral, bacteria, and fungal infections, PML |
| Diroximel fumarate (Vumerity) | CIS, RRMS, SPMS | Twice daily | Flushing, abdominal pain, diarrhea | Immunosuppression | Lymphopenia, transaminitis | Anaphylaxis, angioedema, PML, fatal opportunistic infections (PJP, disseminated HSV, etc.) |
| Ozanimod (Zeposia) | CIS, RRMS, SPMS | Daily | URIs, orthostasis, UTIs, back pain | Bradyarrhythmias, hypertension, decreased pulmonary function, macular edema | Transaminitis | |
| **Infused Medications** | | | | | | |
| Alemtuzumab (Lemtrada) | RRMS, SPMS | Two treatment courses, each over 5 consecutive days | Rash, headache, pyrexia, nausea, UTIs | Immune thrombocytopenia, glomerulonephropathy, thyroid disorders, TTP, hemophilia | Transaminitis, decreased cell counts | Opportunistic viral, bacteria, and fungal infections, PML |
| Mitoxantrone (Novantrone) | RRMS, PRMS, SPMS | Every three months | Nausea, alopecia, depression | CHF, menstrual disorders including amenorrhea | Leukopenia | Secondary AML, opportunistic infections |
| Ocrelizumab (Ocrevus) | PPMS, CIS, RRMS, SPMS | Every 6 months | Transfusion reactions | Herpetic infections/lesions, immunosuppression, breast cancer | Reduction in immunoglobulins | Disseminated herpes, herpes encephalitis, PML |
| Natalizumab (Tysabri) | CIS, RRMS, SPMS | Every 4 weeks | Headache, fatigue, arthralgias | Immunosuppression | Transaminitis, thrombocytopenia | Herpes encephalitis, liver failure, anaphylaxis, PML |

AML: acute myelogenous leukemia; AV: atrioventricular; CHF: congestive heart failure; CIS: clinically isolated syndrome; DRESS: drug rash with eosinophilia and systemic symptoms; HSV: herpes simplex virus; ITP: immune thrombocytopenia; PJP: *Pneumocystis jerovicii* pneumonia; PML: progressive multifocal leukoencephalopathy; PPMS: primary progressive multiple sclerosis; PRES: posterior reversible encephalopathy syndrome; PRMS: progressive ( or primary) relapsing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; TMA: thrombotic microangiopathies; TTP: thrombotic thrombocytopenic purpura; URIs: upper respiratory infections, UTIs: urinary tract infections

judgment, as well as processing and memory impairment.[40,41]

When communicating with MS patients in the ED, provide enough time for the patient to verbalize understanding, allow digestible fragments of information, and provide written summaries of results and plans.

MS patients are at a significantly higher risk of developing depression and anxiety.[42] This likely is the result of a combination of the inflammatory changes of the brain parenchyma as well as the social impact of a disability.[43] Depression is more common in men,

which is different from the non-MS population.[44] This is exacerbated by the lack of control and uncertainty of the progression of symptoms.[45] Depression can reduce compliance with treatments, and many MS medications can exacerbate depression.[46] (*See Table 2.*) There have been multiple proposed screening tools for depression in MS.[47] The most practical in the ED is the PHQ-2, since it is simple and efficient. It consists of these two questions.[48]

1. In the last two weeks, how many days have you had little interest or pleasure in doing things?
2. In the last two weeks, how many days have you felt down, depressed, or hopeless?

The PHQ-2 has an accuracy of 0.84 and a negative predictive value of 0.96.[47] This can be a rapid aid in the ED to screen for ongoing depression in MS patients to help guide management, therapy regimens, and disposition decisions.

If a patient presents with complaints of new or worsening psychiatric effects, the etiology usually is multifaceted. Changes in mood could be related to physical deficits and their impact on livelihood. Mood changes can be affected by the medications used to treat MS, as noted in Table 2. Medication reconciliation and review of recent changes in medications should be performed in detail.

Behavioral changes can be a result of frontal lobe plaques inherent to the disease process as well, resulting in a lack of normal verbal inhibitions. New psychiatric symptoms may be a sign of a relapse, even in the absence of physical deficits. Dementia is unlikely to be a contributing factor in MS patients, since MS does not increase the risk of dementia or affect intelligence.[49]

## Diagnostic Tools

MS is a clinical diagnosis that requires an array of data and historical factors over time to make. In the history of present illness, elicit the historical neurologic abnormalities that are relevant to the algorithm outlined in the 2017 McDonald criteria.[50] (*See Table 3.*) The 2017 McDonald criteria are not intended to rule out non-MS diagnoses and should not be used by the ED physician to make a final diagnosis.

Alternate diagnoses should be considered as well to ensure a separate phenomenon is not causing the new symptoms (e.g., ischemic stroke, infections, metabolic disturbances). Along with a thorough history and physical exam, obtain a visual field test. A unilateral loss of vision suggests optic neuritis with a scotoma of the central or cecocentral visual field. The monocular vision loss is associated with the presence of relative afferent pupillary defect (RAPD) on exam, otherwise known as a Marcus Gunn pupil. RAPD is elicited by shining a bright flashlight at the unaffected eye in a dark room and swinging the light to the affected eye (with visual loss). In a patient with optic neuritis, this results in a diminished or absent pupillary constriction.

The Lhermitte phenomenon is a relatively unique exam finding of MS that occurs when MS affects the spine. This also is known as the barber chair phenomenon, which is an electric shock-like sensation that occurs in the neck on flexion of the neck. Urinary retention can be seen with a bladder scan. The level of spinal cord involvement determines which symptoms will affect the patient.

MRI is the primary imaging modality that provides diagnostic information by determining a new diagnosis or an exacerbation of MS, or demonstrable progression of chronic MS, and serves to guide treatments.[51-53] An MRI is positive in 80% of CIS and is abnormal in nearly 100% of patients with an established diagnosis.[54] A spinal MRI is important because almost 50% of patients with a CIS and up to 90% of those with chronic forms of MS have a lesion seen in the spine, usually the cervical spine.[55-58] Most commonly, there are foci of abnormalities identified within the white matter, located in the periventricular, infratentorial, or the juxtacortical areas.[54]

In the ED, obtain a workup that includes a complete blood count, comprehensive metabolic panel, urinalysis, and an electrocardiograph. Check for any signs of neutropenia, lymphopenia, or other signs of immunocompromise. Consider additional testing to evaluate other entities that increase the risk of MS that include a mononucleosis spot test and EBV nuclear antigen immunoglobulin G (IgG) levels.[17] Send extra tubes of blood to the lab to add on further possible MS workups, such as myelin-oligodendrocyte glycoprotein (MOG-IgG) antibodies.

When the history, exam, and MRI are not able to provide a clear diagnosis of MS, a lumbar puncture (LP) may be necessary. The cerebrospinal fluid (CSF) in MS demonstrates a normal white blood cell (WBC) count or slight pleocytosis (up to 25 WBCs per $cm^3$), increased protein (under 1 g/L), elevated IgG index, and IgG oligoclonal bands.[54] CSF oligoclonal bands are present up to 90% of the time when patients are diagnosed with MS.[59]

Non-MS-related diagnoses need to be considered. MS is diagnosed incorrectly in up to 10% of cases.[60] Common misdiagnoses include fibromyalgia, small vessel cerebrovascular disease, migraine headache, and other functional neurological conditions.[60,61]

The ED physician should be able to integrate history and clinical exam findings and facilitate further diagnostic studies. Ultimately, a definitive diagnosis of MS should be made by either an MS subspecialist or a neurologist who is familiar with MS diagnostic criteria and treatment.

## Management

The most common life-threatening problem is sepsis, typically related to respiratory infections or urinary tract infections.[62] Less commonly, complications of medical management listed in Table 1 can occur, including anaphylaxis, immunosuppression leading to fatal opportunistic infections, or hepatic failure. The options of treatment include intravenous (IV) steroids, oral steroids, adrenocorticotropic hormone (ACTH), plasma exchange, disease-modifying treatments (DMTs), and nonpharmacologic modalities, such as physical therapy.

Treatment for an MS relapse is initially 1,000 mg of methylprednisolone IV or orally daily for three to five days.[63] A three-day course has fewer side effects compared to the five-day course. Inform the patient about the side effects of methylprednisolone that include facial flushing, dysgeusia,

**Table 3. The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients with an Attack at Onset**

| | Number of lesions with objective clinical evidence | Additional data needed for a diagnosis of multiple sclerosis |
|---|---|---|
| ≥ 2 clinical attacks | ≥ 2 | None* |
| ≥ 2 clinical attacks | 1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†) | None* |
| ≥ 2 clinical attacks | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ |
| 1 clinical attack | ≥ 2 | Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶ |
| 1 clinical attack | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡<br>AND<br>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶ |

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5.

¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.



hyperglycemia, gastrointestinal upset, elevated blood pressure, insomnia, anxiety or agitation, hypokalemia, and peripheral edema. Consider providing prophylactic prescribed or over-the-counter medications to mitigate these side effects (e.g., a proton pump inhibitor or sucralfate and metoclopramide for gastrointestinal symptoms).[64] Oral steroids may be preferred over IV, since they are less cumbersome, less expensive, and appear to be equally as effective as IV.[65] The dosing of oral steroids is 25 50-mg prednisone tablets or 32 6-mg dexamethasone tablets per day for three to five days. Intravenous corticosteroids have been the standard treatment in the past for optic neuritis, but there is recent evidence that oral corticosteroids are not inferior to IV steroids for optic neuritis.[66] Steroids typically alleviate symptoms within one week. If there is no improvement by two weeks, this is considered a treatment failure.[67,68] If there is no improvement, patients can receive a second course of steroids, ACTH, or plasma exchange.[68-71]

Treating true relapses with high-dose corticosteroids mitigates inflammation leading to a reduction in new neurologic deficits. True relapses should be suspected with a new neurologic territory impairment. This diagnosis can be made clinically and does not always require an MRI, although further imaging may be considered in the ED in consultation with the patient's neurologist.

When a pseudorelapse is diagnosed, treat the underlying cause. Avoid steroids in patients who present with a pseudorelapse, since steroids can be immunosuppressive, which may exacerbate underlying pathology. Evaluate for urinary tract infections, respiratory infections, and viral infections. Treat the underlying etiology of the pseudorelapse with appropriate antibiotics, antifungals, or antivirals as appropriate.

Treat fever with antipyretics, since increased body temperature worsens MS symptoms.[72,73] Elucidate any difficulties with medication compliance, dosing schedule, or side effects, since noncompliance may lead to pseudorelapse as well.

Consider and counsel selected patients on "needle fatigue," which is a condition in MS patients that occurs when they stop taking DMTs (i.e., high-frequency interferon beta and glatiramer acetate) because of intolerable

side effects from the injections, which can happen in 17% to 46% of those in their first year of treatment.[74-76] Oral treatments or parenteral treatments that are given once every two weeks have been shown to be an effective alternative to improve compliance when needle fatigue is present.[7]

Nonpharmacologic modalities and patient preference of treatment should be based on acceptance and adherence by the patient. Options include exercise, nutritional counseling, psychosocial therapy, occupational therapy, physical therapy, and speech therapy, which have been demonstrated to improve outcomes in MS.[77-79] This will improve the patient's overall quality of life by improving the patient's physical, mental, and social health.[80] Recommending outdoor activity may be important also because sun exposure has protective effects against MS.[81,82]

Address modifiable risk behaviors that can reduce the relapse and/or progression of MS that include cessation of cigarette smoking, increased sun exposure, increased exercise, Mediterranean diets, reduced exposure to air pollution, and weight loss in obese patients.[17]

MS relapses often will improve spontaneously or resolve without medications. Therefore, after a careful discussion with the patient and his/her neurologist, patients may opt to forego initiation or alterations in medications. Shared decision-making is important to deliver good and compliant care.

## Disposition

Unless the patient otherwise meets inpatient criteria, outpatient management in a patient with an MS relapse is preferred for cost savings, patient wellness, and avoidance of overtreating.[83]

Inpatient criteria can be considered in patients with suspected new-onset MS. An admission may be indicated to evaluate whether the patient is presenting with MS vs. a non-MS diagnosis, such as a stroke. An MS workup can include MRIs and neurology consultation as well as possible LP for CSF analysis and further laboratory tests. A neurologist will establish the diagnosis of MS.

Outpatient workup can be considered if the patient can follow up soon and demonstrates good compliance, and if urgent outpatient MRI testing and neurology consultation are available. Outpatient treatment of a relapse or a pseudorelapse (e.g., infection) also should include the clinical stability or functional safety of the outpatient setting. Evaluate the patient's ability to care for himself or herself and the need for IV medications, oxygen, physical therapy, or other inpatient medical interventions that are required. If the patient is stable to be discharged, involve the consultation of a neurologist to assist with an outpatient treatment plan and ensure close outpatient follow-up. When discharging the patient from the ED, make the patient aware of the various treatment options, adverse effects, drug interactions, compliance, identification of treatment failures, evaluation of readiness to initiate treatment, and barriers to treatment, and counsel patients on fertility and reproduction-related concerns.[73]

## Summary

MS is a complex disease that often is challenging to diagnose and initiate management in the ED. Patients who have been previously diagnosed with MS often will be knowledgeable about their condition, treatments, and disposition management. Many diagnostic considerations must be weighed when an MS patient presents to the ED, including differentiating between a new-onset presentation of MS, a relapse, and a pseudorelapse, which will guide the workup and disposition. Development of new neurologic signs or symptoms also may be a non-MS problem. Therefore, it is important that the emergency physician performs a careful history and physical exam and is familiar with the various presentations of MS, MS mimics, and conditions that can exacerbate the MS disease course. In addition to good communication, patient counseling and shared decision-making are important aspects of high-quality care. Each presentation will require a thorough evaluation and workup, patient involvement, neurology consultation, and a disposition and management plan that addresses the patient's unique circumstances. As imaging technology advances, new pharmacologic and non-pharmacologic therapies are developed, and protocols evolve, high-quality outcomes in MS depend on a well-informed emergency physician.

## References


1. Farber R, Hannigan C, Alcauskas M, Krieger S. Emergency department visits before the diagnosis of MS. *Mult Scler Relat Disord* 2014;3:350-354.
2. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. *Am J Manag Care* 2013;19(17 Suppl):s321-s331.
3. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* 2014;83:278-286.
4. Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. *Lancet Neurol* 2012;11:157-169.
5. Zeydan B, Kantarci OH. Impact of age on multiple sclerosis disease activity and progression. *Curr Neurol Neurosci Rep* 2020;20:24.
6. Amato MP, Fonderico M, Portaccio E, et al. Disease-modifying drugs can reduce disability progression in relapsing multiple sclerosis. *Brain* 2020;143:3013-3024.
7. Thompson AJ, Baranzini SE, Geurts J, et al. Multiple sclerosis. *Lancet* 2018;391:1622-1636.
8. Vidal-Jordana A, Montalban X. Multiple sclerosis: Epidemiologic, clinical, and therapeutic aspects. *Neuroimaging Clin N Am* 2017;27:195-204.
9. Wallin MT, Culpepper WJ, Campbell JD, et al. The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology* 2019;92:e1029-e1040. [Published correction appears in *Neurology* 2019;93:688.]
10. Yamasaki R, Kira J. Multiple sclerosis. In: Sango K, Yamauchi J, Ogata T, Susuki K, eds. *Myelin: Basic and Clinical Advances*. Springer; 2019.
11. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. *Rev Neurol (Paris)* 2016;172:3-13.
12. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;2:162-173.
13. Compston A, McDonald IR, Noseworthy J, et al, eds. *McAlpine's*

*Multiple Sclerosis*, 4th ed. Churchill Livingstone; 2005.

14. Hirst C, Ingram G, Pickersgill T, et al. Increasing prevalence and incidence of multiple sclerosis in South East Wales. *J Neurol Neurosurg Psychiatry* 2009;80:386-391.
15. Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol* 2007;6:903-912.
16. Belbasis L, Bellou V, Evangelou E, et al. Environmental risk factors and multiple sclerosis: An umbrella review of systematic reviews and meta-analyses. *Lancet Neurol* 2015;14:263-273.
17. Waubant E, Lucas R, Mowry E, et al. Environmental and genetic risk factors for MS: An integrated review. *Ann Clin Transl Neurol* 2019;6:1905-1922.
18. Laribi B, Shekarabi M, Zarnani AH, et al. Differential serostatus of Epstein-Barr virus in Iranian MS patients with various clinical patterns. *Med J Islam Repub Iran* 2018;32:118.
19. Houen G, Trier NH, Frederiksen JL. Epstein-Barr virus and multiple sclerosis. *Front Immunol* 2020;11:587078.
20. Wasko NJ, Nichols F, Clark RB. Multiple sclerosis, the microbiome, TLR2, and the hygiene hypothesis. *Autoimmun Rev* 2020;19:102430.
21. Smith KJ, McDonald WI. The pathophysiology of multiple sclerosis: The mechanisms underlying the production of symptoms and the natural history of the disease. *Philos Trans R Soc Lond B Biol Sci* 1999;354:1649-1673.
22. Margolin E. The swollen optic nerve: An approach to diagnosis and management. *Pract Neurol* 2019;19:302-309.
23. Henderson AP, Altmann DR, Trip SA, et al. Early factors associated with axonal loss after optic neuritis. *Ann Neurol* 2011;70:955-963.
24. Nij Bijvank JA, van Rijn LJ, Balk LJ, et al. Diagnosing and quantifying a common deficit in multiple sclerosis: Internuclear ophthalmoplegia. *Neurology* 2019;92:e2299-e2308.
25. Brassington JC, Marsh NV. Neuropsychological aspects of multiple sclerosis. *Neuropsychol Rev* 1998;8: 43-77.
26. Rao SM. Neuropsychology of multiple sclerosis. *Curr Opin Neurol* 1995;8: 216-220.
27. Ciccarelli O, Cohen JA, Reingold SC, et al. International Conference on Spinal Cord Involvement and Imaging in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders. Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders. *Lancet Neurol* 2019;18:185-197.
28. Rodríguez de Antonio LA, García Castañón I, Aguilar-Amat Prior MJ, et al. Non-inflammatory causes of emergency consultation in patients with multiple sclerosis. *Neurología* 2021;36:403-411.
29. Kalincik T, Buzzard K, Jokubaitis V, et al. Risk of relapse phenotype recurrence in multiple sclerosis. *Mult Scler* 2014;20:1511-1522.
30. Mahadeva A, Tanasescu R, Gran B. Urinary tract infections in multiple sclerosis: Under-diagnosed and undertreated? A clinical audit at a large University Hospital. *Am J Clin Exp Immunol* 2014;3:57-67.
31. Sakakibara R. Neurogenic lower urinary tract dysfunction in multiple sclerosis, neuromyelitis optica, and related disorders. *Clin Auton Res* 2019;29:313-320.
32. Guan XL, Wang H, Huang HS, Meng L. Prevalence of dysphagia in multiple sclerosis: A systematic review and meta-analysis. *Neurol Sci* 2015;36:671-681.
33. Davis SL, Jay O, Wilson TE. Thermoregulatory dysfunction in multiple sclerosis. *Handb Clin Neurol* 2018;157:701-714.
34. Tzelepis GE, McCool FD. Respiratory dysfunction in multiple sclerosis. *Respir Med* 2015;109:671-679.
35. Howard RS, Wiles CM, Hirsch NP, et al. Respiratory involvement in multiple sclerosis. *Brain* 1992;115:479-494.
36. Perez CA, Smith A, Nelson F. *Multiple Sclerosis, A Practical Manual for Hospital and Outpatient Care*. Cambridge University Press. March 2021.
37. Taus C, Giuliani G, Pucci E, et al. Amantadine for fatigue in multiple sclerosis. *Cochrane Database Syst Rev* 2003;(2):CD002818.
38. Witenko C, Moorman-Li R, Motycka C, et al. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. *P T* 2014;39:427-435.
39. Benedict RH, Munschauer, F, Zarevics P, et al. Effects of l-amphetamine sulfate on cognitive function in multiple sclerosis patients. *J Neurol* 2008;255:848.
40. Benedict RHB, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006;12:549-558.
41. Olivares T, Nieto A, Sánchez MP, et al. Pattern of neuropsychological impairment in the early phase of relapsing-remitting multiple sclerosis. *Mult Scler* 2005;11:191-197.
42. Brenner P, Piehl F. Fatigue and depression in multiple sclerosis: Pharmacological and non-pharmacological interventions. *Acta Neurol Scand* 2016;134(Suppl 200):47-54.
43. Barker AB, Lincoln NB, Hunt N, das-Nair R. Social identity in people with multiple sclerosis: An examination of family identity and mood. *Int J MS Care* 2018;20:85-91.
44. Berzins SA, Bulloch AG, Burton JM, et al. Determinants and incidence of depression in multiple sclerosis: A prospective cohort study. *J Psychosom Res* 2017;99:169-176.
45. Pérez Martín MY, González-Platas M, María Pilar PT. Perception of the disease in patients with multiple sclerosis. *J Neur Diseases* 2019;405:303.
46. Bruce JM, Hancock LM, Arnett P, Lynch S. Treatment adherence in multiple sclerosis: Association with emotional status, personality, and cognition. *J Behav Med* 2010;33:219-227.
47. Marrie RA, Zhang L, Lix LM, et al. The validity and reliability of screening measures for depression and anxiety disorders in multiple sclerosis. *Mult Scler Relat Disord* 2018;20:9-15.
48. Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2: Validity of a two-item depression screener. *Med Care* 2003;41:1284-1292.
49. Fischer JS. Cognitive impairment in multiple sclerosis. In: Cook SD, ed. *Handbook of Multiple Sclerosis*. Marcel Dekker;2001:233-256.
50. Mantero V, Abate L, Balgera R, et al. Clinical application of 2017 McDonald diagnostic criteria for multiple sclerosis. *J Clin Neurol* 2018;14:387-392.
51. Barkhof F, Hommes OR, Scheltens P, Valk J. Quantitative MRI changes in gadolinium DTPA enhancement after high-dose intravenous methylprednisolone in multiple sclerosis. *Neurology* 1991;41:1219-1222.
52. Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology* 2001;9:1239-1247.
53. Zivadinov R, Zorzon M, De Masi R, et al. Effect of intravenous

methylprednisolone on the number, size and confluence of plaques in relapsing-remitting multiple sclerosis. *J Neurol Sci* 2008;267:28-35.

54. Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: Progress and challenges. *Lancet* 2017;389:1336-1346.
55. Mahajan KR, Ontaneda D. The role of advanced magnetic resonance imaging techniques in multiple sclerosis clinical trials. *Neurotherapeutics* 2017;14: 905-923.
56. Sombekke MH, Wattjes MP, Balk LJ, et al. Spinal cord lesions in patients with clinically isolated syndrome: A powerful tool in diagnosis and prognosis. *Neurology* 2013;80:69-75.
57. Bot JCJ, Barkhof F, Lycklama à Nijeholt G, et al. Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: Value of spinal MR imaging. *Radiology* 2002;223:46-56.
58. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: A 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008;131:808-817.
59. Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: A meta-analysis of prevalence, prognosis and effect of latitude. *J Neurol Neurosurg Psychiatry* 2013;84:909-914.
60. Solomon AJ, Weinshenker BG. Misdiagnosis of multiple sclerosis: Frequency, causes, effects, and prevention. *Curr Neurol Neurosci Rep* 2013;13:403.
61. Solomon AJ, Klein EP, Boudette D. "Undiagnosing" multiple sclerosis: The challenge of misdiagnosis in MS. *Neurology* 2012;78:1986-1991.
62. Castelo-Branco A, Chiesa F, Conte S, et al. Infections in patients with multiple sclerosis: A national cohort study in Sweden. *Mult Scler Relat Disord* 2020;45:102420.
63. Tremlett HL, Luscombe DK, Wiles CM. Use of corticosteroids in multiple sclerosis by consultant neurologists in the United Kingdom. *J Neurol Neurosurg Psychiatry* 1998;65:362-365.
64. Chataway J, Porter B, Riazi A, et al. Home versus outpatient administration of intravenous steroids for multiple-sclerosis relapses: A randomised controlled trial. *Lancet Neurol* 2006;5:565-571.
65. Le Page E, Veillard D, Laplaud DA, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): A randomised, controlled, double-blind, non-inferiority trial. *Lancet* 2015;386:974-981.
66. Morrow SA, Fraser JA, Day C, et al. Effect of treating acute optic neuritis with bioequivalent oral vs intravenous corticosteroids: A randomized clinical trial. *JAMA Neurol* 2018;75:690-696.
67. Stoppe M, Busch M, Krizek L, Then Bergh F. Outcome of MS relapses in the era of disease-modifying therapy. *BMC Neurol* 2017;17:10-17.
68. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 1999;46:878-886.
69. Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: Predictors of response. *Neurology* 2002;58:143-146.
70. Cortese I, Chaudhry V, So YT, et al. Evidence-based guideline update: Plasmapheresis in neurologic disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2011;76,3:294-300.
71. Flanagan EP. Neuromyelitis optica spectrum disorder and other non-multiple sclerosis central nervous system inflammatory diseases. *Continuum* 2019;25:815-844.
72. Ontaneda D, Rae-Grant AD. Management of acute exacerbations in multiple sclerosis. *Ann Indian Acad Neurol* 2009;12:264-272.
73. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:777-788
74. McKay KA, Tremlett H, Patten SB, et al. Determinants of nonadherence to disease-modifying therapies in multiple sclerosis: A cross-Canada prospective study. *Mult Scler* 2017;23:588-596.
75. Clerico M, Barbero P, Contessa G, et al. Adherence to interferon-beta treatment and results of therapy switching. *J Neurol Sci* 2007;259:104-108.
76. Tan H, Cai Q, Agarwal S, et al. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Adv Ther* 2011;28:51-61.
77. National Institute for Health and Care Excellence (UK). NICE Clinical Guidelines, No. 186. Multiple Sclerosis: Management of multiple sclerosis in primary and secondary care. National Institute for Health and Care Excellence; 2014.
78. McNicholas N, Lockhart A, Yap SM, et al. New versus old: Implications of evolving diagnostic criteria for relapsing-remitting multiple sclerosis. *Mult Scler* 2019;25:867-870.
79. Craig J, Young CA, Ennis M, et al. A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. *J Neurol Neurosurg Psychiatry* 2003;74: 1225-1230.

## CME/CE INSTRUCTIONS

**To earn credit for this activity, please follow these instructions:**

1. Read and study the activity, using the references for further research.
2. Log onto ReliasMedia.com and click on My Account. First-time users *must register on the site.*
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%. Tests are taken with each issue.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.


80. World Health Organization. WHO Guidelines on Physical Activity and Sedentary Behaviour. World Health Organization; 2020.
81. Tremlett H, Zhu F, Ascherio A, Munger KL. Sun exposure over the life course and associations with multiple sclerosis. *Neurology* 2018;90:e1191-e1199.
82. Espinosa-Ramírez G, Ordoñez G, Flores-Rivera J, Sotelo J. Sunlight exposure and multiple sclerosis in a tropical country. *Neurol Res* 2014;36:647-650.
83. Abboud H, Mente K, Seay M, et al. Triaging patients with multiple sclerosis in the emergency department: Room for improvement. *Int J MS Care* 2017;19:290-296.


## CME/CE Questions

1. Which of the following is a risk factor for multiple sclerosis (MS)?
   a. Smoking
   b. Cytomegalovirus infection
   c. Sunlight
   d. Air pollution
2. Which of the following is a first-line treatment for MS relapse?
   a. Corticosteroids
   b. Toradol
   c. Plasma exchange
   d. Rehabilitation
3. Which of the following is true regarding oral steroids to treat MS?
   a. They are contraindicated, since only intravenous (IV) steroids are indicated.
   b. They are equally as expensive as IV steroids.
   c. They are more convenient, less expensive, and no less effective in treating MS relapses.
   d. They are more likely to cause gastrointestinal bleeding in MS patients compared to other populations.
4. Patients with MS are particularly prone to which of the following infections?
   a. Urinary and respiratory tract
   b. Central nervous system
   c. Biliary tract
   d. Gastrointestinal tract
5. Patients with optic neuritis present with which type of pain?
   a. Only in the dark
   b. With extraocular movement
   c. When reading
   d. When there is light pressure applied to the eye
6. Which of the following is true of pseudorelapsing MS?
   a. It occurs when the patient imagines new symptoms.
   b. It is always caused by depression.
   c. It can be caused by exposure to hot conditions.
   d. It is brought on by bed rest.
7. Which laboratory abnormalities should be expected during treatment with disease-modifying treatments?
   a. Decreased leukocyte count
   b. Lipase elevation
   c. Creatinine elevation
   d. Proteinuria

## EMERGENCY MEDICINE REPORTS

### *CME/CE Objectives*

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

*EMERGENCY MEDICINE REPORTS™*
**(ISSN 0746-2506) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to Emergency Medicine Reports, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.**

**Executive Editor:** Shelly Morrow Mark
**Associate Editor:** Mike Gates
**Editorial Group Manager:** Leslie Coplin
**Accreditations Director:** Amy M. Johnson, MSN, RN, CPN

**GST Registration No.: R128870672**





**Back issues: $30.** Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

## SUBSCRIBER INFORMATION

**CUSTOMER SERVICE: (800) 688-2421**

Customer Service Email Address:
customerservice@reliasmedia.com

Editorial Email Address:
smark@relias.com

Online:
ReliasMedia.com

**MULTIPLE COPIES:**
Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at groups@reliasmedia.com or (866) 213-0844.

Relias Media
From **Relias**


## ACCREDITATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

3 ANCC contact hours will be awarded to participants who meet the criteria for successful completion

Approved by the American College of Emergency Physicians for a maximum of 3 hour(s) of ACEP Category I credit.

This Enduring Material activity, Emergency Medicine Reports, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 01/01/2020. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 3 AAFP Prescribed credits.

The American Osteopathic Association has approved this continuing education activity for up to 2.5 AOA Category 2-B credits.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME/CE activity is intended for emergency and family physicians and nurses. It is in effect for 36 months from the date of the publication.

EMERGENCY MEDICINE REPORTS

# Multiple Sclerosis in the Emergency Department

## Medication Side Effects

| Name | Types of MS Treated | Frequency | Most Common Side Effects | Possible Clinical Syndromes | Possible Lab Abnormalities | Rare Life-Threatening Conditions |
|---|---|---|---|---|---|---|
| **Injectable Medications** | | | | | | |
| Interferon beta-1a (Avonex, Rebif) | CIS, RRMS, SPMS | Avonex: weekly; Rebif: 3 times/week | Headache, flu-like symptoms, injection site symptoms, depression | Psychosis, CHF, TMA, seizures | Transaminitis, decreased cell counts, UTIs | Suicidality, liver failure, anaphylaxis |
| Interferon beta-1b (Betaseron, Extavia) | CIS, RRMS, SPMS | Every other day | Flu-like symptoms, headache, injection site reactions (including necrosis), hypertonia | Drug-induced SLE, CHF, TMA | Lymphopenia, transaminitis | Anaphylaxis, fatal capillary leak syndrome |
| Glatiramer acetate (Copaxone, Glatopa) | CIS, RRMS, SPMS | Daily (20 mg) or 3 times/ week (40 mg) | Injection site reactions (including lipoatrophy), infection, flushing | | Transaminitis | Liver failure |
| Ofatumumab (Kesimpta) | CIS, RRMS, SPMS | Monthly | URIs, flu-like symptoms, injection site reactions, UTIs | Immunosuppression | Reduction in immunoglobulins | PML, hepatic failure (due to hepatitis B) |
| Peginterferon beta-1a (Plegridy) | CIS, RRMS, SPMS | Every 2 weeks | Injection site symptoms, flu-like symptoms, headache, pyrexia | CHF, TMA, autoimmune disorders, seizures | Transaminitis, decreased cell counts | Liver failure, anaphylaxis |
| **Oral Medications** | | | | | | |
| Teriflunomide (Aubagio) | CIS, RRMS, SPMS | Daily | Headache, diarrhea, alopecia | Immunosuppression, DRESS, interstitial lung disease | Transaminitis, decreased cell counts | Liver failure |
| Monomethyl fumarate (Bafiertam) | CIS, RRMS, SPMS | Twice daily | Flushing, abdominal pain, nausea | Immunosuppression | Transaminitis, lymphopenia | Anaphylaxis, angioedema, PML, opportunistic infections (PJP, disseminated HSV, etc.) |
| Dimethyl fumarate (Tecfidera) | CIS, RRMS, SPMS | Twice daily | Flushing, abdominal pain, diarrhea | Immunosuppression | Transaminitis, lymphopenia, eosinophilia | Anaphylaxis, angioedema, PML, fatal opportunistic infections (PJP, disseminated HSV, etc.) |
| Fingolimod (Gilenya) | CIS, RRMS, SPMS | Daily | Infections, hypertension | Immunosuppression, bradycardia, AV blocks, QT prolongation, Kaposi's sarcoma, macular edema, cutaneous malignancies, lymphoma | Lymphopenia, transaminitis | Opportunistic viral, bacteria, and fungal infections, PRES |
| Cladribine (Mavenclad) | CIS, RRMS, SPMS | Two separate treatment cycles | URIs, headache, nausea | Immunosuppression, malignancy, TB, GVHD with blood transfusion, cardiac failure | Lymphopenia, transaminitis, pancytopenia | Opportunistic viral, bacteria, and fungal infections, liver failure (due to direct liver injury or hepatitis), PML (*continued*) |

## The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients with an Attack at Onset

| | Number of lesions with objective clinical evidence | Additional data needed for a diagnosis of multiple sclerosis |
|---|---|---|
| ≥ 2 clinical attacks | ≥ 2 | None* |
| ≥ 2 clinical attacks | 1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†) | None* |
| ≥ 2 clinical attacks | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ |
| 1 clinical attack | ≥ 2 | Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶ |
| 1 clinical attack | 1 | Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡<br>AND<br>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶ |

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5.

¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

## Medication Side Effects (*continued*)

| Name | Types of MS Treated | Frequency | Most Common Side Effects | Possible Clinical Syndromes | Possible Lab Abnormalities | Rare Life-Threatening Conditions |
|---|---|---|---|---|---|---|
| **Oral Medications** | | | | | | |
| Siponimod (Mayzent) | CIS, RRMS, SPMS | Daily | Headache, hypertension | Immunosuppression, bradycardia, AV blocks, QT prolongation, macular edema, cutaneous malignancies, PRES | Lymphopenia, transaminitis | Opportunistic viral, bacteria, and fungal infections, PML |
| Ponesimod (Ponvory) | CIS, RRMS, SPMS | Daily | Headache, hypertension | Immunosuppression, bradycardia, AV blocks, QT prolongation, macular edema, cutaneous malignancies, PRES | Lymphopenia, transaminitis | Opportunistic viral, bacteria, and fungal infections, PML |
| Diroximel fumarate (Vumerity) | CIS, RRMS, SPMS | Twice daily | Flushing, abdominal pain, diarrhea | Immunosuppression | Lymphopenia, transaminitis | Anaphylaxis, angioedema, PML, fatal opportunistic infections (PJP, disseminated HSV, etc.) |
| Ozanimod (Zeposia) | CIS, RRMS, SPMS | Daily | URIs, orthostasis, UTIs, back pain | Bradyarrhythmias, hypertension, decreased pulmonary function, macular edema | Transaminitis | |
| **Infused Medications** | | | | | | |
| Alemtuzumab (Lemtrada) | RRMS, SPMS | Two treatment courses, each over 5 consecutive days | Rash, headache, pyrexia, nausea, UTIs | Immune thrombocytopenia, glomerulonephropathy, thyroid disorders, TTP, hemophilia | Transaminitis, decreased cell counts | Opportunistic viral, bacteria, and fungal infections, PML |
| Mitoxantrone (Novantrone) | RRMS, PRMS, SPMS | Every three months | Nausea, alopecia, depression | CHF, menstrual disorders including amenorrhea | Leukopenia | Secondary AML, opportunistic infections |
| Ocrelizumab (Ocrevus) | PPMS, CIS, RRMS, SPMS | Every 6 months | Transfusion reactions | Herpetic infections/lesions, immunosuppression, breast cancer | Reduction in immunoglobulins | Disseminated herpes, herpes encephalitis, PML |
| Natalizumab (Tysabri) | CIS, RRMS, SPMS | Every 4 weeks | Headache, fatigue, arthralgias | Immunosuppression | Transaminitis, thrombocytopenia | Herpes encephalitis, liver failure, anaphylaxis, PML |

AML: acute myelogenous leukemia; AV: atrioventricular; CHF: congestive heart failure; CIS: clinically isolated syndrome; DRESS: drug rash with eosinophilia and systemic symptoms; HSV: herpes simplex virus; ITP: immune thrombocytopenia; PJP: *Pneumocystis jerovicii* pneumonia; PML: progressive multifocal leukoencephalopathy; PPMS: primary progressive multiple sclerosis; PRES: posterior reversible encephalopathy syndrome; PRMS: progressive ( or primary) relapsing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; TMA: thrombotic microangiopathies; TTP: thrombotic thrombocytopenic purpura; URIs: upper respiratory infections, UTIs: urinary tract infections

## Differential Diagnosis

| | |
|---|---|
| Vascular | Ischemic stroke, hemorrhagic stroke, transient ischemic attack (TIA), cerebral aneurysm, vertebral/carotid dissection, central venous thrombosis, amaurosis fugax, anemia |
| Infectious/inflammatory | Severe infection (sepsis), viral encephalitis (including herpes simplex virus [HSV]), bacterial meningitis, Lemierre syndrome, human immunodeficiency virus (HIV), neurosyphilis, systemic lupus erythematosus, polyarteritis nodosa, Lyme disease |
| Toxicologic/traumatic | Concussion/traumatic brain injury (TBI), neuropraxia, spinal injury, rhabdomyolysis, ciguatera poisoning, coral snake bite, bark scorpion sting, tick paralysis, botulism, organophosphates, methanol poisoning |
| Autoimmune | Guillain-Barré syndrome, myasthenia gravis, Lambert-Eaton syndrome, autoimmune encephalitis |
| Metabolic | Hypoglycemia, hypokalemia, hypocalcemia, vitamin B12 deficiency |
| Neoplastic | Intracranial tumors, spinal cord tumors, Schwannoma, metastatic lesions |
| Congenital | Arnold-Chiari malformation |
| Degenerative | Diabetic neuropathy, amyotrophic lateral sclerosis (ALS), Huntington's disease |
| Endocrine | Hypothyroidism, hyperthyroidism |

(In particular, the close mimickers that have a relapsing and remitting course are: neuromyelitis optica, neurosarcoidosis, central nervous system vasculitis, Susac's syndrome, CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy], systemic lupus erythematosus, Sjögren's syndrome, antiphospholipid syndrome, Behçet's disease, CLIPPERS [chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids], and Leber's hereditary optic neuropathy.)

Supplement to *Emergency Medicine Reports*, September 15, 2021: "Multiple Sclerosis in the Emergency Department."
Authors: Jay Bernstein, MD, MPH, MS, FACEP, Assistant Professor, Department of Emergency Medicine, Wright State University, Dayton, OH; Shannon Lyon, MD, Emergency Medicine Resident, Wright State University, Dayton, OH; and Rachel Tabbouche, University of Maryland, College Park.