Accordant
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Clinical Practice Guidelines

Multiple Sclerosis

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Accordant Clinical Practice Guidelines:
Multiple Sclerosis (MS)

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INTRODUCTION

The AccordantCare™ program works with health plans to assess, monitor, and support those with certain complex, chronic conditions. The focus of the program is to improve health outcomes and prevent or limit disease-related complications. AccordantCare offers unique services at no additional charge to the patients, putting them in a strong position to adhere to their treatment plan.

There are several ways Accordant augments physicians' efforts. Through regular telephone contact, Accordant nurses:

- Keep patients informed about the disease process
- Coach patients in self-motivation and self-care skills
- Encourage patients to alert their physician when new symptoms arise
- Direct patients to resources that help pay for medication, transportation, home modifications, etc.
- Ensure preventive and screening measures are accomplished
- Provide emotional support to patients and caregivers
- Screen for depression
- Find local support groups

We invite physicians to make use of the services offered by Accordant and to suggest ways we can further patients' treatment goals. To offer feedback, get more information, ask questions or voice concerns; call toll-free 1-800-948-2497 to speak with a program representative from 8 a.m. to 9 p.m., Monday through Thursday, and from 8 a.m. to 5 p.m. on Friday, Eastern Time. Messages left after hours will be returned the next business day.

Intent of Guidelines

The purpose of this Clinical Practice Guideline is to describe current patterns of practice where there is no fully established national guideline for diagnosis and management. It is not meant to dictate care of patients. Decisions about care are made by the physician and the patient based on the individual needs of that patient.

A patient's health plan may or may not pay for all the medicines, tests, equipment, or services mentioned in this document. Benefits should be checked with the individual's health plan to assure payment.

Accordant Clinical Practice Guidelines:
Multiple Sclerosis (MS)

DISEASE OVERVIEW

Definition

Multiple sclerosis (MS) is a chronic, inflammatory, neurodegenerative disease that attacks the central nervous system (CNS)—the brain, spinal cord, and optic nerves. These assaults are triggered by the body's immune system and appear to be directed against myelin, oligodendrocytes, and axons.

The inflammation results in injury and removal of the myelin sheath, damage to the axons, and plaque/lesion formation (sclerosis). The name of the disease denotes that the sclerosis occurs in multiple areas, disrupting the ability of the affected nerves to conduct impulses to and from the brain. MS is a complex disorder, in which both environmental and genetic factors are thought to contribute to the underlying etiology.[1]

Classification

MS patients may experience one out of three typical disease courses.[2] The course of MS can vary greatly from individual to individual.[3]

- Relapsing-remitting MS (RRMS): This is the most common form of the disease; approximately 90% of people with MS begin with this course. RRMS is characterized by clearly defined acute attacks of worsening neurological function with full recovery or with residual deficit upon recovery. Periods between disease relapses are characterized by a lack of disease related to worsening.
- Primary-Progressive MS (PPMS): Approximately 10% to 15% of people with MS begin with this course. It is characterized by steadily worsening neurologic function from the beginning. The rate of progression may vary over time (with occasional plateaus and temporary, minor improvements). Patients may also experience later acute superimposed relapses with or without full recovery.
- Secondary-progressive MS (SPMS): This course begins as RRMS, but transitions after several years to progressive, slow-worsening MS.[4] This may include occasional relapses and minor remissions and plateaus. Typically, secondary-progressive disease is characterized by less recovery following attacks, and/or fewer attacks (or none at all) accompanied by progressive disability. Many patients with RRMS ultimately develop SPMS (e.g., some natural history studies show that of patients who start with relapsing-remitting MS, more than 50% will transition to secondary-progressive MS within 10 years).

Prevalence of Disease

MS affects approximately 400,000 Americans and more than two million individuals worldwide.[5] It is potentially the most frequent cause of neurological disability in young adults, generally presenting in most individuals between the ages of 20 and 40.

Prevalence and incidence are higher for women than for men, with more than twice as many women as men having the disease. The one exception is primary progressive MS, which affects men and women in about equal numbers and is usually associated with a later age at presentation. Incidence rates for MS are increasing among women.

Cost of the Disease

With the advent of disease modifying agents (DMAs) to treat MS the proportion of expenses spent for medications has increased. A 2010 study estimated the total cost of treatment for an MS patient over a 10-year period. For patients taking Avonex, e.g., the average total cost was $467,712. Other interferons had a similar cost. The average 10-year cost for a patient who was not taking a DMA was $267,710. Many factors went into the overall cost of treatment of MS. However, the cost of the medication, loss of productivity, inpatient admissions, and in-home nonmedical care accounted for over 90% of the costs. The cost of the medication (53% for Avonex, e.g.) was a big part of the overall cost.[6]

DIAGNOSIS OF DISEASE

Often individuals first seek medical attention after having a clinically isolated syndrome (CIS). Making an initial, accurate diagnosis as early as possible is critical. One study found that after four years of follow up, 52% or 75% of patients converted to clinically definite MS (depending on the criteria used).[7] Currently no specific test, symptom, or physical finding can definitively conclude that an individual has MS. The diagnosis of MS is based on the individual's medical history, an assessment of the signs and symptoms, and any tests the clinician determines necessary.

Diagnostic Criteria[8]

The 2010 revisions to the McDonald Criteria are the standard guidelines for diagnosing MS. They emphasize the importance of demonstrating dissemination of lesions in space and time and to exclude alternative diagnoses. They also allow that MS can be diagnosed on clinical grounds alone or by careful and standardized integration of clinical and MRI findings. In addition, a diagnosis of MS can be made following a CIS if MRI dissemination in space and time are met. (The presence of both gadolinium-enhancing and nonenhancing asymptomatic lesions on the baseline MRI can substitute for a follow-up scan to confirm dissemination in time as long as it can be reliably determined that the gadolinium-enhancing lesion is not caused by non-MS pathology.)

Table 3. 2010 McDonald MRI Criteria for MS

Dissemination in Time	Dissemination in Space
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI compared to baseline scan, regardless of the timing of the baseline MRI. (Lesions should be greater than 3 mm in size.)	One or more T2 lesions in at least two of the four areas of the CNS: • periventricular • juxtacortical • infratentorial • spinal cord
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time.	Gadolinium enhancement of lesions is not required. If the patient has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and don't contribute to lesion count.

Adapted from: Polman C, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69:292-302.

Doctors can diagnose MS based on a clinical presentation that includes two or more attacks. "Attacks" are defined as patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of the attack being at least 24 hours, in the absence of fever or infection.

Before a definite diagnosis of MS can be made, at least one of the attacks must be corroborated. Corroboration can be by findings on neurological examination, visual evoked potential (VEP) response in patients reporting prior visual disturbance, or by MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

Tests for MS

Neurological examination:

- An eye exam with an ophthalmoscope can reveal a pale optic nerve, often indicative of earlier damage; the doctor also tests visual acuity and looks for signs of diplopia, nystagmus, or other vision problems.
- The finger-to-nose test can show coordination problems, and the arm/leg resistance test and hand-squeezing test can demonstrate weakness issues.
- The tandem gait test and the walking-on-the-heels/toes test can reveal balance and strength difficulties.
- Reflex tests can uncover unequal reflexes on the two sides of the body. A positive Babinski's reflex (dorisflexion of the big toe and fanning out of the other toes after the sole of the foot has been firmly stroked) indicates corticospinal tract damage.
- Lhermitte's phenomenon can help to confirm a diagnosis of MS.

MRI[9]

Magnetic resonance imaging (MRI) is able to detect lesions in different parts of the CNS and distinguish new and active lesions from old ones, which is crucial in satisfying the diagnosis criterion of dissemination in time.[10] MRI findings can aid doctors in making the diagnosis and in predicting who will develop clinically definite MS.

For example, patients who present with a CIS and have one to three typical periventricular lesions (>3 mm in size) on brain MRI have an 89% chance of developing clinically definite MS over a 14-year period.[11] Nevertheless, a diagnosis of MS cannot be made solely on the basis of MRI results because other diseases can cause similar lesions in the brain or spinal cord. And a normal MRI cannot be used to exclude an MS diagnosis because a small percentage of confirmed MS patients do not show macroscopic brain lesions on MRI.

Analysis of Cerebrospinal Fluid (CSF)

Cerebrospinal fluid may be sampled by a spinal tap.[9] The most characteristic abnormalities of the CSF are the presence of oligoclonal bands on electrophoresis or an elevated IgG index. An elevated IgG index indicates intrathecal Ig production. CSF may also show a low grade pleocytosis. Spinal fluid analysis is useful to help diagnose MS, particularly in the case of PPMS.[12] Doctors use such findings to support the inflammatory demyelinating nature of the underlying condition, to evaluate alternative diagnoses, and to aid diagnosis of MS.

Evoked Potential (EP) Tests[9]

Evoked potential tests record the electrical responses elicited by stimulations to specific sensory pathways in the CNS. Because demyelination results in a slowing of response time, EP testing may demonstrate functional nerve problems that are not apparent from clinical examination and may be used to provide evidence of dissemination in space.[13]

The EP test most valuable in the diagnosis of MS is the visual evoked potential (VEP) test. The finding of a prolonged P100 wave on VEP in an individual, even if there are no clinical signs or symptoms of an optic nerve lesion, indicates subclinical involvement of the optic nerve.[13] However, EP tests can be initially normal in 50% of MS patients.[11]

Blood Tests

Blood tests can be used to rule out other causes (e.g., Lyme disease, vitamin B_{12} deficiency, collagen-vascular diseases, AIDS) of neurological symptoms.[9]

Serum testing for autoantibodies to aquaporin-4 (AQP4) in patients with symptoms of neuromyelitis optica spectrum disorder (NMOSD) help to diagnose NMOSD vs MS.[8]

Note: The development and validation of the McDonald Criteria have been limited to patients with typical presentations (CIS suggestive of MS or symptoms consistent with a CNS inflammatory demyelinating disease). Therefore, the McDonald Criteria should be applied only to patients with such typical presentations, or in the case of suspected PPMS, patients with progressive paraparesis/cerebellar/cognitive syndrome.

Differential Diagnosis
Only a few diseases cause neurological deficits that regress spontaneously and relapse in different areas of the CNS over the course of many years. Because of the remarkably varied symptoms of MS, many disorders may resemble MS, especially in the first years of active disease.

In applying the McDonald criteria, it is essential to consider and exclude alternative diagnoses. The 2010 consensus panel focused specifically on the differential diagnosis for MS vs NMOSD. The panel agreed that this phenotype should be separated from typical MS because of its different clinical course, prognosis, underlying pathophysiology, and poor response to some MS disease-modifying therapies.

APPROACH TO MANAGEMENT OF PRIMARY CONDITION

Goals of Treatment
In general, the priorities of MS treatment include[14,15]:

- Attaining a better understanding of MS pathogenesis and variability to guide the development of better monitoring and improved therapies;
- Preventing or postponing disability because of disease progression;
- Reducing the frequency, severity, and duration of relapses with additional treatment options;
- Finding effective therapies for progressive forms of the disease;
- Relieving specific symptoms, like bladder dysfunction or spasticity; and
- Promoting the repair of neural damage and restoration of function.

General Treatment of MS
Axonal damage, which occurs early in the disease course, is the pathology underlying permanent disability. Disease modifying agents (DMAs) can modify disease worsening and reduce future disability. The earlier they are utilized as treatment, the more beneficial DMAs become.[16] A 2014 Consensus Paper by the MS Coalition recommends starting treatment with an FDA-approved DMA[17]:

- As soon as possible following a diagnosis of relapsing MS;

- For individuals with a first clinical event and MRI features consistent with MS, in whom other possible causes have been excluded;
- For individuals with secondary-progressive MS who continue to demonstrate clinical relapses and/or demonstrate inflammatory changes on MRI;
- Treatment with a given DMA should be continued indefinitely unless any of the following occur:
  - Suboptimal treatment response as determined by the individual and his or her treating clinician;
  - Intolerable side effects;
  - Inadequate adherence to the treatment regimen; or
  - Availability of a more appropriate treatment.
- Movement from one DMA to another should occur only for medically appropriate reasons.
- When evidence of additional clinical or MRI activity while on treatment suggests suboptimal response, an alternative regimen (e.g., with a different mechanism of action) should be considered to optimize therapeutic benefit.
- The factors affecting choice of treatment at any point in the disease course are complex; they are most appropriately analyzed and addressed collaboratively by the individual and his or her treating clinician.

First-Line Agents to Treat MS

Today the first-line arsenal of DMAs approved for the treatment of relapsing MS includes[15,18]

- Beta interferon 1a (intramuscular Avonex® ,subcutaneous Rebif®, and pegylated subcutaneous Plegridy™)
- Beta interferon 1b (subcutaneous Betaseron® & subcutaneous Extavia®)[19]
- Glatiramer acetate (subcutaneous Copaxone®)
- Natalizumab (Tysabri®) (in patients who are JC virus antibody negative)[20,21]
- Fingolimod (oral Gilenya®)
- Teriflunomide (oral Aubagio®)[22]
- Dimethyl fumarate (oral Tecfidera™)[23,24]

Second-Line Agent to Treat MS

If treatment with a first-line agent is not effective, treatment with mitoxantrone (Novantrone®) may be considered,[18] although it is rarely used.

Other Treatment Options

Plasmapheresis and IVIG

Plasmapheresis may be considered as second-line treatment of steroid-resistant exacerbations in relapsing forms of MS. Plasmapheresis is **not** proven effective and should not be offered for progressive disease without relapses or secondary progressive MS.[25] Intravenous immunoglobulin (human) (IVIG) is not approved for use in MS, and randomized, double-blind, placebo-controlled trials showed no benefit of IVIG over placebo in either RRMS or SPMS.[26,27] Some experts believe IVIG may be useful in the postpartum period to prevent relapses.

Other medication treatment options exist for patients who do not respond favorably to, or who have reached dose limitations for, one or more of the above disease modifying agents. Other options include medications that have not been approved by the FDA for MS treatment and are being used off-label. These options also include promising new agents that are being investigated for their potential value with MS patients.

Complementary and Alternative Medicine (CAM)

Most patients with MS use therapies proposed by complementary and alternative medicine (CAM)—usually diet and diet supplements. Omega-3 fatty acid was tested in a 2-year, multi-center, randomized, double-blind, placebo-controlled trial. No beneficial effects on disease activity were found when it was used as monotherapy (6 months) or in combination with beta interferon (18 months) in patients with RRMS, when compared to those taking placebo.[28]

Gingko biloba compared with placebo failed to demonstrate improvement in cognitive performance.[29]

Medical marijuana, also known as cannabis, can be prescribed by doctors legally in 23 states. Different formulations of marijuana have been studied in MS patients according to the American Academy of Neurology.[30] However, it should be used with caution in the context of MS, a progressive neurologic disease where cognitive dysfunction is a known complication.

High levels of vitamin D are associated with lower incidence of MS and less disease activity.[31] However, it is not known whether vitamin D supplementation improves the course of MS. Even so, most MS specialists do supplement with vitamin D to achieve serum levels of 25-hydroxyvitamin D to 50 nmol/L.[32] Some doctors recommend a serum level of vitamin D of 70 nmol/L. Nearly ¼ of Americans are at risk of vitamin D inadequacy (serum 25-hydroxyvitamin D 30 to 49 nmol/L).[33]

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Accordant helps patients prevent and manage complications by teaching them to recognize early warning signs, encouraging adherence to treatment plans, offering supportive care, and recommending physician contact when needed. The list of goals and cooperative interventions listed below does not represent a comprehensive list of complications but reflects some of the more common clinical situations specific to MS. General health topics (e.g., age-appropriate cancer screening) are beyond the scope of this document.

Goal: Improve Self-management Skills
Cooperative interventions: Teach patients to:

- Strengthen their personal motivation skills.
- Develop prevention-focused, self-management skills.
- Develop purposeful communication skills and maintain open, ongoing communications with their physician.
- Work with Accordant for education, information, and self-care needs.

Goal: Improve Patient's Knowledge of Disease
Cooperative interventions:

- Advise patients to seek information from national and community-based MS foundations and resources.
- Provide an approved list of educational materials and Web site listings with assessments on an as-needed basis.
- Educate patients about MS and the specific complications they may be experiencing.
- Educate patients on treatment options, benefits, risks, and side effects, to enhance adherence through informed decision making.

Goal: Encourage Adherence
Cooperative interventions

- Educate patients about the importance of taking their medication as prescribed, its dosing, potential side effects, interactions, etc.
- Inform physician of any patient medication errors or unreported side effects.
- Encourage patients to carry all prescription and over-the-counter medications to physician visits.
- Monitor adherence with follow-up lab work as needed for medications.
- Build trust and become problem-solving partners with patients, ultimately leading to patients who are more willing to adhere to their treatment regimens.[34]
- Reassure family members, including children, that their understanding, love, support, and feedback are essential to the patient's treatment.[34]

Goal: Promote Healthy Behavior
Cooperative interventions

- Provide educational resources that promote proper nutrition programs that prevent obesity and comorbid conditions such as heart attack/stroke.
- Recommend exercise as part of a patient's overall, long-term treatment plan. Help with setting goals for exercise type, timing, frequency, duration, and intensity.[35]
- Encourage not smoking and provide information and education on resources that help patients to stop smoking.
- Encourage flu vaccination/pneumococcal vaccine, polyvalent (Pneumovax), unless contraindicated, to high-risk patients with MS. The varicella vaccine (Zostavax) may be safe and beneficial for people with MS who have had chicken pox in the past (or who currently have antibodies to the varicella zoster virus).[36]

Goal: Prevent and Manage Bladder Problems
Cooperative interventions

- Identify patients who are experiencing signs and symptoms of neurogenic bladder for appropriate management.
- Recommend that patients avoid spicy foods (containing capsaicin) and caffeine, because they may irritate the bladder wall and precipitate spasm.
- Suggest patients try pelvic floor exercises for at least three months before determining if they are effective. Bladder training with scheduled voiding may be helpful, also.[11]
- Monitor closely for signs of secondary symptoms such as urinary tract infections, benign prostatic hypertrophy in men, or kidney stones and other kidney damage.[37]

Goal: Prevent and/or Manage Exacerbations
Cooperative interventions:

- Monitor and enhance adherence to prescribed DMAs.
- Educate patients about flares and encourage early contact with their treating physician.
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- Explain that similar symptoms may result from fever, infection, heat, or stress (pseudoexacerbation), and not from the underlying MS, and that it is important to determine if the symptoms result from new lesions/plaques.[38]
- Educate patients and provide tips about how to avoid fatigue.
- For acute exacerbations, ensure coordination of corticosteroid treatment and adherence with the prescribed therapy.
- With a few exceptions, avoid live vaccines because they can increase disease activity.[36]

Goal: Prevent and Manage Infections
Cooperative interventions

- Educate patients about the risks, signs and symptoms of common infections.
- Encourage patients to report signs and symptoms of infections to a nurse or doctor for rapid diagnosis and treatment to minimize emergency room visits and inpatient stays.
- Identify and treat patients with symptoms indicating systemic infection as soon as possible.
- Identify patients who are experiencing swallowing problems to prevent aspiration pneumonia and other infections.[39]
- Provide ongoing education to avoid injection-site infections such as cellulitis and soft-tissue abscesses.[40]

Goal: Prevent Falls and Fractures
Cooperative interventions

- Encourage patients to discuss risk of falls with their physician and to determine if they need an in-depth falls exam (e.g., Get Up and Go Test)[41]
- Reduce risk of falls by facilitating pre-emptive home safety evaluations, physical therapy, or durable medical equipment for high-risk patients.
- Consider interventions that provide additional sensory input to the lower or upper extremities and provide additional proprioceptive information about the position of the body in space.[42]
- Encourage patients to participate in exercise that improves balance, gait, and strength.[41]
- Educate about the importance of osteoporosis and adherence to medication regimen for osteoporosis.
- Encourage patients to discuss calcium and vitamin D supplements.[41]

Goal: Prevent and Manage Skin Problems
Cooperative interventions

- For wheelchair-bound or bed-ridden patients, stratify patient's risk for skin breakdown using Kurtzke Extended Disability Status Scale and scripted inquiries.
- Educate patients about the warning signs of skin breakdown and the need to inform their physician as soon as possible.
- Identify any patient with apparent skin breakdown and notify physician.
- Ensure that a physician treatment plan and follow-up is in place.
- Inquire about ongoing skin issues, assess skin reactions, and periodically review injection technique.[40]

Goal: Prevent and Manage Depression/Emotional Disturbances
Cooperative interventions

- Evaluate adequacy of support systems and work with physician, the patient, caregiver, family and health plan to correct deficiencies.

- Assist physician in detecting mood disturbances using the two-question screening tool[43] with each contact.
- Facilitate corrective plan as approved by the patient and physician.
- Enhance the patient's access to support groups and encourage communication with physician.
- Establish with patients that depression is a disease with biological and chemical components, that it is common in MS patients, and that it is treatable.[34]

Goal: Manage Dysphagia
Cooperative interventions: Teach patients to:

- Focus on exercises and other means to restore disturbed swallowing functions.
- Learn new postures and swallowing techniques to compensate for swallowing problems.
- Modify their environment (food texture, eating utensils, etc.) to facilitate eating and drinking.

PATIENT FOLLOW-UP

Please inform Accordant of any issues that require monitoring or follow-up with your patient so that we may effectively communicate the specifics of the physician treatment plan. For example, follow-up with the patient may be helpful after home safety evaluations, physical therapy, or the acquisition of new durable medical equipment.

With the high cost of disease modifying agents to treat MS, and the huge social cost of cognitive impairment, ongoing follow-up with MS patients to evaluate their coping status is essential.[44] Accordant can work with the patient to coordinate referrals, community resources, and government services. We also can collaborate with other healthcare professionals on behalf of the patient.

PATIENT EDUCATION

The Accordant Health Communities Web site at:
https://www.accordant.com offers resources for patients with MS.

Other approved and informative Web sites for patient education include the following.

The National Multiple Sclerosis Society
http://www.nationalmssociety.org

National Institutes of Health

http://health.nih.gov/topic/MultipleSclerosis

The Consortium of Multiple Sclerosis Centers
http://www.mscare.org/cmsc/index.php

National Institute for Health and Clinical Excellence (NICE)
http://guidance.nice.org.uk/CG8

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