Relapse Management in Multiple Sclerosis

Ben W. Thrower, MD

Abstract: Relapses, exacerbations, and attacks are synonymous for new or worsened neurologic symptoms that are the hallmark of relapsing-remitting multiple sclerosis. Management of relapses is not always straightforward. The clinician must distinguish between true relapses, symptom fluctuation, and pseudo-relapses. Risks and benefits of treating a relapse must be considered. Once the decision to treat is made, most clinicians would pursue a course of corticosteroids. Consensus may end there, as there is no clear-cut “best” route of administration or dosing schedule. The patient presenting with their first relapse or clinically isolated syndrome may be at risk for the development of multiple sclerosis. Clinical presentation, CSF findings, and MRI may all give clues as to the risk for future demyelinating events.

Key Words: multiple sclerosis, clinically isolated syndrome, relapse, exacerbation, prednisone, methylprednisolone, intravenous immunoglobulin, plasma exchange, pseudo-relapse

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Multiple sclerosis (MS) is a leading cause of nontraumatic disability for young adults worldwide. Each week, 200 new cases are diagnosed. Most of these will present as relapsing-remitting MS (RRMS). Without intervention, natural history predicts that most of these patients will transit to secondary progressive MS (SPMS). This transition is characterized by fewer relapses and increasing disability.

MS is an autoimmune disorder directed against myelin in the CNS. Although it is felt to be primarily a T-cell driven disease, B-cells may also contribute to the immunopathology. Before 1998, MS was felt to be a demyelinating disease with less focus given to the role of axonal pathology. In 1998, Trapp et al confirmed what had been described by Charcot in 1868, namely that axonal transaction occurs in MS and may occur early in the course.

Management of MS can be divided into 3 areas; relapse management, symptom management, and therapies to alter the long-term course of the disease. This review will focus on clinical issues surrounding the acute management of relapses, not on long-term use of immune therapies in MS. Ongoing relapses despite immunomodulatory therapy may be an indication of an inadequate treatment response. The subjects of the long-term management of MS including inadequate responders, although crucially important, are outside of the scope of acute relapse management. Special topics including pregnancy, vaccinations, and clinically isolated syndromes (CIS) will also be covered.

Relapse Definition

The term “relapse” in MS, is synonymous with “attack” and “exacerbation.” A relapse is defined as a new neurologic symptom lasting for more than 24 hours. There must be no better alternative explanation. A relapse may also present as worsening of a neurologic symptom that had previously been stable for at least 30 days. Again, there must be no better alternative explanation.

Although these definitions are helpful, sorting out what is a relapse and what is not can be tricky at times. Many MS patients mistakenly interpret the term “remission” to mean symptom-free. Unfortunately, most people with MS are always symptomatic in some way. Fatigue, for instance, is the most common MS symptom and is usually present even during periods of clinical stability or remission. Factors such as stress or sleep deprivation can worsen these baseline symptoms. These symptom fluctuations do not represent relapses.

Pseudo-relapses and infections can also muddy the clinical waters. New or worsened symptoms in the setting of heat exposure or overexertion are usually not felt to represent true attacks. Events associated with heat or exertion should resolve with rest or cooling. These transient worsenings are likely because of conduction block within demyelinated axons. The effect of infections on MS relapses may depend upon the nature and severity of the infection. Viral upper respiratory infections and simple UTIs are most likely to be associated with pseudo-relapses. Systemic infections, however, can cause true clinical relapses, new MRI lesions, and an increase in T-cell activation.

Stress, Pregnancy, and Vaccinations

Many patients with MS report an increase in symptoms with psychosocial stress. When we look at the relationship between stress and relapses or new MRI lesions, studies have yielded mixed results. Some studies have found no correlation between stress and increased clinical/MRI activity, whereas others have. Self-reported stressful events have been associated with a doubled risk for exacerbation in the 4 weeks after the stressor. Psychosocial stress and its relationship to gadolinium-enhancing lesions were examined in 36 RRMS patients. Psychosocial stress or distress increased the odds ratio (1.64; P = 0.00083) of a new enhancing lesion on brain MRI in the following 8 weeks.

Pregnancy can have significant short-term effects on relapse rates for the woman with MS. Relapses become less frequent during pregnancy, especially during the third trimester. Relapse rates then tend to increase during the 3 months after delivery. However, the majority (72%) of postpartum women with MS will not experience a relapse. Postpartum relapse rates may be best predicted by the prepregnancy rate. The effects of pregnancy and the postpartum period do not alter the overall course of MS.

Although relapses are less frequent during pregnancy in the woman with MS, they are still possible. Corticosteroids are relatively contraindicated during pregnancy (pregnancy category C). Intravenous immune globulin (IVIG) is also listed as a pregnancy category C drug, but there is some data on its use during pregnancy in MS and in other health conditions (ie, thrombocytopenia). The use of IVIG during pregnancy is discussed under the section of this article dealing with treatment options.

The decision whether to breast-feed or not is an individual one. Relapse rates are similar in women with MS who breast-fed their infants compared with those who did not. Breastfed infants of mothers with MS have been shown to have a lower risk for otitis media, lower respiratory infections constipation, and
milk intolerance.\textsuperscript{11} This benefit needs to be weighed against the need to withhold immunomodulatory therapy until the baby has weaned.

There has been concern over the risk of relapse after certain vaccines for the person with MS. Years ago, influenza vaccines were discouraged in the MS patient for fear of provoking an exacerbation. More recently, questions have arisen regarding MS risk after hepatitis B vaccination. After reviewing all available data, the National MS Society has concluded that vaccines for influenza, hepatitis B, varicella, and diphtheria/tetanus, were not associated with a risk of developing or worsening MS.\textsuperscript{12–14} MS patients on immunosuppressants should not receive live, attenuated vaccines such as MMR (measles, mumps, rubella). Immunosuppressants include mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and chronic corticosteroids. Beta-interferons and glatiramer acetate are not immunosuppressants.

The Importance of MS Relapses

Relapses in MS matter. Relapses are associated with disruption of the patient’s life, economic expense, and anxiety about future relapses. Inpatient management of a relapse cost $12,870 in 2002. Outpatient management generated $1847 in expenses. These represent direct medical costs and do not include time lost from work.\textsuperscript{15}

There is no guarantee of complete neurologic recovery after a relapse. The nature of untreated RRMS is that it transitions to SPMS. Relapses become less frequent as disability accumulates. Lublin\textsuperscript{16} demonstrated persistence of disability for many patients after an attack. When examined 6 months after a relapse, 42% remained worsened by 0.5 points on the Expanded Disability Status Score (EDSS) and 28% by 1 point.

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The frequency of relapses early in the course of MS has predictive value in regards to future disability. An EDSS of 6.0 is an important milestone in MS. At this score, the patient is using a unilateral assistive device, ie, a cane or forearm crutch. The likelihood of reaching an EDSS of 6.0 was 20% at 10 years if the patient had 1 or fewer exacerbations in the first 2 years of their disease. In contrast, most patients with 5 or more relapses in the first 2 years had progressed to cane usage at 10 years.\textsuperscript{17}

Relapses: To Treat or Not to Treat?

Before discussing treatment options for relapses, one needs to ask whether all relapses need to be treated. Several studies have given insight into the acute and long-term effects of treating a relapse. Corticosteroids have been the mainstay of MS relapse therapy. Multiple regimens exist, however, using varying doses and routes of administration. This review will focus on steroids administered for acute relapse management, not those used on a pulse basis for long-term disease modification.

The optic neuritis treatment trial (ONTT) divided optic neuritis patients into 3 therapeutic groups; oral prednisone for 14 days, oral placebo for 14 days, or intravenous methylprednisolone (IVMP) 250 mg 4 times daily for 3 days followed by oral prednisone 1 mg/kg/d for 11 days. At 6 months, the IVMP group showed faster visual recovery of visual function compared with the placebo group ($P < 0.001$). At 1 year, there was no difference in visual outcomes between the 3 groups. Thus, IVMP led to a speedier but not better recovery. Interestingly, at 2 years, the oral prednisone group had a higher risk (30%) of recurrent optic neuritis compared with the IVMP (14%) and placebo groups (16%). There is no consensus on whether this increased risk is real or due to baseline differences in treatment groups at randomization. The risk for a second demyelinating event of any kind at 2 years was 7.5% in the IVMP group, 14.7% in the oral prednisone group, and 16.7% in the placebo.\textsuperscript{18}

The presence of short-term but not long-term clinical benefits from steroid therapy\textsuperscript{19,20} seems to be mirrored by the duration of effects on immune markers and MRI. High-dose IVMP results in a decrease in peripheral CD4\textsuperscript{+} lymphocytes and interferon-\gamma.\textsuperscript{21,22} However, these effects are not present at 6 months. Treatment with IVMP results in a rapid reduction in blood brain barrier abnormalities on MRI. Enhancing lesions are reduced by 96%. This benefit persists for a month, with new and/or re-enhancing lesions developing afterward.\textsuperscript{23}

It is possible that high-dose steroids could play a larger role than that of just speeding clinical recovery. Tissue recovery within an enhancing lesion was measure by magnetization transfer ratios (MTR). Lesion recovery measured 12 to 18 months after the initial enhancement was higher for the group treated with 5 days of IVMP 1 g/d.\textsuperscript{24} Several small prospective studies have suggested improvements in EDSS and reductions in relapse rates persisting for up to a year after a single course high-dose steroids in RRMS.\textsuperscript{24,26}

The risk of steroid side effects must be considered when deciding whether to treat a relapse or not. There is significant variability in tolerance for steroids from one individual to the next. Potential side effects include mood changes, ranging from anxiety, to agitation, to psychosis. Increases in serum glucose and blood pressure may make steroid use more difficult in some patients. Hypokalemia and gastric upset may also be seen. Chronic steroid usage may be associated with premature cataracts, osteoporosis, weight gain, thinned skin, and other side effects.

The decision to treat or not largely depends upon the functional impact of the exacerbation on activities of daily living.

The patient should be advised to notify the provider of all potential relapses. The decision to treat or not largely depends upon the functional impact of the exacerbation on activities of daily living. As stated earlier, recovery from the relapse will be the same with or without steroid therapy. However, treatment may hasten recovery. Even if a relapse is not treated, documentation is still desirable. Recurrent attacks will factor into the decision of whether a patient’s immunomodulatory therapy is adequate.

Once the decision to treat is made, what do we treat with? First-line options generally include 3 to 5 days of IVMP (500–1000 mg/d) with or without an oral taper, high-dose oral steroid. Adrenocorticotropic hormone (ACTH), IVIG, and plasma exchange may be alternatives. Based upon unproven efficacy and the results of the ONTT, low-dose oral steroids are not as commonly used.
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Steroids: Intravenous Versus Oral

Most US neurologists use 3 to 5 days of high-dose IVMP, 1 g/d typically, as their treatment of choice for MS relapses. Oral prednisone tapers are used by some. Canadian neurologists may be more likely to use 3 to 5 days of high-dose oral prednisone/methylprednisolone for relapse management. Both routes of administration have shown efficacy for relapse therapy. Individual and regional practice patterns may be determined by observation, training, or habit. Is there a single best steroid protocol for management of MS exacerbations?

Serum steroid concentrations after the administration of 1 g of IVMP were compared with those after 1250 mg of oral prednisone. At 24 hours, the mean areas under the concentration-time curve were the same, demonstrating similar bioavailability. Gastric tolerance, as measured by permeability, was not significantly different between high-dose IVMP and high-dose prednisone groups. Several studies have shown similar efficacy between high-dose oral and intravenous regimens. The decision to select one route of administration over another is one of patient/clinician preference. Cost and convenience may also factor into the decision.

Steroid Alternatives

ACTH was once the mainstay of MS relapse management. ACTH was typically given intramuscularly as a 2-week tapering dose. Several trials have shown equal efficacy for more conveniently administered courses of IVMP. Recently, there has been some interest in using shorter courses of ACTH administered subcutaneously. As of August 2007, there was a significant price increase in the commercially available form of ACTH (Acthar) to over $23,000 per vial. For now, ACTH plays no realistic role in the management of MS relapses.

Intravenous immune globulin may be considered for the treatment of relapses in patients who are unresponsive to steroids or have a contraindication to steroid use.

IVIG may be considered for the treatment of relapses in patients who are unresponsive to steroids or have a contraindication to steroid use. Anecdotal experience suggests that some patients may benefit, but clinical trials have been disappointing. A trial looking at IVIG versus placebo for acute optic neuritis management found no differences in visual recovery up to 6 months. The addition of IVIG 1 g/kg/d to 3 days of IVMP 1 g/d did not further improve recovery in a significant way. IVIG may play a role in reducing the risk of postpartum relapses. Protocols using IVIG during gestation and the postpartum period were shown to decrease relapse rates during both periods compared with control groups. IVIG was dosed at 0.4 g/kg/d for 5 days within 6 to 8 weeks of gestation with additional booster doses of 0.4 g/kg once every 6 weeks until 12 weeks postpartum. Relapse rates during or after pregnancy were reduced compared with untreated controls. A second group was only treated during the postpartum period with 0.4 g/kg/d for 5 days within 1 week of delivery, followed by booster doses of 0.4 g/kg/d for 1 day at 6 and 12 weeks postpartum. Postpartum relapse rates were reduced compared with untreated controls. The referenced studies are aimed at preventing relapses during or after pregnancy. There are no studies examining the use of IVIG to treat an established relapse during pregnancy. Based upon safety data with IVIG during pregnancy and anecdotal reports of benefit from IVIG for acute relapse management, a course of IVIG 0.4 g/kg/d for 5 days may be considered for severe gestational relapses.

Plasma exchange may be considered for relapses that are unresponsive to steroid therapy.

Based upon the reports of Weinshenker, plasma exchange (PE) may be considered for relapses that are unresponsive to steroid therapy. PE was examined in a variety of acute demyelinating events. All patients were unresponsive to a course of high-dose IVMP. Twelve patients had RRMS, whereas 10 had other demyelinating conditions. A crossover design was used, with patients randomized to sham PE or real PE. Forty-two percent of PE patients had moderate or greater improvement with 2 weeks of treatment. Only 6% of sham patients improved. Three sham failures improved when crossed over to PE.

A Role for Rehabilitation

Rehabilitation plays a significant role in the comprehensive management of MS. Education, prevention, and symptom management improve function and help adapt to limitations. The exact role of rehabilitation in the long-term management has not been as well defined as it has been with spinal cord injury, stroke, or traumatic brain injury. This is at least in part because of the lower prevalence and progressive nature of MS. Relapses may temporarily or permanently reduce a patient’s ability to function at home or work. The addition of comprehensive rehabilitation to standard IVMP therapy resulted in improved performance on measures of disability and quality of life after a relapse.

Putting It All Together

The flow chart for potential relapse management at the MS Institute at Shepherd is included below. The reader is reminded that there are many protocols and individual preferences for relapse management.

Shepherd MS Relapse Protocol

1. Rule out possible precipitating events (heat exposure, overexertion, UTI, URI).
2. If any infection is suspected, screen and treat accordingly. Hold steroids.
3. If there are no clear cut precipitating events, determine the severity of the symptoms and any impact on activities of daily living.
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The importance of identifying and treating high-risk clinically isolated syndromes patients has been demonstrated in 3 studies. 

The importance of identifying and treating high-risk CIS patients has been demonstrated in 3 studies. ETOMS, CHAMPS, and BENEFIT have examined the effect of varying doses and dose frequencies of interferon-β in the CIS patient. All have shown that the time to the second clinical event is delayed by early treatment. Three-year data from BENEFIT (interferon-β-1b 250 µg subcutaneously every other day) recently showed that disability is also delayed by early initiation of therapy in CIS patients. 

CONCLUSIONS

Relapses are a defining clinical feature of the most common form of MS. They can have vocational, financial, and psychosocial impact. Exacerbations may be associated with incomplete recovery and future disability. Acute steroid therapy may lead to faster, but not necessarily better recovery. There is great variability in steroid dosing and routes of administration. Studies would support the use of high-dose intravenous or oral steroids over a course of 3 to 5 days. Pregnancy is associated with a reduction in relapse risk in the second and third trimesters. The risk of exacerbation then rises for a period of 6 months after delivery. Overall, these 2 factors probably balance out, resulting in no significant long-term effect of pregnancy on disability. Despite past fears, vaccinations for influenza, hepatitis B, varicella, and diphtheria/tetanus are not associated with an increased risk of relapse. CIS may represent the earliest clinical manifestation of RRMS. Although the acute management of the attack is important, consideration must be given as well to the risk for future events. Clinical presentation, CSF, and brain MRI all have predictive value for future MS risk. Thus far, all completed trials of disease modifying therapies have shown that the second relapse is delayed with early treatment. Three-year data from BENEFIT (interferon-β-1b in CIS patients. At 3 years after a CIS, 51% of these same patients had been diagnosed. 

REFERENCES


4. If the symptoms are not significantly affecting activities of daily living, you may observe.
5. If activities of daily living are affected, consider steroid therapy. Review medical history for any relative contraindications (diabetes mellitus, hypertension, pregnancy, poorly controlled psychiatric disease, past history of poor tolerance for steroids).
6. If there are no contraindications, proceed with steroids.
   a. IVMP 1 g/d for 3 days. No oral taper.
   or
   b. Oral prednisone 300 mg BID for 3 days. No oral taper. An oral taper may be considered in patients who report general malaise after 3 days of intravenous or oral steroids as above. Prednisone 20 mg, 3 po daily for 3 days, then 2 po daily for 3 days, then 1 po daily for 3 days, then 1/2 po daily for 3 days, then stop.
7. Consider lorazepam 1 mg po Q 8 hours for patients with a history of anxiety while on steroids or 1 mg po QHS for insomnia.
8. We do not routinely prescribe antacids or H2 blockers during steroids, some do.
9. For patients intolerant to steroids or pregnant women, consider IVIG 0.4 g/kg/d for 5 days. In our experience, some patients do seem to respond to IVIG for relapses.
10. For patients with tightly controlled diabetes mellitus, steroids can be used with caution by using sliding scale insulin. May consider IVIG as above for these patients as well.

Clinically Isolated Syndromes

Relapsing remitting MS starts with a first relapse. This initial clinical manifestation of demyelination is referred to as a CIS. Optic neuritis, transverse myelitis, and brainstem syndromes are the most common CIS presentations. The challenge for the clinician faced with the CIS patient is not only the acute management but also predicting what the risk for future demyelinating events will be. Clinical presentation, CSF findings, and brain MRI can all help with risk stratification.

For the patient presenting with optic neuritis leading to MS, certain clinical features are more common. Female gender, unilateral symptoms, retro-orbital pain, onset in young adulthood, and a normal optic disc are all associated with a higher risk for future demyelinating events. In the CIS patient presenting with transverse myelitis, higher MS risk is predicted by asymmetric sensory symptoms, smaller cord lesions, and the absence of cord edema. The location of the demyelinating lesion in the CNS does not have predictive value. Lesions affecting the optic nerve, spinal cord, and brainstem all have the same risk of MS at 3 years after a CIS.

CSF examination at the time of the first demyelinating event may also give clues as to the risk of future MS. The presence of oligoclonal bands (OCB) unique to the CSF was determined in CIS patients using isoelectric focusing. At 6 years, the majority of CIS patients who had OCB had been diagnosed with MS. In contrast, OCB negative individuals were unlikely to have had more demyelinating events. Sensitivity was 91% and specificity was 94% for predicting MS.

The presence of brain lesions suspicious for demyelination is associated with a higher risk of MS in CIS patients. In the ONTT, the risk of MS at 10 years more than doubled from 22% to 56% when brain MRI lesions were present. One lesion was just as predictive as several. O’Riordan et al demonstrated a more dramatic spread in the difference between CIS patients with normal versus abnormal brain MRIs. For those with brain lesions, 83% had developed MS at 10 years compared with 11% with normal studies.

It should be noted that both the referenced studies above, defined MS by a second clinical event (Poser criteria). The McDonald criteria and the more recent Polman revisions allow for new MRI lesions to substitute for clinical attacks. RRMS is diagnosed more effectively at 3, 12, and 36 months after a CIS by using the McDonald criteria as compared with the Poser criteria. BENEFIT examined the early institution of interferon-β-1b in CIS patients. At 6 months, 20% of placebo patients met Poser guidelines for clinically definite MS. Using the McDonald criteria, 51% of these same patients had been diagnosed.

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