

Mellen Center Approaches: Management of MS relapses.

What is the definition of an MS relapse?

In 70-80% of patients, MS begins with a relapsing-remitting course in which neurologic manifestations develop in the context of acute relapses. A relapse (exacerbation, attack) is defined as new, worsening, or recurrent neurologic symptoms consistent with those caused by MS; typically evolving over days to weeks; lasting at least 24-48 hours; accompanied by objective change on the neurologic exam corresponding to the patient's symptoms. Even without treatment, most relapses recover partially or completely over weeks-months, particularly early in the disease. However, not all relapses recovery completely; and early in the disease most impairment/disability accrual is the result of incomplete relapse recovery.¹ Relapses are variable within and between patients in terms of the neurologic manifestations involved, frequency, severity, and degree of recovery.

Although relapses are a clinical event, MS disease activity, indicated by MRI lesion activity, can occur without clinical manifestations (i.e., an MRI relapse).

Relapses conceptually are distinct neurologic events. However, in practice relapses often are indistinct or equivocal. Also, MS relapses must be distinguished from:

- Transient day-to-day fluctuations in neurologic symptoms common in MS patients.
- Progression – gradual worsening over months.
- Pseudo-relapses – worsening in (typically pre-existing) neurologic manifestations in association with intercurrent illness (particularly febrile) or metabolic derangement.
- Neurologic manifestations due to development of a superimposed medical condition.

What is the general approach to evaluation and treatment of acute MS relapse?

The evaluation and treatment of acute MS relapses involves several aspects:

- The patient is evaluated to determine whether the change in neurologic status represents a relapse. Evaluation also is intended to assess intercurrent medical conditions that may have triggered the relapse or may be causing pseudo-relapse. Most often the evaluation is carried out in the office, although in some special circumstances the evaluation may be arranged locally or carried out by phone.
- Treatment of underlying infection (if necessary).
- Symptomatic therapy e.g., for vertigo from a brainstem relapse.
- Corticosteroids to accelerate recovery and (in theory) improve degree of recovery.
- Rehabilitation to develop compensatory strategies e.g., for gait impairment and promote functional recovery.²⁻⁴
- Reconsideration of long-term disease therapy. The occurrence of a relapse may indicate the need to initiate or alter disease modifying therapy.

Is MRI necessary to evaluate a suspected relapse?

MRI typically is not necessary to diagnose an acute relapse. MRI sometimes is obtained in the setting of a suspected acute relapse 1) to rule-out an alternative explanation for the change in neurologic status, or 2) to assess the level of disease activity to help assess the need to initiate or alter disease therapy.

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What is the purpose of corticosteroid treatment of an acute MS relapse?

Short courses of high-dose corticosteroids are routinely used to treat acute MS relapses. The potential goals of therapy include:

- Accelerate recovery.⁵⁻⁹
- Limit damage and improve degree of recovery. Some studies support this,^{9, 10} although in other studies there was little difference in the ultimate degree of recovery.^{6, 8}
- Delay the next relapse. Some^{11, 12} but not all¹³ studies support this.

What is the typical Mellen Center corticosteroid regimen?

The typical corticosteroid regimen employed at the Mellen Center is methylprednisolone (MP) 1000 mg IV as a single daily dose on 3 consecutive days as an outpatient with a subsequent 12-day tapering dose of oral Prednisone 60 mg/d for 4 days, 40 mg/d for 4 days, and 20 mg/d for 4 days.^{6, 14}

What variations could be employed and why?

The standard corticosteroid regimen can be modified for several reasons:

- Reduced MP dose: Some patients, including those with small body mass, tolerate a lower dose, e.g., 500 mg, better.
- Dosing interval: Some patients tolerate divided doses of MP, e.g., 250 mg q6h, better.
- Treatment duration: For more severe relapses or relapses that are not improving, the duration of IV MP sometimes is extended to 5-7 days.
- Oral Prednisone taper. We typically employ an oral Prednisone taper to lessen rebound symptoms, except in patients with known poor tolerability from side effects or a complicating condition, e.g., diabetes, hypertension, or osteoporosis. We typically taper Prednisone over 12 days but may shorten it to lessen adverse effects or prolong it in patients with a known tendency to experience rebound symptoms with the standard taper.
- Corticosteroid other than methylprednisolone: Limited experience suggests other corticosteroids e.g., dexamethasone at comparable doses are equally efficacious.

- Treatment setting: Relapses are routinely treated as an outpatient, either in the Mellen infusion center, another infusion center, or at home via homecare. The first course of IV MP for an individual patient typically is administered under observation until tolerability is confirmed. Patients are hospitalized if felt to be unsafe at home due to neurologic manifestations, e.g., inability to walk; require symptomatic therapy, e.g., IV fluids for vertigo with nausea and dehydration; or to manage steroid complications, e.g., hyperglycemia or severe mood disorder/psychosis.

Do all relapses require treatment?

Relapses that cause significant impairment and interfere with daily function and/or are failing to improve spontaneously typically are treated, unless there is a strong contra-indication to corticosteroids. Mild relapses that are already improving may not require treatment.

How soon does treatment need to be initiated after the onset of symptoms to be effective?

In general, treatment should be started as soon as a relapse is confirmed. However, initiation of treatment typically is not considered urgent. An exception is Devic's neuromyelitis optica (NMO). Relapses in NMO often evolve rapidly, are fulminant, and tend to recovery incompletely. Therefore, NMO relapses should be treated as soon as suspected.

What adverse effects are associated with corticosteroid treatment of relapses?

Short courses of high-dose corticosteroids generally are safe and well-tolerated. However, potential adverse effects are myriad.¹⁵

The most common adverse effects associated with short courses of corticosteroids (both IV and oral) include:

- Metallic taste
- Insomnia
- Dysphoria
- Anxiety
- Increased appetite
- Edema
- Headache

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- Myalgia
- Easy bruising
- Acne
- Gastrointestinal distress/heartburn
- Flushing
- Palpitations

Uncommon but important adverse effects associated with short courses of corticosteroids include:

- Anaphylaxis
- Osteonecrosis/aseptic necrosis
- Psychosis
- Euphoria or depression
- Exacerbation of pre-existing peptic ulcer disease, diabetes mellitus, hypertension, affective disorders

Chronic corticosteroids increase the risk of bone mineral density loss, cataracts, fatty liver, Cushingoid habitus, infection diathesis, and impaired healing. Several studies showed intermittent, short courses of corticosteroids to treat MS are not associated a significantly increased risk of these conditions.¹⁶⁻¹⁸

How are routine corticosteroid-related side effects managed?

Approaches to treat corticosteroid-related side defects include:

- Diet: Patients are advised a diet with no concentrated sweets (to lessen risk of hyperglycemia), no added salt (to decrease fluid retention), and foods rich in potassium (to prevent hypokalemia).
- GI prophylaxis: We typically prescribe Pepcid 20 mg daily or BID, to lessen risk of gastritis, although there are limited data confirming benefit.
- Insomnia: Patients frequently experience insomnia during corticosteroid treatment. Typically this is managed by providing a short-acting hypnotic to be taken at bedtime.
- Hyperglycemia: Blood sugar should be monitored in patients with known diabetes mellitus or past history of corticosteroid-associated hyperglycemia. It usually is advisable to involve the patient's primary care provider.
- Hypertension: Blood pressure should be monitored, particularly in patients with known essential or

corticosteroid associated hypertension. It usually is advisable to involve the patient's primary care provider.

- Mood disorder: Mood should be monitored, particularly in patients with known affective disorder.
- Patient education about potential corticosteroid side effects is an important aspect of management.

Can corticosteroids be administered orally only?

Several studies and clinical experience suggest that low-dose oral Prednisone (approximately 1 mg/kg daily) is not as effective as high-dose IV MP (approximately 1000 mg/day) to treat acute MS relapses.⁶ Therefore, relapses typically are not treated with low-dose oral Prednisone alone.

Substantial evidence supports the rationale for substituting comparable doses of oral corticosteroids for high-dose IV MP. Arguments in favor include:

- Feasibility; comparable doses can be administered orally.
- Greater convenience.
- Reduced cost.¹⁹
- Comparable bio-availability.²⁰
- Good tolerability.²¹
- Reported equivalence in other disorders e.g., asthma²² and rheumatoid arthritis.²³

Comparable high doses of PO and IV steroids have been reported to have similar benefit in treating MS relapses in several small studies.^{7, 24-26} An adequately sized study to confirm equivalence has not been done. Therefore, acute MS relapses typically are treated with IV MP at the Mellen Center. However, high-dose oral corticosteroids are used in certain situations, e.g., poor venous access, needle phobia, or lack of insurance coverage for IV infusion. Regimens include PO methylprednisolone (500-1000 mg daily)^{7, 26} or PO prednisone (1250 mg daily).²⁰

Can acute relapses be treated during pregnancy?

In general, we have a somewhat higher threshold for treating relapses that occur during pregnancy, particularly in the first trimester. However, if needed, relapses in pregnancy can be treated using the standard regimen, in collaboration with the patient's obstetrician.

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How are relapses that fail to respond to a standard corticosteroid regimen treated?

Options for treating relapses that fail to respond to a standard course of IV MP include:

- Repeat IV MP; sometimes we'll extend the second course to 5-7 days.
- Plasma exchange.²⁷
- IV gamma globulin.²⁸

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