Neuromyelitis Optica

*Dean M. Wingerchuk, MD, MSc, FRCP(C)**
Brian G. Weinshenker, MD, FRCP(C)

Address
*Department of Neurology, Mayo Clinic, 13400 East Shea Boulevard, Scottsdale, AZ 85259, USA.
E-mail: wingerchuk.dean@mayo.edu

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Opinion statement

Neuromyelitis optica (Devic's syndrome) is an uncommon, idiopathic, demyelinating syndrome of the central nervous system that preferentially affects the optic nerves and spinal cord. It frequently is misdiagnosed as severe multiple sclerosis, but usually is readily distinguished from multiple sclerosis in fully developed cases because of its severity, typical magnetic resonance imaging (MRI) findings (normal brain MRI; longitudinally extensive lesions on spinal cord MRI), and cerebrospinal fluid analysis (polymorphonuclear pleocytosis and absence of oligoclonal banding). A serum autoantibody marker, NMO-IgG, is highly specific for the disorder. Most patients have relapsing disease, and natural history studies confirm early and severe disability. We treat acute myelitis and optic neuritis exacerbations with parenteral corticosteroids and use rescue plasmapheresis for severe, refractory attacks. Immunomodulatory drugs used for typical multiple sclerosis seem ineffective for relapse prevention. We recommend systemic immunosuppression, usually with azathioprine and oral corticosteroids, for most patients. Fulminant disease and breakthrough disease may respond to other forms of humoral immunotherapy such as rituximab.

Introduction

DIAGNOSIS OF NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO; Devic's syndrome) is an idiopathic demyelinating syndrome of the central nervous system with a predilection for the optic nerves and spinal cord [1•]. It usually has been considered a severe and unusual variant of multiple sclerosis (MS) and variably defined as "bilateral optic neuritis and myelitis occurring in close succession" [1•,2]. However, contemporary case series focusing on clinical manifestations, in addition to advances in neuroimaging and immunopathology, have allowed simultaneous expansion of the "NMO spectrum" of disorders and refinement of diagnostic criteria that seem to have high diagnostic accuracy in discriminating NMO from typical MS [1•,2–4]. This is important because the natural history, prognosis, and treatment of NMO differ markedly from MS [1•,5].

Patients with fully developed NMO experience optic neuritis (unilateral or bilateral) and myelitis. Although there is substantial overlap in clinical features and their severity with MS, clinical features that favor NMO over MS include non-Caucasian ethnicity, more severe attacks with greater residual deficits, simultaneous bilateral optic neuritis, and "complete," near-symmetric transverse myelitis. The clinical spectrum of NMO now is recognized to include patients with unilateral optic neuritis, any interval between the first events of optic neuritis and myelitis (even years), and a relapsing course [1•,5].

The most helpful diagnostic test probably is spinal cord magnetic resonance imaging (MRI), which reveals a longitudinally extensive, expansile, gadolinium-enhancing lesion of the central cord that is three or more vertebral segments in craniocaudal length. Additional evidence in favor of NMO includes normal or nonspecific brain MRI white matter abnormalities and cerebrospinal fluid abnormalities, such as polymorphonuclear lymphocytosis of greater than 50 leukocytes/mm^3 and absence of oligoclonal banding. Diagnostic criteria are summarized in Table 1 [1•; 6, Class III].

Definition of an expanded spectrum of NMO has been partially validated by the discovery of a serum autoantibody marker termed NMO-IgG [7••]. This marker has

Table 1. Neuromyelitis optica diagnostic criteria*

Absolute criteria
Optic neuritis
Acute myelitis
No clinical disease outside of the optic nerves and spinal cord
Major supportive criteria
Negative brain MRI at disease onset that is normal or does not meet radiologic diagnostic criteria for MS
Spinal cord MRI with T2 signal abnormality extending over ≥3 vertebral segments
Cerebrospinal fluid pleocytosis† or >5 neutrophils/mm^3
Minor supportive criteria
Bilateral optic neuritis
Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye
Severe, fixed, attack-related weakness‡

MRI—magnetic resonance imaging; MS—multiple sclerosis
*Diagnosis requires all absolute criteria and one major supportive criterion or two minor supportive criteria
†>50 leukocyte/mm^3
‡MRC grade 2 or less in one or more limbs

Table 2. Evidence supporting humoral immune mechanisms in neuromyelitis optica

Co-existing systemic autoimmune disorders or autoimmune seroposivity
IgG deposition and activated complement in spinal cord lesions
Excellent response to plasma exchange
Discovery of NMO-specific IgG autoantibody
Analogy with myelin oligodendrocyte glycoprotein-associated experimental allergic encephalomyelitis

NMO—neuromyelitis optica

approximately 75% sensitivity and greater than 90% specificity for NMO. Approximately 60% of patients with Japanese opticospinal MS, relapsing transverse myelitis, and relapsing optic neuritis with negative brain MRI are seropositive for NMO-IgG, strongly suggesting that these disorders represent the same disease or a forme fruste of NMO [7••,8•]. The autoantibody discovery also is congruent with the growing body of clinical, immunologic, and pathologic evidence that NMO is a humorally mediated syndrome (Table 2) [5; 6, Class III; 8•,9••].

Patients with monophasic disease experience their initial optic neuritis and myelitis events in close succession (generally within hours to a few days) in keeping with the classical definition. However, relapsing disease is much more common (probably >90% of cases) and ultimately more disabling [1•]. Patients accrue disability in stepwise fashion with each successive attack because of poor recovery. Within 5 years, more than 50% of relapsing NMO patients are functionally blind (visual acuity worse than 20/200) or require at least unilateral ambulatory assistance [1•,10]. They also are at risk for neurogenic respiratory failure attributable to ascending cervical myelitis. Relapsing disease requires early preventative therapy to prevent future attacks and protect neurologic function. Unfortunately, no diagnostic test yet has been proven to predict relapsing disease. Some clinical criteria that are predictive, in order of magnitude, include longer interval between the first and second attacks, female gender, and better motor recovery after the first myelitis event [10]. This suggests that patients who meet NMO criteria are likely to have relapsing disease if their first inter-attack interval is several weeks or more in length. These patients should be treated with preventative immunotherapy as soon as possible.

Treatment

Diet and lifestyle

- There are no dietary, nutritional, or lifestyle factors that are known to alter the natural history of NMO.

Pharmacologic treatment

- Acute exacerbations of optic neuritis and myelitis usually are severe and cause functional impairment. There are no studies that evaluate pharmacologic interventions for acute NMO attacks, but they usually are treated in the same manner as MS exacerbations or idiopathic optic neuritis. In the setting of MS, corticosteroids increase the likelihood of clinical improvement during the first 5 weeks after therapy; there may be a benefit of methylprednisolone compared with ACTH [11]. Intravenous administration is favored, but increasing the duration of therapy to greater than 5 days does not seem beneficial. For optic neuritis, the Optic Neuritis Treatment Trial showed that intravenous methylprednisolone (1000 mg/d for 3 days followed by oral prednisone 1 mg/kg/d for 11 days and a 4-day taper), but not oral prednisone monotherapy, increased the speed of visual recovery compared with placebo [12]. At 6-month follow-up, methylprednisolone therapy was associated with slightly better visual function (color vision and contrast sensitivity, but not visual acuity) compared with placebo, but there was no significant impact on long-term visual function (more than 5-year follow-up) [12,13]. Patients presenting with visual acuity of 20/40 or better did not benefit in this trial; if the results are translatable to NMO, a greater proportion of NMO patients may experience enhanced recovery speed because of the severity of optic neuritis in this disorder. A meta-analysis including the Optic Neuritis Treatment Trial and several smaller controlled investigations showed that intravenous methylprednisolone reduced the risk of failure to improve by day 30, but did not improve long-term visual outcome [14]. Plasmapheresis (see Interventions) is used for corticosteroid-refractory myelitis exacerbations and it also may benefit refractory optic neuritis [15••,16•].

Parenteral corticosteroids

	Intravenous corticosteroids are first-line therapy for acute exacerbations [6, Class III]. They seem to stabilize or improve function within 1 to 5 days in most patients and generally are well-tolerated.
Standard dosage	Intravenous methylprednisolone (1000 mg/d) for 5 consecutive days. Most patients will begin or resume oral prednisone after completion of parenteral therapy (see Relapse Prevention section).
Contraindications	Hypersensitivity to any constituent of the corticosteroid preparation, systemic fungal infections. Relative contraindications include peptic ulcer, pregnancy or current breast-feeding, psychotic tendencies, renal insufficiency, tuberculosis (active or latent), systemic infection, hypertension, and myasthenia gravis.
Main drug interactions	Bupropion (decreased seizure threshold), anticonvulsants, diltiazem (hepatic enzyme inhibitor resulting in increased methylprednisolone levels), fluoroquinolones, hydrochlorothiazide (increased risk of hypokalemia and secondary cardiac arrhythmia), oral anticoagulants (effects increased or decreased), chronic use of high-dose aspirin (increased aspirin clearance; possible increased risk of gastric ulceration), and quetiapine (decreased concentration).
Main side effects	Short-term administration of intravenous methylprednisolone is well-tolerated and relatively safe when administered to young, healthy adults and is routinely administered in outpatient infusion centers or through home care services [17, Class I]. Euphoria/depression, gastrointestinal distress, peptic ulcer, mild elevations in liver function tests, metallic taste, hyperglycemia, hypertension, sodium and fluid retention, hypokalemia, increased risk of infection. Avascular necrosis of the hip is a serious, but rare side effect.
Special points	Live vaccine or attenuated live vaccine is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Lower dosages (500 or 750 mg/d methylprednisolone) may still benefit patients who have a history of corticosteroid intolerance at higher dosages. Selected patients with diabetes, labile or poorly controlled hypertension, or on multiple medications may best be treated in a hospital.

Cost/cost effectiveness Relatively inexpensive. Administration costs can be substantial for outpatient infusion centers and many people require hospitalization for myelitis attacks. Cost effectiveness is unknown.

Relapse prevention

- Many patients with relapsing NMO receive an initial diagnosis of MS and are subsequently treated with one of the approved immunomodulatory MS therapies such as beta-interferon or glatiramer acetate. Although there are some case reports of success using these therapies, most North American clinicians who treat NMO consistently note that MS immunotherapies fail to alter relapse frequency for individual patients [5; 6, Class III]. In most cases, we establish immunosuppression using a combination of azathioprine and oral prednisone for long-term relapse prevention. Patients with relapsing NMO accrue disability from repeated attacks and progressive disease, the main contributor to permanent disability in typical MS, seems rare (although it may be difficult to appreciate in the presence of severe deficits) in NMO. Therefore, successful relapse prevention will likely have a major impact on physical, quality of life, and economic outcomes.

Azathioprine

One uncontrolled, open-label case series of seven patients showed that the combination of oral azathioprine and prednisone seemed to stabilize previously very active relapsing NMO and neurologic function, as measured by the Expanded Disability Status Scale, improved accordingly [18•, Class III]. This is congruent with other anecdotal observations by clinicians experienced in treating NMO.

Azathioprine and prednisone combination therapy is considered the standard immunosuppressive regimen for patients with relapsing NMO who do not need immediate "induction"-type therapy because they have not had recent clusters of severe attacks or have been attack-free for a few months. Typically, these are patients who are referred for a management opinion regarding "severe MS" or because they have noted no significant benefit from MS immunomodulatory therapy. The rationale for the combination therapy is that the onset of action of azathioprine may be delayed up to 6 months and corticosteroids provide a means of more rapid immunosuppression.

Standard dose Begin azathioprine at 50 mg/d and increase in 50 mg increments every week to a target dose of 2.5 to 3 mg/kg/d. Divided doses or taking azathioprine with food can improve drug tolerability. Dose adjustments are required if the leukocyte count falls below 3000/mm^3 or the platelet count drops below 100,000/mm^3.

Contraindications A history of treatment with alkylating agents (increased risk of lymphoma), hypersensitivity to azathioprine, and pregnancy.

Main drug interactions Angiotensin-converting enzyme inhibitors, allopurinol, cyclosporine, methotrexate, mycophenolate mofetil, warfarin.

Main side effects Gastrointestinal and other hypersensitivity reactions, nausea and/or vomiting, rash, drug fever, hepatotoxicity, infection, leukopenia, anemia, thrombocytopenia, megaloblastic anemia, pancreatitis, alopecia, cancer (rare). Possible impaired fertility.

Special points Female patients should not become pregnant. There is a small increased risk of malignancy with long-term use. Obtain baseline complete blood count, liver function tests, chest radiograph, and purified protein derivative. Thiopurine methyltransferase levels can be checked before treatment initiation since deficiency increases risk of azathioprine-induced toxicity (one should consider substituting mycophenolate mofetil in this setting). Patients should report signs of infection, bleeding, or bruising. The onset of immunosuppression is delayed by 1 to 6 months and is associated with mild reduction in the leukocyte count and increase in mean corpuscular volume (MCV). Monitor complete blood count weekly during first month, twice monthly during second and third months, and monthly thereafter; monitor liver function tests monthly.

Cost/cost effectiveness Azathioprine is inexpensive, but laboratory monitoring costs are moderate. Cost effectiveness is unknown, but is potentially very high if observations that immunosuppression can reduce the frequency of relapses, the main cause of permanent disability.

Prednisone

Standard dosage Initiate oral prednisone 1 mg/kg/d (usually 60 to 80 mg/d) with azathioprine. After the target azathioprine dose is reached and there is laboratory evidence of its effect (modest reduction in lymphocyte count and increase in mean corpuscular volume), and if the disease is stable, the prednisone dose may be tapered slowly. We usually reduce the dose by no more than 5 mg/week to achieve alternate day prednisone dosing (if prednisone 60 mg/d was the starting dose, the taper consists of a 5 mg dose reduction every week until the patient is taking 60 mg and 0 mg on alternate days). At that point, the dose is decreased more slowly, usually by 5 mg every 2 weeks, and discontinued if possible. Some patients seem to require continuous low-dose therapy (5 to 15 mg/d) or they experience breakthrough attacks [6, Class III].

Contraindications Hypersensitivity to prednisone or systemic fungal infection. Live vaccine or attenuated live vaccine is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Precautions include: peptic ulcer, pregnancy, psychotic tendencies, renal insufficiency, tuberculosis (active or latent), systemic infection, hypertension, cirrhosis, diverticulitis, osteoporosis, ulcerative colitis, and myasthenia gravis.

Main drug interactions Bupropion, anticonvulsants, ethinyl estradiol, diltiazem, fluoroquinolones, hydrochlorothiazide, oral anticoagulants, quetiapine, itraconazole, and mycophenolate mofetil.

Main side effects Fluid retention and/or edema, hyperglycemia, hypertension, increased appetite, weight gain, gastrointestinal distress, peptic ulcer, mild elevations in liver function tests, impaired skin healing, hypokalemia, increased risk of infection, osteoporosis, skin atrophy, cataracts, acne, adrenocortical insufficiency, Cushing's syndrome, euphoria and/or depression, tuberculosis reactivation. Avascular necrosis of the hip is a serious, but rare side effect.

Special points In preparation for long-term therapy, check baseline complete blood count, electrolytes, fasting glucose, blood pressure, chest radiography, purified protein derivative, bone densitometry. Prescribe calcium 1000 to 1500 mg/d, vitamin D 800 to 1000 IU/d, and consider bisphosphonate therapy. Monitor complete blood count, electrolytes, glucose, blood pressure periodically and consider annual bone densitometry and eye examination (cataract screening). Live vaccines are contraindicated, but influenza and pneumococcal vaccines should be administered.

Some patients experience breakthrough attacks during the latter portion of the prednisone taper. In our experience, many of these patients seem to require small doses of long-term oral prednisone (5 to 15 mg/d) in addition to azathioprine, but at least two attempts to discontinue prednisone are warranted for most patients.

Cost/cost effectiveness Inexpensive. Cost effectiveness is unknown, but potentially high if effective for attack prevention, the main cause of permanent disability.

Mycophenolate mofetil

This drug suppresses B and T cell proliferation while theoretically leaving hemopoiesis and neutrophil number and activity unchanged, a potential advantage over azathioprine. It is favored by some because it lacks the idiosyncratic gastrointestinal reaction that occasionally occurs with azathioprine. However, in a recent controlled organ transplantation study, the drugs were equally well-tolerated (leukopenia was more common with azathioprine but there was no greater objective evidence for bone marrow toxicity) [19, Class I]. Mycophenolate mofetil is a good substitute for patients at risk for azathioprine-induced toxicity attributable to thiopurine methyltransferase deficiency. The onset of action may not be any faster than azathioprine. We use it for some patients who do not tolerate azathioprine, but do not require immediate-onset therapy.

Standard dose Start 500 mg twice daily and after 1 week, increase to 1000 mg twice daily. A negative pregnancy test should be obtained in women with childbearing potential.

Contraindications Hypersensitivity to mycophenolate, pregnancy. Live attenuated vaccines should not be used during treatment with mycophenolate mofetil, and other vaccines may be less effective. Precautions include bone marrow suppression and hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase.

Main drug interactions Antacids containing magnesium and aluminum hydroxides, ethinyl estradiol and other similar oral contraceptives, acyclovir, cholestyramine, Echinacea, and azathioprine.

Main side effects Constipation, diarrhea, nausea, vomiting, hypertension, peripheral edema, headache, confusion, tremor, gastrointestinal bleeding, increased susceptibility to infections, sepsis, myelosuppression, and increased risk for developing lymphomas or other malignancies.

Special notes Women should use contraception during therapy and for 6 weeks after stopping the drug. Because of potential mycophenolate-oral contraceptive drug interactions, additional contraceptive methods should be used. Monitor complete blood count weekly during first month, twice monthly for second and third months, then monthly through the first year.

Cost/cost-effectiveness Very expensive. Less likely to be cost-effective as a first-line oral agent.

Rituximab

This anti-CD20 monoclonal antibody deletes B cells and seems to be a rational choice for NMO and other humorally-mediated disorders [20]. A recent case series suggests that some patients experience disease stabilization for at least several months after rituximab administration [21•, Class III]. We recommend initiation of rituximab therapy for patients with relapsing NMO who have breakthrough disease despite other immunosuppressive therapy or who require rapid-onset "induction" therapy because of recent severe attack(s).

Standard dose 1000 mg intravenously, repeated 2 weeks later. Consider retreatment at 1 year.

Contraindications Known type I hypersensitivity or anaphylactic reactions to rituximab or murine proteins. Precautions include hepatitis B infection (may reactivate), human anti-chimeric antibodies (<1%), severe mucocutaneous reactions.

Main drug interactions Live vaccines.

Main side effects Infusion reactions (fever, chills/rigors, nausea, urticaria, angioedema, bronchospasm, hypotension), asthenia, dizziness, headache, nausea, vomiting, pruritus, rash, angina, cardiac arrhythmias, bronchiolitis obliterans, pneumonitis, lymphopenia (frequent), hemolytic anemia (rare), transient aplastic anemia (rare), neutropenia, thrombocytopenia, infection, sepsis, lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, renal toxicity, toxic epidermal necrolysis, and vesiculobullous dermatitis.

Special points Obtain baseline complete blood count, renal and hepatic function tests. Monitor complete blood count and platelet counts at regular intervals and increase monitoring frequency if cytopenia is noted. Premedicate with acetaminophen 1000 mg and diphenhydramine 50 to 100 mg before each infusion. Hypersensitivity reactions are common and may be severe; they may respond to infusion rate reduction. Discontinue treatment in event of serious cardiac arrhythmias.

Intravenous immune globulin

This therapy has a reasonable theoretical basis because of the evidence that NMO is an antibody-mediated disorder. One report described remission in two relapsing NMO patients, one of whom had breakthrough disease despite therapy with azathioprine and prednisone (22, Class III).

Standard dose The standard dose for most neurological indications is 0.4 g/kg/d for 5 days. In the NMO case reports, one patient received 60 g monthly and the other received 0.4 g/kg/d for 5 days followed by 1 g/kg/d for 2 consecutive days every month.

Contraindications Hypersensitivity to immune globulin, human albumin, or thimerosal; isolated immunoglobulin A deficiency with antibodies to IgA. Precautions include conditions predisposing to acute renal failure, including pre-existing renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or co-administration of nephrotoxic drugs; conditions predisposing to thrombotic events including atherosclerosis, multiple cardiovascular risk factors, or known or suspected hyperviscosity.

Main drug interactions	Live virus vaccines (except polio and yellow fever vaccines). Intravenous immune globulin (IVIG) interferes with immune response to the vaccine.
Main side effects	Headache and/or migraine, fever, systemic infusion reaction (myalgias, back pain, chills, flushing, dyspnea, anxiety), aseptic meningitis, rash, transient leucopenia, thromboembolic events (possible attributable to hyperviscosity), acute renal failure, transmission of infection (very rare), anaphylaxis attributable to IgA deficiency (very rare).
Special points	At baseline, complete blood count, renal function; consider quantitative immunoglobulin testing to check for IgA deficiency. IVIG infusion reactions may be reduced by slowing the infusion rate and premedicating with oral acetaminophen 650 to 1000 mg, oral diphenhydramine 25 to 50 mg, and corticosteroids (intravenous hydrocortisone 1 mg/kg or oral prednisone 100 mg). Consider use of commercial preparations (especially for patients with pre-existing renal dysfunction) with lower sucrose content since higher sucrose concentrations are associated with risk of renal failure. Live virus vaccines should be given 6 months after completion of IVIG therapy and should not be administered to patients receiving regular IVIG therapy.
Cost/cost effectiveness	Very expensive. Cost effectiveness is possible only if magnitude of benefit on relapse prevention is high (not known).

Mitoxantrone

	Mitoxantrone is approved by the United States Food and Drug Administration for treatment of rapidly worsening relapsing-remitting or secondary progressive MS [23,24]. It inhibits B cell, T cell, and macrophage proliferation and impairs antigen presentation. Some patients with NMO are treated with mitoxantrone by clinicians who feel it is a severe MS variant. One small case series reported that 4 of 5 patients with relapsing NMO experienced disease stabilization and MRI improvement after mitoxantrone therapy [25•, Class III].
Standard dose	12 mg/m^2 administered intravenously every 3 months for up to 2 years (total 96 mg/m^2) is approved for MS; up to 140 mg/m^2 may be administered with appropriate toxicity monitoring. In the relapsing NMO case series, 12 mg/m^2 was administered monthly for 6 months followed by three more treatments, each 3 months apart.
Contraindications	Hypersensitivity to mitoxantrone, hepatic impairment, left ventricular ejection fraction less than 50%. Precautions include concomitant use of topoisomerase II inhibitors, pre-existing cardiovascular disease; myelosuppression, prior mediastinal/pericardial radiotherapy, and prior therapy with anthracycline/anthracenedione or other cardiotoxic drugs.
Main drug interactions	Live vaccines.
Main side effects	Alopecia, diarrhea, nausea, vomiting, headache, myelosuppression (frequent), menstrual disorders (amenorrhea, irregular periods), mucositis, reduced fertility, urinary tract infection, abnormal liver function tests, cardiac toxicity (related to cumulative total lifetime dose), hepatotoxicity, secondary leukemia, and myelodysplasia.
Special notes	Check baseline complete blood count, hepatic function, electrocardiogram, chest radiograph, and cardiac ejection fraction (either with echocardiography or multigated angiogram scan). Subsequent ejection fraction monitoring if signs of congestive heart failure develop and before all doses administered to patients receiving a cumulative dose of 100 mg/m2 or greater. Pregnancy test before each dose for women capable of becoming pregnant. Obtain complete blood count and liver function tests before each dose. Patients may notice a blue-green color to their urine and sclera for 24 hours after administration.
Cost/cost effectiveness	Moderate cost. Cost effectiveness unknown.

Other immunosuppressive regimens

- Systemic immunosuppression may be achieved using a variety of chemotherapeutic agents and a report of combination intravenous methotrexate and oral prednisone (in some patients, after intravenous cyclophosphamide therapy) suggested disease stabilization [26, Class III]. It remains unclear whether NMO will respond to all forms of general systemic immunosuppression.

Interferon-beta 1b

- North American clinicians anecdotally report that MS immunomodulatory therapies, including the beta-interferons, usually fail to adequately suppress relapses (with minor exceptions [27, Class III]). However, a Japanese randomized controlled trial indicated that subcutaneous interferon beta-1b was effective in reducing attack frequency in MS, including the opticospinal form that seems to be the same disorder as NMO [28•, Class I]. The full report has not yet been published. It is possible that there are genetic or other factors, as yet unidentified, that could determine NMO therapeutic responsiveness to different drug interventions. In the meantime, we do not recommend interferon therapy for NMO.

Other symptomatic therapies

- Patients may need pharmacologic therapies to manage symptomatic complications of NMO such as paroxysmal tonic spasms (anticonvulsants), spasticity (antispasticity drugs, botulinum toxin injections, intrathecal baclofen infusion via an implanted pump), and neuropathic pain (tricyclic antidepressants, anticonvulsants, and analgesics).

Interventional procedures

Rescue plasmapheresis

	Patients with corticosteroid-refractory myelitis exacerbations benefit from rescue plasmapheresis administered seven times on alternate days [14, Class I]. Patients with NMO seem especially likely to experience significant functional benefit (60% of cases) [29, Class III].
Standard procedure	Plasmapheresis with exchanges of 55 mL/kg every other day for a total of seven treatments. Patients without satisfactory peripheral venous access for high flow exchange procedures require central venous access with double lumen catheters.
Contraindications	Hemodynamic instability, coagulopathy, recent myocardial infarction or significant cardiac disease, thrombocytopenia, sepsis. Complications include hypotension, vasovagal reactions, perioral paresthesias attributable to hypocalcemia. Urticaria or allergic reactions are uncommon. Anemia (common, but self-limiting within 1 month), thrombocytopenia, leukocytosis (uncommon). Complications of vascular catheters include thrombotic occlusion, pneumothorax, hemothorax, nerve injury, hemorrhage, infection. Venous thrombosis, coagulopathy, electrolyte disturbances, cardiac arrhythmias (very uncommon) also may occur.
Cost/ cost effectiveness	Very expensive. Cost effectiveness has not been determined.

Assistive devices

- Mechanical ventilation may be temporarily required for some patients with severe, ascending cervical myelitis that causes neurogenic respiratory failure.
- Mechanical gait assistance may be needed by some patients, temporarily or permanently, to manage the effects of myelitis on gait and motor function. This may include an ankle-foot orthosis, cane, Canadian crutches, walker, or manual or power-assisted wheelchair.
- Patients with severe residual visual deficits from optic neuritis may benefit from electronic and optic devices designed for low vision management.

Physical therapy and exercise

- Standard types of physical therapy and exercise may be required to improve physical abilities and reduce symptoms such as pain and spasticity for patients with new or residual symptoms from myelitis attacks.

Emerging therapies

- Cumulative clinical, laboratory, and immunopathologic evidence supports humoral pathogenesis for NMO, and any new agent that disrupts B cell or antibody production may be a therapeutic candidate. Evaluations of current therapies, such as repeated courses of intravenous immune globulin or plasmapheresis, seem warranted. The recent identification of the serum autoantibody marker NMO-IgG is a significant advance because when its target antigen is identified and if there is evidence that it is causative, much more specific therapeutic approaches may be developed. However, a correlation between antibody titer and disease activity/severity has not been established either within a given individual over time or between different individuals with NMO.
- There are no current therapies that speed repair of damaged optic nerve or spinal cord segments after NMO attacks. Trials of intravenous immune globulin for patients with MS with stable visual loss or motor weakness were negative, but similar study designs may be useful in the future [30,31].

Pediatric considerations

- Neuromyelitis optica does affect children. Most of the aforementioned treatments have been used is children and adults, and the same adverse effects and treatment considerations apply to the pediatric age group.

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