

# TREATMENT OF INFLAMMATORY NEUROPATHIES

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## INTRODUCTION

Inflammatory neuropathies are a heterogeneous group of diseases in which there is immune system targeting and injury of constituent structures of the peripheral nervous system. In many of these disorders, the pathogenic mechanisms of the disease are not well understood but in some there is a direct immunologic attack, often in association with autoantibodies reacting to antigenic intracellular proteins or glycoconjugates (including glycoproteins and glycolipids), on neuronal cell surface membranes and peripheral nerve myelin. Additionally, a primary inflammatory attack on the neural vasculature is implicated in vasculitic neuropathy. As a group, these types of neuropathies are relatively common, comprising approximately 9-18% of all causes of neuropathy in a retrospective case-series (1). Along with a spectrum of pathogenic mechanisms, these disorders have distinct clinical phenotypes, electrodiagnostic, and laboratory findings that aid in diagnosis and management. The treatment for these conditions is often overlapping, though not entirely, speaking to distinct pathogenic mechanisms.

## GUILLAIN-BARRE SYNDROME

### Presentation

Guillain-Barre Syndrome (GBS) is a common cause of acute weakness occurring with an annual incidence is 1-2 cases per 100,000 in the general population annually. The typical clinical presentation is the abrupt onset of tingling and symmetric sensory changes beginning in the legs and then ascending to the arms with a nadir reached by 4 weeks. In North America, the most common presentation is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is due to a primary inflammatory attack of the myelin sheath of sensory and motor nerves (2). Less commonly, GBS can present as an axonal neuropathy such as acute motor and sensory axonal neuropathy and acute motor axonal neuropathy, Miller-Fisher syndrome (MFS), a cervical-pharyngeal-brachial variant, and pure autonomic neuropathy (2). AIDP is often preceded by upper respiratory tract infections and diarrheal illness in up to two-thirds of cases with the bacterium *Campylobacter jejuni* implicated in up to 30-40% of cases. As such, AIDP and other forms of GBS are thought to be a consequence of molecular-mimicry in which bacterial cell wall or viral capsid oligosaccharide epitopes share structural and antigenic similarities with peripheral nerve gangliosides causing crossed immunoreactivity to peripheral nerve (3).

### Treatment

The treatment for AIDP is supportive care to address autonomic dysfunction and respiratory failure and immunomodulatory therapies to accelerate recovery from the disease. Only plasma exchange and intravenous immune globulin (IVIG) have been shown to have a greater beneficial impact on the disease than supportive therapy, demonstrating improvement in strength, need for mechanical ventilation, and recovery when used. A 2011 American Academy of Neurology (AAN) guideline on plasma exchange in the treatment of neurologic disorders recommended its use in severe GBS, confirming its effectiveness in this disease (4). Based on a 2012 meta-analysis of six randomized controlled un-blinded trials, compared to placebo, plasma exchange has been shown to shorten the median time to recovery walking with aid and time to onset of motor recovery and was most effective if used within 7 days from symptom onset (5).

IVIG has not been studied in GBS in a randomized controlled trial. However, a number of randomized studies have compared IVIG with plasma exchange in the treatment of GBS, showing comparable results. This conclusion was also reached in a 2012 AAN guideline on IVIG in the treatment of neuromuscular disorders (6). Additionally, a 2014 Cochrane review of these studies found that IVIG, when started within two weeks from the onset of the disease, hastened the onset of recovery from severe GBS as much as plasma exchange without a significant difference in the treatments in the mean change in a seven-grade disability scale after four weeks (7). This meta-analysis also suggested that IVIG may be better tolerated than plasma exchange. Intravenous and oral corticosteroids have not been found to be effective in treating GBS, either as monotherapy or in conjunction with IVIG. Combining IVIG and plasma exchange does not have added benefit based on a large randomized controlled trial that found no significant differences in measures of recovery among patients treated with plasma exchange, IVIG, or therapy with both plasma exchange and IVIG (8). IVIG is generally given as 2.0 grams/kg of

body weight over 2-5 days and plasma exchange as four to 6 exchanges over eight to ten days for a single series of treatment only. Despite timely employment of plasma exchange or IVIG, about 25% of patients have long-term sequela including fatigue, numbness, neuropathic pain, and distal weakness and muscle atrophy.

## **CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY**

### **Presentation**

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a protracted form of immune-mediated neuropathy causing either progressive decline or a relapsing-remitting course (9). CIDP is more common than AIDP with a prevalence of about 8 cases per 100,000 in the general population. Patients with CIDP present with a greater than 8 week history of symmetric sensory loss and weakness that generally begins in the legs but can ascend to the upper extremities similar to AIDP. Compared to patients with AIDP, individuals with CIDP less commonly demonstrate respiratory involvement, autonomic nervous system dysfunction, or pharyngeal weakness. A number of less common forms of CIDP exist, including multifocal acquired demyelinating sensory and motor neuropathy, distal acquired demyelinating symmetric neuropathy, and pure sensory and motor CIDP (9).

### **Treatment**

The mainstay of pharmacological management of CIDP is typically corticosteroids or IVIG. Corticosteroids have been used as therapy for CIDP for decades. While there are no large randomized controlled treatment trials, a few small randomized prospective studies and retrospective studies have been performed showing improvement in disability (10,11,12). Additionally, randomized controlled studies have compared the use of both oral daily prednisolone with pulsed monthly dexamethasone (13) and intravenous methylprednisolone with IVIG (14), showing no significant differences in efficacy in regimens, though the latter study suggested better tolerance and perceived benefit of IVIG by subjects compared with corticosteroids. Current regimens being used for CIDP include daily or alternate day dosing of oral prednisone, usually dosed between 1-1.5 grams/body weight and then tapered over weeks to the lowest dose required to maintain clinical response, and pulsed weekly oral or intravenous methylprednisolone.

There have been five randomized controlled IVIG treatment trials in CIDP, all of which have shown efficacy, improving disability for about two to 6 weeks following each treatment in over half of patients (15). After the completion of the ICE study (16), the largest of these trials consisting of 117 participants which showed that the benefit of IVIG lasts as long as 48 weeks with IVIG given as 1 g/kg every three weeks, IVIG became the first medication approved by the Food and Drug Administration (FDA) for the treatment of CIDP. The 2012 AAN guideline on IVIG in the treatment of neuromuscular disorders has espoused its use as an effective long-term treatment for CIDP (6). The typical administration of IVIG is 2.0 grams/kg of body weight over 2-5 days followed every 2-6 weeks by 0.5-2.0 grams/kg of body weight depending on treatment response. An attempt should be made to discontinue or taper off the medication after a few months of sustained and significant response, though the percentage of patients who can enter into remission without the need for continued therapy remains uncertain but is likely a minority (17).

Plasma exchange has been found to be effective for the short-term treatment of CIDP compared to sham exchange based on two small randomized controlled trials (18). In these studies, about two thirds of patients responded in regard to improved function. The 2011 AAN guideline on plasma exchange in the treatment of neurologic disorders has recommended its use in the short-term management of CIDP (4). Plasma exchange is typically given as five exchanges of 50 ml/kg plasma volume each over eight to ten days followed every three to four weeks by one to two exchanges over one to three days. Overall, about 70% of patients are thought to have a good response to corticosteroids, IVIG, or plasma exchange, with a minority remaining in remission after tapering off all medication.

Other promising immunomodulatory therapies that have been investigated in small randomized or uncontrolled trials have included azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, cyclophosphamide, subcutaneous immunoglobulin, and rituximab. A recent randomized controlled trial has also suggested that subcutaneous immunoglobulin may be equally effective as IVIG as first line initial therapy for CIDP, though IVIG seems to take effect more quickly (19). For refractory CIDP, the evidence is strongest for the use of cyclophosphamide. Both moderate dose pulsed cyclophosphamide (alone or preceded by plasma exchange) (20) as well as high dose cyclophosphamide (21) have been shown to facilitate remission, though significant toxicity from this medication remains a concern.

## **DISTAL ACQUIRED DEMYELINATING SYMMETRIC NEUROPATHY**

### **Presentation**

A subset of patients with CIDP have a variant that is associated with a more distal presentation termed distal acquired demyelinating symmetric neuropathy (DADS) (9,22). These patients demonstrate slowly progressive sensory ataxia and, less commonly, foot drop. On examination, they exhibit significant large fiber sensory compromise with variable distal weakness. Many patients also have a kinetic and postural tremor that resembles an essential tremor. The neuropathy is often associated with a monoclonal gammopathy (DADS-M), usually of unknown significance but sometimes as a consequence of a lymphoproliferative disorder such as Waldenstrom's macroglobulinemia, and it can be seen without one as well (DADS-I). About 50-60% of patients with DADS-M with a monoclonal IgM gammopathy also demonstrate antibodies to myelin-associated glycoprotein (MAG) (22).

### **Treatment**

Patients with DADS-I or DADS-M associated with a monoclonal IgG or IgA typically respond to the immunotherapies discussed about for classic CIDP. Unfortunately, patients with DADS-M associated with a monoclonal IgM gammopathy, especially those with anti-MAG antibodies, rarely respond to such therapies (23). Additionally, a few uncontrolled studies and one randomized controlled study suggested benefit using rituximab, a monoclonal antibody to the surface marker CD20 expressed on B lymphocytes at the pre-B cell stage (24,25). In most of these studies, the medication was administered at 375 mg/m<sup>2</sup> weekly for four weeks. Rituximab appeared to be generally well tolerated. However, in a more recent randomized controlled study, subjects did not appear to have recovery of function with treatment evaluating the primary endpoint, though there was significant improvement based on secondary endpoint measures (26).

## **MULTIFOCAL MOTOR NEUROPATHY WITH CONDUCTION BLOCK**

### **Presentation**

Multifocal motor neuropathy with conduction block (MMN) is a chronic immune mediated neuropathy involving slowly progressive, asymmetric limb weakness, typically of the forearm and intrinsic hand muscles, without sensory loss (27). This neuropathy has a predilection for middle-aged males and occurs with a male:female ratio of 3:1. Rarely, lower extremity, cranial nerve, and respiratory involvement from diaphragmatic weakness may occur. The prevalence of this condition is about 1-2 cases per 1000,000 in the United States. Up to two-thirds of patients with MMN will have fasciculations and this disease may often be misdiagnosed as amyotrophic lateral sclerosis (28). Nerve conduction studies typically demonstrate motor conduction block in multiple nerves while sensory nerve conduction study is normal, including over areas of motor conduction block. Antibodies to GM1 have been identified in about half of all individuals with MMN (29) and are thought to target the nodes of Ranvier and paranodal myelin of motor nerves where this ganglioside is concentrated (30).

### **Treatment**

Based on a number of relatively small randomized controlled studies and a recent larger one (31), the first-line treatment for MMN is IVIG, generally showing benefit in about 70% of patients. The 2012 AAN guideline supports the use of IVIG use as an effective long-term treatment for MMN (6). Additionally, the FDA recently approved IVIG for the treatment of this disease. Dosing is generally similar to that used to treat CIDP, though often patients can be maintained on lower monthly doses. Unfortunately, there is no evidence that patients go into remission, either with treatment or without. Subcutaneous immunoglobulin may also be of benefit in MMN based on small randomized and uncontrolled trials (32,33). Cyclophosphamide is reported to improve function in MMN in smaller, uncontrolled case series but the long-term effectiveness of this medication is unknown and it generally cannot be tolerated for prolonged periods of time (34). Rituximab has also shown promise for the treatment of MMN in a number of uncontrolled trials (35). Corticosteroids and plasma exchange appear to be ineffective for treating MMN and may cause worsening (36). Additionally, mycophenolate mofetil has recently been shown to have no effect on the disease (37).

## **POEMS SYNDROME**

### **Presentation**

POEMS syndrome, also known as Crow-Fukase syndrome, is characterized by the association of polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M), and skin abnormalities (S). Patients generally need to have at least three of these five features to meet criteria for this condition. The polyneuropathy is typically a mixed demyelinating and axonal polyneuropathy on electrodiagnostic study manifesting by distal sensory loss and sensory ataxia as well as distal weakness. Most patients have osteosclerotic myeloma with sclerotic bone lesions representing plasmacytoma and the remainder demonstrating just a monoclonal gammopathy of unknown significance. While pathogenic mechanisms for this disease are not well understood,

there may be a role for vascular endothelial growth factor (VEGF) as these levels appear to be selectively increased in most patients with this disorder compared with other inflammatory neuropathies such as CIDP. Increased VEGF levels are thought possibly to lead to increased vascular permeability and edema of affected tissues, including endoneurial edema, as well as deposition of plasma cell-derived material (38).

### **Treatment**

Treatment of POEMS is typically a combination of corticosteroids with low dose chemotherapies like melphalan or peripheral blood stem cell transplantation following high dose chemotherapies. Patients have limited benefit from corticosteroids alone and no clear benefit from intravenous immunoglobulin therapy or plasma exchange. About 50% of patients with POEMS and osteosclerotic myeloma benefit in particular from the use of prednisone or another form of corticosteroids and melphalan (39). While initial studies suggested a high mortality with autologous stem cell transplantation, more recent series have suggested much lower rates of death, though with frequent morbidity, especially engraftment syndrome (40). Bevacizumab, a monoclonal antibody that selectively targets VEGF, and lenalidomide, which is cytotoxic to plasma cells, have also shown variable benefit in a few case reports (41, 42). Rather than medication, for patients with an isolated plasmacytoma, surgical excision and radiation therapy are the treatment of choice as these may lead to complete resolution of the syndrome.

## **VASCULITIC NEUROPATHY**

### **Presentation**

Vasculitic neuropathy, also known as mononeuritis multiplex, is an asymmetric or multifocal peripheral neuropathy that results from inflammation of the vaso nervorum (43). Patients typically present with the abrupt onset of weakness and numbness, typically in association with dysesthetic pain and constitutional symptoms such as fatigue, weight loss, myalgias, and fever, in the distribution of individual nerves. Within a short time, usually hours or days, additional nerves become involved. In some patients, there is a more protracted and progressive course occurring over months. Uncommonly, patients present with a symmetric polyneuropathy. Most patients have an underlying systemic disease that predisposes to vasculitis including connective tissue diseases such as rheumatoid arthritis or systemic lupus erythematosus, inflammatory disorders such as Churg-Strauss angiitis or Wegener's granulomatosis, infection related conditions, especially hepatitis C with associated cryoglobulinemia, and paraneoplastic syndromes (43). About 10-15% of patients will have non-systemic vasculitic neuropathy. Because vasculitic neuropathy can lead to persistent peripheral nerve damage as well as vasculitis of the skin, renal insufficiency, hepatitis, cardiomyopathy, cerebrovascular accident, and pulmonary involvement, if suspected, it should be treated emergently. The diagnosis of vasculitis is supported by electrodiagnostic testing, which typically shows evidence of a sensory and motor axonal mononeuropathy multiplex.

### **Treatment**

Vasculitic neuropathy is traditionally treated with corticosteroids, typically prednisone, usually in combination with steroid sparing agents such as azathioprine, methotrexate, and, in particular, cyclophosphamide (44). The typical starting dose of prednisone is 40-100 mg a day for 6-8 weeks or until treatment response followed by a slow taper to every other day dosing. Cyclophosphamide is given either orally starting at 1 mg/kg a day or intravenously in monthly pulses of 1000 mg/m<sup>2</sup>, usually for 6 months. There is also limited evidence to support the use of intravenous immunoglobulin as an adjunct therapy. Patients typically need to be on immunosuppression for 6 months to a year or sometimes longer. Patients with hepatitis C and cryoglobulinemia as a cause of vasculitic neuropathy deserve special attention, as the treatment of choice is antiviral therapy. For those intolerant of or ineligible for such therapy, rituximab is likely the best alternative treatment (45). Rituximab may also be another option for other forms of vasculitic neuropathy and is usually dosed at 1000 mg intravenously on Days 1 and 15 and then every 6 months for two years.

## **PARANEOPLASTIC NEUROPATHIES**

### **Presentation**

Peripheral neuropathies as a remote effect of neoplasms other than plasma cell dyscrasias are varied in their presentation and sometimes associated with specific autoantibodies (46, 47). The most common are neuropathies seen with type 1 antineuronal nuclear antigen autoantibodies (ANNA-1), previously known as anti-Hu antibodies (47). A subacute sensory neuronopathy (paraneoplastic dorsal root ganglionitis) has been well characterized in association with these antibodies. Often, patients suffer from small cell carcinoma of the lung but less frequently can have other neoplasms including carcinomas of the breast, ovaries, pancreas, and lymphoma. Often, there is co-existence with autonomic neuropathies associated with symptoms such as orthostatic hypotension, cardiac arrhythmias, and gastroparesis. Paraneoplastic autonomic neuropathies in isolation can also be seen with antibodies to ganglionic nicotinic acetylcholine receptor (48). About 10-15% of patients with solid

tumors, especially lung cancers, have symptomatic chronic sensorimotor polyneuropathies, with more demonstrating subclinical evidence for neuropathy. Acute sensorimotor and demyelinating neuropathies resembling either GBS or CIDP have been seen with Hodgkin's lymphoma and, less commonly, other hematologic malignancies. Paraneoplastic motor neuropathies and neuronopathies resembling amyotrophic lateral sclerosis have rarely been reported, including a subacute motor neuronopathy associated with Hodgkin's lymphoma. Finally, vasculitic neuropathies can be associated with neoplasm, in particular small cell carcinoma of the lungs but also prostate and lymphoma (46).

### **Treatment**

In general, immunosuppression has limited impact on paraneoplastic neuropathies. Treatment is frequently focused on identifying and addressing the underlying neoplasm. In patients with AIDP or CIDP and an associated neoplasm, in addition to addressing the cancer, patients are treated as they would be if they did not have cancer, generally with IVIG or plasma exchange for the former and corticosteroids or IVIG for the latter. Patients with paraneoplastic vasculitic neuropathies often respond to treatment of the cancer but also to corticosteroids and cyclophosphamide. In general, a number of immunomodulatory therapies, including IVIG, corticosteroids, cyclophosphamide, plasma exchange, and rituximab, have been reported to be of benefit in paraneoplastic neuropathies in small series (48) but no randomized controlled studies have confirmed these preliminary findings (49).

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**Table.** Immunomodulatory medications commonly used for inflammatory neuropathies.

Medication	Starting Dose	Dose adjustment	Side Effects	Monitoring
Prednisone	40-100 mg daily	Taper slowly down to alternate day dosing.	Hypertension, diabetes, glaucoma, osteoporosis, aseptic necrosis, cataracts, glaucoma, GI distress, steroid myopathy, infection	BMP, bone density, blood pressure
Azathioprine	50 mg twice daily	Increase by 50 mg as needed every 2-4 weeks until 2-3 mg/kg/day in two to three divided dosages	Systemic reaction, myelosuppression, pancreatitis, hepatotoxicity, infection	Check TPMT level initially, CBC, LFTs,
Cyclosporine	3 to 4 mg/kg/day in two divided doses	Increase slowly up to total 6 mg/kg/day as needed	Hypertension, nephrotoxicity, tremor, PRES, seizure, hepatotoxicity, infection	CBC, LFTs, BMP, drug trough levels
Mycophenolate mofetil	500 mg twice daily	Increase as needed by 500 mg every 2-4 weeks to 1500 mg twice daily	Diarrhea, vomiting, myelosuppression, infection	CBC, Cr
Cyclophosphamide	Oral: 1 mg/kg/ day Intravenous: monthly pulses of 1000 mg/m <sup>2</sup> usually for 6 months	Oral: advance as needed to 2 mg/kg/day	Myelosuppression, infection, secondary malignancies, hemorrhagic cystitis	CBC, UA
Rituximab	375 mg/m <sup>2</sup> /week for 4 weeks (alternatively 1000 mg IV 2 weeks apart)	Repeat infusion every 6 months up to years as needed for recurrence	Infusion reaction, anaphylaxis, myelosuppression, infection, PML	CBC, B cell percentage by flow cytometry
Intravenous immunoglobulin (IVIg)	2 g/kg over 2-5 days	Guillain-Barre: single course only. CIDP: monthly infusions and then taper to lowest dose (0.5-1 g/kg) with longest interval	Infusion reaction, aseptic meningitis, nephrotoxicity, stroke, deep venous thrombosis, pulmonary embolus, fluid overload	BUN, Cr
Plasma exchange	Five exchanges of 50 ml/kg plasma volume each over 8-10 days	Guillain-Barre: single course only. CIDP: initial course and then monthly 1-2 exchanges over 1-3 days	Metabolic alkalosis, hypocalcemia, hypokalemia, hypotension, thrombosis, line infection, anaphylaxis	Fibrinogen, BMP, blood pressure

*BMP: basic metabolic profile; TPMT: thiopurine methyltransferase; PRES: posterior reversible leukoencephalopathy; CBC: complete blood count; BUN: blood urea nitrogen; Cr: creatinine; ECG: electrocardiogram; LFT: liver function test; UA: urinalysis; PML: progressive multifocal leukoencephalopathy; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy*