Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

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Opinion statement
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated, non-length-dependent polyradiculoneuropathy that is progressive or relapsing over a period of at least 8 weeks, often evolving over time to a relatively symmetric pattern. Although the exact pathogenesis is unclear, it is thought to be mediated by both cellular and humoral reaction to the peripheral nerve myelin sheath involving nerve roots and proximal and distal nerves. Early medical treatment of CIDP is important to prevent axonal loss occurring as a secondary effect of progressive demyelination. Only three treatments for CIDP have demonstrated benefit in randomized controlled studies: corticosteroids, plasma exchange, and intravenous immunoglobulin. About 25% of patients fail to respond to these treatments or respond inadequately. These treatments have similar efficacy but differ significantly in cost and adverse effects. These factors are considered in treatment selection.

Introduction
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an inflammatory disorder of the peripheral nerves and nerve roots that, in its classic presentation, is clinically characterized by proximal and distal weakness of the extremities, sensory disturbance, and absent or decreased deep tendon reflexes. The prevalence of CIDP is 2–7 per 100,000 [1], with a slight male predilection. It occurs most commonly in adults 40–60 years of age, but it can be seen in children and the elderly. It is differentiated from acute inflammatory demyelinating polyneuropathy, the most common presentation of Guillain-Barré syndrome (GBS), by the slower progression of symptoms (exceeding 8 weeks) followed by a progressive or relapsing course, as opposed to an acute onset reaching the nadir of symptomatology by 4 weeks and a monophasic pattern in GBS. However, about 16% of CIDP patients present with an acute onset, indistinguishable from GBS [2,3]. In several large series, approximately 15% of patients had a pure sensory clinical syndrome, though many showed motor involvement on nerve conduction studies [4••]. Facial, oropharyngeal, and ocular involvement occurs in less than 15% of patients with CIDP, and ventilatory failure and autonomic symptoms occur in less than 10% [4••]. CIDP accounts for about 20% of initially undiagnosed neuropathies, and in a large series, it accounted
for approximately 10% of all patients referred to a neuromuscular clinic [5].

No biologic marker in the serum, urine, cerebrospinal fluid, or nerve can be detected to verify the diagnosis of CIDP. Early evaluation with electrophysiologic studies classically shows evidence of demyelination with slowed conduction, temporal dispersion, prolonged distal latencies, and prolonged F-wave latencies. Nerve conduction studies performed late in the course or in severe cases may show loss of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs), presumably because of axonal injury, so that the classic demyelinating pattern is absent. Thus, the classic electrophysiologic findings, though often helpful or diagnostic, are not mandatory for the diagnosis. Similarly, as cerebrospinal fluid analysis is often performed in patients suspected of having CIDP, cyttoalbuminologic dissociation is common but not mandatory for the diagnosis. Along with demyelination and inflammation, onion bulbs, similar to those seen in the hereditary demyelinating neuropathies, may be observed in nerve biopsies because of chronic demyelination and remyelination of nerve fibers.

Laboratory studies to eliminate other disorders are indicated for patients suspected of having CIDP. Those studies include complete blood count, basic metabolic profile (including electrolytes, blood urea nitrogen, and creatinine), fasting blood glucose, 2-h glucose tolerance test, HIV titer, antinuclear antibodies, and serum and urine protein electrophoresis with immunofixation. A family history of heritable neuropathies should be sought. If the diagnosis is unclear after electrophysiologic and laboratory testing, a lumbar puncture to look for cyttoalbuminologic dissociation is indicated. Elevated protein (>45 mg/dL) is detected in at least 80–95% of patients [6]. If the diagnosis remains in question or there is concern about concurrent disorders, a further workup may be necessary.

About 10–15% of patients with presumed CIDP have an associated systemic medical disorder, which can complicate the differentiation of a secondary form of CIDP from idiopathic CIDP. These disorders include diabetes mellitus, thyroid disease, several autoimmune or connective tissue diseases, rheumatologic diseases, renal insufficiency, malignancies, organ transplantation, and viral infections. It is not clear whether the concurrent illness alters the response to treatment or prognosis of the neuropathy, but consideration of the systemic medical disorder may guide the choice of therapy [4••].

There are also a few medical conditions that may occur concurrently with CIDP and are implicated in its pathogenesis. These include a monoclonal gammopathy found in 15–20% of CIDP patients; most of these are a monoclonal gammopathy of undetermined significance (MGUS), but they may also include the malignant plasma cell dyscrasias.

Since 1958, when the efficacy of corticosteroid in CIDP was demonstrated [7], only two other first-line treatments have emerged: intravenous immunoglobulin (IVIg) and plasmapheresis. Along with corticosteroids, these remain the mainstay of treatment and effect improvement in 60–80% of CIDP patients [8,9]. Patients who are refractory to individual trials of these conventional therapies are typically considered for an alternative immunomodulatory treatment. Treatment of CIDP should be initiated early in the course of the disease to avoid permanent axonal injury.

The importance of distinguishing CIDP from other types of chronic acquired demyelinating polyneuropathy (CADP) is emphasized because of differences in response to treatment and prognosis. These disorders have distinctive characteristics. Two important CADP disorders are multifocal motor neuropathy (MMN, the pure motor variant) and the anti–myelin associated glycoprotein (anti–MAG) neuropathy. MMN most often responds to IVIg, can worsen with prednisone, and does not respond to plasmapheresis [10]. In anti–MAG neuropathy, corticosteroids have been found to be effective only when combined with other treatments [11]. Other CADP disorders, including MGUS (when not associated with anti–MAG) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM, also known as Lewis Sumner Syndrome [LSS]), are thought to represent subtypes of CIDP because the response of these disorders to immunomodulatory treatments is similar to the response seen in CIDP.

**Diagnostic Criteria**

The Medical Advisory Board of the GBS/CIDP Foundation International recently convened an expert committee comprising international neuromuscular neurologists, an epidemiologist, and a statistician to develop a new set of criteria for establishing the diagnosis of CIDP. Named for the lead investigator, the Koski criteria (Table 1) showed an 83% sensitivity and 97% specificity when validated in 117 patients.
with CIDP. The performance of the criteria exceeded the performance of previously published criteria [12•].

The reader may note that, unlike other established diagnostic criteria, the Koski criteria give no specified values by which the nerve conduction velocity or CMAP must be decreased or which they must exceed. Because the CMAP must be recordable in at least 75% of motor nerves, the recommendation from the committee is to increase the number of nerves studied when motor responses are absent in several nerves. As previously published by Rajabally et al. [13], optimal electrodagnostic practice in the diagnosis of CIDP is performed by the study of multiple motor nerves in both upper limbs rather than attempting to record multiple nonresponsive motor nerves in the lower limbs. The simplicity of these new criteria, in conjunction with the highest sensitivity and specificity among published criteria, may lead to earlier diagnosis and thus earlier treatment.

**Treatment**

- Improvement in functional status and maintenance of long-term remission are the main goals of treatment of CIDP. Early intervention is necessary to avoid the permanent weakness, sensory loss, pain, and imbalance that are commonly seen with axonal loss, as a secondary effect of demyelinating injury of peripheral nerves.
- Corticosteroids, IVig, and plasmapheresis are the three conventional therapies that remain the standard of care and have shown efficacy in randomized controlled trials. Improvement can be expected in 60–80% of patients using one of these three conventional treatments [4••]. Mild cases may resolve spontaneously.
Clinical trials have shown similar efficacy of IVlg and plasmapheresis [14] and similar efficacy of IVlg and prednisolone [15]. There are no studies proving superior efficacy of one of these treatments over the other.

The relatively short-term effects, high cost, and inconvenience of administering IVlg and plasmapheresis, and the high adverse-effect profile of corticosteroids, are compelling reasons to find alternative treatment options for CIDP, but to date, there is insufficient evidence for other therapies to replace these three treatments. Choice of therapy should be determined individually for each patient, keeping in mind considerations such as the pattern of symptoms, the age and comorbidities of the patient, the affordability and availability of therapy, and, in the case of plasmapheresis, the training, experience, and proficiency of the proceduralist implementing the therapy.

If a patient who was initially responsive becomes resistant to treatment, reevaluation is important to detect the emergence of an alternative pathology, such as paraproteinemia.

Change in treatment should be considered if there is no response to
- Prednisone 3–4 weeks after initiation
- IVlg after a second set of infusions, 4–6 weeks after initiation
- Plasma exchange within 2 weeks after a second series of exchanges

Pharmacologic treatment

Corticosteroids

Several small trials and case reports have shown improvement of CIDP with corticosteroids. Dyck et al. [16, Class I] published the results of a randomized, placebo-controlled trial demonstrating the benefit of prednisone over no treatment, with 86% of the treatment group responding. A Cochrane review of corticosteroid treatment for CIDP identified only one study meeting their criteria for diagnosis of CIDP [8]. The Cochrane review concluded that the single randomized controlled trial provided weak evidence to support the conclusion from nonrandomized studies that oral corticosteroids reduce impairment in chronic inflammatory demyelinating polyradiculoneuropathy. Experience from large, nonrandomized studies suggests that steroids are beneficial [8]. Improvement in disability may begin as early as 2 weeks after prescription of corticosteroids; the average time to induce a response is about 2 months, and maximal improvement is not observed until 6 months [4••,8]. Corticosteroids are known to have serious long-term adverse effects. The long-term risk and benefits have not been adequately studied [8].

Prednisone

| Standard dosage | 1–1.5 mg/kg (40–100 mg) per day. After 2–3 months, if the patient demonstrates significant improvement, the dosage may be switched to an alternate-day regimen by tapering 5–10 mg on the alternate day, every 2– |
4 weeks, as determined by the patient's clinical state. If the patient's condition worsens, the minimal effective dose should be resumed [2,8; Class I].

**Contraindications**
Corticosteroids are contraindicated in patients with systemic fungal infections, tuberculosis, or hypersensitivity reactions. Relative contraindications include osteoporosis, diabetes mellitus, hypertension, glaucoma, and history of mania or depression.

**Main drug interactions**
The action of anticoagulants may be reduced with co-administration of corticosteroids. The effects of prednisone may be reduced by hepatic inducers, such as rifampin, phenytoin, and barbiturates. Live-virus vaccines should be avoided while using corticosteroids. Co-administration with mifepristone increases the risk of adrenal insufficiency.

**Main side effects**
Hyperglycemia, gastritis, gastrointestinal bleeding, osteoporosis, bone fractures, hypertension, aseptic necrosis of the femoral or humeral head, hypertension, cataracts, poor wound healing, susceptibility to infection, myopathy, weight gain, Cushinoid features, insomnia, euphoria, depression, and suppression of the hypothalamic-pituitary-adrenal axis.

**Special points**
Maximal improvement occurs after 3–6 months. Because of the potential for severe adverse effects, especially in the elderly, the decision to treat with corticosteroids should be made while considering the patient's age and comorbidities. Patients on chronic steroids require regular monitoring of blood pressure, blood glucose, serum potassium, and bone density, as well as ophthalmologic evaluations for cataracts. They should receive prophylactic treatment with bisphosphonates, calcium, and vitamin D.

**Cost**
Inexpensive direct cost; potential high cost of adverse effects.

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**Methylprednisolone**

**Standard dosage**
*Oral methylprednisolone:* Pulsed dose, 500 mg once a week for 3 months, tapering by 50 mg every 3 months to 100 mg once a week depending on the clinical status [17, Class IV]. *Methylprednisolone sodium succinate* (IV): 1,000 mg intravenously once daily for 3–5 days, then once monthly, followed by tapering the dose or frequency [18, Class III].

**Contraindications**
Same as prednisone.

**Main drug interactions**
Same as prednisone.

**Main side effects**
Same as prednisone.

**Special points**
The goal of pulsed dosing is to minimize the adverse effects of the steroids.

**Cost**
Inexpensive direct cost potential high cost of adverse effects.

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**Intravenous immunoglobulin**

- The largest randomized controlled trial conducted in CIDP patients, the IGIV-C CIDP Efficacy (ICE) trial, has proven the efficacy of IVIg (10% caprylate/chromatography purified IGIV-C) in CIDP patients [19*, Class I]. Both a recent consensus statement from a committee of the American Association of Neuromuscular & Electrodiagnostic Medicine [20] and a Cochrane review [21] provide strong support for the use of IVIg in CIDP. In those patients for whom IVIg is effective, the clinical improvement often occurs within 1–2 weeks after the
initiation of IV Ig, and the benefits of treatment (compared with placebo) extend over 2–6 weeks [21].

**Intravenous immunoglobulin (IV Ig)**

**Standard dosage** Initial dose 2 g/kg over 2–5 days repeat infusions at 0.5 g/kg every 2 weeks, 1 g/kg every 3 weeks, or 2 g/kg every month [1,22,23; Class I].

**Contraindications** Sucrose-containing formulations pose a risk of renal failure, particularly in patients with pre-existing renal disease. Immunoglobulin A deficiency is a risk for anaphylaxis. Rare thrombotic events have been reported in patients with vascular disease.

**Main drug interactions** Live vaccines may interfere with the efficacy of IV Ig and may not provide adequate immunologic protection with concomitant use of IV Ig. The IV Ig dose may need to be lowered with concomitant use of nephrotoxic drugs.

**Main side effects** Headache, mild flu-like symptoms, rash, aseptic meningitis. Rare but serious side effects include thromboembolic events, stroke, myocardial infarction, and oliguric renal failure.

**Special points** Clinical improvement occurs within 1–2 weeks in many patients, but may not occur until after the second infusion. Maximal effects last from several weeks to months.

**Cost** $10,000–$20,000 per month.

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**Plasma exchange**

- The benefit of plasma exchange in CIDP has been demonstrated in two double-blind, sham-controlled trials [24,25; Class I] and is supported by a Cochrane review [26]. The Cochrane review concluded that plasma exchange provides significant short-term benefit in about two thirds of patients with CIDP, but rapid deterioration may occur afterwards. About 3–17% of plasma exchange procedures cause adverse effects, and some are serious, including sepsis, myocardial infarction, hypotension, deep venous thrombosis, and pulmonary embolus [26].

**Plasmapheresis (plasma exchange)**

**Standard dosage** *Initial:* Five exchanges (1–1.5 plasma volume each) every other day over 10 days. *Maintenance therapy:* One exchange (1–1.5 plasma volume) every week to every other week [27, Class I].

**Contraindications** Hemodynamic instability, cardiac disease, coagulopathy, sepsisemia.

**Main drug interactions** Plasmapheresis may increase the clearance of medications.

**Main side effects** Complications of venous access include improper line placement, bleeding, vagus nerve syndrome, air embolism, thrombosis, and infection. Effects related to fluid shifts include hypotension, fluid overload, electrolyte imbalance, fever, chills, nausea, vomiting. Hypocalcemia may occur because of citrate toxicity. Allergic reaction to infused plasma substitutes may occur.

**Special points** The decision to use plasma exchange should consider the proficiency and complication rate of the proceduralists placing the lines, which may vary among institutions. Plasma exchange is typically used for acute exacerbations
and is used less commonly for maintenance therapy. It has been used prior to IVlg to increase the effectiveness of IVlg treatment.

Cost About $10,000 per course of treatment.

Alternative treatments

- Alternative treatments are used in patients who do not respond to one of the conventional therapies, or to minimize the use of steroids. The evidence is inadequate to decide whether azathioprine, the interferons, or any other immunosuppressive drugs are beneficial in chronic inflammatory demyelinating polyradiculoneuropathy. The patients described in these case reports or small studies are usually those who are refractory to the conventional treatments, and these study participants often are using multiple therapies, making it difficult to draw conclusions regarding the efficacy of one therapy over another. The choice of alternative treatments should consider the patient’s age and comorbidities as well as the potential risks, availability, and affordability of the therapy.

Azathioprine

<table>
<thead>
<tr>
<th>Standard dosage</th>
<th>2–3 mg/kg total daily dose as a single daily dose or a divided dose twice daily [28, Class IV].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to drug; pregnancy. Thiopurine methyltransferase (TPMT) deficiency is a relative contraindication.</td>
</tr>
<tr>
<td>Main drug interactions</td>
<td>Angiotensin-converting enzyme (ACE) inhibitors may increase the hematologic toxicity. Concomitant use with allopurinol may increase the toxicity of azathioprine, such that the dose should be reduced by 67–75%. An increased dose of warfarin may be necessary to reach goal INR. Other immunosuppressants are associated with overlapping toxicity, malignancy, and risk of infection.</td>
</tr>
<tr>
<td>Main side effects</td>
<td>Gastritis, anemia, thrombocytopenia, leukopenia, myelosuppression, pancreatitis, hepatotoxicity, hepatic veno-occlusive disease.</td>
</tr>
<tr>
<td>Special points</td>
<td>Often prescribed for steroid-sparing effects, azathioprine is an antimetabolite that suppresses delayed cell-mediated hypersensitivity, producing variable alterations in antibody production; often improvements are seen only after 9–12 months of therapy. TPMT genotyping or phenotyping can identify patients who are at increased risk for severe, life-threatening myelosuppression due to enzyme deficiency.</td>
</tr>
<tr>
<td>Cost</td>
<td>About $100 per month.</td>
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</tbody>
</table>

Mycophenolate mofetil

<table>
<thead>
<tr>
<th>Standard dosage</th>
<th>1–2 g/d in a divided dose twice daily [29, Class IV].</th>
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</thead>
<tbody>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity to the drug.</td>
</tr>
<tr>
<td>Main drug interactions</td>
<td>NSAIDs may potentiate the toxic effects. Decreased efficacy may be seen with vancomycin co-administration.</td>
</tr>
<tr>
<td>Main side effects</td>
<td>Leukopenia, thrombocytopenia, neutropenia, lymphoma, sepsis, susceptibility to infection, gastrointestinal bleeding, peripheral edema, headache, nausea, vomiting, constipation, tremor, insomnia.</td>
</tr>
<tr>
<td><strong>Special points</strong></td>
<td>Often prescribed for steroid-sparing effects.</td>
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<tr>
<td><strong>Cost</strong></td>
<td>Expensive ($550–$1,100 per month).</td>
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</tbody>
</table>

**Cyclophosphamide**

**Standard dosage**
Intravenous pulse dose of 0.75–1.0 g/m² monthly for up to 6 months; treatment course may be shortened if improvement is sustained over 3 months [23, Class IV].

**Contraindications**
Bone marrow suppression, hypersensitivity to drug.

**Main drug interactions**
Increased metabolism and potentiation of leukemic effects with chronic use of barbiturates.

**Main side effects**
Bone marrow suppression, hemorrhagic cystitis, alopecia, vomiting, infertility, teratogenicity, delayed development of hematologic and bladder malignancies.

**Special points**
Cystitis can be reduced by forced diuresis and the use of 2-mercaptopethane sulfonate (MESNA). Follow white blood cell count (WBC) weekly with a goal to decrease the WBC to 1,500–2,000/mm³ at 2 weeks after treatment. If WBC does not respond sufficiently, increase the dose by 25% on subsequent doses.

**Cost**
About $100 per month.

**Interferon-α 2a**

**Standard dosage**
3 million units subcutaneously two to three times per week [30-32].

**Main drug interactions**
Antiretrovirals may cause bone marrow suppression; ACE inhibitors may cause granulocytosis or thrombocytopenia; theophylline will have an increased half-life.

**Main side effects**
Flulike symptoms, anemia, leukopenia, thrombocytopenia, gastrointestinal disturbances, psychiatric effects (primarily mood disorders, psychotic syndromes, and aggravation of preexisting mental disorders).

**Special points**
There is a case report of a patient developing CIDP while being treated with interferon-α [30].

**Cost**
$500–$750 per month.

**Rituximab**

**Standard dosage**
375 mg/m² intravenously once weekly for 4 weeks [33,34; Class IV]

**Contraindications**
Hypersensitivity to drug.

**Main drug interactions**
None.

**Main side effects**
Fever, chills, infection, lymphopenia, asthenia. Serious adverse reactions include progressive multifocal leukoencephalopathy (PML), viral infections, mucocutaneous toxicities, hepatitis B reactions with fulminant hepatitis, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

**Special points**
Complete blood count, renal function tests, and CD20 count should be monitored regularly. Hepatitis B screen is indicated prior to initiation of therapy, with careful monitoring during therapy and for up to 1 year after completion of therapy for signs of infection in patients who are carriers or who have a history of a prior infection. Cardiac monitoring should be per-
formed during the infusions in patients with preexisting cardiac disease or development of arrhythmia.

Cost $2,500 per month.

**Etanercept**

**Standard dosage** 25 mg subcutaneously twice weekly [35, open label].

**Main drug interactions** Live vaccines may not provide the immunologic protection intended or may result in infection; avoid using etanercept with other tumor necrosis factor blockers because of additive effects.

**Main side effects** Rare reports of optic neuritis, multiple sclerosis, myelitis.

**Special points** Etanercept is a recombinant monoclonal antibody directed against tumor necrosis factor \( \alpha \), a pro-inflammatory cytokine. An open-label study of 10 patients with refractory CIDP reported improvement in 3 patients and stabilization in 3 others.

Cost $2,500 per month.

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**Emerging therapies**

**Hematopoietic stem cell transplantation**

Experimental data in animal models have shown that several autoimmune disorders, both congenital and acquired, can be transferred and/or treated by the transplantation of bone marrow stem cells. Hematopoietic stem cell transplantation (HSCT) has been performed with varying success in over 700 patients with autoimmune disorders throughout Europe. The experience in CIDP is limited [36,37].

**High-dose cyclophosphamide without stem cell transplantation**

**Standard dosage** 200 mg/kg divided over 4 days [38, Class III].

**Contraindications** Bone marrow suppression, hypersensitivity to drug.

**Main drug interactions** Live vaccines may not provide the immunologic protection intended. Colony-stimulating factors may produce antagonistic effects during induction.

**Main side effects** Bone marrow suppression, mucositis, rash, hemorrhagic cystitis, alopecia, vomiting, infertility, teratogenicity, delayed development of hematologic and bladder malignancies, cardiomyopathy.

**Special points** Cystitis can be reduced by forced diuresis and the use of MESNA. Rescue granulocyte colony-stimulating factor (G-CSF) should be used after the first treatment. Treatment has resulted in long-term remission.

Cost Expensive (hospitalization in a specialized unit for neutropenic patients, additional drug costs).

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**Disclosure**

Dr. Donofrio is a member of the Steering Committee of Talecris Biotherapeutics. No other potential conflicts of interest relevant to this article were reported.
References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance,
- Of major importance


This article, which is published as a section of the AANEM 2009 course in the Dysimmune Neuropathies, provides a comprehensive review of CIDP, including clinical features, clinical variants, concurrent diseases, laboratory evaluation, electrophysiological criteria, pathology, differential diagnosis, and treatment.


These new diagnostic criteria for CIDP, developed by an international expert committee, have demonstrated higher sensitivity and specificity than all previously published criteria.


This is the publication of the findings of the ICE Study, the largest randomized placebo-controlled trial for any CIDP treatment, showing efficacy of IV Ig (10% caprylate-chromatography purified) over placebo.


