Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired autoimmune disorder directed against the myelin sheath of peripheral nerves. It was initially characterized as chronic inflammatory polyradiculoneuropathy by Dyck et al in 1975, but cases consistent with probable CIDP were described as early as 1958. CIDP is rare, affecting approximately 40,000 patients in the United States. It has a variable course that can be relapsing-remitting, stepwise progressive, or gradually progressive. It also has typical and atypical phenotypes that present with different features. All of these factors likely contribute to diagnostic delays for patients with CIDP. Greater understanding of CIDP is needed because early diagnosis and treatment are crucial to prevent permanent nerve damage and resulting disability. The complexities of diagnosing and treating CIDP provide unique challenges for managed care organizations. The purposes of this article are to provide managed care clinicians with current concepts in the diagnosis and treatment of CIDP as well as highlight recent therapeutic innovations, such as subcutaneous (SC) administration of immunoglobulin (SCIg).

**Pathophysiology**

In CIDP, cellular and humoral components of the immune system attack myelin on large peripheral nerve fibers, leading to demyelination that manifests as weakness, numbness, paresthesia, and sensory ataxia. As the disease progresses, axonal loss occurs secondary to demyelination and is associated with a poor prognosis. CIDP is a heterogenous disorder with typical and atypical phenotypes that may or may not share the same pathogenesis. Although a single autoantibody has not been identified to act as a biomarker for CIDP overall, specific autoantibodies have been identified against paranodal proteins within the nodes of Ranvier in the peripheral nerves of about 10% of patients. Autoantibodies identified so far include vinculin, LM1, neurofascin-155, neurofascin-186, gliomedin, and contactin-1. Some of these may have prognostic significance and may also predict a poor response to specific immunomodulating drugs. For example, contactin-1 antibodies have been associated with a later onset of CIDP and a more aggressive course.
Emerging data suggest a possible genetic contributor to CIDP. In a recent study, patients with CIDP had a high frequency of perforin gene variations that impair the function of cytotoxic T and natural killer cells. Identification of potential genetic determinants, in addition to the autoantibodies found in subsets of patients, illustrates the need for large registries and biobanks to collect data from patients with CIDP.3,8,18

**Epidemiology and Disease Description**

Although CIDP is the most common treatable chronic neuropathy worldwide, it is still a rare disease.9 CIDP has an estimated incidence of 0.7 to 1.6 cases per 100,000 persons per year.5,10 The overall prevalence is estimated at 4.8 to 8.9 cases per 100,000 persons.5,20 The prevalence in children is estimated at 0.5 cases per 100,000 persons.21 In an epidemiologic study of residents in Olmstead County, Minnesota, in 2000, the median age at diagnosis was 58 years (range, 4-83).3 The median disease duration at diagnosis was 10 months (range, 2-64).3 The disorder is more common in men than in women.22

Experts have debated for decades whether diabetes is a risk factor for CIDP.1,12 Epidemiologic studies conducted in the United States and Italy did not find a higher risk of CIDP in patients with diabetes, but an analysis of health insurance claims data for more than 100 million patient-lives found a 9-fold higher prevalence of CIDP in patients with diabetes.1,23,24 Difficulties in diagnosing CIDP may contribute to the controversy.20

CIDP has a variable course and treatment response; some patients experience a cure or remission, whereas a minority progress despite treatment. Among the first cohort of 53 patients with CIDP reported by Dyck et al in 1975, approximately 60% remained ambulatory, 25% became confined to a wheelchair or bed, and 10% died from their disease over a mean follow-up of 7.5 years.4 A more recent cohort of 38 Japanese patients with CIDP who had received immune-modulating therapy were followed for 5 years.25 Although 26% had achieved a complete remission lasting at least 2 years without treatment, 61% had a partial remission and 13% had severe disability and were unable to walk. In a larger cohort of 106 patients with CIDP for a mean of 6.4 years (range, 3 months to 23 years), 11% of patients were in remission without treatment for at least 5 years, 44% had active disease that was stabilized with treatment, 7% were improving after recent treatment initiation, and 18% were treatment naïve or treatment refractory with unstable active disease.24 In a recent survey of 41 patients with CIDP for a mean duration of more than 7 years, almost 40% reported needing assistance with activities of daily living.4

Motor and proprioceptive deficits predominate over autonomic symptoms and pain in CIDP.1 This is attributed to greater susceptibility of motor and proprioceptive nerve fibers to demyelination because they are surrounded by a thicker myelin coat than autonomic and pain fibers. Although pain is usually considered a secondary symptom of CIDP, studies evaluating pain intensity have reported severe pain in 13% to 17% of patients with CIDP.27

The typical form of CIDP that occurs in about 50% of patients is characterized by proximal and distal weakness.1,9 Atypical subtypes include a predominantly distal distribution (distal acquired demyelinating symmetric, 2%-17% of patients), an asymmetric distribution (multifocal acquired demyelinating sensory and motor neuropathy or Lewis-Sumner syndrome, 6%-15%), pure sensory (4%-35%, including chronic immune sensory polyradiculopathy, which affects 5%-12% of patients), and pure motor (4%-10%).20 Focal CIDP is extremely rare (1% of patients). There is a temporal continuum between the demyelinating form of Guillain-Barre syndrome, which is referred to as acute inflammatory demyelinating polyneuropathy (AIDP), and CIDP in patients initially diagnosed with AIDP that do not recover and may later be diagnosed with CIDP.1

**Diagnosis**

Although many sets of diagnostic criteria have been developed for CIDP, the criteria used most often in current clinical practice were developed by the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS).20 Although other diagnostic criteria are highly specific, they lack sensitivity, which may lead to underdiagnosis of CIDP. In a study of 151 patients with CIDP and 162 control patients, the EFNS/PNS criteria had sensitivity of 81.3% and specificity of 96.2% for definite or probable CIDP.20 Sensitivity of other diagnostic criteria in this study ranged from 45.7% to 79.5%.20 As shown in Table 1, the diagnosis of CIDP according to EFNS/PNS criteria is based on clinical history, physical examination, electrophysiology, and supporting laboratory tests.

EFNS and PNS recommend that the diagnosis of CIDP should be considered in any patient with progressive symmetrical or asymmetrical polyradiculopathy that is relapsing and remitting or that progresses for longer than 2 months.28 Commonly reported signs and symptoms of CIDP are shown in the Sidebar.1,19 Electrophysiologic testing, the sensitivity of which is improved by testing more than 4 nerves, is necessary to confirm the diagnosis. The testing of 3 limbs may improve the diagnostic certainty of electrophysiologic testing.23 Supportive criteria, such as somatosensory-evoked potentials for sensory CIDP, can help confirm the diagnosis.23 High-resolution ultrasound is a readily available tool that can be used at the bedside. Recent study results have demonstrated the potential utility of measuring abnormal nerve enlargement, both in the brachial plexus and proximal median nerve segments in the arm, with high-resolution ultrasound in the differential diagnosis of CIDP.10,11

Misdiagnosis is common in CIDP, especially in the atypical subtype. In a retrospective study of 59 patients with presumed CIDP referred to
CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

A university neurology group, 47% did not meet EFNS/PNS diagnostic criteria. Almost half of misdiagnosed patients met clinical criteria for atypical CIDP. Misinterpretation of nerve conduction studies was a major contributor to misdiagnosis. Almost 80% of patients who had been misdiagnosed with CIDP had received treatment with intravenous immunoglobulin (IVIg) or a corticosteroid for a mean of 18.6 and 16.2 months, respectively. Some experts estimate that up to one-third of patients in the United States with a diagnosis of CIDP do not have the disease. It is encouraged to seek referrals to Centers of Excellence designated by the GBS-CIDP Foundation.

TABLE 1. EFNS/PNS Diagnostic Criteria for CIDP

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Criteria</strong></td>
<td>One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs):</td>
</tr>
<tr>
<td>• Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities</td>
<td>• Predominantly distal (DADS)</td>
</tr>
<tr>
<td>• Developing over ≥2 months</td>
<td>• Asymmetric (MADSAM or Lewis-Sumner syndrome)</td>
</tr>
<tr>
<td>• Absent or reduced tendon reflexes in all extremities</td>
<td>• Focal (eg, involvement of brachial or lumbosacral plexus or 1 or more peripheral nerves in 1 upper or lower limb)</td>
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<tr>
<td>• Cranial nerves may be affected</td>
<td>• Pure motor</td>
</tr>
<tr>
<td></td>
<td>• Pure sensory (including chronic immune sensory polyradiculopathy)</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>Lyme disease, diphtheria, or drug or toxin exposure likely caused the neuropathy</td>
</tr>
<tr>
<td></td>
<td>Hereditary demyelinating neuropathy</td>
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<tr>
<td></td>
<td>Prominent sphincter disturbance</td>
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<tr>
<td></td>
<td>Diagnosis of multifocal motor neuropathy</td>
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<tr>
<td></td>
<td>Other causes of demyelinating neuropathy (eg, POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy)</td>
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</table>

**Electrophysiologic Criteria**

<table>
<thead>
<tr>
<th>Typical</th>
<th>Atypical</th>
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<tbody>
<tr>
<td><strong>Definite</strong></td>
<td>One or more of the following:</td>
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<tr>
<td>• Motor distal latency prolongation ≥50% above ULN in 2 nerves (excluding median wrist neuropathy from carpal tunnel syndrome)</td>
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<tr>
<td>• Reduction of motor conduction velocity ≥30% below LLN in 2 nerves</td>
<td></td>
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<tr>
<td>• Prolongation of F-wave latency ≥30% above ULN in 2 nerves (≥50% if amplitude of distal negative peak CMAP)</td>
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<tr>
<td>• Partial motor conduction block: ≥50% amplitude reduction of proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥20% of LLN in 2 nerves, or in 1 nerve and ≥1 other demyelinating parameter in ≥1 other nerve</td>
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<tr>
<td>• Abnormal temporal dispersion (&gt;30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves</td>
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<tr>
<td>• Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median, ≥6.6 ms; ulnar, ≥6.7 ms; peroneal, ≥7.6 ms; tibial, ≥8.8 ms) and ≥1 other demyelinating parameter in ≥1 other nerve</td>
<td></td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>≥30% amplitude reduction of proximal negative peak CMAP relative to distal, excluding posterior tibial nerve, if distal negative peak CMAP ≥20% of LLN, in 2 nerves, or in 1 nerve and ≥1 other demyelinating parameter in ≥1 other nerve</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>As in “definite” but in just 1 nerve</td>
</tr>
</tbody>
</table>

**Supportive Criteria**

| | Elevated CSF protein with leukocyte count <10/mm³ |
| | MRI abnormalities: gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or brachial or lumbosacral plexuses |
| | Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial SNAP amplitudes |
| | Sensory conduction velocity <80% LLN (<70% if SNAP amplitude <80% LLN) |
| | Delayed somatosensory evoked potentials without CNS disease |
| | Objective clinical improvement from immunomodulatory treatment |
| | Nerve biopsy with unequivocal demyelination and/or remyelination by electron microscopy or teased fiber analysis |

CIDP indicates chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; CNS, central nervous system; CSF, cerebrospinal fluid; DADS, distal acquired demyelinating symmetric; EFNS, European Federation of Neurological Societies; LLN, lower limit of normal value; MADSAM, multifocal acquired demyelinating sensory and motor; MRI, magnetic resonance imaging; PNS, Peripheral Nerve Society; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SNAP, sensory nerve action potential; ULN, upper limit of normal value.
International Advisory Board for expert advice and second opinions, which can be found at gbs-cidp.org/support/centers-of-excellence.

Clinical Burden and Healthcare Utilization

Healthcare resource utilization and costs are substantial for patients with CIDP. In 2011, a study analyzed insurance claims data for 73 patients with CIDP among 6.5 million covered lives in 9 US commercial health plans. The annual health plan cost per patient was almost $57,000. Pharmacy claims were the primary cost driver, accounting for 57% of health plan costs. Just 49% of patients received immunomodulatory treatment for CIDP, including IVIg (26%), prednisone (16%), and immunosuppressants (7%); 2 patients received plasma exchange. IVIg accounted for 90% of drug costs, with a mean cost of $108,016 (± $18,437) per patient. Frequent use of anticonvulsants, opiates, and antidepressants suggested a burden of neuropathic pain.

Treatment

Initial treatment options for CIDP include immunoglobulin, corticosteroids, or therapeutic plasma exchange (TPE). Considerations that drive the selection of initial therapy include disease severity, comorbid disorders, venous access, potential adverse effects (AEs), availability, and cost. Goals of therapy are to improve muscle strength and prevent permanent disability due to demyelination and secondary axonal loss. In addition to drug therapy, patients with CIDP benefit from an interprofessional approach that may include strength training, physical and occupational therapy, and assistive devices to improve their gait. In a recent clinical trial, aerobic and resistance exercise improved muscle strength in patients with CIDP.

Three clinical trials have attempted to compare first-line treatment options for CIDP; results are limited by inadequate power, imbalances in patient characteristics in treatment arms, and other methodologic issues that are common to studies of patients with rare diseases. In an observer-blinded comparative trial, plasma exchange and IVIg had comparable improvements in neurologic disability scores, weakness subset scores, and summed muscle action potentials. Two studies compared a corticosteroid with IVIg. A double-blind crossover trial compared oral prednisolone tapered from 60 mg to 10 mg once daily over 6 weeks with IVIg 2 g/kg given over 1 or 2 days. In 24 patients who completed at least 2 weeks of treatment with both regimens, improvement in disability grade after 2 weeks was slightly higher with IVIg than with prednisolone. Disability grade improvement was 0.71 (± 1.27) with IVIg and 0.58 (± 0.93) with prednisolone, with a mean difference of 0.16 (95% CI, −0.35 to 0.66). The burden of AEs was comparable with prednisolone and IVIg.

A double-blind, placebo-controlled trial compared monthly administration of IVIg (0.5 g/kg/day for 4 days/month) and intravenous (IV) methylprednisolone (0.5 g/day for 4 days/month) for 6 months in 45 patients with CIDP. The primary outcome, discontinuation due to any cause, was higher with methylprednisolone than IVIg (52% vs 13%; relative risk, 0.54; 95% CI, 0.34-0.87). In patients who responded to therapy, the risk of CIDP worsening and requiring additional therapy after treatment discontinuation was higher with IVIg than with methylprednisolone (38% vs 0%; P = .03).

Corticosteroids

Although corticosteroids have been used for more than 40 years, their efficacy in CIDP has not been established in a large-scale clinical trial. In a nonblinded, randomized, 12-week trial, neuropathy impairment scores improved in 12 of 19 patients receiving prednisone compared with 5 of 15 patients receiving no treatment. The double-blind, randomized PREDICT trial compared standard doses of oral prednisolone with high-dose oral dexamethasone given for 4 days each month in 40 patients. Both regimens appeared to have similar efficacy, but the monthly dexamethasone regimen had fewer AEs (moon-shaped face and insomnia). An intermittent IV methylprednisolone regimen has also been noted to have a lower risk of AEs than regular oral doses of prednisone. Patients from the PREDICT study were followed for a median of 4.5 years after the study ended. The cure or remission rate was 26% after treatment with either corticosteroid. An alternate diagnosis was subsequently made in 17.5% of patients who did not respond to either corticosteroid, again pointing to the need for diagnostic reevaluation and second opinions in patients with presumed CIDP who did not respond to immunomodulatory treatment. An analysis of the PREDICT trial results suggests that patients with a focal distribution pattern of demyelination and less sensory involvement on electrophysiology may have a higher risk of early deterioration after treatment with a corticosteroid.

There is no consensus on the optimal corticosteroid regimen for CIDP. Prolonged treatment with corticosteroids has a substantial burden of dose- and duration-related AEs. These may include osteoporosis and fractures, adrenal suppression and Cushing
Therapeutic Plasma Exchange

TPE is a procedure that passes the patient’s blood through an extracorporeal medical device to remove plasma and replace it with another fluid. Twice-weekly TPE is effective for short-term improvement of disability in CIDP, based on a Cochrane review of 2 studies (n = 59) that compared it with sham exchange. In these studies, response rates were 33% and 66%, respectively. The improvement in neurologic function with plasma exchange can be dramatic, with some patients who are unable to stand recovering their ability to walk. Although the primary mechanism of action in treatment of CIDP and other autoimmune disorders is removal of autoantibodies, TPE may also have immune-modulating activity.

The American Society for Apheresis recommends that patients with CIDP initially receive 1 to 1.5 total plasma volume exchanges 3 times per week until they experience improvement. Plasma is usually replaced with albumin. After a response, TPE may be required at weekly to monthly intervals to maintain a response. Remission of CIDP symptoms has been maintained, with monthly plasma exchange for as long as 21 years.

Common AEs of the procedure include fatigue, nausea, dizziness, perioral and extremity paresthesia, allergic reactions, and hypotension. In a large observational study of apheresis performed for any reason, complications occurred in 3.9% of procedures. Rare, serious complications include arrhythmias, seizures, electrolyte abnormalities, and unexplained bleeding. Laboratory monitoring is required to detect and manage TPE-related anemia, hypocalcemia, hypomagnesemia, and coagulopathies. Citrate, which is used as an anticoagulant during the procedure, contributes to hypocalcemia and hypomagnesemia. Angiotensin-converting enzyme inhibitors must be held for 24 to 48 hours before each session to prevent bradykinin reactions that cause flushing and prolonged hypotension. Drug administration is usually held during TPE to prevent removal of drugs found in the plasma fraction. Drugs used to treat CIDP that can be removed by TPE include IVIg and rituximab. TPE requires reliable peripheral venous access or a central venous catheter. Central venous catheter complications, including infection and pneumothorax, contribute to AEs in patients undergoing TPE.

TPE is a technically challenging process that requires expertise and coordination among an apheresis team, blood bank, pharmacy, and clinical laboratory. Access may be limited to specialized treatment centers. Rough estimates suggest that up to 125,000 TPE procedures are performed in the United States annually. Over a 10-year period at one apheresis center, approximately 5% of procedures were performed to treat CIDP. In 2011, direct hospital costs for 5 TPE procedures were estimated at approximately $4600. Immunoglobulins

Immunoglobulins have been evaluated for CIDP much more extensively than other first-line treatment options. This includes 3 phase 3 clinical trials to support Food and Drug Administration (FDA) approval of 1 SCig and 2 IVIg products to treat CIDP in adults. In 2008, immune globulin injection (Human) 10% caprylate/chromatography purified (Gamunex-C) received FDA approval on the basis of the IGV-C CIDP Efficacy (ICE) trial results. In September 2017, immune globulin IV (Human), 10% liquid (Privigen), a formulation stabilized with proline, received FDA approval on the basis of the Privigen study results. In March 2018, immune globulin SC (Human) 20% liquid (Hizentra) received FDA approval specifically for maintenance therapy on the basis of the PATH trial results. Selected properties of these products, including dosage and administration, are compared in Table 2. The benefit of immunoglobulin in CIDP is attributed to anti-inflammatory activity. It is thought to reduce proinflammatory responses by upregulating FcRiIB on effector macrophages.

Intravenous administration. IVIg has demonstrated response rates of 54% to 61% in 2 phase 3 clinical trials. The ICE trial had 2 phases: a 24-week crossover comparison with placebo followed by an extension phase in which participants responding to IVIg were rerandomized to either IVIg or placebo. At 24 weeks, clinically meaningful improvement in disability on the Inflammatory Neuropathy Cause and Treatment (INCAT) score (≥1-point improvement on the adjusted INCAT disability score) was significantly greater with IVIg than with placebo (54% vs 21%), with an absolute difference of 33.5% (95% CI, 15.4%-51.7%). An improvement in INCAT score occurred between 3 to 6 weeks. In some responders, INCAT scores continued to increase over 24 weeks. In the extension phase, the time to relapse was longer and the relapse rate was significantly lower with IVIg than placebo (33% vs 45%; HR, 0.19; 95% CI, 0.05-0.70). The Privigen study was a 24-week single-arm trial. The primary outcome was a preset success criterion of at least 35% response rate, with response defined as at least a 1-point improvement on the INCAT disability score. The response rate was 60.7% (95% CI, 42.4%-76.4%).

The ICE trial accounted for almost half of the patients in a 2013 Cochrane review that evaluated 5 placebo-controlled trials (n = 235) of IVIg for CIDP. In this meta-analysis, the relative risk

syndrome, hyperglycemia, hypertension, psychiatric disturbances, cataracts, weight gain, and immunosuppression. The risk of corticosteroid-induced osteoporosis is a particular concern for patients with CIDP who have gait disturbances and are at risk of falling. Patients with CIDP who require prolonged corticosteroid treatment should be assessed for fracture risk and receive preventive treatment according to assessed risk. The low acquisition cost of corticosteroids is often cited as a potential benefit. This falls to consider that corticosteroid AEs cause substantial morbidity and increase the cost of care, with some analyses showing that the cost of care increases with higher corticosteroid doses and duration of use.
of improvement with IVIg was 2.4 (95% CI, 1.72-3.36), translating to a number needed to treat (NNT) for a patient to benefit of 3 (95% CI, 2.33-4.55). The relative risk of an AE with IVIg was 2.62 (95% CI, 1.81-3.78), translating to a number needed to harm of 3 (95% CI, 2.56-4.76). There was no difference in the risk of serious AEs with IVIg and placebo (7% vs 8%; relative risk, 0.82; 95% CI, 0.36-1.87). Mild transient AEs associated with IVIg infusion (eg, headache, nausea, chills, and fever) occurred in 49% of patients; serious reactions were less frequent at 6%. Rare serious AEs with IVIg include potentially fatal hypersensitivity reactions, aseptic meningitis, noncardiogenic pulmonary edema, and hemolysis; reversible renal impairment is more likely to occur in patients with preexisting renal impairment. IVIg product labeling contains a black box warning about the risks of renal impairment and a potential increase in thromboembolic events due to an increase in serum viscosity.

There is little consensus about optimal maintenance dosing requirements of IVIg in CIDP. The recommended dose in IVIg product labeling is the dose that was established as effective in the ICE trial (see Table 2). In clinical practice, the maintenance dose is considered to range from 0.4 to 1.2 g/kg given every 2 to 6 weeks, with variable dosing requirements attributed to a variable half-life for IVIg that ranges from 18 to 33 days. Some treatment centers individualize the dose and the dosing interval based on the patient’s response to optimize treatment and minimize cost. Ongoing research should provide clinicians with additional guidance. A phase 3 clinical trial, ProCID, is currently underway to establish whether 0.5, 1, or 2 mg/kg every 3 weeks is the optimal maintenance dose of IVIg. The ongoing DRIP trial is evaluating how more frequent dosing affects efficacy and tolerability of IVIg.

Considering that CIDP remits in a minority of patients, some may be able to discontinue treatment after an initial 6 months of treatment with IVIg. This is supported by data from the ICE trial of IVIg and the PATH trial of SCIg, which show that 58% and 37% of patients, respectively, did not relapse during treatment with placebo. Concern has been raised that continued IVIg treatment of patients who may be in remission creates a burden of unnecessary treatment, AEs, and cost. However, a standardized approach to identifying these patients and how to stop treatment is lacking. Some centers recommend that attempts should be made to reduce the IVIg dose in patients who have been stable for more than 6 months.

Subcutaneous administration. Although SCIg has been evaluated for initial treatment in a small short-term trial, it is currently FDA approved for maintenance therapy in adults with CIDP. The PATH trial evaluated SCIg for maintenance therapy in patients who had been previously treated with IVIg. After a run-in period designed to confirm that patients were IVIg-responders, patients (n = 172) were randomized to receive 24 weeks of weekly SCIg at 0.2 g/kg or 0.4 g/kg or placebo. The primary outcome was relapse or withdrawal from the study for any reason. In an intent-to-treat analysis, the primary outcome was 63% with placebo, 39% with low-dose SCIg (P = .007 vs placebo), and 33% with high-dose SCIg (P = .0005 vs placebo). There was no significant difference in response.

### TABLE 2. Properties of FDA-Approved Immunoglobulin Products for CIDP

<table>
<thead>
<tr>
<th>Formulations</th>
<th>IVIg</th>
<th>SCIg</th>
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<tbody>
<tr>
<td>10% caprylate/chromatography purified liquid (Gamunex-C)</td>
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</tr>
<tr>
<td>O.2 g/kg (20 mL/kg) in divided doses over 2 to 4 consecutive days</td>
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</tr>
<tr>
<td>Maintenance dose: 1 g/kg (10 mL/kg) administered in 1 or 2 infusions on consecutive days</td>
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<td></td>
</tr>
<tr>
<td>Load dose: 2 g/kg (20 mL/kg) in divided doses over 2 to 4 consecutive days</td>
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</tr>
<tr>
<td>Maximum dose: 8 g/kg (80 mL/kg) in divided doses over 2 to 4 consecutive days</td>
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<td></td>
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<tr>
<td>Infusion Rate and Volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial: 0.5 mg/kg/min (0.005 mL/kg/min) or 2 mg/kg/min (0.02 mL/kg/min)</td>
<td>Maximum of 8 infusion sites. Initial volume: 20 mL/site</td>
<td></td>
</tr>
<tr>
<td>Maximum: 8 mg/kg/min (0.08 mL/kg/min)</td>
<td>Maximum volume: 50 mL/site Initial rate: 20 mL/h</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Every 3 Weeks</td>
<td>Weekly</td>
</tr>
<tr>
<td>Gamunex: headache (27%), pyrexia (13%), hypertension (6%), chills (7%), nausea, rash (both 5%); arthralgia, asthenia (both 5%)</td>
<td>Headache (24.5%); diarrhea (10.2%); fatigue, back pain, nausea, extremity pain, cough (all 8.2%); vomiting, upper abdominal pain, migraine, pain (all 6.1%)</td>
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</tr>
<tr>
<td>Privigen: headache (28.6%); asthenia, hypertension (both 14.3%); nausea, extremity pain (both 10.7%); hemolysis, flu-like illness, leukopenia, rash (all 7.1%)</td>
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</table>

CIDP indicates chronic inflammatory demyelinating polyneuropathy; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.
rate for the 2 SCIg doses. Relapse rates were 58.8%, 35.0%, and 22.4%, respectively ($P < .02$ for low-dose vs placebo; $P < .001$ for high-dose vs placebo). The NNT to prevent a relapse with low- and high-dose SCIg was 2.7 and 4.4, respectively.  

In the PATH trial, treatment-emergent AEs occurred in 37% of patients receiving placebo compared with 58% receiving low-dose SCIg and 52% receiving high-dose SCIg. Respective rates for local reactions were 7%, 19%, and 29%. Local reactions were characterized primarily as erythema, induration, or swelling, and 95% were mild reactions.  

A meta-analysis evaluated 8 studies that compared IVIg and SCIg in patients with autoimmune neuropathies, including multifocal motor neuropathy (n = 50) and CIDP (n = 88). Results found no differences in muscle strength outcomes with the 2 routes of administration. The relative risk of systemic AEs (eg, fever, headache, nausea) was 28% lower with SCIg (95% CI, 0.11-0.76).  

SCIg offers an additional treatment option for patients with CIDP who respond to IVIg that may improve quality of life. After training, patients can self-administer SCIg at home with an infusion pump. Approximately 88% of patients in the PATH trial reported that self-administration of SCIg was easy. Although 18% of SCIg-treated patients preferred their previous treatment with IVIg, 53% preferred SCIg and cited greater independence and fewer AEs. The usual initial SC dose is 0.2 g/kg (1 mL/kg) given once weekly in 1 or 2 sessions over 1 or 2 days. If CIDP symptoms worsen on this dose, the patient can temporarily return to treatment with IVIg and then restart SCIg at a higher dose. In the PATH trial, the infusion time was approximately 1 hour via 2 to 8 infusion sites.  

**Monitoring Treatment Response**  
Experts recommend that objective measures be used to document and monitor the response to immunomodulating therapy. Numerous assessment tools have been used in clinical trials, but they may not be practical for clinical practice. Assessment tools suggested for use in clinical practice include the Rasch-Built Overall Disability Scale (R-ODS) to measure disability and the Martin Vigorimeter to measure grip strength. The R-ODS is a 24-item patient questionnaire that captures activity and social participation with items that range in difficulty from reading a book and eating to running and standing for hours. The Martin Vigorimeter is an air pressure tool that measures handgrip strength (0-160 kPa) with a minimum clinically important different cutoff value for grip strength of greater than 8 kPa. Daily self-monitoring can be used to direct therapy, but a potential limitation is that it just assesses hand strength.  

**Other Treatment Options**  
Additional treatment strategies are needed to manage CIDP, especially for patients who do not respond to first-line therapy. Data from the Italian Network for CIDP Register suggest that about 20% of patients become refractory to first-line CIDP therapy. In respective randomized clinical trials, azathioprine and methotrexate did not significantly decrease disability in patients with CIDP. However, experts do not consider these studies adequate to conclude that these drugs are ineffective for CIDP. Additional clinical trials are needed to establish whether they reduce disability or have corticosteroid-sparing effects. In small noncomparative studies, cyclosporine reduced disability in patients who were unresponsive to first-line treatment. Case series report inconsistent benefit with mycophenolate, with some patients responding and others experiencing no benefit. Clinical trials are currently evaluating cyclosporine and mycophenolate for CIDP.  

A few biologic response modifiers and drugs for multiple sclerosis, another demyelinating disease, have been evaluated in patients with CIDP. The use of alemtuzumab, a monoclonal antibody against the CD52 antigen on lymphocytes and monocytes, was associated with remission in 2 of 7 patients with severe IVIg-dependent CIDP. Interferon beta-1a was ineffective for treatment-resistant CIDP in a placebo-controlled clinical trial. A phase 3 trial evaluated fingolimod 0.2 mg/day in 106 patients previously treated with IVIg or a corticosteroid. The study was discontinued early when an interim analysis concluded that the study was unlikely to show benefit at study completion. Hematopoietic stem cell transplant is under evaluation for the management of refractory CIDP, with a phase 2 trial expected to complete data collection in December 2018.  

A retrospective observational study evaluated the response to second-line therapy in 110 patients with CIDP refractory to first-line therapy. A response was defined as improvement on the Rankin scale of at least 1 point. Response rates were 27% for azathioprine (n = 77), 33% for rituximab (n = 18), 38% for cyclophosphamide (n = 13), 25% for mycophenolate (n = 12), 25% for cyclosporine (n = 12), 17% for methotrexate (n = 12), 36% for interferon-alpha (n = 11), and 0% for interferon beta-1a (n = 3). AEs were reported in 30 patients and led to treatment discontinuation in 16 patients (10 with azathioprine; 5 with cyclosporine).  

**Treatment Guidelines**  
The 2010 EFNS/PNS guideline outlines a comprehensive approach to the management of CIDP. It recommends the use of a corticosteroid or IVIg for patients with moderate to severe CIDP. IVIg should be considered instead of a corticosteroid for patients with pure motor CIDP based on evidence of deterioration in these patients soon after initiation of a corticosteroid. When a corticosteroid is used, a treatment duration of up to 12 weeks (prednisone 60 mg with a gradual taper is usual) should be considered before determining whether the patient is a responder. In responders, the dose should be tapered slowly to a low maintenance dose over 1 to 2 years, with consideration of eventual withdrawal. TPE should be considered when patients do not respond to IVIg or a corticosteroid; it may...
also be an initial option for severe CIDP when a rapid response is needed. An immunosuppressant can be considered when first-line therapy does not provide an adequate response, but data are insufficient to guide drug selection. Patient education and shared decision making are key components of treatment selection. An interprofessional approach that includes referral to rehabilitation specialists, management of neuropathic pain, and physical and occupational therapy is recommended.

Two guidelines from the American Academy of Neurology address the use of IVIg and plasmapheresis to treat CIDP. A guideline focused on the use of IVIg to treat neurologic disease recommended that IVIg should be offered for long-term treatment of CIDP. However, it found that data are insufficient to determine comparative efficacy with other treatment modalities. Another guideline focused on the use of TPE to treat neurologic diseases and recommended that it should be offered for short-term treatment of CIDP. The American Society for Apheresis also recommends TPE for CIDP.

Conclusions

CIDP is a rare heterogeneous disease with complex pathophysiology and diagnosis, and few treatment options. Despite these obstacles, substantial gains have been made by dedicated experts in the field to clarify the pathogenesis and simplify the diagnosis of CIDP. SC Ig provides patients with an alternative to IVIg that increases their independence and may be more tolerable. The results of ongoing clinical trials will provide clinicians with information that informs better treatment strategies. All of these research advances offer hope to patients with CIDP.

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