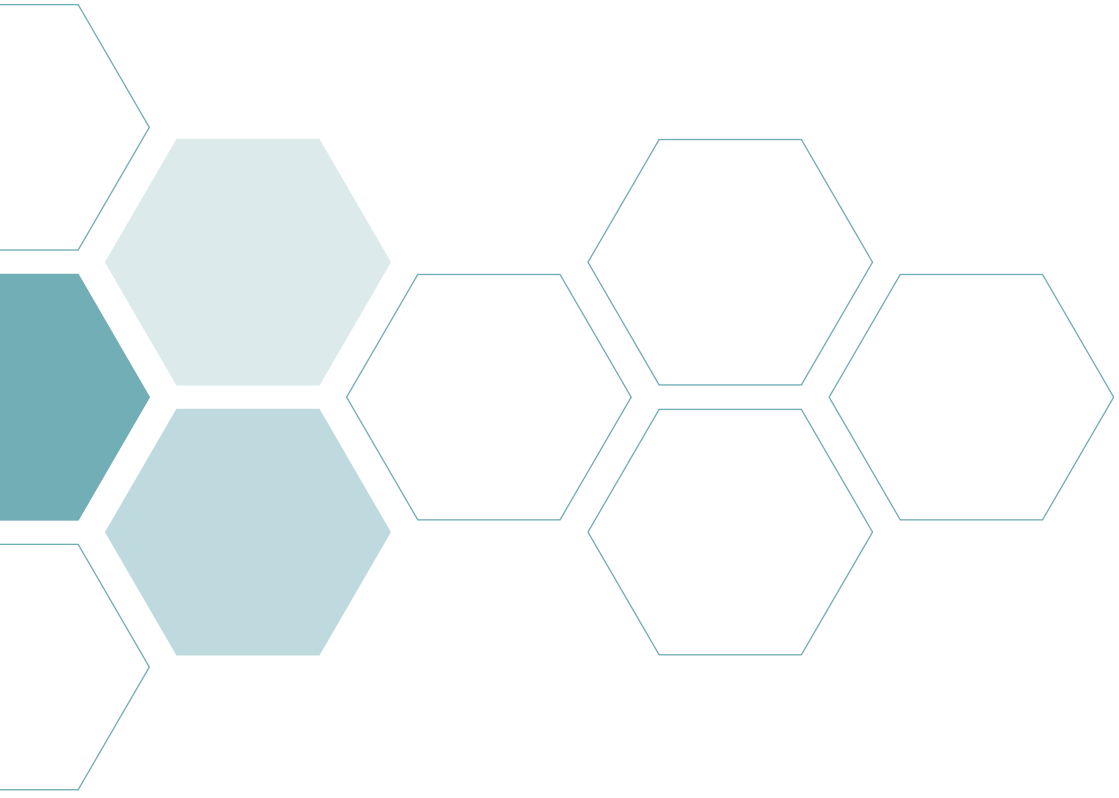
# Evolving Treatment Paradigms in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):

## Managed Care Considerations on Immunoglobulin Replacement Therapy

A CME/CNE Approved Activity



JOURNAL of MANAGED CARE MEDICINE

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Instructions for CME/CNE: Activity is valid from February 1, 2019 to January 31, 2021.

A score of 70% must be achieved on the post-test to receive continuing education credits.
Read the monograph, answer the post-test, complete the evaluation form, and send completed post-test and evaluation to:

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**Learning Objectives:**
1. Identify the clinical and electrophysiological signs and symptoms of chronic inflammatory demyelinating polyneuropathy (CIDP).
2. Examine the safety and efficacy of currently available and emerging immunoglobulin (Ig) replacement therapies for the management of CIDP and apply them to patient cases using evidence-based medicine.
3. Employ shared decision-making when choosing treatment for patients with CIDP in the initial management and maintenance settings.
4. Analyze novel administration methods for immunoglobulin (Ig) replacement therapies and how they are changing the treatment paradigm.
5. Examine the total cost of care for CIDP, including direct costs associated with drug therapy and associated infections from non-treatment, as well as indirect costs.
6. Apply methods to enable optimal cost management of Ig replacement therapies to be realized by multiple CIDP stakeholders including managed care organizations.

**Faculty Disclosure:**
Dr. Owens has disclosed no relevant financial relationships.

All material has been peer reviewed for bias.

**Planning Committee Disclosure**
Bill Williams, MD; Jacqueline Cole, RN, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

**Accreditation and Designation**
The National Association of Managed Care Physicians (NAMCP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
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This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN recertification requirements.

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# Evolving Treatment Paradigms in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Managed Care Considerations on Immunoglobulin Replacement Therapy

## Post-Test Questions

1. Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder of the _____.
   - **a.** Peripheral nervous system
   - **b.** Central nervous system
   - **c.** Parasympathetic nervous system
   - **d.** Sympathetic nervous system
2. Patients with CIDP usually present with weakness _____.
   - **a.** Proximally **b.** Distally
   - **c.** Both proximal and distal **d.** Centrally
3. Which of the following is a correct statement about the epidemiology of CIDP?
   - **a.** Prevalence is estimated at 40 cases per 100,000 persons.
   - **b.** The median age at diagnosis is 20 years.
   - **c.** The disorder is more common in women than men.
   - **d.** The incidence is estimated at 0.7 to 1.6 cases per 100,000 persons per year.
4. The goal of CIDP therapy is to reverse demyelination and secondary axonal loss.
   - **a.** True **b.** False
5. Which of the following is an accurate statement about the use of corticosteroids to treat CIDP?
   - **a.** Corticosteroids efficacy in CIDP has been established in a large-scale clinical trial.
   - **b.** A high dose 4 day/month dexamethasone regimen was equivalent for efficacy and safety to daily prednisolone.
   - **c.** Prolonged use carries a significant risk of adverse effects.
   - **d.** Corticosteroids are more effective than plasma exchange and immunoglobulins.
6. Therapeutic plasma exchange has been shown in clinical trials to significantly improve disability scores and reduce risk of relapse.
   - **a.** True **b.** False
7. A meta-analysis of five trials of intravenous immunoglobulin in CIDP found that the number needed to treat (NNT) for a patient to benefit from the therapy was ___ and the number needed to harm was ___.
   - **a.** 3 and 3 **b.** 12 and 4 **c.** 3 and 8 **d.** 17 and 56
8. Which of the following is the major advantage of using subcutaneous immunoglobulin compared with intravenous immunoglobulin?
   - **a.** Improved efficacy for initial treatment of CIDP
   - **b.** A significantly lower number needed to treat
   - **c.** Significantly reduced adverse effect rates
   - **d.** Improved quality of life
9. The estimated cost of a CIDP hospitalization is _____.
   - **a.** $20,364 **b.** $48,598 **c.** $68,231 **d.** $125,138
10. Which is the most common current strategy for managing immunoglobulin costs?
    - **a.** Value based contracting
    - **b.** Required use of biosimilars
    - **c.** Personalized treatment with biomarkers
    - **d.** Prior authorization

## Activity Evaluation and Improvement Process

*Please rate this activity on the following scale:*
*4 - Excellent 3 - Good 2 - Fair 1 - Poor*

1. Based on the content presented, I am better able to:

   Identify the clinical and electrophysiological signs and symptoms of chronic inflammatory demyelinating polyneuropathy (CIDP).

   4 3 2 1

   Examine the safety and efficacy of currently available and emerging immunoglobulin (Ig) replacement therapies for the management of CIDP and apply them to patient cases using evidence-based medicine.

   4 3 2 1

   Employ shared decision-making when choosing treatment for patients with CIDP in the initial management and maintenance settings.

   4 3 2 1

   Analyze novel administration methods for immunoglobulin (Ig) replacement therapies and how they are changing the treatment paradigm.

   4 3 2 1

   Examine the total cost of care for CIDP, including direct costs associated with drug therapy and associated infections from non-treatment, as well as indirect costs.

   4 3 2 1

   Apply methods to enable optimal cost management of Ig replacement therapies to be realized by multiple CIDP stakeholders including managed care organizations.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

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ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: P.O. Box 71895, Richmond, VA 23255-1895; Tel (804) 387-7580; Fax (703) 997-5842. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316. 

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.



# Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

CIDP Monograph

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# Evolving Treatment Paradigms in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP):

## Managed Care Considerations on Immunoglobulin Replacement Therapy

Gary M. Owens, MD

### Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder of the peripheral nervous system. In CIDP, the myelin sheath, the protective covering of the nerves, is damaged.[1] It is characterized by progressive weakness and impaired sensory function in the legs and arms and is sometimes called chronic relapsing polyneuropathy. CIDP effects can worsen over time, leading to significant activity limitations and a decreased quality of life.

Because myelin is the main target of the condition, nerve fibers with the most myelin (largest fibers) are the most involved and patients present with weakness, numbness, and sensory ataxia (symptoms of large myelinated fiber dysfunction). CIDP is a progressive neuropathy. The course of CIDP can be varied--presentations include relapsing-remitting, stepwise progressive, or gradually progressive. The clinical pattern of CIDP is unlike typical peripheral neuropathies that are length-dependent (meaning that the most distal segments are most involved).

CIDP usually presents as a polyradiculoneuropathy with weakness in both proximal and distal segments.[2] Patients are weak both distally (e.g., intrinsic hand weakness and foot drop) and proximally (e.g., difficulty going up stairs or lifting objects onto shelves). In most cases, motor deficits are the most problematic symptoms that patients experience. Patients may have difficulty walking, often fall, and may require gait aids. They may also have difficulty with fine finger control. Numbness, paresthesia and sensory ataxia (not knowing where one's limbs are in space) are also common features.[2] Autonomic symptoms and neuropathic pain are less common.

The most common presentation of CIDP is the "classical" symmetrical polyradiculoneuropathy.[2] The second most common subtype of CIDP is multifocal CIDP, which has also been called Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy. Another subtype of CIDP is one that is clinically and pathologically confined to the sensory nerve roots which defies easy diagnosis because the results of nerve conduction studies are normal. These cases have been described as CISP and noted that they present with profound sensory ataxia, numbness, and no weakness.

The pathophysiology of CIDP involves cellular and humoral components of the immune system attacking myelin on large peripheral nerve fibers, leading to demyelination. CIDP is a heterogenous disorder with typical and atypical phenotypes that may or may not share the same pathogenesis. In about 10 percent of patients, specific autoantibodies have been identified against paranodal proteins within the nodes of Ranvier in the peripheral nerves. Autoantibodies identified so far also include vinculin, LM1, neurofascin-155, neurofascin-186, gliomedin, and contactin-1.[3-5]

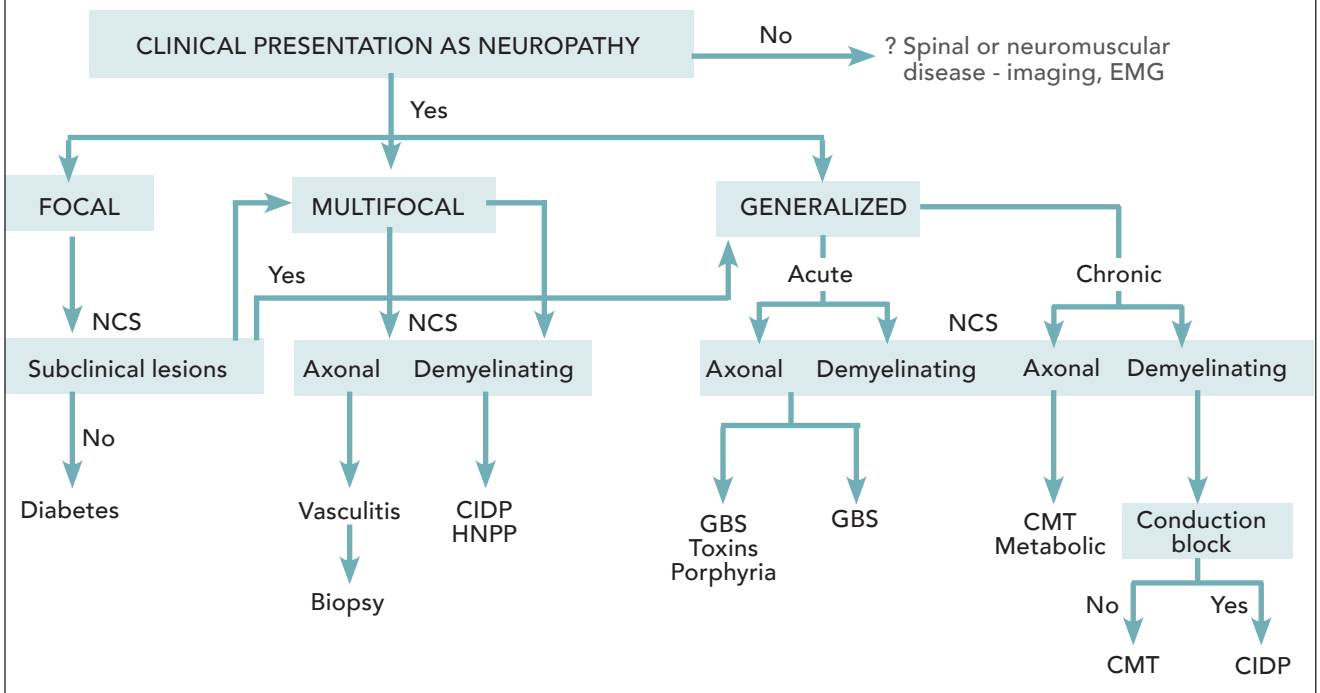
The diagnosis of CIDP requires that it be distinguished from other neuropathies (Exhibit 1).[6] The diagnosis of CIDP is made by using a combination of clinical history, physical examination, and electrodiagnostic and laboratory evaluation. Although many sets of diagnostic criteria have been developed 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 (Exhibit 2).[7]

CIDP is the most common treatable chronic neuropathy worldwide, but it is still a rare disease, with an incidence of 0.7 to 1.6 cases per 100,000 persons per year.[8,9] Prevalence is estimated at 4.8 to 8.9 cases per 100,000 persons.[8,9] In an epidemiologic study of residents in Olmstead County, Minnesota, in 2000, the median age at diagnosis was 58 years and median disease duration at diagnosis was 10 months (range, 2-64).[8] The disorder is more common in men than in women.

Initial treatment options for CIDP include corticosteroids, therapeutic plasma exchange, or immunoglobulin (Ig). Considerations that drive the selection of initial therapy include: disease severity, comorbid disorders, venous access, potential adverse effects, and cost.[10] The goals of therapy are to improve muscle strength and prevent permanent disability due to demyelination and secondary axonal loss. A significant portion of patients subsequently become dependent on these treatments to maintain function.[11]

Although commonly used, corticosteroids efficacy in CIDP has not been established in a large-scale

**Exhibit 1: Differentiating CIDP[6]**




CIDP = chronic inflammatory demyelinating polyradiculoneuropathy

CMT = Charcot-Marie-Tooth

EMG = electromyography

GBS = Guillain-Barré syndrome

HNPP = hereditary neuropathy with liability to pressure palsies

NCS = nerve conduction studies

clinical trial. In a nonblinded, randomized, 12-week trial, neuropathy impairment scores improved in 12 of 19 patients receiving prednisone compared with five of 15 patients receiving no treatment.[12] The double-blind, randomized PREDICT trial compared standard daily doses of oral prednisolone with high-dose oral dexamethasone given for four days each month in 40 patients.[13] At 4.5 years of follow-up, the cure or remission rate was 26 percent after treatment with either corticosteroid. The dexamethasone regimen caused fewer adverse effects (moon-shaped face and insomnia) than prednisolone. It is important to note that patients with presumed CIDP, who do not respond to an immunomodulatory treatment, should have a diagnostic reevaluation and second opinions; 17 percent of those in this trial received another diagnosis. There is no optimal dosing regimen for corticosteroids in CIDP and prolonged use carries a significant risk of adverse effects (osteoporosis and fractures, adrenal suppression and Cushing's syndrome, hyperglycemia, hypertension, psychiatric disturbances, cataracts, and weight gain).

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. The primary mechanism of action in treatment of CIDP and other autoimmune disorders is removal of autoantibodies. Twice-weekly TPE is effective for short-term improvement of disability in CIDP, based on a Cochrane review of two studies (n = 59) that compared it with sham plasma exchange.[14] In these studies, response rates were 33 percent and 66 percent. The improvement in neurologic function with plasma exchange can be dramatic, with some patients, who are unable to stand, recovering their ability to walk. Patients with CIDP initially receive 1 to 1.5 total plasma volume exchanges three times per week until they experience improvement.[15] Plasma is usually replaced with albumin. After a response, TPE may be required at weekly to monthly intervals to maintain the response; monthly TPE has maintained remission out to 21 years. Adverse effects can include infections, anemia, hypocalcemia, hypomagnesemia, and coagulopathies. TPE is a technically challenging process that requires expertise and coordination among an apheresis team, a blood bank, a pharmacy,

| Exhibit 2: CIDP Diagnostic Criteria[7] |
|---|
| **Typical:** Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities: |
| • Developing over ≥ 2 months |
| • Absent or reduced tendon reflexes in all extremities |
| • Cranial nerves may be affected |
| **Atypical:** One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs): |
| • Predominantly distal (DADS) |
| • Asymmetric (MADSAM or Lewis-Sumner syndrome) |
| • Focal (e.g., involvement of brachial or lumbosacral plexus or 1 or more peripheral nerves in 1 upper or lower limb) |
| • Pure motor |
| • Pure sensory (including chronic immune sensory polyradiculopathy) |
| One or more of the following: |
| • Motor distal latency prolongation ≥50% above ULN in 2 nerves (excluding median wrist neuropathy from carpal tunnel syndrome) |
| • Reduction of motor conduction velocity ≥30% below LLN in 2 nerves |
| • Prolongation of F-wave latency ≥30% above ULN in 2 nerves (≥50% if amplitude of distal negative peak CMAP) |
| • Partial motor conduction block: ≥50% amplitude reduction of proximal negative peak CMAP relative to distal |
| • Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves |
| • Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve and ≥1 other demyelinating parameter in ≥1 other nerve |
| Supporting Diagnostics |
| • Elevated CSF protein with leukocyte count <10/mm$^3$ |
| • MRI abnormalities: gadolinium enhancement and/or hypertrophy of the cauda equina |
| • 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 |

and a clinical laboratory. Access to specialized treatment centers offering TPE can be limited.

Intravenous immunoglobulin (IVIg) is frequently used as the initial treatment of CIDP and is the best studied intervention.[2] The benefit of Ig in CIDP is attributed to anti-inflammatory activity. IVIg is particularly useful in patients with diabetes or patients with other medical comorbidities that would make the use of corticosteroids less than ideal. Prior to FDA approval, IVIg was used off label for this indication. A total of three Phase III clinical trials supported the FDA approval of two IVIg products to treat CIDP in adults and one subcutaneous infusion IG (Exhibit 3).[16-18]

A prospective randomized controlled trial evaluating IVIg in 117 patients with CIDP, which included a crossover period for non-responders and an extension phase for responders, found significant improvement

| Exhibit 3: FDA Approved Ig Preparations for CIDP[16-18] | | |
|---|---|---|
| Product | 10% caprylate/chromatography purified liquid (Gamunex-C®)<br>10% liquid (Privigen®) | 20% liquid (Hizentra®) |
| FDA approved Indication* | CIDP in adults | Chronic maintenance in adults with CIDP |
| Frequency | Every 3 weeks | Weekly |
| Common adverse effects (incidence >5% in Phase III 3 clinical trial) | Gamunex: headache (27%), pyrexia (13%), hypertension (6%), chills (7%), nausea, rash (both 5%); arthralgia, asthenia (both 5%)<br>Privigen: headache (28.6%); asthenia, hypertension (both 14.3%); nausea, extremity pain (both 10.7%); hemolysis, flu-like illness, leukopenia, rash (all 7.1%) | 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%) |

* CIDP indications only listed, each has other indications

in inflammatory neuropathy and treatment disability scores after 24 weeks in the IVIg group (54% vs 21% with placebo).[16] During the extension phase in the trial, there was a lower rate of relapse in patients treated with IVIg (13% vs 45%). A meta-analysis of five trials of IVIg in CIDP found that the number needed to treat (NNT) for a patient to benefit from the therapy was 3 and the number needed to harm was also 3.[19] There was no difference in the risk of serious adverse effects with IVIg and placebo (7% vs 8%).[19] Mild transient AEs (e.g., headache, nausea, chills, and fever) occur in almost 50 percent of patients. Rare serious AEs with IVIg include potentially fatal hypersensitivity reactions, aseptic meningitis, noncardiogenic pulmonary edema, hemolysis, renal impairment, and thromboembolic events.[20]

Subcutaneous immunoglobulin (SCIg) has been studied for maintenance therapy in patients who had been previously treated with IVIg, and it is now FDA approved for maintenance therapy in CIDP.[18] 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 0.2 g/kg or 0.4 g/kg or placebo. Fifty-eight percent of those receiving the placebo had relapse, 35 percent with low-dose SCIg, and 22.4 percent with high-dose SCIg (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. The low dose (0.2 g/kg) is the recommended dose in the approved package labeling. Adverse effects with subcutaneous infusion and intravenous infusion are very similar.

Subcutaneous infusion 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 percent of patients in the published trial reported that self-administration of SCIg was easy.[18] Although 18 percent of SCIg-treated patients preferred their previous treatment with IVIg, 53 percent preferred SCIg and cited greater independence and fewer adverse effects.

The CIDP indication has held the second most market share of the IVIg market.[21] Subcutaneous administration of Ig is predicted to grow exponentially at a rate of 9.8 percent annually.[21] Growth potential of this segment of therapy is associated with the advantages of subcutaneous administration, which includes the rapid action of the drug once administered, faster patient responses, and fewer adverse effects associated with these formulations.

Other immunosuppressants have been investigated in small studies for managing CIDP and are used some for long-term management.[2] Agents used include methotrexate, azathioprine, mycophenolate mofetil, rituximab, and alemtuzumab. None of these has an FDA indication for CIDP.

Because it is a chronic disease, it is important to engage CIDP patients in their treatment. Shared decision making (SDM) can be an integral part of the decision pathway. Patients want to participate more actively in their health care overall. Goals of SDM include ensuring that patients understand their disease and encouraging patients to increase the roles they assume in their own disorder and its management. This means collaborating with them to be more aware of their symptoms and the adverse effects of therapy, essentially promoting optimal interaction between

patients and clinicians. The SHARE approach to therapeutic treatment decisions involves five steps:

1. Seek patient participation.
2. Help the patient explore and compare treatment options.
3. Assess the values and preferences of the patient.
4. Reach a decision with the patient.
5. Evaluate the patient's decision.[22]

Instead of just telling the patient what to do, the clinician works with the patient to make and evaluate the decision together and ensure it is the optimal one for the individual patient. Tailoring CIDP therapy and management for each patient is crucial and has long-term implications.

CIDP is costly to treat. In 2011, a study analyzed insurance claims data for 73 patients with CIDP among 6.5 million covered lives in nine United States (U.S.) commercial health plans and found the annual health plan cost per patient was almost $57,000.[23] Pharmacy claims were the primary cost driver, accounting for 57 percent of health plan costs. Just 49 percent of patients received immunomodulatory treatment for CIDP, including IVIg (26%), prednisone (16%), and immunosuppressants (7%). Two patients received plasma exchange. IVIg accounted for 90 percent of drug costs, with a mean cost of $108,016 (± $18,437) per patient. The other primary driver of total costs were inpatient hospital stays and care in outpatient hospital settings (infusion centers). Frequent use of anticonvulsants, opiates, and antidepressants suggested a burden of neuropathic pain in these patients.

Suryavanshi and Khanna identified data surrounding discharges of adult patients with CIDP identified from the 2010 pooled Healthcare Cost and Utilization Project National (Nationwide) Inpatient Sample (HCUP-NIS).[24] The estimated cost of hospitalizations for CIDP from 2010 to 2012 was $2.1 billion in the U.S. alone, with a mean cost of CIDP-related hospitalization of $68,231. [24] Those with CIDP had a 50 percent longer length of stay (LOS) and higher total charges than control patients without CIDP. Predictors of hospitalization outcomes included patient age, hospital bed size, location and teaching status; discharge to long-term care or skilled nursing facilities; presence of complications; and administration of IVIg or plasmapheresis treatments.

Because of the cost-of-care, payers are actively managing CIDP treatments. In a survey, U.S. payers indicated that Ig products are typically managed with a prior authorization (PA) based on indication.[25] Payers emphasized that a correct diagnosis is a critical component for a PA. The survey noted that when the various Ig agents have different FDA-approved indications, PA does not differentiate agents based on variable indications or routes of administration. Fifty-six percent of participants indicated that failure of oral immunosuppressants and/or corticosteroids was required before they approve an Ig product. Those whose health plan did not require prior treatment failure indicated that Ig is usually not the primary treatment of choice by their patients.

In these cases, there is not a strong perceived need to have treatment failure requirements for disease management with Ig products. Immunoglobulin products are primarily handled as part of medical benefits instead of pharmacy benefits. When asked specifically about coverage status and tier placement of specific agents, payers stated that Ig products were covered on the highest tier. There was minimal preference for any specific agent. Payers overwhelmingly considered these drugs to be interchangeable therapeutic equivalents from a health plan perspective. There was strong concern about the site of administration and its relationship to cost, with preference given to infusion at a health clinic, at an infusion center under the health plan, or at home. Other specific concerns cited by payers relating to management of Ig included drug price, off-label or questionable use, correct diagnosis before approval of use, complexities and differences in treatment strategies across the country making contracting more difficult, and difficulties associated with switching to home-based administration. There is a need for more data for decision making, especially surrounding resource usage, cost-impacting care variations, and head-to-head agent comparisons.

Many payers also require that once treatment of CIDP with Ig is initiated for any approved indication, documentation of patient progress is required. If improvement is noted and continued treatment is still necessary, objective clinical assessment to monitor patient progress is required.

Payer management of specialty drugs may impact CIDP therapies. Payer strategies in 2018 and beyond are evolving rapidly and include newer benefit designs, multiple tiers of specialty benefit, consideration of the emerging biosimilar marketplace, specialty specific formularies, and alignment of patient incentives. Change in specialty drug management is on the way. Today's management is driven by medication class with tiered co-payment, preferred brands, co-insurance and deductibles, specialty management carve outs, step therapy, and prior authorization. The future is value-based insurance design where plans pay for what works, accountable care organizations, and personalized medicine with targeted therapy where medication is only given if it will work based on companion diagnostics. Value means different

things to different stakeholders; therefore, payers need to take these multiple views into consideration to develop value-based coverage.[26] In addition to the plan's view, payers will need to consider the view of providers, patients, and manufacturers.

## Conclusion

Despite available treatment options, many CIDP patients continue to struggle with daily disease and lifestyle challenges. Fortunately, for these patients, novel immunoglobulin replacement therapies have recently become available that have shown improved efficacy and safety as a maintenance therapy in CIDP.

## Author Bio

**Gary M. Owens, MD** is President of Gary Owens and Associates.

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## Notes

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