Guillain-Barre Syndrome Treatments

Number: 0732

POLICY

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers any of the following therapies medically necessary for the treatment of Guillain-Barre syndrome (GBS):

A. Intravenous immunoglobulin (IVIG) when criteria in CPB 0206 - Parenteral Immunoglobulins (../200_299/0206.html) are met.

B. Outpatient pulmonary rehabilitation program when criteria listed in CPB 0032 - Pulmonary Rehabilitation (../1_99/0032.html) are met.

C. Plasmapheresis when criteria in CPB 0285 - Plasmapheresis/Plasma Exchange/Therapeutic Apheresis (../200_299/0285.html) are met.

II. Aetna considers the use of any of the following therapies for the treatment of GBS experimental and investigational because their effectiveness for this indication has not been established (not an all-inclusive list).

A. Acupuncture

B. Alemtuzumab (CPB 0764 - Alemtuzumab (Campath) (../700_799/0764.html))

C. Amantadine

D. Bifidobacterium infantis
E. Brain-derived neurotrophic factor
F. Cerebrospinal fluid filtration
G. Corticosteroids
H. Eculizumab
I. Interferons (CPB 0404 - Interferons (../400_499/0404.html))
J. Leukocyte trafficking inhibitors (e.g., efalizumab, etrolizumab, natalizumab and vedolizumab)
K. Neuromuscular electrical stimulation in rehabilitation of GBS
L. Per-oral endoscopic myotomy (for the treatment of GBS-associated achalasia)
M. Rituximab
N. Sugammadex.

BACKGROUND

Guillain-Barre syndrome (GBS) is an acquired acute peripheral neuropathy causing limb weakness that progresses over a period of days to weeks. It occurs with a median annual incidence of 1.3 cases per population of 100,000, with men being more frequently affected than women. The prognosis of GBS is generally favorable, but it is a serious disease with a mortality of about 10% and approximately 20% of patients are left with severe disability. Guillain-Barre syndrome is considered to be an autoimmune disease triggered by a preceding bacterial or viral infection. Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, and mycoplasma pneumoniae are commonly identified antecedent pathogens. It is a heterogeneous disorder representing at least 5 different entities -- 3 are predominantly motor; namely acute inflammatory demyelinating polyneuropathy (AIDP), acute motor sensory axonal neuropathy (AMSAN), and acute motor axonal neuropathy (AMAN); and the remaining 2 variants are Fisher syndrome, and acute panautonomic neuropathy (Lindenbaum et al, 2001; Kuwabara, 2004).

In the AMAN form of GBS, the infecting organisms probably share homologous epitopes to a component of the peripheral nerves and, therefore, the immune responses cross-react with the nerves causing axonal degeneration; the target molecules in AMAN are likely to be gangliosides GM1, GM1b, GD1a and GalNAc-GD1a expressed on the
motor axolemma. In the AIDP form of GBS, immune system reactions against target epitopes in Schwann cells or myelin result in demyelination; however, the exact target molecules in the case of AIDP have not yet been identified. Acute inflammatory demyelinating polyneuropathy is by far the most common form of GBS in Europe and North America, whereas AMAN occurs more frequently in eastern Asia, namely China and Japan (Kuwabara, 2004).

Treatment of GBS entails management of severely paralyzed patients with intensive care and ventilatory support, and specific immunomodulating therapies that shorten the progressive course of GBS, presumably by limiting nerve damage. High-dose intravenous immunoglobulin (IVIG) and plasmapheresis (PP)/plasma exchange (PE)/therapeutic apheresis aid more rapid resolution of the disease. The predominant mechanisms by which IVIG exerts its action appear to be a combined effect of complement inactivation, neutralization of idiotypic antibodies, cytokine inhibition and saturation of Fc receptors on macrophages.

There is insufficient evidence that patients with GBS respond to corticosteroids (Lindenbaum et al, 2001; Czapinski and Steck, 2004; Newswanger and Waren, 2004; Kuwabara, 2004). Furthermore, a Cochrane review on corticosteroids for GBS (Hughes et al, 2006) stated that limited evidence demonstrates that oral corticosteroids markedly slow recovery from GBS. Substantial evidence shows that intravenous methylprednisolone alone does not produce significant benefit or harm. The authors noted that further investigation is needed and more effective treatments for GBS should be sought.

In a multi-center, randomized controlled study (n = 233), van Koningsveld et al (2004) reported that there was no significant difference between methylprednisolone plus IVIG and IVIG alone in the treatment of patients with GBS. Odaka et al (2005) compared side effects in 9 patients with GBS treated with standard IVIG only and in 9 patients treated with combined methylprednisolone and IVIG therapy. Headache occurred in 2 patients in both groups, suggesting that pre-infusion with steroids does not prevent headache.
In a Cochrane review, Hughes and colleagues (2010) examined the effectiveness of corticosteroids in the treatment of GBS. These investigators searched the Cochrane Neuromuscular Disease Group Trials Specialized Register (June 2009), Medline (January 1966 to June 2009) and Embase from (January 1980 to June 2009). They included quasi-randomized or randomized controlled trials of any form of corticosteroid or adrenocorticotrophic hormone. The primary outcome was change in disability grade on a 7-point scale after 4 weeks of treatment; secondary outcomes included time from randomization until recovery of un-aided walking, time from randomization until discontinuation of ventilation (for those ventilated), death, death or disability (inability to walk without aid) after 12 months, relapse, and adverse events. Two authors extracted the data. No new trials were discovered in the new search in June 2009; 6 trials with 587 subjects provided data for the primary outcome. According to moderate quality evidence, the disability grade change following 4 weeks in the corticosteroid groups was not significantly different from that in the control groups, weighted mean difference (WMD) 0.36 less improvement (95% confidence intervals [CI]: 0.16 more to 0.88 less improvement). In 4 trials of oral corticosteroids with 120 participants in total, there was significantly less improvement after 4 weeks with corticosteroids than without corticosteroids, WMD 0.82 disability grades less improvement, 95% CI: 0.17 to 1.47). In 2 trials with a combined total of 467 participants, there was no significant difference, WMD 0.17 (95% CI: -0.06 to 0.39) of a disability grade more improvement after 4 weeks with intravenous corticosteroids. According to moderate-to-high quality evidence, there were no significant differences between the corticosteroid-treated and the control groups in any of the secondary outcomes. Diabetes was significantly more common and hypertension significantly much less common in the corticosteroid-treated participants. The authors concluded that according to moderate quality evidence, corticosteroids given alone do not significantly hasten recovery from GBS or affect the long-term outcome. According to low quality evidence oral corticosteroids delay recovery. Diabetes requiring insulin was significantly more and hypertension less common with corticosteroids.

Interferon has not been shown to be effective for GBS. Pritchard et al (2003) performed a pilot double-blind, randomized, placebo-controlled safety trial of interferon beta 1a on patients with GBS. Participants
received interferon beta 1a or placebo subcutaneously thrice-weekly, 22 ug for the first week and then 44 ug for up to 24 weeks, in addition to IVIG. These researchers reported that interferon beta 1a did not have any unexpected interaction with IVIG and there was no significant difference in rate of improvement.

Practice parameter on immunotherapy for GBS furnished by the Quality Standards Subcommittee of the American Academy of Neurology (Hughes et al, 2003) has the following recommendations:

- Corticosteroids are not recommended for the management of GBS;
- IVIG is recommended for non-ambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms. The effects of PE and IVIG are equivalent;
- PE and IVIG are treatment options for children with severe GBS;
- PE is recommended for non-ambulant adult patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms. PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms; and
- Sequential treatment with PE followed by IVIG, or immunoadsorption followed by IVIG is not recommended for patients with GBS.

Monaco and colleagues (2004) stated that in GBS and related variants, randomized clinical trials show that PE and IVIG are equally effective as disease-modifying treatments, although IVIG has been adopted as the favorite treatment in most centers. Finsterer (2005) stated that concerning the treatment of GBS, there is no significant difference between IVIG, PE, and PE followed by IVIG. Because of convenience and absent invasiveness, IVIG is usually preferred.

A Cochrane review (Hughes et al, 2006) stated that randomized trials in severe cases of GBS show that IVIG started within 2 weeks from onset hastens recovery as much as PE, which is known to be more effective than supportive care. Treatment with IVIG is significantly more likely to be completed than PE. Giving IVIG after PE did not confer significant extra benefit. In children, IVIG probably hastens recovery compared with
supportive care alone. The authors stated that more research is needed in mild disease and in treatment starting more than 2 weeks following the onset of the condition. These findings are in agreement with the afore-mentioned recommendations of the American Academy of Neurology.

Raphael (2005) noted that PE is the first-line treatment for GBS. Two PE are recommended in patients who are able to walk (mild) with 2 additional PE if they deteriorate. In patients who are unable to walk without assistance (moderate), 4 PE are sufficient, likewise in those who require mechanical ventilation (severe form). It is not useful to add further PE in more severe disease or if there is no response. High-dose of IVIG (0.4 g/kg daily for 5 days) and PE are equally effective in the treatment of intermediate and severe forms of GBS. The choice between the 2 options depends on their respective contraindications and local availability.

Amantadine has not been proven effective for treatment of GBS. In a randomized, double-blind, placebo-controlled, cross-over trial (n = 80), Garssen et al (2006) examined the effect of amantadine on severe fatigue related to GBS. During the pre-treatment phase, all patients were monitored for 2 weeks. Only patients with severe fatigue, defined as a mean fatigue score of greater than or equal to 5.0 on the Fatigue Severity Scale (FSS), were included in this study. Primary outcome measure was improvement of at least 1 point on the FSS. Secondary outcome measures were impact of fatigue, anxiety and depression, handicap, as well as quality of life. A total of 80 patients were randomized, of whom 74 were included for analysis. Fatigue appeared to be reduced already during the pre-treatment phase (p = 0.05), probably due to increased attention provided to the patients. No significant differences in any of the primary and secondary outcome measures were found. These researchers concluded that amantadine was not superior to placebo.

A multi-disciplinary consensus group reviewed the published medical literature and made recommendations regarding supportive care of persons with GBS (Hughes et al, 2005). In the acute phase in bed-bound adult patients, the group recommended the use of heparin and graduated pressure stockings to prevent deep vein thrombosis, monitoring for blood pressure, pulse, autonomic disturbances, and respiratory failure, and the timely institution of artificial ventilation and tracheostomy. The group
noted that pain management is difficult, but carbamazepine or gabapentin may help. The cautious use of narcotic analgesics may be needed. Disabled patients should be treated by a multi-disciplinary rehabilitation team and should receive an assistive exercise program. Persistent fatigue following GBS is common and may be helped by an exercise program. The group stated that, because of a very small and possibly only theoretical increase in the risk of recurrence following immunization, the need for immunization should be reviewed on an individual basis. The group reported that more research is needed to identify optimal methods for all aspects of supportive care.

van Doorn (2009) noted that epidemiological studies have shown that the incidence of GBS remains stable at about 2/100,000 per year; but that there have been changes in hospitalization use, likely due to the widespread availability of IVIG. Research into mechanisms has shown the importance of single amino acids in campylobacter jejuni and the importance of ganglioside conformation. In a murine model of anti-ganglioside antibody-mediated neuropathy, eculizumab was effective in reversing clinical disease and preventing pathology. This suggested trials of eculizumab in GBS should be considered. However, there are no new randomized controlled trials in GBS to report.

In a Cochrane review, Hughes et al (2011) reviewed systematically the evidence from randomized controlled trials for pharmacological agents other than PE, IVIG and corticosteroids. These investigators searched the Cochrane Neuromuscular Disease Group Specialized Register (July 5, 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 2), MEDLINE (January 1966 to June 2010) and EMBASE (January 1980 to June 2010) for treatments for GBS. They included all randomized or quasi-randomized controlled trials of acute (within 4 weeks from onset) GBS of all types, ages and degrees of severity; and discarded trials that only tested corticosteroids, IVIG or PE. These researchers included other pharmacological treatments or combinations of treatments compared with no treatment, placebo treatment or another treatment. Change in disability after 4 weeks was the primary outcome. Two authors checked references and extracted data independently. One author entered and another checked data in Review Manager (RevMan). They assessed risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions. They
calculated mean differences and risk ratios with their 95% CIs. They assessed strength of evidence with GradePro software. Only very low quality evidence was found for 4 different interventions. One randomized controlled trial with 13 participants showed no significant difference in any outcome between interferon (IFN) beta-1a and placebo. Another with 10 participants showed no significant difference in any outcome between brain-derived neurotrophic factor and placebo. A third with 37 participants showed no significant difference in any outcome between cerebrospinal fluid filtration and PE. In a fourth with 20 participants, the risk ratio of improving by one or more disability grades after 8 weeks was significantly greater with the Chinese herbal medicine tripterygium polyglycoside than with corticosteroids (risk ratio 1.47; 95% CI: 1.02 to 2.11). The authors concluded that the quality of the evidence was very low. Three small randomized controlled trials, of IFN beta-1a, brain-derived neurotrophic factor and cerebrospinal fluid filtration, showed no significant benefit or harm. A 4th small trial showed that the Chinese herbal medicine tripterygium polyglycoside hastened recovery significantly more than corticosteroids but this result needs confirmation. It was not possible to draw useful conclusions from the few observational studies.

In a Cochrane review, Liu and colleagues (2013) evaluated the safety and effectiveness of pharmacological treatments for various pain symptoms associated with GBS, during both the acute and convalescent (3 months or more after onset) phases of GBS. On August 27, 2012, these investigators searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL (2012, Issue 8) in The Cochrane Library, MEDLINE (January 1966 to August 2012) and EMBASE (January 1980 to August 2012). In addition, they searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform. These researchers included randomized controlled trials (RCTs) and quasi-RCTs in participants with confirmed GBS, with pain assessment as either the primary or secondary outcome. For cross-over trials, an adequate washout period between phases was required for inclusion. Two review authors independently screened the titles and abstracts of identified records, selected studies for inclusion, extracted eligible data, cross-checked the data for accuracy and assessed the risk of bias of each study. A total of 3 short-term RCTs, which enrolled 277 randomized participants with acute phase GBS, were included. Risk of
bias in the included studies was generally unclear due to insufficient information. None of the included studies reported the primary outcome selected for this review, which was number of patients with self-reported pain relief of 50% or greater. One small study investigated 7-day regimens of gabapentin versus placebo. Pain was rated on a scale from 0 (no pain) to 10 (maximum pain). Among the 18 participants, significantly lower mean pain scores were found at the end-point (day 7) in the gabapentin phase compared to the end-point of the placebo phase (mean difference -3.61, 95% CI: -4.12 to -3.10) (very low quality evidence). For adverse events, no significant differences were found in the incidence of nausea (risk ratio (RR) 0.50, 95% CI: 0.05 to 5.04) or constipation (RR 0.14, 95% CI: 0.01 to 2.54). A second study enrolling 36 participants compared gabapentin, carbamazepine and placebo, all administered over 7 days. Participants in the gabapentin group had significantly lower median pain scores on all treatment days in comparison to the placebo and carbamazepine groups (p < 0.05). There were no statistically significant differences in the median pain scores between the carbamazepine and placebo groups from day 1 to day 3, but from day 4 until the end of the study significantly lower median pain scores were noted in the carbamazepine group (p < 0.05) (very low quality evidence). There were no adverse effects of gabapentin or carbamazepine reported other than sedation. One large RCT (223 participants, all also treated with IVIG), compared a 5-day course of methylprednisolone with placebo and found no statistically significant differences in number of participants developing pain (RR 0.89, 95% CI: 0.68 to 1.16), number of participants with decreased pain (RR 0.95, 95% CI: 0.63 to 1.42) or number of participants with increased pain (RR 0.85, 95% CI: 0.52 to 1.41) (low quality evidence). The study did not report whether there were any adverse events. The authors concluded that while management of pain in GBS is essential and pharmacotherapy is widely accepted as being an important component of treatment, this review did not provide sufficient evidence to support the use of any pharmacological intervention in people with pain in GBS. Although reductions in pain severity were found when comparing gabapentin and carbamazepine with placebo, the evidence was limited and its quality very low. They stated that larger, well-designed RCTs are needed to further investigate the safety and effectiveness of potential interventions for patients with pain in GBS. Additionally, interventions for pain in the convalescent phase of GBS should be investigated.
Pena et al (2015) noted that pain is a common symptom in patients with GBS. Intensity is moderate to severe in most cases and pain may persist after resolution of the disease. These researchers identified the most appropriate analgesic therapy for pain management in patients with GBS. They performed a systematic review and selection of scientific articles on treatment of pain in GBS patients, published between January 1985 and December 2012. They included only double-blind RCTs assessing the effectiveness of drugs for pain management in these patients. A total of 4 articles met the inclusion criteria. One evaluated the use of gabapentin, another evaluated carbamazepine, a third compared gabapentin to carbamazepine, and the last evaluated use of methylprednisolone. Both carbamazepine and gabapentin were useful for pain management. Patients experienced lower-intensity pain with gabapentin treatment in the study comparing that drug to carbamazepine. Methylprednisolone was not shown to be effective for reducing pain. The published data did not permit completion of a meta-analysis. The authors concluded that there is no robust evidence at present that would point to a single treatment option for this disorder. Moreover, they stated that further clinical studies of larger patient samples and with a longer duration are needed to characterize types of pain for each patient and measure pain intensity in an objective way.

Furthermore, an UpToDate review on “Treatment and prognosis of Guillain-Barré syndrome in adults” (Vriesendorp, 2014) states that “Aside from plasma exchange and intravenous immune globulin (IVIG), no other pharmacologic agents have been found to be effective for GBS. Interferon-beta has been reported to be beneficial in individual cases, but in a small randomized controlled trial, interferon-beta therapy was not associated with significant clinical improvement, and possible medication-related side effects were common”.

Tzachanis et al (2014) reported on the case of a 79-year old man with chronic lymphocytic leukemia who presented with GBS with features overlapping with the Miller Fisher syndrome and Bickerstaff brainstem encephalitis and positive anti-ganglioside GQ1b antibody about 6 months after treatment with bendamustine and rituximab. His clinical and neurologic condition continued to deteriorate despite sequential treatment with corticosteroids, IVIG and plasmapheresis, but in the end, he had a
complete and durable response to treatment with alemtuzumab. The findings of this single-case study needs to be validated by well-designed studies.

Zhang et al (2014) stated that GBS is an immune-mediated acute inflammatory disorder of the peripheral nervous system (PNS) in humans characterized by inflammatory infiltration and damage to myelin and axon. Experimental autoimmune neuritis (EAN) is a useful animal model for studying the pathogenesis and treatment of GBS. Immunocompetent cells together with cytokines produced by various cells contribute to the inflammatory process of GBS and EAN by acting as mediators or effectors. Both GBS and EAN have long been attributed to T helper (Th) 1 cell-mediated autoimmune disorders. Interferon-gamma (IFN-γ) acts as a central mediator of Th1-mediated autoimmune disorders by deflecting the immune response toward a Th1 phenotype by inducing the differentiation of T cells to a Th1 phenotype and inhibiting the development of Th2 cells in autoimmune disorders such as GBS. These investigators presented an overview of current knowledge on the inflammatory and immune-regulatory role of IFN-γ in GBS and EAN, which is important for evaluating whether IFN-γ can become a potential therapeutic target in GBS. The authors concluded that analysis of immuno-pathogenesis of GBS and EAN revealed the significance of IFN-γ in both diseases, even though the complex mechanism of the delicate modulation of the cytokine is still under debate. They stated that more work is needed to rule out its potential in immune-regulatory function and pave the way for new therapeutic strategies for GBS.

Pritchard and colleagues (2016) noted that PE and IVIG, but not corticosteroids, are beneficial in the treatment of GBS. The effectiveness of other pharmacological agents is unknown. This review was first published in 2011 and updated in 2013 and 2016. These researchers evaluated the effects of pharmacological agents other than PE, IVIG and corticosteroids for GBS. On January 18, 2016, these investigators searched the Cochrane Neuromuscular Specialized Register, Cochrane Central Register of Controlled Trials, Medline, and Embase for treatments for GBS. They also searched clinical trials registries. These researchers included all RCTs or quasi-RCTs of acute GBS (within 4 weeks from onset) of all types and degrees of severity, and in individuals of all ages. They discarded trials that investigated only corticosteroids, IVIG or PE.
They included other pharmacological treatments or combinations of treatments compared with no treatment, placebo or another treatment. The authors concluded that the quality of the evidence was very low; 3 small RCTs, comparing IFN beta-1a or brain-derived neurotrophic factor with placebo, and cerebrospinal fluid filtration with PE, showed no significant benefit or harm for any of the interventions. A 4th small trial showed that the Chinese herbal medicine, tripterygium polyglycoside, hastened recovery in people with GBS to a greater extent than corticosteroids, but this result needs confirmation. The authors stated that they were unable to draw any useful conclusions from the few observational studies that they identified.

Per-Oral Endoscopic Myotomy for Guillain-Barre Syndrome-Associated Achalasia

Shin and colleagues (2017) stated that GBS-associated achalasia is a very rare disease of uncertain cause. These researchers reported the case of a patient diagnosed with GBS-associated type I achalasia who was successfully treated with per-oral endoscopic myotomy (POEM). A 30-year old man who was diagnosed with GBS 3 months before was referred to the authors’ department with dysphagia and meal-related regurgitation. The results of esophagography, endoscopy, and high-resolution manometry (HRM) revealed type I achalasia. POEM that utilized a sub-mucosal tunneling technique was performed to treat the GBS-associated type I achalasia. After POEM, smooth passage of a contrast agent into the stomach was shown in follow-up esophagography, and follow-up HRM revealed a decrease in the mean integrated relaxation pressure of 22.9 mmHg to 9.6 mmHg. The patient remained without dysphagia for 7 months, even though the patient’s neurological problems were not fully resolved. The authors concluded that POEM may be a safe and effective treatment for GBS-associated type I achalasia.

Rituximab for the Treatment of Guillain-Barre Syndrome

Motamed-Gorji and colleagues (2017) addressed emerging biological approaches for the treatment of GBS. These researchers carried out an extensive electronic literature search from April 2016 to July 2016. Original articles, clinical trials, systematic reviews (with or without meta-analysis) and case reports were selected. Titles and abstracts of papers
were screened by reviewers to determine whether they met the eligibility criteria and full texts of the remaining articles were retrieved. They focused on data concerning emerging biological therapeutic agents, namely anti-C5 monoclonal antibody (eculizumab), anti-C1q monoclonal antibody, anti-T cell monoclonal antibody, anti-CD2 monoclonal antibody, anti L-selectin monoclonal antibody, anti-CD20 monoclonal antibody (rituximab), anti-CD52 monoclonal antibody (alemtuzumab) and cytokine targets. By far, none of these agents has been approved for treatment of GBS by the Food and Drug Administration (FDA). The authors concluded that these findings represented in current review herald promising results for using these biological targets.

In a systematic review and meta-analysis, MacIsaac and colleagues (2018) examined the safety and efficacy of rituximab in autoimmune diseases that are also treated with IVIG. The most common indications for immune modulation with IVIG, as identified from a 2012 regional audit in Canada, were chronic inflammatory demyelinating polyneuropathy (CIDP), immune thrombocytopenia (ITP), myasthenia gravis (MG), multifocal motor neuropathy, GBS, systemic lupus erythematosus (SLE), Sjogren’s syndrome (SS), and pemphigus vulgaris. These investigators searched Medline, Embase, and the Cochrane Library until July 2016 for studies evaluating rituximab in each of these conditions. The primary outcome in this meta-analysis was clinical response at 6 months as defined by disease-specific criteria in randomized trials. These researchers also calculated pooled proportions of responders within disease types from observational studies. A total of 95 rituximab studies were identified: 86 were observational studies in patients with ITP (n = 1,746), SLE (n = 1,047), pemphigus vulgaris (n = 564), SS (n = 138), MG (n = 66), and CIDP (n = 31) and 9 were RCTs (n = 992) in patients with ITP, SLE, and SS that compared rituximab with placebo plus standard of care. Among randomized trials, response rates were higher with rituximab (RR, 1.38; 95 % CI: 1.05 to 1.83). The pooled proportion of rituximab responses ranged from 94 % (95 % CI: 88 % to 98 %) for pemphigus vulgaris to 48 % (95 % CI: 30 % to 66 %) for CIDP. Rituximab was generally well-tolerated in observational studies although in the randomized trials, AEs were more common in the rituximab group. The authors concluded that rituximab is an immune-modulating agent with biologic activity across many autoimmune conditions. These researchers
stated that these findings support the use of comparative trials with broad eligibility criteria to evaluate rituximab as an alternative to IVIG in autoimmune diseases.

Sugammadex for the Treatment of Guillain-Barre Syndrome

Tezcan and colleagues (2017) noted that sugammadex encapsulates and inactivates rocuronium and vecuronium. It is used to reverse neuromuscular blockade from these non-depolarizing agents. The safety of sugammadex in patients with neuromuscular disease has not been established. Guillain-Barre Syndrome (GBS) is a neuromuscular disease characterized by acute inflammatory polyneuropathy. Patients with GBS may exhibit autonomic dysfunction, chronic pain, abnormal reactions to neuromuscular blocking agents, and may require post-operative mechanical ventilation. These investigators reported the successful use of sugammadex to reverse rocuronium in a patient with chronic GBS, who presented for a hemi-colectomy. These findings need to be validated in well-designed studies.

Bifidobacterium infantis

Shi and colleagues (2018) stated that GBS is a rare, autoimmune-mediated disease. The use of Bifidobacterium infantis is reportedly effective in alleviating GBS since they act by regulating T helper (Th) cells. In this study, these researchers explored the differentiation of T helper cell subsets in patients with GBS. They also evaluated the effect of GBS on Bifidobacterium levels in patients and the likely protective influence of this bacterium in alleviating the disease in an animal model. These investigators used flow cytometry, and real-time polymerase chain reaction (PCR) to determine the T cell subsets differentiation among 30 GBS patients and 20 healthy controls (HC). The concentration of Bifidobacterium was assayed by real-time PCR. Experimental autoimmune neuritis (EAN) animal model was established to support the protective role of Bifidobacterium in GBS. The expression of Th cells, Th2 and Th17 in the patients was significantly higher than that in the HC, while Treg cells decreased substantially. Moreover, the levels of Bifidobacterium in the GBS patients were considerably lower than those in the HC, the concentration of Bifidobacterium correlating with Th2 and Th17 subsets negatively. Treatment with Bifidobacterium significantly
reduced the levels of Th2 and Th17 and promoted the levels of Treg cells. The authors concluded that Bifidobacterium alleviated GBS by regulating Th cells, although in-depth studies are needed to fully understand the mechanism of action.

Eculizumab

In a multi-center, double-blind, randomized phase-II clinical trial, Misawa and colleagues (2018) examined the safety and efficacy of eculizumab, a humanized monoclonal antibody against the complement protein C5, in patients with severe GBS. This was a 24-week, placebo-controlled trial carried out at 13 hospitals in Japan. Eligible patients with GBS were aged 18 years or older and could not walk independently (GBS functional grade 3 to 5). Patients were randomly assigned (2:1) to receive 4 weeks of IVIG plus either eculizumab (900 mg) or placebo; randomization was done via a computer-generated process and web response system with minimization for functional grade and age. The study had a parallel non-comparative single-arm outcome measure. The primary outcomes were efficacy (the proportion of patients with restored ability to walk independently [functional grade of less than or equal to 2] at week 4) in the eculizumab group and safety in the full analysis set. For the efficacy end-point, these investigators pre-defined a response rate threshold of the lower 90 % CI boundary exceeding 50 %. Between August 10, 2015 and April 21, 2016, a total of 34 patients were assigned to receive either eculizumab (n = 23) or placebo (n = 11). At week 4, the proportion of the patients able to walk independently (functional grade of less than or equal to 2) was 61 % (90 % CI: 42 to 78; n = 14) in the eculizumab group, and 45 % (20 to 73; n = 5) in the placebo group. Adverse events (AEs) occurred in all 34 patients; 3 patients had serious AEs: 2 in the eculizumab group (anaphylaxis in 1 patient and intra-cranial hemorrhage and abscess in another patient) and 1 in the placebo group (depression). The possibility that anaphylaxis and intra-cranial abscess were related to eculizumab could not be excluded. No deaths or meningococcal infections occurred. The authors concluded that the primary outcome measure did not reach the pre-defined response rate. However, these researchers noted that because this was a small study without statistical comparison with the placebo group, the safety and efficacy of eculizumab need to be examined in larger RCTs.
Leukocyte Trafficking Inhibitors

Liu and co-workers (2018) noted that GBS, the most common cause of acute neuromuscular weakness and paralysis worldwide, encompasses a group of acute immune-mediated disorders restricted to peripheral nerves and roots. Immune-mediated attack of peripheral nervous system myelin, axons or both is presumed to be triggered by molecular mimicry, with both cell- and humoral-dependent mechanisms implicated in disease pathogenesis. Good circumstantial evidence exists for a pathogenic role for molecular mimicry in GBS pathogenesis, especially with its axonal forms, providing insights that could guide future immunotherapy; IVIG and PE are the most commonly prescribed immunotherapies for GBS with variable efficacy dependent on GBS subtype, severity at initial presentation and other clinical and electrophysiologic prognostic factors. The mechanisms of action of IVIG and PE are not known definitely. Despite recent significant advances in molecular biology that provide insights into GBS pathogenesis, no advances in therapeutics or significant improvements in patient outcomes have occurred over the past three decades. We summarize the clinical aspects of GBS, its current pathogenesis and immunotherapy, and highlight the potential of leukocyte trafficking inhibitors as novel disease-specific immunotherapeutic drugs.

Neuromuscular Electrical Stimulation in Rehabilitation of Guillain-Barre Syndrome

Harbo and colleagues (2019) noted that in GBS, patients often develop muscle atrophy from denervation and immobilization. In a pilot study, these researchers examined the feasibility, safety, and effectiveness of neuromuscular electrical stimulation (NMES) on muscle wasting in the early phase of GBS. A total of 17 patients were randomized to receive 20 mins of muscle fiber stimulation followed by 40 mins of NMES of the right or left quadriceps muscle with the untreated side as control. Cross-sectional area (CSA) of the muscle measured by ultrasound (US) and isometric knee extensor strength were the primary and secondary outcome measures. No treatment related adverse effects were recorded. Change in CSA was -0.25 cm² (CI: -0.93 to 0.42) on the stimulated side versus -0.60 cm² (CI: -1.32 to 0.11) on the non-stimulated side (p = 0.08). No effect was observed on muscle strength. The authors concluded that
NMES appeared safe and feasible in the early phase of GBS. Moreover, these researchers stated that further studies are needed to examine the effect on muscle function.

Rescue Treatment (Intravenous Immunoglobulin or Plasma Exchange)

Walgaard and associates (2018) noted that 1 course of IVIG of 2 g/kg is standard treatment in GBS patients unable to walk independently. Despite treatment some patients recover poorly, in part related to rapid consumption of IVIG, indicating that they may benefit from a 2nd course of IVIG. These investigators examined if a 2nd course of IVIG, administered 1 week after start of the 1st course in patients with GBS and predicted poor outcome improves functional outcome on the GBS disability scale after 4 weeks. Secondary outcome measures included AEs, Medical Research Council sum score and GBS disability score after 8, 12, and 26 weeks, length of hospital and intensive care unit (ICU) admission, mortality, and changes in serum IgG levels. GBS patients of 12 years and older with a poor prognosis, based on the modified Erasmus GBS outcome score (mEGOS) at 1 week after start of the 1st IVIG course are eligible for randomization in this double-blind, placebo-controlled (IVIG or albumin) clinical trial. This study will determine if a 2nd course of IVIG administered in the acute phase of the disease is safe, feasible, and effective in patients with GBS and a poor prognosis.

Alboudi and colleagues (2019) examined the effectiveness of rescue treatment (IVIG or PE) in patients with GBS who did not respond or deteriorated after the initial management with IVIG. These investigators carried out a retrospective review of the medical records of patients who responded poorly or did not respond to IVIG treatment. The disability parameters of those who received 2nd-line treatment with IVIG or PE (20 patients) were compared with those who did not receive 2nd-line treatment (19 patients). There was a statistically significant improvement in disability scores at 1 month in the patients who received the rescue treatment (p = 0.033). However, there was no significant difference in the disability scores at 3 and 6 months, or in length of ICU stay. The authors concluded that the best strategy to be applied for GBS patients who did not respond to the 1st course of treatment is yet to be determined. Some trials showed benefit or a trend of benefit of a 2nd modality of treatment.
They noted that this study showed that a 2nd course of treatment to carefully selected patients may be beneficial. These researchers stated that RCTs should be performed and include only patients who did not respond to 1st-line treatment to be randomized to either a 2nd-line treatment or supportive management.

The authors stated that this study had several drawbacks. First, this was a retrospective study, and there were no clear criteria recognized to choose patients who should receive the rescue treatment. Instead, the decision was made by the responsible physician depending on his or her interpretation of the patient's clinical situation. Second, follow-up was limited because most patients were expatriates. Moreover, it was clear that more patients in the control group were lost to follow-up, and the increasing disability score at follow-up suggested that the less severely patients were the ones lost. Third, the wide range of ages introduced more variability in the results. Finally, financial issues were sometimes a factor in not giving a 2nd course of treatment to some patients who may have otherwise benefited from the treatment.

The Zipper Method

Kesici and colleagues (2019) noted that IVIG and PE are proven treatments for GBS. Despite these treatments, the prognosis for severe GBS is still unsatisfactory. These researchers sought for a logical timing for PE-IVIG synergy, which may improve outcome in severe GBS requiring mechanical ventilation. In an open-label study, a total of 9 pediatric severe GBS patients requiring mechanical ventilation were treated with novel treatment strategy named as "zipper method". In this method, following diagnosis of GBS, PE was started immediately. In the 1st session of PE, 1.5 volume of patients' plasma was removed by using 5% albumin as replacement solution. At the end of the PE session, 0.4 g/kg IVIG infusion was started immediately; 2nd PE session was applied with 1 volume change after 24 hours from the end of the IVIG infusion. Each PE session was followed by IVIG infusions. This PE-IVIG cycle was repeated for 5 times. Among the 9 patients, the mean mechanical ventilation duration was 7 (5 to 14) days and the mean hospital stay was 18 (10 to 30) days. Medical Research Council sum score was increased in all patients, especially after the 3rd session. All patients survived and all patients were able to walk unaided on the 28th day of admission. The
authors concluded that the zipper method as a novel treatment modality appeared to reduce mortality, expedite weaning from mechanical ventilation, and shorten hospital stay, with excellent outcome in severe GBS patients, who required intensive care. These researchers stated that this technique stands as a promising immunomodulation strategy for various scenarios.

**Acupuncture**

Fan and colleagues (2020) noted that GBS is the most common acute paralytic neuropathy. Many clinical trials indicated acupuncture provides a good effect as a complementary therapy of Western medicine for GBS. The objective of this systematic review protocol is to provide the evidence to examine the safety and effectiveness of acupuncture for the treatment of GBS. These investigators will search relevant RCTs examining the effect of acupuncture for GBS in following data-bases from start to October 2019: PubMed, Embase, the Cochrane Library, CINAHL Complete, National Digital Science Library, China National Knowledge Infrastructure, and Wanfang Database without language restriction. For articles that meet inclusion criteria, 2 researchers will extract the data information independently, and evaluate the risk of bias and trial quality by the Cochrane collaboration's tool. All data will be analyzed by RevMan V.5.3.3 statistical software. According to the Barthel index of activities of daily living (ADL) and the Medical Research Council (MRC) muscle scale, the safety and efficacy of acupuncture for GBS will be determined in this study. The authors concluded that this systemic review will provide high quality evidence to examine if acupuncture provides benefits for the treatment of GBS.

**Second Course of IVIG**

Algahtani and associates (2020) stated that GBS is a life-threatening form of inflammatory polyneuropathy. Immunotherapy with IVIG has been used successfully in the treatment of GBS. In this case report, these researchers presented a severe axonal form of GBS that showed improvement after 3 cycles of IVIG. Repeated cycles of IVIG may be an option for treating severe forms of GBS not responding to the 1st course of such treatment. The recent work suggested that patients who are severely affected and have severe gadolinium enhancement on the
magnetic resonance imaging (MRI) of the spine should be considered for re-treatment with IVIG. Although the cost of management was high, the outcome was excellent, which is definitely considered a reasonable approach. The authors concluded that this case report is an urgent call for conducting large, multi-center studies on the use of repeated cycles of IVIG in the management of severe cases of GBS.

Verboon and colleagues (2020) compared disease course in patients with GBS with a poor prognosis (defined as being unable to walk independently) who were treated with 1 or with 2 IVIG courses. From the International GBS Outcome Study, these researchers selected patients whose modified Erasmus GBS Outcome Score at week 1 predicted a poor prognosis. They compared those treated with 1 IVIG course to those treated with 2 IVIG courses. The primary end-point, the GBS disability scale at 4 weeks, was evaluated with multi-variable ordinal regression. Of 237 eligible patients, 199 patients received a single IVIG course; 20 received an “early” 2nd IVIG course (1 to 2 weeks after start of the 1st IVIG course) and 18 patients a “late” 2nd IVIG course (2 to 4 weeks after start of IVIG). At baseline and 1 week, those receiving 2 IVIG courses were more disabled than those receiving 1 course. Compared with the 1-course group, the adjusted odds ratio (OR) for a better GBS disability score at 4 weeks was 0.70 (95 % CI: 0.16 to 3.04) for the early group and 0.66 (95%CI 0.18 to 2.50) for the late group. The secondary end-points were not in favor of a 2nd IVIG course. The authors concluded that this observational study did not show better outcomes after a 2nd IVIG course in GBS with poor prognosis. The study was limited by small numbers and baseline imbalances; lack of improvement was likely an incentive to start a 2nd IVIG course. These researchers stated that a prospective, randomized trial is needed to examine if a 2nd IVIG course would improve outcome in GBS; and it is being conducted in the SID-GBS RCT.

CPT Codes/ HCPCS Codes/ICD-10 Codes
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by “+”
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>36514</td>
<td>Therapeutic apheresis; for plasma pheresis</td>
</tr>
<tr>
<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
</tr>
<tr>
<td>97810 - 97814</td>
<td>Acupuncture, 1 or more needles</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized, (e.g., powder), 500 mg</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>S9473</td>
<td>Pulmonary rehabilitation program, non-physician provider, per diem</td>
</tr>
<tr>
<td>J0202</td>
<td>Injection, alemtuzumab, 1 mg</td>
</tr>
<tr>
<td>J0702</td>
<td>Injection, betamethasone acetate and betamethasone sodium phosphate, per 3 mg</td>
</tr>
<tr>
<td>J1020</td>
<td>Injection, methylprednisolone acetate, 20 mg</td>
</tr>
<tr>
<td>J1030</td>
<td>Injection, methylprednisolone acetate, 40 mg</td>
</tr>
<tr>
<td>J1040</td>
<td>Injection, methylprednisolone acetate, 80 mg</td>
</tr>
<tr>
<td>J1094</td>
<td>Injection, dexamethasone acetate, 1 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>J1100</td>
<td>Injection, dexamethasone sodium phosphate, 1 mg</td>
</tr>
<tr>
<td>J1300</td>
<td>Injection eculizumab 10 mg</td>
</tr>
<tr>
<td>J1700</td>
<td>Injection, hydrocortisone acetate, up to 25 mg</td>
</tr>
<tr>
<td></td>
<td>(Hydrocortone acetate)</td>
</tr>
<tr>
<td>J1710</td>
<td>Injection, hydrocortisone sodium phosphate, up to 50 mg</td>
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<tr>
<td>J1720</td>
<td>Injection, hydrocortisone sodium succinate, up to 100 mg</td>
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<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
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<tr>
<td>J2650</td>
<td>Injection, prednisolone acetate, up to 1 ml</td>
</tr>
<tr>
<td>J2920</td>
<td>Injection, methylprednisolone sodium succinate, up to 40 mg</td>
</tr>
<tr>
<td>J2930</td>
<td>Injection, methylprednisolone sodium succinate, up to 125 mg</td>
</tr>
<tr>
<td>J3300</td>
<td>Injection, triamcinolone acetonide, preservative free, 1 mg</td>
</tr>
<tr>
<td>J3301</td>
<td>Injection, triamcinolone acetonide, per 10 mg</td>
</tr>
<tr>
<td>J3302</td>
<td>Injection, triamcinolone diacetate, per 5 mg</td>
</tr>
<tr>
<td>J3303</td>
<td>Injection, triamcinolone hexacetonide, per 5 mg</td>
</tr>
<tr>
<td>J3380</td>
<td>Injection, vedolizumab, 1 mg</td>
</tr>
<tr>
<td>J7509</td>
<td>Methylprednisolone, oral, per 4 mg</td>
</tr>
<tr>
<td>J7510</td>
<td>Prednisolone, oral, per 5 mg</td>
</tr>
<tr>
<td>J7512</td>
<td>Prednisone, immediate release or delayed release, oral, 1 mg</td>
</tr>
<tr>
<td>J8540</td>
<td>Dexamethasone, oral, 0.25 mg</td>
</tr>
<tr>
<td>J9212</td>
<td>Injection, interferon alfacon-1, recombinant, 1 mcg</td>
</tr>
<tr>
<td>J9213</td>
<td>Interferon alfa-2A, recombinant, 3 million units</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>J9214</td>
<td>Interferon alfa-2B, recombinant, 1 million units</td>
</tr>
<tr>
<td>J9215</td>
<td>Interferon alfa-N3, (human leukocyte derived), 250,000 IU</td>
</tr>
<tr>
<td>J9216</td>
<td>Interferon gamma-1B, 3 million units</td>
</tr>
<tr>
<td>J9312</td>
<td>Injection, rituximab, 10 mg</td>
</tr>
<tr>
<td>Q3027</td>
<td>Injection, interferon beta-1a, 1 mcg for intramuscular use</td>
</tr>
<tr>
<td>S8930</td>
<td>Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient</td>
</tr>
<tr>
<td>S9559</td>
<td>Home injectable therapy, interferon, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- G61.0 Guillian-Barre syndrome

The above policy is based on the following references:


57. Walgaard C, Jacobs BC, Lingsma HF, et al; Dutch GBS Study Group. Second IVIg course in Guillain-Barré syndrome patients


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0732 Guillain-Barre Syndrome Treatments

The need to meet criteria in Clinical Policy Bulletin CPB 0206 does not apply to Pennsylvania Medicaid.

For the Pennsylvania Medical Assistance Plan, effective 1/1/20 medication coverage requests for medications on the statewide preferred drug list will be reviewed using the guidelines for determination of medical necessity developed by the Pennsylvania Department of Human Services.

updated 09/30/2021