Inpatient Management of Guillain-Barré Syndrome

Matthew Harms, MD¹

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Abstract

Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis in the developed world. Guillain-Barré syndrome typically presents with ascending paralysis and is usually severe enough to warrant hospital admission for management. In the United States alone, GBS results in more than 6000 hospitalizations each year. Although GBS patients were historically cared for at tertiary referral centers, changing treatment practices have broadened the number of neurologists who care for the disease. This article provides a review of key issues in the inpatient management of GBS. A survey of the evidence base for treatment with plasma exchange or intravenous immunoglobulins is presented. Although either of these treatments can limit the severity of GBS, patients are still at risk for a broad range of complications, including respiratory failure, autonomic dysfunction, thromboembolic disease, pain, and psychiatric disorders. Awareness of these complications, their detection and management, may help limit the morbidity of GBS.

Keywords

Guillain-Barre syndrome, neurocritical care, polyradiculoneuropathy

Introduction

Guillain-Barré syndrome (GBS) and its related variants comprise a group of acute radiculoneuropathies, with an inflammatory or autoimmune pathophysiology. The classical form of GBS is also known as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and accounts for 90% of cases seen in the United States and Europe.¹ Acute inflammatory demyelinating polyradiculoneuropathy typically presents with progressive flaccid paralysis that is often ascending and reaches its nadir within 4 weeks. After a plateau phase of variable duration, recovery begins and often results in a significant return of function. Associated clinical features include areflexia, variable sensory loss, an albumin-cytological dissociation in the cerebrospinal fluid, and variable degrees of demyelination on electrophysiologic testing. An axonal form of GBS (acute motor axonal neuropathy, or AMAN) is more prevalent in Asia and South America, while other GBS variants (including the Miller Fisher syndrome, acute motor and sensory axonal neuropathy, or AMSAN, and acute pandysautonomia) are uncommon.² Detailed clinical characteristics of GBS and its variants, including electrophysiological classification, associated serum antibodies, and prognostic features, are available online.³

With the near-eradication of polio, GBS has become the most common cause of acute flaccid paralysis in developed countries. The incidence of GBS is best known for the United States and Europe, with a consistent annual incidence of

0.84 to 1.9 cases/100 000 population.⁴ Despite improved recognition and treatment, GBS continues to be a severe disease. One-quarter of patients will require mechanical ventilation for respiratory failure or airway protection,⁵⁻⁷ and 3-11% will die of GBS-related complications.^{5,7,8} Although most patients make substantial recoveries, 20% to 38% experience residual disability,^{5,9} and more than one-third are forced to make adjustments to their work and social lives.¹⁰

Because most patients require hospitalization, GBS results in more than 6000 hospital admissions annually in the United States alone.¹¹ Recent trends in the treatment of GBS are resulting in fewer patient transfers to tertiary care centers,¹¹ broadening the number of hospitals and neurologists who need familiarity and expertise in the management of GBS. This review aims to provide guidelines for the inpatient care of GBS, focusing first on treatment of the underlying disease process and then turning to the prevention and management of potential complications.

¹ Department of Neurology, Washington University School of Medicine, St Louis, MO, USA

Corresponding Author:

Matthew Harms, Department of Neurology, Washington University School of Medicine, Campus Box 8111, St Louis, MO 63110, USA
Email: harmism@neuro.wustl.edu

Disease Modifying Therapies

In as many as two-thirds of GBS patients, the onset of weakness occurs 1 to 3 weeks following an upper respiratory illness, gastrointestinal infection, or vaccination.^{6,12} This fact suggests an antibody-mediated pathogenesis and initially led researchers to investigate the use of immune modulating therapies as treatment for GBS.

Plasmapheresis

Plasmapheresis, or plasma exchange (PE), nonselectively removes immunoglobulins, complement, and cytokines, all of which may play a role in the pathogenesis of GBS.¹³ Plasma exchange was the first therapy for GBS shown to be effective by a randomized controlled trial.¹⁴ Results from 6, high-quality, randomized trials were recently summarized by the Cochrane Review,¹⁵ 5 of which clearly demonstrated the efficacy of PE.^{14,16-20} For severe GBS, the relative risk of improving one or more functional grades by 4 weeks after PE treatments was 1.64 (95% CI 1.37 to 1.96). Treatment also significantly reduced the number of patients requiring mechanical ventilation, shortened the time to extubation, increased the number of patients achieving full strength at 1 year, and reduced the number of patients experiencing severe sequelae at 1 year. These studies also demonstrated that treatment within 7 days is the most effective and that patients with mild GBS (able to ambulate at time of treatment) still benefit from PE.²⁰

Plasma exchange is initiated as early as possible but up to 30 days from the onset of weakness. Although the clinical trial regimens varied slightly, PE is typically administered as 4 to 6 total plasma volumes exchanged over a span of 10 to 14 days. Alternate day PE reduces the risk of coagulopathy by permitting hepatic synthesis to regenerate serum clotting factors. It allows time for antibodies initially located outside of the plasma compartment to redistribute back into the serum, where they can be removed during subsequent exchange. Replacement with albumin is preferred over fresh frozen plasma due to a lower complication rate.¹⁸ Prothrombin time, PTT, CBC, and calcium levels are typically followed daily to detect coagulopathy, thrombocytopenia, occult bleeding, or the hypocalcemia caused by citrate anticoagulation.

The optimal dose of PE has not been firmly established, but the French Cooperative Group study has provided several guidelines²⁰—in mild GBS (patients able to walk, but not run), 2 exchanges are better than none. Similarly, in moderate GBS (unable to walk, but not mechanically ventilated), 4 exchanges are better than 2. However, more is not always better and in severe GBS (requiring mechanical ventilation), 6 exchanges were not superior to four. Approximately 10% of patients treated with PE may have relapsing weakness (“treatment related fluctuations”) after their initial improvement.²¹ These fluctuations may occur due to rebound antibody release or production. Anecdotal evidence supports the efficacy of repeating PE in these cases.^{21,22}

Although the expense of PE is offset by shorter ICU and hospital stays,^{23,24} it is still only available in specialized centers. Additionally, contraindications to PE are found in 4% to 27% of GBS patients,^{18,20,25} including unstable hemodynamics, coagulopathy, sepsis, and problems with vascular access. In another 2% to 18%, PE must be curtailed or discontinued secondary to complications.^{14,18,20,26,27} These issues ultimately prompted searches for easier-to-administer therapies.

Intravenous Immunoglobulins

Intravenous immunoglobulin (IVIg) is the other GBS therapy for which trial-based evidence exists. Although IVIg versus placebo has never been studied in adults, 5 trials comparing IVIg to PE for GBS have been reported.^{26,28-31} A recent meta-analysis of these studies found no difference between IVIg and PE in terms of mortality, improvement at 4 weeks, residual disability, or time on mechanical ventilation.³² A single study found that IVIg added after PE offered a small, but statistically insignificant, benefit over IVIg alone.²⁶ The mechanism by which IVIg exerts its beneficial effect in GBS is not firmly established, but it may neutralize autoantibodies or cytokines, saturate macrophage Fc receptors, or inhibit complement activation.³³

The most common IVIg dose is 2 g/kg split evenly over 5 days, but the optimal dose and dosing regimen remains unknown. The only study addressing the amount of IVIg administered suggested a trend toward greater improvement with 6 days versus 3 days of therapy.²⁵ However, this study included only 39 patients and therefore definite conclusions could not be drawn. Recent data suggests that a “one-size fits all” approach to IVIg dosing may be inadequate. Kuitwaard et al measured total serum IgG 2 weeks after IVIg treatment, showing that patients whose IgG rose the least had worse outcomes at 6 months.³⁴ Whether this implies that additional doses of IVIg should be given to those with smaller treatment-related increases in serum IgG remains to be established.

Because studies have administered IVIg within 14 days of symptom onset, it is also unknown whether IVIg is effective after this time point. There is no evidence favoring one IVIg preparation/brand over another in the treatment of GBS. Sparse anecdotal data suggests that some patients treated with IVIg with “treatment-related fluctuations” receive further benefit from retreatment.²²

Although IVIg is relatively safe to administer, adverse events occur in about 5% of patients and commonly include infusion-related headache, myalgias, chills, and nausea.³⁵ These are typically managed with symptomatic medications and by stopping the infusion temporarily before resuming at a slower rate. Aseptic meningitis is rarer complication and typically develops after the infusion is completed. Treatment often requires nonsteroidal anti-inflammatories and/or opiates.³⁶ Serious side-effects from IVIg are rare but include

congestive heart failure, stroke, myocardial ischemia, renal failure, thrombocytopenia, hemolysis, and anaphylactic shock. Slower infusion rates may prevent cardiac complications in patients with cardiac disease.³⁷ Risk of anaphylaxis appears greatest in patients with IgA deficiency and circulating antibodies against IgA. Checking qualitative IgA levels prior to administering IVIg will identify those at risk and permit the use of IgA-depleted formulations of IVIg or favor the use of PE.

Because treatment with PE and IVIg are equally effective, the choice between them is dictated by treatment availability, facility expertise, and patient comorbidities or contraindications. The fact that most hospitals stock IVIg and have familiarity with its use has dramatically changed GBS treatment practices. For example, in the decade following the first IVIg study, rates of plasmapheresis in the United States plummeted from 24.5% to 14.7% of admissions, while the rate of IVIg usage increased by a reciprocal amount.¹¹ A similar sea change in European treatment practices even forced the early termination of a GBS treatment trial in Germany.³¹

Corticosteroids

Although corticosteroids are a highly effective therapy for chronic inflammatory demyelinating polyneuropathy (CIDP), they are generally avoided in GBS. Meta-analysis of relevant studies has shown no advantage of intravenous methylprednisolone and actually suggested less improvement in patients treated with oral corticosteroids.³⁸ This finding seems counterintuitive but may be due to a negative effect of corticosteroids on denervated muscle, or to corticosteroid-induced inhibition of macrophage-dependent repair processes.

Treatment of GBS in Children

GBS occurs in children with a more variable and benign clinical course than in adults.³⁹ Intravenous immunoglobulin and PE both appear to be effective treatment options in children, but most data come from retrospective series with historical controls or from extrapolated adult data. Three small, randomized studies have suggested improved speed of recovery for children treated with IVIg,⁴⁰⁻⁴² but PE for childhood GBS has not been studied in a randomized fashion. Until additional studies are carried out, it is recommended that either IVIg or PE be reserved for severe childhood GBS.⁴³

Treatment of GBS in Pregnancy

Pregnancy complicated by GBS is rare,⁴⁴ precluding large, prospective studies. To gain some insight, 30 cases from the English literature (1986-2002) were recently reviewed.⁴⁵ Symptom onset was in the later portions of pregnancy, with only 13% of cases beginning in the first trimester. Antecedent infection with *Campylobacter jejuni* was not seen, but the incidence of recent cytomegalovirus (CMV) was high (30%). More than two thirds of patients received PE, IVIg,

or both. Reassuringly, in patients treated during pregnancy with PE (n = 10) or IVIg (n = 8), there were no cases of treatment-related fetal harm. This is consistent with the fact that both therapies are routinely and safely used for other pregnancy-associated conditions. Therefore, in pregnant women, a disease-modifying therapy should be administered as soon as possible, especially given that early treatment is associated with improved response. The choice between PE and IVIg will depend on specific patient factors and institutional expertise and is best made by a multidisciplinary team involving neurologists, obstetricians, and neonatologists. This team will also prove helpful in predicting how GBS may impact labor and modes of anesthesia.

Supportive Care

Despite the improved prognosis with IVIg or PE treatment, patients with moderate or severe GBS still spend an average of 1 to 2 months in the hospital.²⁶ During that stay, patients are at risk for several well-recognized complications. Improved supportive care can minimize the morbidity these complications produce.

Respiratory Care

Respiratory failure is one of the most common and dreaded complications of GBS. Prior to mechanical ventilation, the mortality rate in GBS exceeded 30%, mostly from respiratory failure.² The percentage of patients with GBS ultimately requiring mechanical ventilation depends on study methodology (clinical trials versus population-based) but ranges from 25% to 44%.^{5,6,18,20} Phrenic and intercostal nerve demyelination produce restrictive lung mechanics while bulbar muscle weakness may prevent adequate airway protection and place patients at risk for aspiration.

Respiratory failure can occur precipitously in patients with GBS and, if unnoticed, can be life-threatening or result in significant morbidity. The respiratory status of patients with GBS must therefore be carefully and frequently monitored. Pulse oximetry and blood gases are inadequate for early detection of failure because hypoxemia and hypercarbia are very late manifestations. Instead, regular bedside monitoring of the vital capacity, maximal inspiratory pressure (MIP or P_Imax), and maximal expiratory pressures (MEP or P_Emax) should be used. Admission or transfer to an ICU is warranted if measured values fall below the "20/30/40 rule" that is, the VC falls below 20 mL/kg, MIP above -30 cm H₂O, or MEP below 40 cm H₂O).⁴⁶ ICU admission should also be considered if the values are falling quickly (>30%/24 hours) or if significant bulbar weakness is present.⁴⁶ If followed, these guidelines permit carefully planned, elective intubation when the VC has fallen below 15 mL/kg⁴⁷ or the MIP and MEP have reached -25 cm H₂O and 40 cm H₂O, respectively.⁴⁸

The recovery of independent breathing can be slow in GBS, resulting in prolonged periods of mechanical

ventilation. One half of intubated patients with GBS ultimately require tracheostomy,⁴⁹ but the optimal timing of tracheostomy is debated. Delaying tracheostomy >14 days after intubation has been associated with a higher incidence of ventilator-associated pneumonia and longer duration of mechanical ventilation,⁵⁰ but earlier intervention will result in some patients getting an unnecessary tracheostomy. Some have advocated waiting 10 to 14 days prior to tracheostomy,^{47,51} but individual patient characteristics must be considered.

Dysautonomia

Autonomic dysfunction occurs to some degree in 65% of patients with GBS.¹² Manifestations are protean, including brady- or tachy-arrhythmias, episodic hypertension, orthostatic hypotension, abnormal hemodynamic responses to vasoactive medications, gastrointestinal dysfunction, and sweating abnormalities. Signs of autonomic over- and under-activity may coexist or alternate in the same patient.

Severe autonomic dysfunction occurs in those with severe disease. This has 2 important implications. First, the same patients who are at risk for autonomic complications are at risk for other complications producing arrhythmia, cardiovascular collapse, and blood pressure fluctuations (sepsis, pulmonary embolism, heart failure, etc). These causes should be considered and excluded before attributing symptoms to GBS-related autonomic failure. Second, the GBS patients who are at highest risk for autonomic complications are typically already being managed in the ICU, where continuous cardiac and blood pressure monitoring are routine and readily available for diagnostic and management purposes.

Episodic bradycardia, sinus arrest, and asystole have been blamed for deaths in GBS or necessitated pacemaker placement.¹² These arrhythmias can be triggered by tracheal suction or other vagotonic stimulation, but also occur spontaneously. Caution should be used in tracheal suctioning, with ready access to atropine and external pacing devices. Paroxysmal hypertension also occurs but is generally short-lived and rarely requires treatment. If fluctuations are severe enough to cause end-organ damage, quickly titratable, short-acting medications are recommended to avoid hypotension. Orthostatic hypotension generally resolves by the time patients have regained the ability to walk and responds to volume expansion with intravenous hydration. If refractory, sodium chloride tablets, fludrocortisone, or midodrine could be considered.

Gastrointestinal autonomic dysfunction results in constipation, gastric immotility, and ileus. Retrospective series have identified ileus in up to 15% of patients with GBS requiring ICU care.⁵² Demyelinated nerves, immobility, and opiate medications are likely contributing factors. Detection with careful examination, output monitoring, and radiography should allow early institution of treatments to prevent perforation. Cessation of enteral feeding, gastric decompression,

promotility agents, reduced opiate medications, and even parental nutrition may be needed.

Some degree of urinary dysfunction is found in 25% of patients and complete urinary retention in up to 9%.^{53,54} The severity of these symptoms correlate with the severity of weakness and are therefore more commonly seen in ICU patients. To minimize infection risks, intermittent catheterization is preferred over indwelling urinary catheters, but the latter may be necessary for patient tolerance or nursing convenience.

Thromboembolism

Deep-vein thrombosis and subsequent pulmonary embolism are recognized complications of immobility from GBS. The incidence of this potentially lethal outcome in GBS is unknown, but pulmonary embolism has long been recognized as a cause of death.^{55,56} Studies have not addressed specific antithrombotic prophylaxis for GBS, but it is recommended that all minimally-ambulant or nonambulant patients receive thromboembolism prophylaxis according to the American College of Chest Physician guidelines.⁵⁷ This approach will typically include either unfractionated heparin (5000 units twice daily) or low-molecular-weight heparin (40 mg daily) but might also utilize compression stockings or sequential compression devices. Prophylaxis should be tailored to the patient's comorbidities, including bleeding risk, renal function, recent spinal tap, etc.⁵¹ Some centers withhold pharmacological prophylaxis on plasma exchange days (due to PE-associated anticoagulation), relying instead on compression stockings or sequential compression devices. The optimum duration of prophylaxis is unclear but should extend into the rehabilitation phase and until ambulation is regained. Even with these measures, thromboembolism can still occur in GBS, sometimes with fatal outcome.⁵⁶ As a result, deep-vein thrombosis and pulmonary embolism should figure prominently in the differential diagnosis of asymmetric leg edema, chest pain, shortness of breath, or hemodynamic instability—even in patients on appropriate prophylaxis.

Malnutrition

Patients with GBS are at high risk for inadequate nutrition throughout the course of their illness. Gastrointestinal symptoms produce dehydration and weight loss even prior to hospital admission. Progressive bulbar dysfunction or adynamic ileus can limit or eliminate oral intake. Furthermore, GBS is a hypermetabolic and hypercatabolic state on the same order as sepsis or trauma.⁵⁸ Inadequate nutrition is associated with increased risk for fluid and electrolyte abnormalities, decubitus ulcers, as well as nosocomial infections. Therefore, nutritional support should begin as quickly as possible by appropriate means (eg, modified diet, nasogastric tube, or parenteral nutrition). To combat the hypermetabolic/hypercatabolic state, it has been recommended that patients receive a

high-protein diet at 1.35 to $1.58 \times$ their calculated basic energy expenditure (BEE) plus an additional 30% to 50% for weight stabilization.⁵⁸ Close monitoring of hydration status, weight, vital proteins, and nitrogen balance will help guide adjustments to this initial diet. If patients undergo PE with albumin replacement, it should be noted that serum albumin will be an unreliable gauge of nutritional status. Other markers such as prealbumin or transferrin may be more reliable in this setting.

Other Immobility Complications

The prolonged immobility experienced by many patients with GBS puts them at significant risk for position-related nerve compression, skin ulceration, and contractures. Patients that are intubated/sedated and those with significant sensory loss may not notice the symptoms that typically occur with these injuries. Careful body positioning, appropriate bracing, pressure point padding, and frequent position changes are all warranted. Patients with incomplete eye closure from facial weakness are also at risk for exposure keratitis. Good corneal hygiene with artificial tears, lubricants, careful lid-taping, or protective eye domes is essential. Multidisciplinary physical therapy should be initiated as soon as possible. In severely affected patients, passive range-of-motion exercises are utilized to prevent contractures. As patients improve and strength returns, other modalities are often employed based on institutional experience and practice. Despite a paucity of efficacy data, physical therapy for GBS as an inpatient and continuing upon discharge is associated with better outcomes and recommended for all but the mildest cases.⁵⁹

Pain

Pain is a common but often overlooked feature of GBS, occurring in 55% to 89% of patients.^{60,61} Frequently, it precedes the development of weakness and persists long after recovery. Proposed mechanisms include inflammation of proximal nerve roots, sensory nerve fiber dysfunction during degeneration or regeneration, and musculoskeletal pain from immobility.⁶² A successful pain treatment strategy begins with frequently inquiring about the presence and severity of pain as a symptom. Opiates have a reliable analgesic effect, but sedation and potential ileus may limit their use. Data on nonopiate pharmacological interventions are limited, but 1 study suggested that gabapentin or carbamazepine may reduce pain and lower narcotic requirements in some patients.⁶³ Because of teratogenicity concerns, carbamazepine should be avoided in pregnant patients.

Psychiatric Complications

Guillain-Barré syndrome produces severe and sudden disability in otherwise healthy adults. This dramatic loss of independence, prolonged hospitalization, and even the loss of

communication produces several psychiatric complications. Anxiety occurs in 82% of patients, with moderate or severe depression occurring in two thirds of patients.⁶⁴ However severe the symptoms may be, patients often remain silent as they develop. Care providers must specifically ask patients about symptoms of anxiety or depression in order to detect and treat them. Selective serotonin reuptake inhibitors (SSRIs) and anxiolytics are often helpful, as evidenced by case report literature.⁶⁵

In severe GBS cases, depersonalization and frank psychosis have also been noted, possibly as a sign of central nervous system inflammation. In a prospective study, episodes of illusion and hallucination meeting criteria for brief reactive psychosis were present in 25%.⁶⁴ The rate was significantly higher (85%) in those with severe tetraparesis, cranial nerve dysfunction, and on mechanical ventilation. Another prospective series found similar mental status changes in one third of patients with GBS admitted to the ICU and correlated their presence with autonomic dysfunction and abnormal sleep morphology.⁶⁶ Data regarding the management of psychosis and sleep is lacking, but a range of neuroleptics have been utilized.

Conclusions

The advent of plasma exchange and intravenous immunoglobulins has dramatically improved the prognosis of patients with GBS. Despite this fact, mortality and morbidity rates remain unacceptably high. Until better therapies are developed, the appropriate utilization of immune-modulating therapy and careful attention to supportive care issues will help to minimize these unfavorable outcomes.

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