CLINICAL SUMMARY SHEET
Guillain-Barré Syndrome (GBS) With a Focus on Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)
OVERVIEW

Guillain-Barré syndrome (GBS), characterized by symmetrical weakness of limbs and hyporeflexia or areflexia, is a common cause of acute flaccid paralysis that reaches maximum severity within four weeks of onset.1,2 This autoimmune disease is preceded by infection, often gastrointestinal or respiratory in nature, in two-thirds of cases.3 There are two major subtypes of GBS: acute inflammatory demyelinating polyradiculoneuropathy (AIDP); and axonal subtypes, acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN).2 Miller Fisher syndrome, a less common subtype of GBS, is characterized by ophthalmoplegia, ataxia, and areflexia.4 AIDP is the most common form of GBS,1 and the bulk of literature and this clinical summary sheet focus on AIDP.

EPIDEMIOLOGY

The annual incidence of GBS in adults in western countries is about 1.1 to 1.8 cases per 100,000 population3,5 and is lower in children (0.34 to 1.34 per 100,000 population).1 The mean age of onset is 40 years, and annual incidence increases after 50 years of age to 1.7 to 3.3 cases per 100,000.3 The lifetime likelihood of developing GBS is 1:1,000.6,7 Males are slightly more likely than females to develop GBS.1,6

ASSOCIATIONS

Uncommon antecedent events for GBS include surgery and parturition.5 Though rare, GBS has occasionally been associated with vaccinations, including measles,8-10 tetanus toxoid,11 rabies,12 oral polio,13 polysaccharide meningococcal,14 measles-rubella,15 influenza,16 and hepatitis B.16 However, little evidence is available to support a causal link between most vaccines and GBS;17 most associations are temporal.17,18 Most cases of AIDP are sporadic in nature, but small clusters of cases have been associated with public outbreaks of infectious diseases, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza virus, and most recently Zika virus.6,19 The most common types of infections are upper respiratory tract infection and gastroenteritis. Campylobacter jejuni (in 13% to 39% of cases), CMV (5% to 22%), EBV (1% to 13%), and Mycoplasma pneumoniae (5%) are among the most common infectious triggers.20,21 For patients with C. jejuni infection, AIDP/GBS develops approximately 9 days following gastroenteritis, and 1 in every 1,000 C. jejuni infections in the U.S. occur in patients with a genetic susceptibility to develop GBS.1 The association of C. jejuni infections with GBS is strongest with the axonal forms of GBS1 and precedes about 60% to 70% of AMAN and AMSAN cases.23 As mentioned, there has been a notable increase in GBS cases in areas of Central and South America affected by Zika virus, which is transmitted by Aedes mosquitoes. This spike in the incidence of GBS in areas of increased Zika virus infection has led to speculation that Zika virus infection may trigger GBS in certain individuals.19 This connection has not yet been proven, but recent data suggest there may be an association between GBS and Zika virus infection. The potential association between Zika virus infection and GBS stems from the link between GBS and other autoimmune neurological complications, which were first suspected during the 2013/2014 Zika outbreak in French Polynesia.19,24,25 A case-control study evaluated patients with GBS diagnosed during the outbreak in French Polynesia and aimed to assess the role of Zika virus infection in developing GBS.26 Forty-two cases of GBS (AMAN subtype) were recorded during the outbreak. There were 98 patients admitted for non-febrile illness in the control group. The risk of GBS was estimated to be 0.24 per 1,000 Zika virus infections, which was calculated based on a 66% attack rate of Zika virus infection in the general population. Of the 42 patients with GBS, 41 (98%) had anti-Zika virus IgM or IgG (versus 36% in the control group), and 100% had neutralizing antibodies against the Zika virus (versus 56% in the control group; P < 0.0001). This is the first study to confirm that the Zika virus infection may lead to GBS.26 Additional data and research are needed to fully establish the link between Zika virus infection and GBS.27 However, considering the rapid spread of Zika virus infection, at-risk countries should be prepared to manage patients with GBS. In addition to the presence of Zika virus in French Polynesia, as of February 2016, it has also been reported in New Caledonia, the Cook Islands, Easter Island, Samoa, Vanuatu, Brazil, and 25 countries of the Americas.28 Health authorities in several of these countries have reported increases in cases of GBS.28
PATHOPHYSIOLOGY

While the precise antigen and antibody combination for the most common GBS/AIDP subtype is not known, there is strong evidence supporting an important role for antibodies to gangliosides in the pathogenesis of GBS (Figure 1).29

Figure 1. Immunopathogenesis of GBS: molecular mimicry and anti-ganglioside antibodies

Infections with pathogens, such as *C. jejuni*, can trigger humoral immune and autoimmune responses that result in nerve dysfunction and the symptoms of GBS. Lipooligosaccharides on the *C. jejuni* outer membrane may elicit the production of antibodies that cross-react with gangliosides, such as GM1 and GD1a, on peripheral nerves. The antigens targeted in AMAN are located at or near the node of Ranvier. The anti-GM1 and anti-GD1a antibodies bind to the nodal axolemma, leading to complement activation followed by membrane attack complex (MAC) formation and disappearance of voltage-gated sodium channels. This damage can lead to detachment of paranodal myelin and nerve conduction failure. Macrophages then invade from the nodes into the periaxonal space, scavenging the injured axons. The antigens targeted in AIDP are, presumably, located on the myelin sheath. The antibodies can activate complement, which leads to formation of the MAC on the outer surface of Schwann cells, initiation of vesicular degeneration, and invasion of myelin by macrophages.

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; APC: antigen-presenting cell; GBS: Guillain-Barré syndrome; MAC: membrane attack complex.

Confirming the presence of specific antibodies can be helpful when diagnosing GBS (Table 1). Following *C. jejuni* infection, antibodies that cross-react with specific gangliosides are generated; this is a critical step in GBS pathogenesis. In particular, antibodies to ganglioside GM1 are present in the axonal AMAN variant of GBS. In *C. jejuni*-related AMAN, this is likely due to a previous infection with *C. jejuni*, the bacterial cell wall of which contains a ganglioside-like structure. The autoimmune attack on axons in AMAN is therefore an unfortunate side effect of the clearance of the bacterial infection. Antibodies to the ganglioside GQ1b are over-represented in the Miller Fisher variant, supporting the hypothesis that antibody specificity defines the pattern of peripheral nerve involvement. Additional antibodies have been identified that are linked to specific variants of GBS, including GM1b, GD1a and GalNac-GD1a, but it is not expected that these antibodies are the primary pathogenic link for AIDP forms of GBS.

<table>
<thead>
<tr>
<th>GBS subgroup</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)</td>
<td>GM1, GM1b, GD1a, GalNac-GD1a</td>
</tr>
<tr>
<td>Miller Fisher syndrome/GBS overlap syndrome</td>
<td>GQ1b, GD3, GT1a</td>
</tr>
</tbody>
</table>

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor sensory axonal neuropathy; APC: antigen-presenting cell; GBS: Guillain-Barré syndrome.

Van Doorn PA. *Presse Med.* 2013; 42 (6 Pt 2): e193–e201. Table reprinted with permission. ©Elsevier Masson SAS Editeur. All rights reserved.

A histological examination of demyelination in AIDP/GBS shows similarity of the disease to experimental autoimmune neuritis (EAN). T-cell responses to any of 3 myelin proteins—P2, PO, and PMP22—induce EAN, and passive transfer of activated T-cells can induce EAN in a naïve animal. This similarity suggests a T-cell-mediated mechanism of demyelination and axonal injury, though this pathophysiology has not been confirmed. Activated T-cells are present in the circulation in acute AIDP/GBS, upregulate matrix metalloproteinases, cross the blood-nerve barrier, and encounter their cognate antigens. Evidence of this process includes the presence of inflammatory infiltrates in nerves and nerve roots. The precise target antigens for AIDP and its chronic cousin, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), are unknown. Candidates for the pathogenic target in AIDP and CIDP include peripheral myelin, Schwann cells, axons, or some combination thereof, but no clear culprit has been identified.

Macrophages are the most predominant cells associated with demyelination in AIDP/GBS and are found in nerves, nerve roots, and nerve plexuses. Still, the invasion of intact myelin sheaths by activated macrophages is difficult to explain according to a purely T-cell-mediated mechanism. It is therefore hypothesized that GBS/AIDP, like other autoimmune peripheral neuropathies, arises owing to a loss of immunogenic tolerance to myelin, the axon, or other peripheral nerve components. This could be due to pathogenic antibodies, T-cells, complement, or macrophages working alone or in concert to induce demyelination and varying amounts of axonal loss. Importantly, it appears that multiple syndromes are represented by GBS, due in part to potentially different pathophysiological effectors.
SYMPTOMS AND SIGNS

The primary features of GBS are rapid, symmetrical-onset weakness and paresthesia in the limbs that begins distally and spreads to the trunk. Most patients have an initial presentation of arm and leg weakness (32%) or selective proximal and distal leg weakness (56%). A much smaller percentage (12%) have onset in the arms only. Reflexes are reduced or absent (areflexia). Most patients, 80% to 90%, will become non-ambulatory during the illness. It is critical to closely monitor patients with AIDP/GBS in the acute phase, as the potential for respiratory complications is high; 30% of patients will require mechanical ventilation.

Patients with AIDP may report sensory disturbances. Raised protein concentrations in cerebrospinal fluid (CSF) are a sign of AIDP. The time course and onset of symptoms differentiate AIDP from CIDP, which progresses slowly. With AIDP, the clinical nadir is reached by 2 weeks in 50% of patients and by 4 weeks in more than 90% of patients (Figure 2). The progression of symptoms follows a variable pattern, where some patients become rapidly non-ambulatory, some accumulate disability slowly, and others will not become non-ambulatory at all. A plateau of symptom severity is followed by a recovery phase, which can last from weeks to months. Most patients will spontaneously recover from AIDP/GBS, and recovery follows a proximal-to-distal pattern.

Figure 2: The course of GBS

The majority of patients with GBS report an infection before the onset of weakness. Antiganglioside antibodies are often detected; their levels decrease over time. Different types of antibodies are related to the preceding infection and the GBS subtype. Progressive weakness reaches its maximum within 4 weeks (often within 2 weeks). The recovery phase may last many weeks, months or even years.


Additional symptoms may include those related to facial and cranial nerves, including nerves involved in swallowing and eye movements. Autonomic dysfunction is common, resulting in symptoms such as hypertension or hypotension, heart rhythm disturbances (tachycardia and bradycardia), flushing, urinary retention, and reduced bowel contractions. Pain is experienced by a majority of GBS patients; 36% experience pain in the two weeks preceding weakness, 66% report pain during the acute phase, and 36% are still in pain one year after symptom onset.
DIAGNOSTIC CRITERIA AND TESTS

Diagnostic Criteria
The diagnosis of GBS is relatively straightforward, especially when weakness is preceded by an infection. Asbury and Cornblath proposed the diagnostic criteria for GBS in 1990 (Table 2). Criteria required for diagnosis included progressive weakness in both arms and both legs, accompanied by hyporeflexia or areflexia. A revision to these criteria was proposed by Barohn in 1998, where the required features were upgraded to include the Asbury criteria as well as a progression of less than 4 weeks and symmetric weakness. The important distinction with this revision is the duration of symptom progression; for cases in which the symptoms progress or worsen for more than 4 weeks, a diagnosis of acute-onset CIDP or CIDP should be considered.

Table 2: Criteria for diagnosis of GBS

<table>
<thead>
<tr>
<th>Required for diagnosis</th>
<th>Supportive for diagnosis</th>
<th>Exclusionary criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive weakness in both arms, both legs</td>
<td>Progression of symptoms over days and up to 4 weeks</td>
<td><strong>Definite exclusionary criteria</strong></td>
</tr>
<tr>
<td>Hyporeflexia or areflexia</td>
<td>Relative symmetry of symptoms</td>
<td>Diagnosis of botulism, myasthenia, poliomyelitis, toxic neuropathy</td>
</tr>
<tr>
<td><strong>Criteria added by Barohn</strong></td>
<td>Mild sensory involvement</td>
<td>Abnormal porphyrin metabolism</td>
</tr>
<tr>
<td>Symmetric weakness</td>
<td>Bilateral weakness of facial muscles, other cranial nerve symptoms</td>
<td>Recent diphtheria</td>
</tr>
<tr>
<td>Symptom progression of less than 4 weeks</td>
<td>High protein concentration in CSF in the absence of cellular increases (cytoalbuminous) dissociation</td>
<td>Purely sensory syndrome without weakness</td>
</tr>
<tr>
<td></td>
<td>Recovery of symptoms beginning 2 to 4 weeks following plateau</td>
<td><strong>Potential exclusionary criteria</strong></td>
</tr>
<tr>
<td></td>
<td>Autonomic dysfunction</td>
<td>Persistent, overt asymmetry of weakness</td>
</tr>
<tr>
<td></td>
<td>Absence of fever at onset</td>
<td>Bladder/bowel dysfunction at onset</td>
</tr>
<tr>
<td></td>
<td>Typical electrodiagnostic features</td>
<td>Sharp sensory symptoms, limited weakness at onset</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Severe pulmonary dysfunction with limited limb weakness at onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased mononuclear cells or the presence of polymorphonuclear cells in CSF</td>
</tr>
</tbody>
</table>

CSF: cerebral spinal fluid; GBS: Guillain-Barré syndrome.

Diagnostic Tests
The neurological exam for AIDP/GBS is abnormal and reveals distal and proximal weakness, symmetrical symptoms, motor neuropathy with occasional sensory symptoms, and potential facial, pharyngeal, and diaphragmatic weakness. Severity of disease can be assessed using the GBS disability score, which is displayed in Table 3. This scoring system is widely accepted and is used to assess the functional status of patients with GBS. Scores of 2 or more indicate considerable disability. The pretreatment GBS disability score is an important predictor of prognosis, underscoring the importance of early intervention.

Table 3: GBS disability score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Healthy state</td>
</tr>
<tr>
<td>1</td>
<td>Minor symptoms and capable of running</td>
</tr>
<tr>
<td>2</td>
<td>Able to walk 10 m or more without assistance but unable to run</td>
</tr>
<tr>
<td>3</td>
<td>Able to walk 10 m across an open space with help</td>
</tr>
<tr>
<td>4</td>
<td>Bedridden or chairbound</td>
</tr>
<tr>
<td>5</td>
<td>Requiring assisted ventilation for at least part of the day</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

There are certain predictive factors in GBS that indicate the need for mechanical ventilation or a higher risk of long-term disability (Table 4). Because respiratory failure is a serious complication for approximately one-third of patients, a validated bedside test can be performed upon admission to the hospital that can robustly predict the likelihood of needing ventilatory support during disease course.

Table 4: Predictive factors in GBS

| Predicts the need for mechanical ventilation<sup>47–49</sup> | Bulbar symptoms  
|                                                         | Inability to raise the head or flex the arms  
|                                                         | Inadequate cough  
|                                                         | Maximum expiratory pressure: < 40 cm H₂O  
|                                                         | Maximum inspiratory pressure: < 30 cm H₂O  
|                                                         | Time from onset of symptoms to hospital admission is less than seven days  
|                                                         | Vital capacity: < 60 percent of predicted or < 20 mL per kg  
|                                                         | Vital capacity, maximum inspiratory pressure, or maximum expiratory pressure reduced by at least 30 percent  

| Predicts long-term disability<sup>32,47</sup> | Absence of motor response  
|                                                | Antecedent diarrheal illness  
|                                                | Axonal involvement  
|                                                | C. jejuni or cytomegalovirus infection  
|                                                | Inability to walk at 14 days  
|                                                | Older age  
|                                                | Rapid progression of symptoms  
|                                                | Severity of symptoms at their peak  

Diagnostic tests for AIDP/GBS are important. Standard lab tests (complete blood count [CBC], chemistry panels) are, however, not particularly useful, as most values will be in the range of normal or only slightly elevated (transaminases and creatine kinase, for example). CSF analysis, on the other hand, is particularly useful. Cytoalbuminous dissociation, the presence of elevated protein levels (> 45 mg/dL) in the absence of elevated cell counts (< 10 cells/mm<sup>3</sup>), is frequently associated with AIDP/GBS. While cytoalbuminous dissociation is present in about half of GBS patients early after onset, there is frequently a delay in protein elevation, and it should not, therefore, be considered strictly exclusionary for the diagnosis. CSF testing can be used to rule out Lyme disease and HIV-related radiculitis, which both show increased mononuclear cells in the CSF; CSF pleocytosis is generally considered a signal that there is a complicating disease or additional diagnostic criteria to consider.

Electromyography (EMG) is used as a further confirmation of the AIDP/GBS diagnosis and to exclude additional diagnoses. In particular, EMG is used to identify features of demyelination, such as temporal dispersion, slow conduction velocity, and prolonged distal and F-wave latencies. Slowing of nerve conduction is frequently identified 2 to 3 weeks following onset. These abnormal findings are primarily expected within the motor neurons over sensory neurons. EMG is also important for differentiation between demyelinating (AIDP) and axonal (AMAN) forms of GBS, which can potentially impact important treatment decisions. Further, EMG is useful in the identification of polyneuropathy prior to the onset of clinical symptoms.
Supportive Care and First-Line Treatment

AIDP/GBS requires multidisciplinary supportive care. A multidisciplinary consensus group constructed a thorough set of recommendations for supportive care, which are outlined in Table 5, based on a literature review over the years of 1966 to 2003. In addition to these potential complications, the consensus group also addressed the issue of rehabilitation following recovery from the acute symptoms. Importantly, there are no long-term follow-up studies of the role of rehabilitation following AIDP/GBS. Still, the group does recommend a program of gentle strengthening during the acute phase and beyond.

Table 5: Recommendations for supportive care for patients with GBS

<table>
<thead>
<tr>
<th>Risk</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis due to muscle weakness and paralysis</td>
<td>Heparin and support stockings for non-ambulatory patients.</td>
</tr>
<tr>
<td>Cardiac and hemodynamic instability due to autonomic disturbances;</td>
<td>Monitoring of pulse and blood pressure, especially in the case of ventilated</td>
</tr>
<tr>
<td>includes arrhythmias and extreme hypertension or hypotension</td>
<td>patients.</td>
</tr>
<tr>
<td>Loss of respiratory function or loss of airway due to weakness in or</td>
<td>Close monitoring of respiration, with additional recommendations regarding the</td>
</tr>
<tr>
<td>loss of function of the muscles of respiration</td>
<td>timing of tracheostomy.</td>
</tr>
<tr>
<td>Pain management</td>
<td>Simple analgesics should be tried first but are often insufficient to provide</td>
</tr>
<tr>
<td></td>
<td>pain relief. Additional options for pain management include gabapentin or</td>
</tr>
<tr>
<td></td>
<td>carbamazepine in the ICU, as well as tricyclic antidepressants and other pain</td>
</tr>
<tr>
<td></td>
<td>modulation agents. Narcotics should be used sparingly and with careful</td>
</tr>
<tr>
<td></td>
<td>monitoring of autonomic function.</td>
</tr>
<tr>
<td>Bladder and bowel dysfunction due to immobility or axonal involvement</td>
<td>Monitoring for evidence of gut silencing, treatment of ileus with suspension</td>
</tr>
<tr>
<td></td>
<td>of gut-feeding and erythromycin or neostigmine. Promotility agents are</td>
</tr>
<tr>
<td></td>
<td>contraindicated owing to potential autonomic dysfunction. Bladder catheterization</td>
</tr>
<tr>
<td></td>
<td>is generally standard of care for bedbound patients and is usually needed.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Customized and intensive exercise program.</td>
</tr>
<tr>
<td>Rare complications for future immunizations, if GBS is immunization-</td>
<td>No additional immunizations during acute GBS and suspension of immunizations</td>
</tr>
<tr>
<td>related</td>
<td>for 1 year following onset. No additional restrictions on vaccination.</td>
</tr>
</tbody>
</table>

Because of the very real risk of respiratory failure, many patients, especially those who rapidly become non-ambulatory, are admitted to a neuro-intensive care unit or to a unit where respiration can be closely monitored. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) was derived from a Dutch study. The EGRIS model can be used in the emergency room setting to predict the probability for respiratory insufficiency during the first week following admission in patients with GBS. The most important predictors of needing mechanical ventilation are rate of disease progression, Medical Research Council sum score, and presence of facial or bulbar weakness. For patients with a high risk of developing respiratory insufficiency, it may be advisable to admit the patient to the intensive care unit (ICU) as opposed to the general neurology ward.

Immunotherapy

In addition to supportive care, the standard therapy for AIDP/GBS is either therapeutic plasma exchange (TPE) or intravenous immunoglobulin (IVIg). TPE was the first successful immunotherapy proposed for AIDP/GBS and a significant benefit for treatment with TPE over supportive care alone was reported in 1985. Because of this, TPE was briefly considered the “gold-standard” treatment against which all other treatments were measured. Additional data suggest that IVIg leads to equivalent disease improvements as TPE, and both TPE and IVIg are considered first-line therapies for AIDP/GBS.

AIDP/GBS is most responsive to immunotherapy early after symptom onset (before 2 weeks or slightly less so before 4 weeks). Thus, immunotherapy-based treatment is recommended prior to disease confirmation and based on clinical suspicion of AIDP/GBS when potential mimicking disorders, such as spinal cord injury, poliomyelitis, Lyme disease, myasthenia gravis, and botulism, have been excluded.
Therapeutic Plasma Exchange (TPE)

TPE, also known as plasmapheresis, is a blood purification procedure performed in patients with autoimmune diseases to remove antibodies from the blood and return blood along with fresh plasma (or albumin) to the patient. The American Academy of Neurology (AAN) and the American Society for Apheresis (ASFA) have each published guidelines on the use of TPE. The AAN practice parameters for TPE in AIDP/GBS recommend TPE for non-ambulatory patients within 4 weeks of symptom onset (Level A). TPE should be considered as a potential therapy for ambulatory patients within 2 weeks of onset (Level B), as it is particularly curative during the early rehabilitation of patients. Highlights from the ASFA guidelines are below (Table 6).

In a study of 230 patients, 88% underwent TPE for the treatment of GBS. Results showed that TPE is generally safe, with the most common complications being paresthesia and/or cramps and hypotension.

**Table 6: Evidence-based approach to therapeutic apheresis**

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Disease condition</th>
<th>Recommendation grade</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP/GBS</td>
<td>TPE</td>
<td>1A</td>
<td>I</td>
</tr>
<tr>
<td>AIDP/GBS, after IVIg</td>
<td>TPE, Post IVIg</td>
<td>2C</td>
<td>III</td>
</tr>
<tr>
<td>RCT</td>
<td>CT</td>
<td>CS</td>
<td>CR</td>
</tr>
<tr>
<td>AIDP/GBS</td>
<td>19 (1,770)*</td>
<td>0</td>
<td>10 (11)*</td>
</tr>
<tr>
<td>AIDP/GBS, after IVIg</td>
<td>0</td>
<td>0</td>
<td>1 (46)*</td>
</tr>
</tbody>
</table>

*Number of trials (number of enrolled participants).

Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatment.

Category III: Optimum role of apheresis therapy is not established. Decision-making should be individualized.

Grade 1A: Strong recommendation with high-quality evidence based on randomized controlled trials without important limitations or overwhelming evidence from observational studies. Implies a strong recommendation that can be applied to most patients in most circumstances and without reservations.

Grade 2C: Weak recommendation with low-quality or very low-quality evidence based on observational studies or case series. Implies a very weak recommendation, where other alternative treatments may be equally reasonable.

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; CR: case report; CS: case series; CT: controlled trial; GBS: Guillain-Barré syndrome; IVIg: intravenous immunoglobulin; RCT: randomized controlled trial; TPE: therapeutic plasma exchange.

KEY STUDIES COVERING TPE

Table 7 contains key studies covering TPE that were included in a systematic review of the literature from 1966 through June 2011.62 There were six trials with a total of 649 participants, which provided data that compared the outcomes of using TPE with the outcomes of using supportive treatment alone. All patients had GBS, fulfilling the criteria established by Asbury et al.41

Based on these studies, the authors concluded that TPE is the first treatment proven to be superior to supportive treatment alone in GBS. TPE is more beneficial when started within seven days after onset of symptoms but is still beneficial in patients treated up to 30 days after onset of symptoms.62

Table 7: Key studies covering TPE62

<table>
<thead>
<tr>
<th>Trial details</th>
<th>TPE intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farkkila 1987:63 RCT, N = 29</td>
<td>3 to 5 exchanges, 3 L per exchange, diluted albumin replacement fluid</td>
<td>Hand-grip force at 3 weeks after first TPE was significantly better in TPE group compared to control (no TPE) group; no difference between hospitalization or recovery periods</td>
</tr>
<tr>
<td>Greenwood 1984:64 RCT, N = 29</td>
<td>5 exchanges in 5 days, 55 mL/kg per exchange</td>
<td>Functional ability at 4 weeks after completion of treatment: comparable between groups (TPE versus no TPE); results do not support the recommendation of TPE for treatment of severe AIDP</td>
</tr>
<tr>
<td>McKhann 1985:65 RCT, N = 245</td>
<td>3 to 5 exchanges in 5 days, 40 mL/kg per exchange</td>
<td>Functional ability at 4 weeks, time to independent walking, outcome at 6 months: significantly better in TPE group; plasmapheresis was not effective for all patients, but was best within 7 days of onset of symptoms or for patients who required ventilatory support</td>
</tr>
<tr>
<td>Osterman 1984:66 RCT, N = 38</td>
<td>3 to 8 exchanges in 7 to 10 days, 3 L per exchange</td>
<td>Functional ability at 4 weeks, time to improvement, muscle weakness, working capacity after 1 month were all better in TPE group; cost-benefit analysis showed net financial savings of TPE</td>
</tr>
<tr>
<td>Raphaël 1987:67 RCT, N = 220</td>
<td>4 exchanges in 8 days, 2 plasma volumes per exchange</td>
<td>Time to recover walking with assistance: significantly faster in TPE group; reduction in the proportion of TPE patients ventilated after randomization; improvement in time to ventilator weaning, motor recovery delay in TPE group; no significant difference between albumin and fresh-frozen plasma as replacement fluid</td>
</tr>
<tr>
<td>Raphaël 1997:68 RCT, N = 556</td>
<td>Between 0 and 6 exchanges every other day, 3 L per exchange with diluted albumin and gelatin as replacement fluid</td>
<td>Mild GBS responded well to 2 exchanges; moderate and severe forms responded well to 4 exchanges, with no additional improvement at 6 exchanges</td>
</tr>
</tbody>
</table>

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; GBS: Guillain-Barré syndrome; RCT: randomized controlled trial; TPE: therapeutic plasma exchange.

Intravenous Immunoglobulin (IVIg)

IVIg was first recommended in 1988 as an alternative to TPE for GBS.69 A subsequent study comparing the outcomes following IVIg with those following TPE was completed in 1992, and the results indicated that the treatment effects of IVIg were equivalent to those of TPE.59 These results have been repeated in several studies. IVIg is therefore considered an alternative first-line therapy for GBS. In patients with CIDP, IVIg is very effective; however, in patients with pain or difference in weakness between arms and legs, IVIg is less effective.71

The postulated mechanism behind improvement following IVIg treatment in GBS includes interference with co-stimulatory molecules and antigen presentation, modulation of autoantibodies, cytokines, or adhesion molecules and the macrophage Fc receptor.68

AAN recommends IVIg for non-ambulatory adult GBS patients within 4 weeks (Level B) or ideally within 2 weeks (Level A) of symptom onset.59 Sequential treatments (that is, TPE followed by IVIg or immunoadsorption followed by IVIg) are not recommended.59,72
The key studies covering IVIg are outlined in Table 8. In a systematic review of the literature through August 2011, seven randomized trials compared the outcomes using IVIg versus outcomes using TPE versus combination therapy, in 623 severely affected AIDP/GBS patients. A meta-analysis of five of these trials involving 536 patients with severe disease revealed no statistically significant difference between treatment groups, suggesting that IVIg and TPE are equivalent for the treatment of AIDP/GBS. No trials were found that compare IVIg to placebo.

Table 8: Key studies covering IVIg

<table>
<thead>
<tr>
<th>Trial details</th>
<th>Treatment groups</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bril 1996: RCT, N = 50</td>
<td>IVIg 0.5 g/kg daily for 4 days versus TPE 40 mL/kg to 50 mL/kg on 5 occasions over 7 to 10 days</td>
<td>Median time to recover ability to do manual work: IVIg group, 65 days; TPE group, 90 days</td>
</tr>
<tr>
<td>Diener 2001: RCT, N = 74</td>
<td>IVIg 0.4 g/kg for 5 days versus TPE 40 mL/kg to 50 mL/kg on 5 occasions within 14 days, versus immunoadsorption on 5 occasions (4,000 mL on 2 occasions and then 2,000 mL on 3 occasions) within 14 days</td>
<td>No significant differences between the treatments were found</td>
</tr>
<tr>
<td>El Bayoumi 2011: RCT, N = 41 (children)</td>
<td>IVIg 0.4 g/kg daily for 5 days versus one plasma volume TPE daily for 5 days</td>
<td>Duration of mechanical ventilation was slightly but statistically significantly shorter in the 21 participants who received TPE than in patients who received IVIg</td>
</tr>
<tr>
<td>Gürses 1995: qRCT, N = 18 (children)</td>
<td>IVIg 1 g/kg/day for 2 days versus supportive care</td>
<td>Recovered full strength after 4 weeks (P = 0.06); IVIg group, 77.6%; control group, 22.2%</td>
</tr>
<tr>
<td>Haupt 1996: NR, N = 34</td>
<td>Immunoadsorption followed by IVIg 0.4 g/kg daily for 5 days versus immunoadsorption alone; additional group treated by TPE alone</td>
<td>Significant difference in favor of the sequentially treated group</td>
</tr>
<tr>
<td>Korinthenberg 2005: RCT, N = 21 (children)</td>
<td>IVIg 1.0 g/kg over 2 days versus no treatment; IVIg 1.0 g/kg daily for 2 days versus 0.4 g/kg daily for 5 days (same total dose)</td>
<td>Significant differences favoring IVIg in the secondary outcome measures, time to onset of signs of improvement and time to improvement on a slightly expanded version of the GBS disability grade scale</td>
</tr>
<tr>
<td>Nomura 2001: RCT, N = 47</td>
<td>IVIg 0.4 g/kg daily for 5 days versus TPE total 200 mL/kg to 250 mL/kg in up to 7 sessions over 4 weeks</td>
<td>No significant differences between groups</td>
</tr>
<tr>
<td>PSGBS Study Group 1997: RCT, N = 383</td>
<td>IVIg 0.4 g/kg daily for 5 days versus TPE 250 mL/kg over 8 to 13 days versus TPE followed by IVIg</td>
<td>Disability grade change after 4 weeks</td>
</tr>
<tr>
<td>Raphaël 2001: RCT, N = 39</td>
<td>IVIg 0.4 g/kg/day for 3 days versus 6 days</td>
<td>Not applicable (trial terminated prematurely)</td>
</tr>
<tr>
<td>Van der Meche 1992: ACT, N = 150</td>
<td>IVIg 0.2 mL/kg daily for 5 days versus TPE 200 mL/kg to 250 mL/kg over 7 to 14 days</td>
<td>Patients improved by one or more grades (P = 0.024) after 4 weeks: IVIg group, 53%; TPE group, 34%</td>
</tr>
<tr>
<td>Wang 2001: RCT, N = 54 (children)</td>
<td>Dexamethasone 5 mg/day to 10 mg/day for 5 or 7 days, tapered over 7 to 10 days versus IVIg 0.2 g/kg to 0.3 g/kg daily for 5 or 6 days and dexamethasone 4 mg to 5 mg daily for 5 or 6 days, tapered over 7 days versus TPE 500 mL to 1,500 mL over 5 to 10 days and dexamethasone 5 mg/day for 5 or 6 days, tapered over 7 days</td>
<td>Children who received IVIg achieved recovery of bulbar or respiratory function or a two-grade improvement in muscle strength in a mean (SD) of 17 (6) days compared with 30 (7) days in the TPE group (P = 0.0001)</td>
</tr>
</tbody>
</table>

ACT: allocation controlled trial; IVIg: intravenous immunoglobulin; RCT: randomized controlled trial; qRCT: quasi-randomized controlled trial; NR: not randomized; TPE: therapeutic plasma exchange; PSGBS: Plasma Exchange/Sandoglobulin Guillain-Barré syndrome.

Please note: an outcome score of less than zero indicates an advantage for IVIg in disability improvement.
IVIg treatment that is started within 2 weeks of onset of AIDP symptoms hastens recovery as much as TPE treatment.\textsuperscript{73} Administering IVIg after giving TPE did not confer additional benefit.\textsuperscript{73}

Important notes regarding immunotherapy for AIDP/GBS:

- The standard treatment regimen for TPE in AIDP/GBS is 200 mL to 500 mL plasma per kg body weight over 10 to 14 days, usually with exchanges on alternating days. The standard replacement fluid is 5% albumin, though there is no definitive evidence for one replacement fluid over another.\textsuperscript{57,67}
- TPE is most beneficial when started before 4 weeks (and ideally prior to 2 weeks) after onset of symptoms.\textsuperscript{30,67}
- TPE is contraindicated for hemodynamically unstable patients because changes in the total blood volume during treatment may result in exaggerated disruptions to blood pressure.\textsuperscript{1}
- The relapse rate following TPE is approximately 5% to 10%, compared to approximately 1% in the control group.\textsuperscript{57,68} Still, additional evidence suggests that, even in light of potentially increased relapses, it is better to treat with immunotherapy than not.\textsuperscript{1}
- IVIg is as effective as TPE when started within 2 weeks of onset and is readily available in most hospitals.\textsuperscript{70,73} Importantly, this applies primarily to AIDP variants of GBS; AMAN (axonal) forms of GBS do not respond robustly to IVIg.\textsuperscript{82}
- IVIg is easier to administer than TPE and is considered slightly safer.\textsuperscript{73}
- TPE followed by IVIg does not appear to improve patient outcomes over single therapy alone.\textsuperscript{83}
- The AAN practice parameters for TPE in AIDP/GBS recommend TPE for non-ambulatory patients within 4 weeks of symptom onset (Level A). TPE should be considered as a potential therapy for ambulatory patients within 2 weeks of onset (Level B).\textsuperscript{59}
- AAN also recommends IVIg for non-ambulatory adult GBS patients within 4 weeks (Level B) or ideally within 2 weeks (Level A) of symptom onset. Sequential treatments (such as TPE followed by IVIg or immunoadsorption followed by IVIg) are not recommended.\textsuperscript{59,72}
- TPE and IVIg are recommended therapies for AIDP/GBS in children, where a decrease in mechanical ventilation rate was noted in children treated with TPE as compared to supportive care alone.\textsuperscript{51,59}
- Adverse events are more frequent in TPE than in IVIg patients. Adverse events following TPE include hypotension, septicemia, pneumonia, abnormal clotting, and hypocalcemia.\textsuperscript{6}
- Immunoadsorption therapy has been proposed as an alternate immunotherapy to TPE. Immunoadsorption removes pathogenic immunoglobulins from circulation without the need for replacement fluids. Interestingly, several studies show that there is no difference between patients treated with immunoadsorption or with TPE and double filtration plasmapheresis.\textsuperscript{77,84}
- While most patients will respond well to either TPE or IVIg, a small percentage will not improve following a single treatment by either method. No RCTs have been completed to address this complication, and no insight is available for why this occurs. The standard of care here is often to repeat the treatment, frequently with better results following a second treatment.\textsuperscript{30}

Corticosteroids

Corticosteroids were first suggested as treatment for AIDP/GBS in the early 1950s,\textsuperscript{85} but the first RCT showed no significant effect.\textsuperscript{86} Additional studies have shown a potential short-term positive effect when corticosteroids are used in combination with IVIg,\textsuperscript{87} but the significance of these findings has been debated, and corticosteroids are not considered a first-line treatment option for AIDP/GBS.\textsuperscript{1} Combinatorial treatment is discussed in more detail below.

KEY STUDIES COVERING CORTICOSTEROIDS

A systematic search and review of data through June 2009 examined six trials with a total of 587 participants.\textsuperscript{88} Based on the gathered results, the authors identified no statistically significant difference in the disability grade change at 4 weeks between the corticosteroid-treated and control groups.\textsuperscript{88} Additional outcome measures that were assessed included time until recovery of walking, time to discontinuation of ventilation, mortality, proportion of patients dead or unable to walk unassisted after 12 months, change in disability grade at 6 or 12 months, relapse rate, and occurrence of specific adverse events potentially attributable to corticosteroids during treatment or within 1 week after stopping treatment.\textsuperscript{88} No significant differences were noted between groups in any of these categories, suggesting that corticosteroids do no harm but also do not help GBS patients.\textsuperscript{88} Importantly, the authors indicate that the available data do not support the treatment of AIDP/GBS with corticosteroids.\textsuperscript{88}
Combination Treatment

TPE followed by IVIg is not significantly better than either TPE or IVIg alone. Oral steroids and intravenous methylprednisolone are not beneficial in patients with GBS. Combination of IVIg and methylprednisolone is no more effective than IVIg alone, although this combined treatment might have some additional short-term benefits when known prognostic factors are taken into account. Small randomized placebo-controlled trials of IFN-β1a and brain-derived neurotrophic factor and one trial studying a 6-week course of mycophenolate mofetil combined with standard IVIg versus IVIg alone did not indicate beneficial effects of these treatments.

PROGNOSIS

The prognosis for patients with AIDP/GBS is variable. Most patients will begin to recover around 28 days following onset, and the mean time to complete recovery is approximately 200 days for 80% of patients. Even so, many patients (up to 65%) will still have minor residual signs and symptoms, a small minority (10% to 15%) will have major residual neurologic deficits, and a high proportion of patients report severe fatigue at 1 year post-onset. Axonal forms of GBS have a more delayed recovery than AIDP forms. The relapse rate for GBS is low, around 5%, and and relapse usually occurs within the first 8 weeks following onset. If relapses occur later than 8 weeks post-onset, the diagnosis of CIDP should be considered.

Mortality due to AIDP/GBS is approximately 10%. In a study of 79 cases, 8% of patients had died within 1 year of onset; all of these patients were over the age of 60. Death in GBS is frequently due to critical illness, including complicating infections, adult respiratory distress syndrome, or pulmonary embolism. Dysautonomia and respiratory failure may also contribute to mortality in GBS. Most deaths occur either at admittance to the ICU due to autonomic failure or pulmonary complications or during the recovery phase, following discharge from acute care.

Because of the variety of disease severity and outcomes with GBS, efforts have been focused on outcome prediction. Factors that may indicate a poor prognosis regardless of treatment with plasmapheresis include age (> 50 years), rapid onset before presentation within 7 days, the need for mechanical ventilation, and severely reduced distal motor amplitudes. A validated bedside scoring method, the Erasmus GBS outcome score, was developed based on 388 patients otherwise enrolled in 3 additional studies. This seven-point score is based on the age of the patient, the presence or absence of preceding diarrhea, and the modified GBS disability score at 2 weeks after entry. In the patients assessed, 27% with an Erasmus GBS score of 5 at 2 weeks were unable to walk independently at 6 months, whereas 52% with a score of 5.5 at 2 weeks were unable to walk at 6 months.

SUMMARY

- AIDP/GBS is an acute polyneuropathy characterized by varying degrees of weakness that usually follows an antecedent infection.
- In areas of Central and South America affected by the Zika virus, there has been a notable increase in GBS; the link between GBS and Zika virus infection is being investigated.
- The time course of AIDP/GBS is rapid, with the height of symptom severity occurring within 4 weeks following onset.
- Clinical course, severity, and outcomes of GBS are highly variable.
- TPE and IVIg provide roughly equivalent degrees of improvement following treatment, and either treatment is recommended early in the disease course (within 2 to 4 weeks). Corticosteroids are not strongly recommended.
- The primary life-threatening complication associated with AIDP/GBS is respiratory failure, and mechanical ventilation is required for approximately 20% of patients.
- Most patients will spontaneously recover from AIDP/GBS, though a high proportion will still have neurological symptoms at 1 year post-onset.
REFERENCES


