

# Treatment guidelines for Guillain–Barré Syndrome

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## Introduction

Guillain–Barré syndrome (GBS) is an acute onset, usually monophasic immune-mediated disorder of the peripheral nervous system. The term GBS is often considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the increasing recognition of variants over the past few decades, the number of diseases that fall under the rubric GBS have grown to include axonal variants and more restricted variants, such as Miller Fisher syndrome (MFS) [Table 1].<sup>[1]</sup>

## Epidemiology

The reported incidence rates for GBS are 1–2 per 100,000 population.<sup>[2–4]</sup> The lifetime likelihood of any individual acquiring GBS is 1:1000.<sup>[5]</sup> The subtypes of GBS have different incidence rates in different parts of the world. In Europe and North America AIDP is dominant contributing to 90% of the cases. In contrast in China and Japan AMAN being the most common subtype.<sup>[6,7]</sup> The picture is intermediate when we look at other population. In Indian series the incidence of AIDP and AMAN are virtually equal although AMAN is more common in younger patients.<sup>[8]</sup> There seems to be a slight preponderance of AIDP in studies by Gupta *et al*<sup>[9]</sup> and by Meena *et al* (unpublished data from NIMS, Hyderabad). Available Indian literature indicates a peak incidence between June–July and Sept–October.<sup>[10]</sup> In western countries, GBS is common in the 5<sup>th</sup> decade,<sup>[11]</sup> but in India it occurs more commonly at a younger age.<sup>[10,12]</sup> GBS is equally common in men and women and can occur at any age. There is a male preponderance among the hospitalized population.<sup>[10,12]</sup>

## Clinical Features

Most often an unremarkable infection, such as upper respiratory infection, often predates the onset of GBS by 14 days.<sup>[2,5]</sup> Many antecedent infections have been identified, including *Campylobacter jejuni*, cytomegalovirus (CMV), *Mycoplasma pneumonia*, Epstein–Barr virus, influenza virus, JEV.<sup>[13,14]</sup> Surgery, immunization, and parturition have also been associated with GBS. GBS usually begins abruptly with distal, relatively symmetrical onset of paraesthesias and quickly followed by progressive limb weakness. Progression is rapid, with 50% of patients reaching clinical nadir by 2 weeks and more than 90% by 4 weeks. The current diagnostic criteria include <4 weeks of progression to clinical nadir. Approximately 80%–90% of patients with GBS become nonambulatory during the illness.<sup>[15,16]</sup> Pain is prominent in 50% of patients.<sup>[16,17]</sup> Neurological examination is characterized by distal and often proximal, relatively symmetrical, weakness. Although GBS is essentially a motor neuropathy, sensory dysfunction is seen in a few patients. It is seen more in a demyelinating form of GBS.<sup>[12,18]</sup> Sensory examination is often normal in the early phase of disease. Facial or pharyngeal weakness is commonly seen in GBS. Diaphragmatic weakness due to phrenic nerve involvement is also common. Approximately one third of hospitalized GBS patients require mechanical ventilation due to respiratory muscle or oropharyngeal weakness.<sup>[18,19]</sup> Tachycardia is common but more serious autonomic nervous system dysfunction may occur, including life-threatening arrhythmias, hypotension, hypertension, and gastrointestinal dysmotility. The incidence is between 27% and 55% and is more common in demyelinating than axonal form.<sup>[12,20]</sup>

## Pathogenesis

Major advances have been made in understanding the mechanisms of some of the subtypes. The histological appearance of the AIDP subtype resembles experimental autoimmune neuritis, which is predominantly caused by T cells directed against peptides from the myelin proteins P0, P2, and PMP22. The role of T-cell-mediated immunity in AIDP remains unclear and there is evidence for the involvement of antibodies and complement. Strong evidence now exists that axonal subtypes of Guillain–Barré syndrome, acute motor axonal neuropathy (AMAN), and acute motor and sensory

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**Table 1: Guillain-Barré syndrome—clinical variants**


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Acute inflammatory demyelinating polyradiculoneuropathy
[Predominantly motor, bilateral facial and pharyngeal, occasional sensory, and autonomic disturbances]
Acute motor axonal neuropathy
[Only motor neuropathy]
Acute motor sensory axonal neuropathy
[Motor and sensory neuropathy]
Miller Fisher syndrome
[Ophthalmoplegia, ataxia, areflexia]
Acute pandysautonomia
[Pure autonomic neuropathy—both sympathetic and parasympathetic]
Pure sensory Guillain Barré syndrome
[Pure sensory neuropathy]
Cervico-brachial-pharyngeal
[Motor weakness predominantly affecting cervico-brachial and pharyngeal muscles]
Bi-brachial
[Motor weakness confining to both the upper limbs with areflexia]
Distal limb variant
[Motor weakness confined to distal muscles of upper and lower limbs with no sensory and cranial nerve involvement]
Oculopharyngeal
[Motor weakness predominantly affecting ocular and pharyngeal muscles]
Paraparetic variants
[Motor weakness predominantly confined to lower limbs]
Pure ophthalmoplegia
[Weakness of bilateral ocular muscles]
Bilateral facial palsy with paresthesias
[Weakness of bilateral facial muscles with paresthesias]
Ropper's variant
[Bilateral sixth and seventh cranial nerve palsy]
Pure generalized ataxia
[Symmetrical limb and axial ataxia]
Polyneuritis cranialis
[Symmetrical or asymmetrical multiple cranial neuropathy]

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axonal neuropathy (AMSAN), are caused by antibodies to gangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier. About a quarter of patients with Guillain-Barré syndrome have had a recent *C. jejuni* infection, and axonal forms of the disease are especially common in these people. The lipo-oligosaccharide from the *C. jejuni* bacterial wall contains ganglioside-like structures and its injection into rabbits induces a neuropathy that resembles acute motor axonal neuropathy.<sup>[21-23]</sup> Antibodies to GM1, GM1b, GD1a, and GalNac-GD1a are in particular implicated in acute motor axonal neuropathy and, with the exception of GalNacGD1a, in acute motor and sensory axonal neuropathy.

## Diagnosis

Progressive weakness in both upper and lower extremities within 4 weeks along with areflexia is essential requirement for the diagnosis. Supportive ancillary testing for GBS includes CSF analysis and electrodiagnostic testing, both of which may be normal in the early phase of GBS. The limitations of ancillary testing in the early phase combined with the importance of prompt treatment of GBS mandates that the clinician at times make the diagnosis based solely on history and examination. An elevated CSF protein concentration (with normal cell

count) is only found on initial CSF analysis in 50% of patients; elevated CSF protein concentration occurs in more than 90% of patients at the peak of the disease. CSF pleocytosis is an important red flag, which raises the question of infectious (HIV, CMV, Lyme, sarcoid), carcinomatous, or lymphomatous polyradiculoneuropathy [Table 2].

## Electrodiagnosis

Electrodiagnostic (EDX) testing is performed to support the clinical impression. EDX testing of GBS patients often demonstrates features of demyelination, such as temporal dispersion, significantly slow conduction velocities, and prolonged distal and F-wave latencies.<sup>[24]</sup> Electrodiagnostic testing features of acquired demyelination (eg, conduction block, temporal dispersion, nonuniform slowing of conduction velocities) are particularly helpful because these findings are characteristic of immune-mediated demyelinating neuropathies. In early GBS, prolonged distal compound muscle action potential (CMAP) latencies and temporal dispersion are more commonly demonstrated than are slow motor conduction velocities and conduction block.<sup>[27]</sup> Another electrodiagnostic testing hallmark of GBS is the “sural sparing” pattern; that is, the finding of a normal sural sensory nerve response in the

setting of abnormal upper extremity sensory nerve results.<sup>[27]</sup> This pattern is very unusual for neuropathies other than GBS. Sural sparing, a marker of demyelinating neuropathy, is more commonly seen in later than in early stages of AIDP. Other electrodiagnostic testing abnormalities are frequently encountered in early GBS but they are less specific to GBS. These include absent H-reflexes, low motor nerve CMAP amplitudes on distal stimulation, and prolonged F-wave responses.<sup>[25-27]</sup> It is reported that the H-reflex was absent in 97% of GBS patients within the first week of symptom onset. It should also be pointed out that motor electrodiagnostic testing findings are more often abnormal than sensory nerve results in early GBS. Blink reflex studies are often abnormal when there is facial nerve involvement.<sup>[26]</sup> Phrenic nerve conduction studies can be used to predict respiratory failure and the need for ventilation.<sup>[28]</sup> Reduced CMAP amplitudes of 0%–20% of the lower limit of normal carry a poor prognosis.<sup>[29]</sup>

The diagnostic yield of various neurophysiological criteria may vary in different subforms of Guillain-Barré syndrome, whose prevalence varies in different geographical areas. In a recent study the diagnostic sensitivity of Albers *et al*,<sup>[30]</sup> Cornblath,<sup>[31]</sup> Ho *et al*,<sup>[32]</sup> Dutch GBS Study Group,<sup>[33]</sup> Italian GBS Study Group,<sup>[34]</sup> and Albers and Kelly criteria<sup>[35]</sup> were evaluated and correlated with clinical subtypes of GBS, duration, severity, and outcome.<sup>[36]</sup> The sensitivity of nerve conduction study in the diagnosis of GBS and in different clinical subtypes of GBS was highest using Albers criteria (88.2%) and lowest using Cornblath criteria (39.2%). As per Ho *et al*, patients could be categorized into AIDP (86.3%), AMAN (7.8%), and AMSAN (5.9%). Electrophysiological findings necessary to diagnose GBS is in Table 3.

Incidence of antiganglioside antibodies in GBS has varied widely in different published series.<sup>[37,38]</sup> Its much more common in AMAN variant than AIDP. The incidence was found to be 58% in a study of 60 patients of GBS by Meena *et al* (Unpublished data from NIMS, Hyderabad). Although antiganglioside antibodies have been implicated in the pathogenesis of GBS, assaying antiganglioside values in a patient with GBS other than MFS at the present time has no diagnostic value in routine practice.

### Variants of Guillain-Barré syndrome

Commonly recognized variants include those with axonal forms, variants based on particular fiber-type involvement (sensory or autonomic), and MFS. Variants with regional or a markedly asymmetric distribution also occur.<sup>[1]</sup> There are also differences in abruptness of onset and time to reach nadir, which can complicate diagnosis and decisions about treatment. For example, some patients have clinical features and disease course similar to GBS except for a slower progression (ie, progression that lasts longer than 4 weeks); this disease is sometimes referred to as subacute inflammatory demyelinating polyradiculoneuropathy (SIDP);<sup>[39,40]</sup> however, in many respects SIDP is like GBS and often should be treated as such. AMSAN and AMAN are two variants characterized by immune attack directed at axons rather than Schwann cells and myelin.<sup>[41-44]</sup>

AMAN occurs in large epidemics during summer in northern

China and more sporadically elsewhere.<sup>[44]</sup> It mostly affects children and young people, usually from rural areas. Onset of motor weakness is abrupt. In addition to acute pure motor paralysis, many patients have transient neck and back stiffness early in the course with resolution within day. Recovery usually begins within 3 weeks and is often complete and may take longer. Mortality rate is roughly 3%–5%. Sensory nerve conduction studies are normal and motor nerve studies are remarkable for low or absent CMAP amplitudes with normal conduction velocities. Denervating potentials are seen on needle electromyography.<sup>[6]</sup>

AMSAN shares many pathological features with acute motor axonal neuropathy but differs clinically from it in patient age of onset (usually adults rather than children), geographic distribution (can occur anywhere), time of onset (not only summertime), involvement of sensory nerves, course (protracted), and outcome (usually severe residual disability).<sup>[40-44]</sup> It has an abrupt onset and rapid progression with most patients requiring mechanical ventilation within a few days of symptom onset. Motor nerves are electrically inexcitable early in the disorder. Sensory nerve conduction studies are also abnormal. Widespread denervation is seen on needle examination. The course is protracted and outcome poor, with only 20% ambulating at 1 year.

**Table 2: Guillain-Barré syndrome—red flags raising other diagnostic possibilities**

Clinical
• Fever at onset
• Severe pulmonary dysfunction with limited weakness at onset
• Severe sensory signs with limited weakness at onset
• Persistent bladder or bowel dysfunction or bladder or bowel dysfunction at onset
• Sharp sensory level
• Marked persistent asymmetry of weakness
Laboratory
• Increased number of mononuclear cells in CSF
• Polymorphonuclear cells in CSF

**Table 3: Electrodiagnostic findings in Guillain-Barré syndrome<sup>[32]</sup>**

### Electrodiagnostic features suggestive of acquired demyelinating neuropathy

Conduction velocity reduced in two or more nerves
CMAP conduction block or abnormal temporal dispersion in 1 or more nerves
Prolonged distal motor latencies in 2 or more nerves
Prolonged minimum F-wave latency or absent F-wave
Electrodiagnostic features suggestive of axonal neuropathy
• No evidence of significant reduction in conduction velocity.
• No evidence of abnormal temporal dispersion.
• Prolonged distal latency NOT considered demyelination if amplitude < 10% LLN.
• Decrease in CMAP (AMAN) and SNAP (AMSAN) to <80% of LLN or inexcitable (absent evoked response) in 2 or more nerves.

CMAP, Compound muscle action potential; AMAN, Acute motor axonal neuropathy; AMSAN, Acute motor and sensory axonal neuropathy; SNAP, Sensory nerve action potential; LLN, Lower limits of normal

MFS: The more recognizable and distinct regional variant of GBS is MFS.<sup>[1,45,46]</sup> Like GBS, the onset of MFS often follows an infection, for example *C. jejuni*.<sup>[47]</sup> MFS patients classically present with external ophthalmoparesis, areflexia, and ataxia,<sup>[2]</sup> although MFS patients often present with fewer components of the classical clinical triad<sup>[1,46,48,49]</sup> or with additional clinical features (facial weakness, oropharyngeal weakness, internal ophthalmoparesis, central nervous system involvement). Bickerstaffs brainstem encephalitis (BBE) is a related syndrome in which alteration of consciousness or corticospinal tract signs are seen in addition to ophthalmoparesis and ataxia. Many patients with MFS or BBE also have “overlapping GBS” with flaccid quadriparesis.<sup>[46,50]</sup> Anti-GQ1b antibodies are present in 95% of patients with acute MFS<sup>[51]</sup> and in approximately two-thirds of patients with BBE. The recognition of various clinical presentations and the high sensitivity and specificity of anti-GQ1b antibody testing suggest rubric name of “anti-GQ1b antibody syndrome.”

Anti-GT1a antibody without anti-GQ1b reactivity is found in patients presenting with the pharyngeal-cervical-brachial (PCB) variant of GBS.<sup>[52,53]</sup> More than half of MFS patients will have cytoalbuminological dissociation on CSF analysis performed within the first 3 weeks of disease onset.<sup>[54]</sup> In MFS, motor nerve conduction studies in the limbs are usually normal or only mildly abnormal with slight reductions in compound muscle action potential amplitudes and conduction velocities.<sup>[55]</sup> Conduction block and temporal dispersion are not a feature of MFS. Sensory nerve action potential amplitudes are usually moderately to severely reduced, more so in the upper extremity sensory nerves (eg, median) than the sural nerve. Blink reflex R1 delayed or absent. MRI of the brain frequently demonstrates cranial nerve enhancement (eg, oculomotor nerves) in MFS<sup>[56]</sup> and high-intensity abnormalities in the posterior fossa, white matter, or thalami in patients with BBE.<sup>[50]</sup> MFS is generally a benign, self-limiting conduction. Almost all treated and untreated patients return to normal activities within 6 months of disease onset, usually with resolution of ophthalmoplegia within 1–2 months and ataxia within 3–4 months.<sup>[57]</sup>

Other regional variants of GBS are those that affect other specific areas of the body, such as only the face or the afferent sensory and autonomic systems.<sup>[58]</sup>

### Management

Patients with GBS who are symptomatic but are able to walk unaided for more than 5 m and who are stable can be managed conservatively at peripheral centers. However, they should be observed for progression of the disease, especially if they are still within the first week of the onset of the disease. Blood pressure and heart rate fluctuations, clinical signs of respiratory failure should be carefully and meticulously monitored. Clinical signs of ileus should be watched. If any of these signs are detected they should be immediately shifted to specialized centers for further management. In the acute phase in bed-bound adult patients require both supportive therapy and immunotherapy can be used taking into consideration the cost factors and the clinical status (staging, complications, and other comorbid conditions) of individual patients.

### Supportive Care

Immunotherapy therapy has not reduced the mortality in

GBS. Mortality is due to disease-related issues or secondary complications developed in hospital due to prolonged disease course. Meticulous and attentive care of these patients are essential in reducing the mortality. Supportive care consensus guidelines have been published.<sup>[59]</sup>

### Management of respiratory failure

GBS is the most common peripheral neuropathy causing respiratory paralysis. Despite advances in respiratory management and immunotherapy, mortality from GBS is as high as 20% for ventilated patients. Mechanical ventilation is usually required by one third of the patients.<sup>[59]</sup> Clinical signs like tachypnea, tachycardia, brow sweating asynchronous movements of chest and abdomen and a vital capacity < 20 mL/kg, maximal inspiratory pressures < 30 mm H<sub>2</sub>O, maximal expiratory pressure < 40 cm H<sub>2</sub>O predicts imminent respiratory failure.<sup>[59]</sup> Time from onset to admission of less than 1 week, facial weakness, bulbar paresis, and neck weakness are other factors associated with respiratory failure.<sup>[59,60,61]</sup> Simple bedside single breath count, which correlates well with vital capacity than phrenic nerve conduction studies is a good predictor of respiratory failure (Unpublished data by Meena *et al* from NIMS, Hyderabad). Percutaneous dilatational tracheostomy may be advantageous over traditional tracheostomy by allowing less risk of accidental extubation and a better cosmetic outcome. In general it takes 2–6 weeks to wean out of ventilatory support.<sup>[62]</sup> Tracheostomy may be performed 2 weeks following intubation and should be based on status of an individual. It is comfortable and provides airway safety but is associated at times with life-threatening complications and disfigurement.<sup>[59]</sup> If pulmonary function is improving, it may be preferable to wait 1 more week to attempt at weaning from ventilator.

### Management of Dysautonomia

Acute dysautonomia is a significant cause of death in patients with GBS. Cardiac and hemodynamic disturbance manifesting as hypertension, postural hypotension, and tachycardia occur in a majority of GBS patients.<sup>[69]</sup> This is due to excessive sympathetic over activity and parasympathetic under activity. Severe dysautonomia occurs usually in severe cases at the peak of the deficit.<sup>[69]</sup> Tachycardia is most common, usually in the range of 100–120/min, which does not require treatment. Approach to inserting a pacemaker for serious bradycardia or sinus arrest has varied widely because of the uncertainty that exists in anticipating such events at the bed side by different ways. However, the presence of tachycardia, increased daily variation in systolic blood pressure, reduced normal respiratory-induced heart rate variation, and first episode of severe bradyarrhythmia reduce the threshold for insertion of pacemaker.<sup>[70,71]</sup> Endotracheal suction may provoke bradycardia or systole, and this can be reduced by hyperoxygenation. Hypertension is seen in one third of patients with GBS and can be labile or be followed by hypotension.<sup>[63-65]</sup> If hypertension is severe (mean pressure greater than approximately 125 mmHg) and sustained, specific therapy may be necessary. Antihypertensives with short half-lives (labetolol, esmolol, or nitroprusside infusions) should be considered.<sup>[65]</sup> Beta-adrenergic or calcium channel blockers should be used with caution, especially if episodes of hypertension alternate with



hypotension. Hypotension can be managed by maintaining intravascular volume and avoid using diuretics. Patients with a risk of hypotension should not be left unattended in a sitting or upright position. Pronounced and persistent hypotension should warrant search for other causes, such as sepsis myocardial infarction and pulmonary thromboembolism or use of narcotics or positive pressure ventilation. Gastrointestinal motility disorders occur in 15% of severely affected GBS patients. Ileus is associated with other features of dysautonomia (tachycardia and hypertension). Dysmotility can be effectively managed by suspension of enteral feeds, nasogastric suctioning, and erythromycin or neostigmine.<sup>[59,69]</sup>

*Hyponatremia* is the common electrolyte abnormality in GBS and is due to SIADH (in majority of the cases) and natriuresis. The treatment is different for both. Both require replenishment of sodium but SIADH need fluid restriction and in case of natriuresis requires intravascular volume expansion. The best way to differentiate these two conditions is by measuring central venous pressure.

### Deep vein thrombosis prophylaxis

All patients should be given subcutaneous fractionated or unfractionated heparin and support stockings until they are able to walk independently to prevent deep vein thrombosis.<sup>[59]</sup> If a prolonged bedridden period is anticipated and a tracheostomy has already been performed, institute oral anticoagulant treatment with warfarin coumadin.

*Pain* and sensory symptoms are reported in majority of patients with GBS and should be treated effectively with opioid analogues. Sedation and bowel hypomotility may become a problem. Other drugs, such as gabapentin, carbamazepine acetaminophen, NSAIDs, and tricyclic antidepressants also can be tried.

### Nutrition

Nasogastric or gastric tube feeding should be instituted early and slowly. High energy (40–45 nonprotein kcal) and high protein diet (2–2.5 g/kg) have been recommended so has to reduce muscle wasting and assist respiratory weaning. Continuous enteral feeding seems to be better tolerated than bolus feeding in these patients.

*Surveillance for infections* with weekly or more frequent sputum and urine cultures and blood count may be useful but the use of these tests should be guided by clinical circumstances.

### Immunotherapy

Both plasma exchange and IVIg are effective immunotherapies for adult and pediatric patients with GBS if given during the first few weeks of disease.

### Plasmapheresis

In a meta-analysis of 6 class II trails comparing plasma exchange (PE) to supportive care alone for adults with GBS, it was found that PE reduced the risk of developing respiratory failure.<sup>[72,73]</sup> Patients treated with PE fared significantly better in the following secondary outcome measures: Time to recover walking without aid, percentage of patients requiring artificial ventilation, duration of ventilation, full muscle strength

recovery after 1 year, and severe sequelae after 1 year. Time to onset of motor recovery in mildly affected patients was significantly shortened in the PE group. However, the cost of PE has been shown to be offset by the savings of shorter hospital stay.<sup>[74]</sup>

*The volume* of plasma removed and the optimum number of PE has not been established and it varies in different trials, but many physicians use the protocol of North American trial in which a total of 200–250 mL/kg was exchanged over 7–10 days all over the world.<sup>[75]</sup> There is evidence that the number of PE in GBS should be adjusted to disease severity and that also patients with mild symptoms do benefit from PE.<sup>[76]</sup>

In mild GBS, two sessions of PE are superior to none. In moderate GBS, 4 sessions are superior to 2. In severe GBS, 6 sessions are no better than 4. In line with these findings, Yuki *et al* reported that at least 2 PE are needed to significantly reduce the circulating immunoglobulin complexes.<sup>[77]</sup> In developing countries where cost is the limiting factor, small volume PE may be used. In India small volume PE was used by Tharakan *et al* with comparable results.<sup>[78]</sup> They used 15 mL/kg body weight/day to be continued till the progression of the disease got arrested or recovery started. This protocol is still performed in various centers in developing countries with good results.

### Type of Plasma Exchange

Continuous flow PE is superior to intermittent flow exchanges. The replacement fluids do not affect the outcome of PE according to the French Study Group.<sup>[79]</sup> Although albumin was found to be superior to fresh frozen plasma as the exchange fluid.

*When to use PE?* A better outcome was demonstrated with PE in French Study Group when compared with North American Study Group.<sup>[79]</sup> This is due to the fact that treatment was initiated within 2 weeks in the former study group and within 4 weeks in the latter. Hence PE is more beneficial when started within 7 days after disease onset rather than later, but was still beneficial in patients treated up to 30 days after disease onset.

*Who should be offered PE?* All patients with mild, moderate, and severe GBS benefit from treatment. Patients who need even minimum assistance for walking, who are steadily progressing and those who are bed- and ventilator-bound should be advised PE. The value of PE in children younger than 12 years is not known.

AAN in 2003 concluded that PE hastens recovery in nonambulant patients who get treatment within 4 weeks of onset, and PE hastens recovery of ambulant patients with GBS who are examined within 2 weeks. PE is usually administered as one plasma volume, 50 mL/kg, on 5 separate occasions over 1–2 weeks.<sup>[72]</sup>

Slightly more complications were observed in PE group than the IVIg group. Significant adverse events of PE include hypotension, septicemia, pneumonia, abnormal clotting, and hypocalcemia. Major hemostatic disorders, unstable cardiovascular state, active infection, and pregnancy are contraindications to PE.

*Immunoabsorption* therapy is an alternative technique to PE. This form of therapy removes Ig from the circulation without the need for replacement with albumin or FFP because of loss of albumin. Evidence says that there is no difference in outcomes between patients treated with immunoabsorption and PE or double filtration plasmapheresis.<sup>[80,81]</sup>

## Steroids

In a Cochrane systematic review of 6 trials with 587 patients it has been shown that corticosteroid therapy is ineffective for treating GBS.<sup>[82]</sup>

## Intravenous Immunoglobulins

The first RCT on the use of IVIg was published in 1992, and showed that IVIg is as effective as PE.<sup>[83]</sup> Since the publication of these results, IVIg, in a regimen of 0.4 g/kg bodyweight daily for 5 consecutive days, has replaced PE as the preferred treatment in many centers, mainly because of its greater convenience and availability. The Cochrane review on the use of IVIg in GBS contained 4 additional trials.<sup>[84]</sup> No difference was found between IVIg and PE with respect to the improvement in disability grade after 4 weeks, the duration of mechanical ventilation, mortality, or residual disability. The combination of PE followed by IVIg was not significantly better than PE or IVIg alone. The combination of IVIg and intravenous methyl prednisolone was not more effective than IVIg alone, although there might be a short-term effect of this combined treatment when a correction is made for known prognostic factors.<sup>[85,86]</sup>

In general in patients with renal dysfunction the rate of infusion should be decreased to half of the normal infusion rate.

### Timing of treatment

Most RCTs have included only patients who are treated within the first 2 weeks from onset of weakness and who are unable to walk without assistance. If these criteria are met, there is no doubt that patients with GBS should be treated with IVIg or PE. The question remains as to what to do in patients with rapidly progressive limb weakness or impaired pulmonary function but who are still able to walk. Although not proven effective, it seems logical to treat these patients with IVIg.

### Treatment of mildly affected patients

These patients are able to walk with some support or no support. A retrospective study showed that these patients often have residual disabilities.<sup>[87]</sup> RCTs that have assessed the effect of IVIg have not studied the effect in mildly affected patients. It should be kept in mind that no RCTs have assessed the effect of PE or IVIg in these mildly affected patients with GBS.

### Miller Fisher syndrome

No RCTs have studied the effect of PE or IVIg in patients with MFS.<sup>[88]</sup> Observational studies have suggested that the final outcome in patients with MFS is generally good. In a large uncontrolled observational study,<sup>[89]</sup> IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia. The investigators concluded that IVIg and PE did not influence the outcome of patients with MFS, presumably because of good natural

recovery. Patients with mild or uncomplicated MFS may perhaps be treated conservatively. Patients with more severe or complicated anti-QIB antibody syndrome, an overlapping GBS, should probably receive immunotherapy.

### Treatment of patients who deteriorate in spite of therapy

Some patients with GBS continue to deteriorate after PE or a standard course of IVIg. In these cases, the best option is unknown. Whether these patients need PE after they have been treated with IVIg has not been investigated, but the combination of PE followed by IVIg is no better than PE or IVIg alone. PE after IVIg is also not advised, because PE would probably wash out the IVIg previously administered. A study in a small series of patients investigated the effect of a second course of IVIg in severe unresponsive patients with GBS.<sup>[90]</sup> This uncontrolled study suggested that a repeated course of IVIg could be effective. About 5%–10% of patients with GBS deteriorate after initial improvement or stabilization following IVIg treatment.<sup>[91]</sup> Although no RCTs have assessed the effect of a repeated IVIg dose in this condition, it is common practice to give a second IVIg course (2 g/kg in 2–5 days). These patients are thought to have a prolonged immune response that causes persistent nerve damage that needs treatment for a longer period of time.<sup>[92]</sup> A longer interval between onset and treatment and longer time to nadir may be associated with a greater chance of relapse.

### Cost-effectiveness of PE and IVIg in GBS

When faced with restrictions in financial resources, especially in developing countries cost-effectiveness of any treatment becomes a major issue in treatment decision making. This is very true in GBS in which the currently approved treatment has shown equal efficacy. There are a few available cost analysis studies addressing this issue and the results are controversial.<sup>[93,94]</sup> However, in developing countries use of small volume PE may bring down the cost when compared to IVIg. Hence the decision to use PE or IVIg must be based on multiple factors. The main limitations for use of PE would be availability of the technical expertise and support. Lack of these, ease of administration, and fewer side effects with IVIg may dictate use of IVIg as the first line of therapy.

## Prognosis

GBS has a serious long-term impact on the patients' work and private life, even 3–6 years after the onset of illness. Recovery can be slow and take years. Persistent disability is seen in 20%–30% of adult patients but is less common in children.<sup>[2,95]</sup> Severe fatigue is a sequel of GBS in two thirds of adult patients. In an RCT of amantidine, it was not superior to placebo.<sup>[96]</sup> Twelve weeks bicycle extensive training program had positive effects on fatigue, anxiety, depression, and functional outcome.<sup>[97]</sup>

## Conclusions

GBS is a monophasic immune-mediated neuropathy characterized by acute onset of predominantly motor weakness and is a common cause of respiratory paralysis. There are many variants described with different prognosis and manifestations. Electrodiagnosis aids in the diagnosis. Immunotherapy definitely makes a difference in the recovery

of GBS patients and both PE and IVIg are equally effective. IVIg may be preferred because of its low side-effect profile and ease of administration. However, small volume PE can be used with equal efficacy due to cost constraints. Attentive anticipatory supportive treatment is equally important in reducing the morbidity and mortality in GBS.

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