

Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome

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Guillain-Barré syndrome (GBS) is an important cause of acute neuromuscular paralysis. Molecular mimicry and a cross-reactive immune response play a crucial part in its pathogenesis, at least in those cases with a preceding *Campylobacter jejuni* infection and with antibodies to gangliosides. The type of preceding infection and patient-related host factors seem to determine the form and severity of the disease. Intravenous immunoglobulin (IVIg) and plasma exchange are effective treatments in GBS; mainly for practical reasons, IVIg is the preferred treatment. Whether mildly affected patients or patients with Miller Fisher syndrome also benefit from IVIg is unclear. Despite medical treatment, GBS often remains a severe disease; 3–10% of patients die and 20% are still unable to walk after 6 months. In addition, many patients have pain and fatigue that can persist for months or years. Advances in prognostic modelling have resulted in the development of a new and simple prognostic outcome scale that might also help to guide new treatment options, particularly in patients with GBS who have a poor prognosis.

Introduction

Almost a century ago, the French neurologists Guillain, Barré, and Strohl described two soldiers who developed acute paralysis with areflexia that spontaneously recovered.¹ They reported the combination of increased protein concentration with a normal cell count in the CSF, or albuminocytological dissociation, which differentiated the condition from poliomyelitis.¹ Despite the fact that Landry had already reported similar cases in 1859,² the combination of these clinical and laboratory features became known as Guillain-Barré syndrome (GBS). Until now, GBS has remained a descriptive diagnosis of a disorder for which there are no specific diagnostic tests. The combination of rapidly progressive symmetrical weakness in the arms and legs with or without sensory disturbances, hypoflexia or areflexia, in the absence of a CSF cellular reaction, remains the hallmark for the clinical diagnosis of GBS. Over the past 20 years, randomised controlled trials (RCTs) have shown the efficacy of plasma exchange (PE) and intravenous immunoglobulin (IVIg), and some factors—in particular, *Campylobacter jejuni*, but also other preceding infections that induce antiganglioside antibodies—have been found to be important in the pathogenesis of GBS. We focus on the diagnosis and the expanding clinical spectrum of GBS, the frequent occurrence of pain and autonomic dysfunction, and recent insights into the pathogenesis of the syndrome. In addition, we discuss prognostic modelling and the current treatment options available during the course of GBS. The Review aims to integrate the latest laboratory and clinical developments that could lead to better therapeutic options for patients with GBS.

Epidemiology

GBS is a common cause of neuromuscular paralysis, and has been reported worldwide. The annual incidence of GBS is reported to be 1.2–2.3 per 100 000.^{3–9} Most studies have found that the incidence increases linearly with age and that men are about 1.5 times more likely to be affected than women.^{4,5,7} A recent epidemiological report

from the USA indicated that the incidence of GBS among patients aged 18 years or older did not change over the period from 2000 to 2004.⁶ Reports on temporarily increased incidences of GBS are rare. One of the most striking reports came from a study in China, which showed an increase in the axonal, motor variant of GBS during the summer of 1991 and 1992 in a rural area.¹⁰ We observed a temporary rise in incidence of GBS from 1.6 to 3.1 per 100 000 over the period from 1987 to 1999 on the Caribbean island of Curaçao.¹¹ However, our recent unpublished observations indicate that the temporarily increased incidence in Curaçao had nearly returned to normal by 2006.

Diagnosis

GBS is most commonly a post-infectious disorder that usually occurs in otherwise healthy people, and is not typically associated with an autoimmune or other systemic disorder. In typical cases, among the first symptoms are pain, numbness, paraesthesia, or weakness in the limbs. The main features of GBS are rapidly progressive bilateral and relatively symmetric weakness of the limbs with or without involvement of respiratory muscles or cranial-nerve-innervated muscles.^{12,13} Diagnostic criteria for typical GBS are shown in panel 1. Weakness might equally affect all limb muscles, or predominantly the distal or proximal muscles in the arms or legs. Patients have decreased or absent deep-tendon reflexes, at least in the affected limbs. A lumbar puncture is almost always done in patients suspected of having GBS. CSF examination typically shows increased protein with normal CSF white-cell count. A common misunderstanding is that CSF protein should always be increased in GBS; CSF protein concentrations in patients with GBS are often normal in the first week, but increased in more than 90% of the patients at the end of the second week.¹⁴ In a large study of patients with the Miller Fisher syndrome (MFS) subtype of GBS, the proportion of patients with raised CSF total protein increased from 25% in the first week to 84% in the third week.¹⁵ Recent studies have indicated

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Panel 1: Diagnosis of typical GBS**Features required for diagnosis**

Progressive weakness in both arms and legs (might start with weakness only in the legs)
Areflexia (or decreased tendon reflexes)

Features that strongly support diagnosis

Progression of symptoms over days to 4 weeks
Relative symmetry of symptoms
Mild sensory symptoms or signs
Cranial nerve involvement, especially bilateral weakness of facial muscles
Autonomic dysfunction
Pain (often present)
High concentration of protein in CSF
Typical electrodiagnostic features

Features that should raise doubt about the diagnosis

Severe pulmonary dysfunction with limited limb weakness at onset
Severe sensory signs with limited weakness at onset
Bladder or bowel dysfunction at onset
Fever at onset
Sharp sensory level
Slow progression with limited weakness without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or CIDP)
Marked persistent asymmetry of weakness
Persistent bladder or bowel dysfunction
Increased number of mononuclear cells in CSF ($>50 \times 10^6/L$)
Polymorphonuclear cells in CSF

CIDP=chronic inflammatory demyelinating polyneuropathy. Adapted from Asbury and Cornblath.¹⁷

Panel 2: Differential diagnosis of GBS**Intracranial/spinal cord abnormalities**

Brainstem encephalitis, meningitis carcinomatosa/lymphomatosa, transverse myelitis, cord compression

Anterior horn cell abnormalities

Poliomyelitis, West Nile virus

Spinal nerve root abnormalities

Compression, inflammation (eg, cytomegalovirus), leptomeningeal malignancy

Peripheral nerve abnormalities

CIDP, drug-induced neuropathy, porphyria, critical illness polyneuropathy, vasculitis, diphtheria, vitamin B1 deficiency (beri-beri), heavy metal or drug intoxication, tick paralysis, metabolic disturbances (hypokalaemia, hypophosphataemia, hypermagnesaemia, hypoglycaemia)

Neuromuscular junction abnormalities

Myasthenia gravis, botulism, organophosphate poisoning

Muscular abnormalities

Critical illness polyneuromyopathy, polymyositis, dermatomyositis, acute rhabdomyolysis

CIDP=chronic inflammatory demyelinating polyneuropathy.

with asymmetric weakness, in those with weakness initially only in the arms, in patients with rapidly progressive deterioration in pulmonary function with relative preservation of muscle force in the extremities, and in patients with prominent pain or autonomic dysfunction as the presenting symptom.¹⁸

Preceding events**Antecedent infections**

About two-thirds of patients have symptoms of an infection in the 3 weeks before the onset of weakness. One Japanese study found that the most frequent antecedent symptoms in GBS and related disorders were fever (52%), cough (48%), sore throat (39%), nasal discharge (30%), and diarrhoea (27%).¹⁹ In most GBS studies, symptoms of a preceding infection in the upper respiratory tract or gastrointestinal tract predominate, although many other types of infections have been reported. Furthermore, an argument for the post-infectious nature of GBS is the typical monophasic clinical course of the disease (figure 1). The most frequently identified cause of infection is *C jejuni*. Other well defined types of infection related to GBS are cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*.²⁰⁻²²

Vaccinations and other events

Many reports have documented the occurrence of GBS shortly after vaccinations, operations, or stressful events, but the specific relation with GBS is still debated.^{3,4,23-28} This

that the concentration of haptoglobin, α_1 -antitrypsin, apolipoprotein, and neurofilaments were increased in the CSF of patients with GBS.¹⁶ Whether these increases are of pathogenetic relevance is currently unknown. Electromyography can be helpful to confirm the diagnosis in clinically difficult cases such as in patients who have extreme pain, and is particularly needed for subclassifying GBS into the subgroups of acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP).¹⁷

In a typical patient with GBS, the diagnosis is usually straightforward. However, in atypical patients, a clearly increased CSF cell count should raise the possibility of another illness, such as a leptomeningeal malignancy, Lyme disease, West Nile virus infection, HIV-related GBS, or poliomyelitis, particularly in developing countries. Some features that could raise doubt about a diagnosis of GBS are listed in panel 1.

Clinical manifestations of GBS can vary, and an extensive number of other disorders could cause similar features of acute neuromuscular paresis (panel 2). The diagnosis of GBS can be difficult, particularly in patients

debate mainly arose after the observation of a slight increase in incidence of GBS after swine influenza vaccines were given in the USA in 1976.²⁹ Other influenza vaccines have not been associated with the same risk.²³ A retrospective study of the 1992–1994 vaccine campaigns in the USA identified that vaccines were associated with a very small, but significant, increased risk of developing GBS of about one GBS case per million vaccines above the background incidence.²⁵ A case–control survey involving about 200 patients with GBS from the UK did not show any significant association between GBS and previous immunisation.²⁴ Another study of patients who had had GBS did not show a significantly increased risk of developing GBS again after a vaccination.³⁰ However, in a recent US report on vaccinations and their side-effects, not only influenza vaccinations but also hepatitis vaccinations were suggested to be associated with the occurrence of GBS.²⁷ Special caution might be required when repeating a tetanus vaccination: we have encountered a patient who had a relapse of GBS two times after tetanus vaccinations (van Doorn, P A, unpublished). However, this does not prove that tetanus is a GBS-related agent, and has not been confirmed in large surveys,^{26,28} but it does illustrate that in any person who has recovered from GBS, the risk of any vaccination should be weighed against the risk of exposure.

Immunobiology

Studies in patients and animals have provided convincing evidence that GBS, at least in some cases, is caused by an infection-induced aberrant immune response that damages peripheral nerves.^{31–38} Four key factors have been identified that control this process (figure 2).

Antiganglioside antibodies

In about half of patients with GBS, serum antibodies to various gangliosides have been found in human peripheral nerves, including LM1, GM1, GM1b, GM2, GD1a, GalNAc-GD1a, GD1b, GD2, GD3, GT1a, and GQ1b.^{34,36,39–49} Other antibodies might bind to mixtures or complexes of different gangliosides instead of individual gangliosides.^{50–53} These gangliosides have a specific tissue distribution in peripheral nerves and are organised in specialised functional microdomains called “lipid rafts”, and play a part in the maintenance of the cell membrane structure.⁵⁴ Interestingly, most of these antibodies are specific to defined subgroups of GBS. Antibodies to GM1, GM1b, GD1a, and GalNAc-GD1a are associated with the pure motor or axonal variants of GBS, whereas antibodies to GD3, GT1a, and GQ1b are related to ophthalmoplegia and MFS (table).^{4,34,44,55} Although there is a relation between the presence of these antibodies and the clinical symptoms and severity of GBS, the pathological significance of some of these antibodies has yet to be established. Antibodies to other glycolipids, and even antibodies and T cells to peripheral nerve proteins, have also been found in patients with

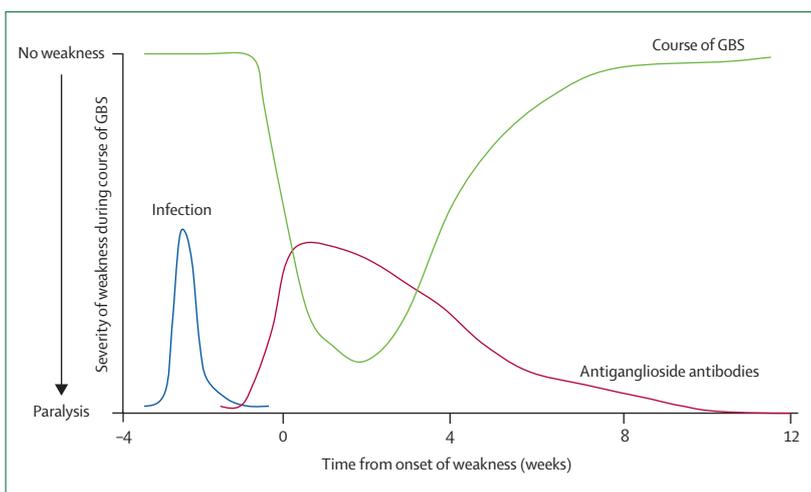


Figure 1: Relation between infections, antiganglioside antibodies, and clinical course of GBS

GBS.^{57,58} Despite intensive research over the past two decades, the immune target is still unknown in a substantial group of patients with GBS. This is particularly the case in patients with sensory-motor AIDP, the most frequent variant of GBS in developed countries.

Molecular mimicry and cross-reactivity

C jejuni isolates from patients express lipo-oligosaccharides (LOS) that mimic the carbohydrates of gangliosides.^{59–61} A gene cluster was identified that enables some *C jejuni* isolates to synthesise these structures.⁶² Specific gene variants in this cluster were associated with *C jejuni* isolates from patients with GBS and are essential for the expression of ganglioside-like LOS.^{61,63,64} The type of ganglioside mimicry in *C jejuni* seems to determine the specificity of the antiganglioside antibodies and the associated variant of GBS. *C jejuni* isolates from patients with pure motor or axonal GBS frequently express a GM1-like and GD1a-like LOS, whereas those isolated from patients with ophthalmoplegia or MFS usually express a GD3-like, GT1a-like, or GD1c-like LOS.^{53,65,66} Antibodies in these patients are usually cross-reactive, and recognise LOS as well as gangliosides or ganglioside complexes.⁵³ In a rabbit model of GBS, immunisation with a GM1-like LOS induced the production of antiGM1 antibodies and was manifest clinically as axonal neuropathy, similar to that found in the GBS patient from which the *C jejuni* was isolated.³⁸ On the basis of these results, GBS, at least in *Campylobacter*-associated GM1-related cases, is thought to be a true case of a molecular-mimicry-related disease.^{55,67} Molecular mimicry and cross-reactive immune responses have also been identified after some types of preceding infection, including *H influenzae*.⁶⁸

Complement activation

Post-mortem studies have shown that local complement activation occurs at the site of nerve damage, such as

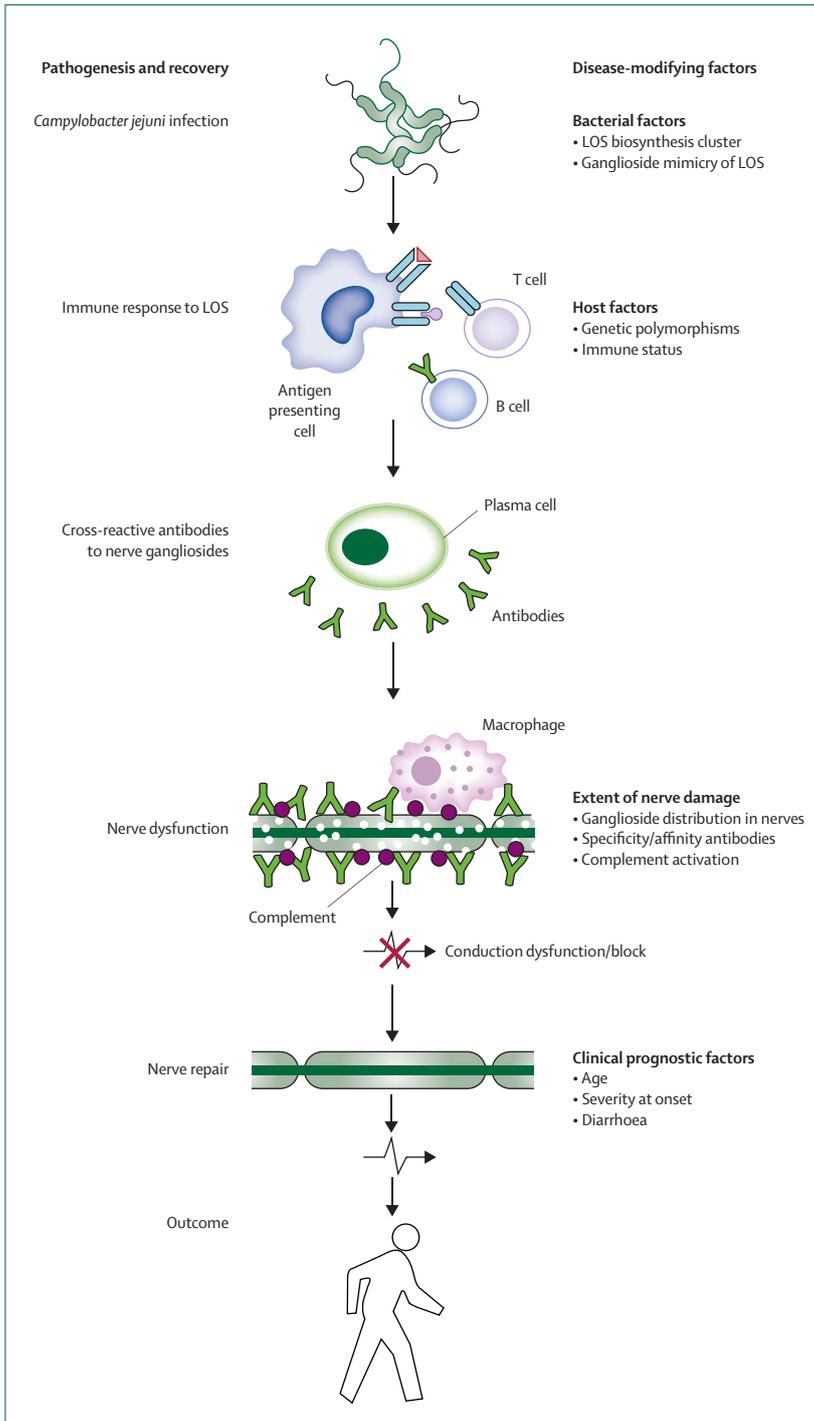


Figure 2: Immunobiology of GBS
 Infections (eg, with *C jejuni*) might induce an immune response that finally leads to GBS. The immune response depends on certain bacterial factors, such as the specificity of lipo-oligosaccharide (LOS), and on patient-related (host) factors. Genetic polymorphisms in the patients might partially determine the severity of GBS. Antibodies to LOS can cross-react with specific nerve gangliosides and can activate complement. The extent of nerve damage depends on several factors. Nerve dysfunction leads to weakness and might cause sensory disturbances. Outcome in patients with GBS can be determined with the Erasmus GBS Outcome Scale (EGOS). Using the EGOS, the chance of walking unaided after 6 months can be calculated on the basis of the age of the patient, the presence of diarrhoea, and severity of weakness in the first weeks. Despite IVIg treatment, many patients only partially recover and have residual weakness, pain, and fatigue.

	Antibodies
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) ^{34,36,44,55}	Unknown
Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN) ^{10,34,36,39,41,44,47,48,55,56}	GM1, GM1b, GD1a, GalNAc-GD1a
MFS and GBS overlapping syndrome ^{34,36,40,44,45,55}	GD3, GT1a, GQ1b

Table: Spectrum of GBS subtypes and serum antiganglioside antibodies

the axolemma in patients with AMAN and the Schwann-cell membrane in patients with AIDP.^{69,70} Accordingly, a mouse model of GBS showed that some anti-ganglioside antibodies are highly toxic for peripheral nerves. An α -latrotoxin-like effect can be induced in mice, which is characterised by a dramatic release of acetylcholine, resulting in a depletion of this neurotransmitter at the nerve terminals, and final blockade of nerve transmission and paralysis of the nerve-muscle preparation.^{71,72} The nerve terminal and perisynaptic Schwann cell are also destroyed.^{33,73} Antibodies to GM1 affect the sodium channels at the nodes of Ranvier of rabbit peripheral nerves.⁷⁴ All these effects seem to be dependent on complement activation and formation of the membrane attack complex. The neurotoxic effects of these antibodies were inhibited by immunoglobulins and the complement inhibitor eculizumab.^{75,76}

Host factors

Fewer than 1 in 1000 patients with a *C jejuni* infection will develop GBS.⁷⁷ Although some temporarily increased incidences have been described,^{10,11} epidemics or outbreaks of GBS have not been reported, not even in families infected with a ganglioside-mimicking variant of *C jejuni*.⁷⁸ Host factors might influence susceptibility to GBS, or the extent of nerve damage and outcome. We found no association between HLA class II alleles and GBS.⁷⁹ In addition, single-nucleotide polymorphisms (SNPs) in other immune-response genes showed no consistent association with susceptibility to GBS.^{80,81} However, these SNPs might play a part as disease-modifying factors. An association has been shown between disease severity or outcome and SNPs in genes coding for mannose-binding lectin, Fc gamma receptor III, matrix metalloproteinase 9, and tumour necrosis factor α .⁸²⁻⁸⁴ These studies require confirmation in large and unselected groups of patients, and a functional effect of these genetic associations needs to be shown.

Clinical spectrum

The extent and distribution of weakness, sensory involvement, and the neurophysiological characteristics vary tremendously between individuals with GBS. The most common subtype of GBS in Europe and North America is the sensory-motor form, AIDP.⁴ In Europe

and North America, fewer than 5–10% of patients have one of the axonal subtypes—AMAN or acute motor and sensory axonal neuropathy.^{4,17,85,86} Facial nerve palsy is the most common form of cranial nerve involvement in GBS, occurring in at least 70% of patients. Bulbar and oculomotor nerves are less often affected, except in patients with the antiGQ1b antibody syndromes.⁸⁷ MFS is a cranial nerve variant of GBS. These patients typically have the triad of ophthalmoplegia, ataxia, and areflexia.^{44,55,88} MFS and overlapping syndromes involving cranial nerve dysfunction and limb weakness are probably more common in Japan than in Europe. The GBS varieties have related and sometimes specific antiganglioside antibodies (table).

Bickerstaff brainstem encephalitis is another overlapping syndrome that generally starts with cranial or peripheral nerve involvement, and can later progress to severe disturbances of consciousness and even coma.⁸⁷ Recognition of Bickerstaff brainstem encephalitis is important, because this disorder might improve after PE, a treatment that, despite the absence of an RCT, could be offered in this severe condition.⁸⁷

Natural history

Rapidly progressive weakness is the core clinical feature of GBS. By definition, maximum weakness is reached within 4 weeks, but most patients have already reached their maximum weakness within 2 weeks.^{12,13} Patients then have a plateau phase of varying duration, which ranges from days to several weeks or months. This phase is followed by a usually much slower recovery phase of varying duration. In Europe, about a third of patients with GBS remain able to walk (mildly affected patients).^{5,89,90} In patients with GBS who are admitted to hospital and are unable to walk (severely affected patients), about 25% need artificial ventilation predominantly because of weakness of the respiratory muscles. Despite the effect of IVIg or PE treatment, about 20% of severely affected patients remain unable to walk after 6 months.⁹¹ Moreover, many patients remain otherwise disabled or severely fatigued.⁹² Even 3–6 years after onset, GBS has a large impact on social life and the ability to perform activities.^{93–95} GBS often remains a severe disease for which better treatment is required, at least in some patients.

General care

Patients with GBS are in particular need of excellent multidisciplinary care to prevent and manage potentially fatal complications (panel 3).⁹⁸ Thus, patients need careful and regular monitoring of pulmonary function (at least vital capacity and respiration frequency) and possible autonomic dysfunction (heart beat frequency, blood pressure), and infections need to be prevented.⁹⁹ Among other issues that need attention early in the course of disease are prophylaxis for deep-vein thrombosis, other symptoms of autonomic dysfunction

(ileus, pupil light unresponsiveness), recognition and management of pain, physiotherapy, rehabilitation, and psychosocial support.⁹⁸ Many patients and their relatives benefit from joining a patient organisation (eg, GBS/Chronic Inflammatory Demyelinating Polyneuropathy [CIDP] Foundation International, the UK GBS Support Group, or the Dutch Association of Muscle Diseases).

For the **GBS/CIDP Foundation International** see <http://www.GBS-CIDP.org/>

For the **UK GBS Support Group** see <http://www.gbs.org.uk/>

For the **Dutch Association of Muscle Diseases** see <http://www.vsn.nl/>

Panel 3: Management of GBS during the course of disease

Diagnosis

Diagnosis of GBS is mainly based on clinical features and CSF findings
Laboratory investigations include blood studies and electromyography

Give good general care

Monitor progression and prevent and manage potentially fatal complications, especially:

- Regularly monitor pulmonary function (vital capacity, respiration frequency), initially every 2–4 h, in stable phase every 6–12 h
- Regularly check for autonomic dysfunction (blood pressure, heart rate, pupils, ileus), initially continuously monitor heart rate (ECG), pulse and blood pressure. If logistically impossible, check every 2–4 h, in stable phase every 6–12 h
- Check for swallowing dysfunction
- Recognise and treat pain: acute nociceptive pain, according to WHO guidelines⁹⁶ (try to avoid opioids); chronic neuropathic pain (amitriptyline or antiepileptic drugs)
- Prevent and treat infections and pulmonary embolism
- Prevent cornea ulceration due to facial weakness
- Prevent decubitus and contractures

Consider specific treatment with IVIg or PE

Indications to start IVIg or PE:

- Severely affected patients (inability to walk unaided, GBS disability scale ≥ 3)^{91,97}
- Start IVIg preferably within first 2 weeks from onset: 0.4 g/kg for 5 days (unknown whether 1.0 g/kg for 2 days is superior); or 5× PE with total exchange volume of five plasma volumes in 2 weeks

Unknown whether IVIg is effective:

- Mildly affected patients (GBS disability scale ≤ 2) or MFS patients

Indications for re-treatment with IVIg:

- Secondary deterioration after initial improvement or stabilisation (treatment-related fluctuation): treat with 0.4 g/kg for 5 days
- No proven effect of re-treatment with IVIg in patients who continue to worsen

Is there an indication for admission to an intensive care unit?

Rapid progressive severe weakness often with impaired respiration (vital capacity <20 mL/kg)

Need for artificial ventilation

Insufficient swallowing with high chance of pulmonary infection

Severe autonomic dysfunction

Fluctuations during the course of disease or continued slow progression?

Consider treatment-related fluctuation: repeat treatment

Consider acute-onset CIDP (A-CIDP) and treat accordingly

Rehabilitation and fatigue

Start physiotherapy early during course of disease

Start rehabilitation as soon as improvement starts

Consider a physical training programme for severe fatigue

Consider contacting patients' organisation for additional information and help

CIDP=chronic inflammatory demyelinating polyneuropathy.

Treatment

Beneficial effects of immunotherapy

The first large trial to show a positive effect of immunotherapy on GBS was the North American PE study.¹⁰⁰ This positive effect was confirmed by a large French PE trial.^{101,102} PE was beneficial when applied within the first 4 weeks of onset, but the largest effect was seen when started early (within the first 2 weeks).^{100,103} The usual regimen is PE five times during 2 weeks, with a total exchange of about five plasma volumes. The first RCT on the use of IVIg was published in 1992, and showed that IVIg is as effective as PE.¹⁰⁴

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 centres, mainly because of its greater convenience and availability. The Cochrane review on the use of IVIg in GBS contained four additional trials.¹⁰⁵ 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.¹⁰⁶

Oral steroids or intravenous methylprednisolone (500 mg daily for 5 consecutive days) alone are not beneficial in GBS.^{107,108} The combination of IVIg and intravenous methylprednisolone 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.^{91,109,110} The well defined lack of a more obvious effect of corticosteroids remains a puzzling issue in an inflammatory neuropathy disorder such as GBS. Possible explanations could include the minor effect of steroids on the toxicity of antiganglioside antibodies and subsequent complement activation, or an adverse effect on macrophages that clear myelin debris and thus hamper remyelination.^{111,112} We recently studied the additional effect of a 6-week course of mycophenolate mofetil in GBS.¹¹³ In this pilot study, there seemed to be no positive effect of mycophenolate mofetil.¹¹³ Although there definitely is a positive effect of immunotherapy on the course of GBS, new research into ways to improve the final outcome of GBS are urgently needed.⁹¹

Assessment of treatment effect and outcome

The selection of trial outcome measurements is important because the assessment scales used should be valid, reliable, and responsive to clinically relevant changes over time to judge whether a treatment is effective. Assessment can be made at the levels of impairment, activities (disability), participation (handicap), and quality of life.¹¹⁴ Most trials of treatment in GBS have used the GBS disability scale as their primary outcome measurement.⁹⁷ This is a seven-point scale, ranging from no symptoms (F=0), able to walk 10 m without assistance (F=2), bedbound (F=4), to death (F=6).⁹⁷ It is used to measure at the levels of activity and participation, and primarily

assesses ambulation and the need for ventilatory assistance, but unfortunately does not assess arm function. This is one of the reasons why the Inflammatory Neuropathy Cause and Treatment (INCAT) group has introduced and evaluated the overall disability sum score, the overall neuropathy limitations scale, and the Rotterdam handicap scale.¹¹⁵⁻¹¹⁷ Secondary outcome measurements in RCTs of GBS have generally been assessed at the impairment level (eg, the Medical Research Council sum score or the number of days the patient is on the ventilator).¹⁰⁴ More recently, quality-of-life measures, such as the 36-item short form questionnaire (SF-36) have been used in studies assessing fatigue in GBS.^{118,119} The INCAT group concluded that the activity and participation level should preferentially be used as the main method of measuring therapeutic response in patients with peripheral neuropathy.^{114,120} The international Peripheral Neuropathy Outcome Measures Standardization (PeriNomS) study is currently assessing different outcome scales in immune-mediated neuropathies.¹²¹

Timing of treatment

The North American PE trial showed an effect of PE when applied within the first 4 weeks after onset of weakness.¹⁰⁰ However, the greatest effect was observed when PE was started within the first 2 weeks from onset in patients who were unable to walk.¹⁰⁰ Since the publication of this trial, 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 reasonable to treat these patients with IVIg. But what about patients who are admitted to the intensive care unit due to severe swallowing problems or autonomic dysfunction but who are still able to walk? In these patients, it also seems reasonable to start treatment.

Treatment of mildly affected patients

“Mildly affected” is arbitrarily defined as being able to walk, with or without assistance. A retrospective study showed that these patients often have residual disabilities.¹²² RCTs that have assessed the effect of IVIg have not studied the effect in mildly affected patients.⁹¹ One large French randomised trial studied the effect of PE in patients who could walk with or without aid, but could not run.⁸⁹ Onset of motor recovery was faster in patients who received two PE sessions than in those who received no PE. On the basis of this study, there might be an indication to treat mildly affected patients who have GBS with PE, but it should be kept in mind that no randomised placebo-controlled trials have assessed the effect of PE or IVIg in these mildly affected patients with GBS.

Treatment of patients with MFS

No RCTs have studied the effect of PE or IVIg in patients with MFS.¹²³ Observational studies have suggested that the final outcome in patients with MFS is generally good. In a large Japanese uncontrolled observational study,¹²⁴ IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia, but the times to resolution of these symptoms were similar among the IVIg, PE, and control groups. The investigators concluded that IVIg and PE did not influence the outcome of patients with MFS, presumably because of good natural recovery. Some patients with MFS can be severely affected and could also have swallowing and respiratory problems; they might even have an overlapping syndrome with additional weakness in the arms and legs. One could argue that particularly in these patients, or in patients with severe autonomic dysfunction, IVIg treatment might be indicated, although there is no positive evidence of a benefit.

Treatment of patients who continue to deteriorate

Some patients with GBS continue to deteriorate after PE or a standard course of IVIg.⁹¹ In these cases, the best option is unknown: wait and see, or start additional treatment. The dilemma is caused by the fact that the course of GBS in individual patients is highly variable and the effect of treatment can be shown only by comparing groups of patients. The reason why some patients continue to deteriorate and could be paralysed for months is not known. These patients might have a severe or prolonged immune attack that causes severe axonal degeneration for which current treatment regimens are insufficient. 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.¹⁰⁶ Thus, 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.¹²⁵ This uncontrolled study suggested that a repeated course of IVIg could be effective.¹²⁵ We are currently involved in setting up an international trial to study the effect of a second IVIg dose in patients with a poor prognosis, based on the Erasmus Guillain-Barré outcome score (EGOS),¹²⁶ which is likely to start soon.

Treatment of patients who deteriorate after initial improvement

About 5–10% of patients with GBS deteriorate after initial improvement or stabilisation following IVIg treatment, a condition named “treatment-related clinical fluctuation” (figure 3).¹²⁷ 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), because these patients are likely to improve after re-initiating this treatment.⁹¹ These patients are thought to

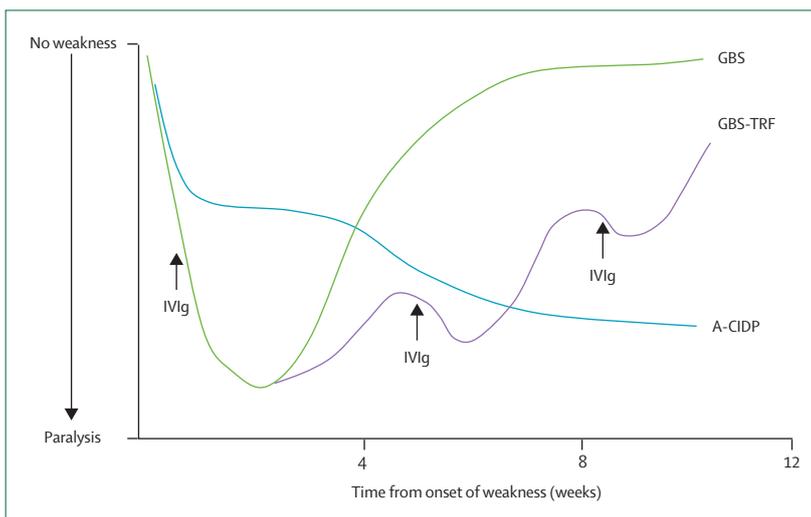


Figure 3: GBS, treatment-related fluctuations (TRF), and acute-onset CIDP (A-CIDP). IVIg=treatment with a course of IVIg (2 g/kg bodyweight) over 2–5 days.

have a prolonged immune response that causes persistent nerve damage that needs treatment for a longer period of time.¹²⁸ Some of these patients with GBS might even have several episodes of deterioration. This often raises the question of whether these patients might have CIDP with acute onset (A-CIDP).

The question of how many episodes of deterioration would alter the diagnosis from GBS to A-CIDP is an important one, but the answer is not yet fully known. The difference between GBS and CIDP is mainly based on the duration of progressive weakness, which is less than 4 weeks in GBS, and, on the basis of research criteria, at least 8 weeks for CIDP.^{12,13,129} A subacute form between GBS and CIDP has been described.¹³⁰ Some patients initially have a course like that of GBS, but finally turn out to have CIDP. We have assessed our patients and concluded that the diagnosis of A-CIDP should be suspected if patients who were initially diagnosed with GBS have three or more of these episodes of deterioration or if they have a subsequent deterioration after 9 weeks from onset of GBS.¹³¹ It is important to look for these episodes of secondary deterioration because patients with GBS might improve after a new course of IVIg and some of these patients turn out to have a variant of A-CIDP that requires chronic maintenance treatment.^{131–133}

Recognition and management of additional symptoms

Pain in the acute and chronic phases

Pain is a common and severe symptom in patients with GBS. Recognition of pain is important, especially in patients who are unable to communicate due to intubation. Pain as a presenting symptom before the onset of weakness might be confusing and can cause a delay in making a diagnosis of GBS. Pain has been described in up to 89% of patients with GBS.^{134–136}

Different symptoms of pain associated with GBS have been distinguished during different phases of disease: paraesthesia or dysaesthesiae, backache or root pain, meningism, muscle pain, joint pain, and visceral pain.^{137,138} Pain in GBS can be very severe, and treatment is often far from successful. There are some reports on the effect of medication to relieve pain in GBS.^{139–145} Corticosteroids, opioids, gabapentin, and carbamazepine are suggested to be effective, although these reports are based on limited numbers of patients, mostly in open studies, and often all types of pain are included together. The likely origin of pain is multifactorial. Pain in the acute phase of GBS might be of nociceptive origin due to inflammation. Small-diameter nerves in the skin, among others responsible for nociception, are affected in GBS. A reduction in intraepidermal nerve fibre density has been found in skin biopsies from patients with GBS.¹⁴⁶ Later in the course of disease, non-nociceptive neuropathic pain might result from degeneration and perhaps even regeneration of sensory nerve fibres. Recognition of the presence and type of pain is important because specific treatments can be offered. Skin biopsies might be helpful to elucidate mechanisms that give rise to a painful neuropathy in GBS.

Autonomic failure

Autonomic dysfunction is a common complication in GBS and occurs in approximately two-thirds of patients.^{135,147–150} The extensive distribution of autonomic nerves might result in an array of signs and symptoms due to sympathetic and parasympathetic failure or over-reactivity. Symptoms include various types of cardiac arrhythmias, blood pressure fluctuations, abnormal haemodynamic responses to drugs, sweating abnormalities, pupillary abnormalities, and bladder and bowel dysfunction.^{147–150}

Although autonomic dysfunction is usually of minor clinical importance, life-threatening cardiovascular complications might develop. 3–10% of patients with GBS die, and in some of these patients the cause is likely to be (sudden) autonomic failure.¹⁴⁸ Therefore, recognition of autonomic dysfunction is important. Predicting which patients will develop serious autonomic failure and will therefore need continuous monitoring is not yet possible. Potentially serious bradyarrhythmias, ranging from bradycardia to asystole, have been found in severely disabled patients, but also in patients who were still able to walk.¹⁵¹ Frequent monitoring of autonomic dysfunction is recommended in all patients with GBS.⁹⁸ In some cases, application of a transcutaneous pacemaker is indicated or atropine has to be given. In general, vasoactive medication and morphine derivatives should be used with caution. Autonomic nerve fibres can be studied by skin biopsy, and a correlation between reduced intraepidermal nerve fibre density values in skin biopsies from patients with GBS who have clinical autonomic dysfunction has been described.¹⁴⁶

Severe fatigue after GBS

Fatigue after GBS is an important problem.⁹⁸ Severe fatigue has been reported in 60% and 80% of patients.^{92,152} In a study of patients with immune-mediated polyneuropathies, including GBS, 80% of patients reported fatigue among their three most disabling symptoms.⁹² Of note, fatigue was independent from severity of weakness during the initial phase of GBS and might remain present for many years.^{92,152} Amantadine is not effective for the relief of fatigue after GBS.¹¹⁸ However, 12 weeks of bicycle exercise training was found to be effective in 16 severely fatigued, but neurologically well recovered patients who had GBS, and in four stable patients with CIDP.¹¹⁹ The intensive, three-times weekly training programme used was well tolerated, and self-reported fatigue scores decreased significantly. Physical fitness, functional outcome, and quality of life also improved.¹¹⁹ A 12-week physiotherapist-prescribed community-based unsupervised training programme was also effective.¹⁵³ However, an RCT still needs to be done. From the physiological point of view, conventional nerve-conduction studies in fatigued patients with GBS showed restored values,¹⁵⁴ although distribution of conduction velocity showed some altered values.¹⁵⁵ More detailed studies that used sustained maximum voluntary contractions suggest that central changes are involved.¹⁵⁶ From a more holistic point of view, changes in fatigue, actual mobility, and perceived functioning seem not to be influenced by changes in physical fitness.¹⁵⁷ A combination of physical and psychological factors seems to determine fatigue after GBS. Although the effect of the physical training programme cannot be fully explained, it does seem to help, possibly by giving self-assurance and by changing the patient's lifestyle.

Prognosis

The prognosis of GBS is difficult to predict in individual patients because of the substantial variation in outcome. Advanced age, however, is generally reported to be indicative of a worse prognosis. The severity of GBS seems to be determined in the early phase of the disease.¹²² RCTs that have investigated the effect of IVIg or PE in patients who were unable to walk have concluded that about 20% of patients remained unable to walk unaided after 6 months.⁹¹ Neurophysiological testing is reported to be helpful for assessing the risk of respiratory failure, which was highest in patients with a reduction in vital capacity of more than 20% and signs of demyelination as expressed by a reduction in peroneal proximal/distal compound action potential.¹⁵⁸ Peroneal nerve conduction block and age above 40 years were independent predictors of disability at 6 months.¹⁵⁸ In a recent study, we developed a simple clinical scoring system (EGOS) that can easily be used at the bedside of a patient with GBS in the acute stage of disease.¹²⁶ It can accurately predict the chance of independent walking after 6 months, and can be calculated within the first 2 weeks of disease onset by use

Search strategy and selection criteria

References for this Review were identified by searches of PubMed, Embase, and the Cochrane Library from January, 1985, to June, 2008, by use of the terms "Guillain-Barré syndrome", "acute inflammatory demyelinating polyneuropathy", "AMAN", "Miller Fisher syndrome", and "Fisher syndrome". Articles resulting from that search and relevant references cited in those articles were considered. The articles were chosen if they focused on the latest advances in the field. Articles were also identified through searches of the authors' own files. With the exception of the papers on the origins of the disease and one Japanese paper³⁵ and one French paper,¹⁴⁰ only papers published in English were included.

of age, presence of preceding diarrhoea, and GBS disability score.¹²⁶ On the basis of the EGOS, the predicted chance of recovery for individual patients varies from 1% to 83%. The accuracy of this scale was confirmed in an independent cohort of patients with GBS. EGOS can be used to inform individual patients about their prognosis, and can also be used in new treatment trials that more specifically target patients with GBS who have the worst prognosis.

Future directions

New treatment options in GBS are necessary because the prognosis in a large proportion of patients with GBS is still far from good. One option in the acute phase could be a second course of IVIg treatment in patients with a bad prognosis. Recent studies indicate that agents that interfere with complement activation are potentially attractive candidates to be tested in the very early phase of GBS.^{74,75} When it is possible to predict outcome in individual patients more accurately, new drugs or regimens could be tested in a restricted GBS population of severely affected patients. New trials that investigate less aggressive treatments are also indicated in mildly affected patients, and possibly also in patients with MFS. More attention should be paid to pain, autonomic dysfunction, and severe fatigue, all of which are often under-recognised conditions in GBS.

Contributors

PAvD wrote the first draft of the manuscript. LR and BCJ contributed to subsequent versions.

Conflicts of interest

PAvD has received a consultation fee for being in the steering committee of the ICE trial (sponsored by Talecris). PAVD's department has received a research grant from Baxter Healthcare. Both Talecris and Baxter are manufacturers of IVIg. BCJ and LR have no conflicts of interest.

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