Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis

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Abstract | Guillain-Barré syndrome (GBS) is a potentially life-threatening postinfectious disease characterized by rapidly progressive, symmetrical weakness of the extremities. About 25% of patients develop respiratory insufficiency and many show signs of autonomic dysfunction. Diagnosis can usually be made on clinical grounds, but lumbar puncture and electrophysiological studies can help to substantiate the diagnosis and to differentiate demyelinating from axonal subtypes of GBS. Molecular mimicry of pathogen-borne antigens, leading to generation of crossreactive antibodies that also target gangliosides, is part of the pathogenesis of GBS; the subtype and severity of the syndrome are partly determined by the nature of the antecedent infection and specificity of such antibodies. Intravenous immunoglobulin and plasma exchange are proven effective treatments but many patients have considerable residual deficits. Discrimination of patients with treatment-related fluctuations from those with acute-onset chronic inflammatory demyelinating polyneuropathy is important, as these conditions may require different treatments. Novel prognostic models can accurately predict outcome and the need for artificial ventilation, which could aid the selection of patients with a poor prognosis for more-individualized care. This Review summarizes the clinical features of and diagnostic criteria for GBS, and discusses its pathogenesis, treatment and prognosis.

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Introduction

Guillain-Barré syndrome (GBS) is a common cause of acute flaccid paralysis, characterized by symmetrical weakness of the limbs, and hyporeflexia or areflexia, which reaches a maximum severity within 4 weeks (Figure 1).¹⁻⁴ Sensory symptoms, such as paraesthesia or numbness, usually start distally and have a symmetrical pattern. The most common subtypes of GBS are acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). 1,3,5-8 A less common subtype is Miller Fisher syndrome (MFS), which is characterized by ophthalmoplegia, ataxia and areflexia. 9,10 Overall, the clinical course, severity and outcomes of GBS are highly variable.

GBS typically occurs after an infectious disease in which the immune response generates antibodies that crossreact with gangliosides at nerve membranes. This autoimmune response results in nerve damage or functional blockade of nerve conduction. The type of preceding infection and the specificity of the antiganglioside

Competing interests

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antibodies largely determine the subtype and clinical course of GBS. Over the past 10 years, much new information has been gathered about the role of antecedent infections and antiganglioside antibodies in the immunopathology of GBS. We now know that the most common pathogen causing the antecedent infection is Campylobacter jejuni, which is associated with the AMAN subtype of GBS.

Currently, intravenous immunoglobulin (IVIg) and plasma exchange are proven effective treatments for GBS.^{11–15} However, despite these treatment options, many patients have a severe disease course, pain, and residual deficits. In this Review, we summarize current data on the immune pathogenesis and clinical characteristics of GBS. We describe the current diagnostic criteria for GBS, and discuss the possible additional diagnostic value of cerebrospinal fluid (CSF) examinations and nerve conduction tests. In addition, we review treatment options and prognosis, including novel predictive models, for patients with GBS.

Epidemiology

GBS is a rare disease with an incidence of 0.81-1.89 (median 1.11) per 100,000 person-years, and is more common in men than in women (ratio 3:2).^{1,16} Worldwide, the incidence is variable; for example, a low rate of 0.40 per 100,000 person-years was reported in Brazil, in contrast to a high rate of 2.5 per 100,000 person-years in Curação and Bangladesh. 16-20 GBS seems to occur less

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Key points

- Guillain-Barré syndrome (GBS) is a heterogeneous disease characterized by rapidly progressive, symmetrical limb weakness with hyporeflexia or areflexia; sensory disturbances and cranial nerve deficits occur in some patients
- The clinical diagnosis of GBS can be supported by additional investigations (such as cerebrospinal fluid examination and nerve conduction studies), which are especially useful in patients with atypical features or diagnostic doubt
- Molecular mimicry, antiganglioside antibodies and, likely, complement activation are involved in the pathogenesis of GBS; a potential role for genetic susceptibility requires further investigation
- Intravenous immunoglobulin and plasma exchange are proven effective treatments, but improved therapies are needed as ~25% of patients require artificial ventilation and 20% are unable to walk after 6 months
- Pain is an important symptom that may be present before onset of weakness, and can impede correct diagnosis, especially in children; other residual features (sensory disturbances and fatigue) may persist for years
- Prognostic models can predict patient outcomes at 4 weeks, 3 months and 6 months, as well as the probability of respiratory insufficiency, even early in the course of the disease

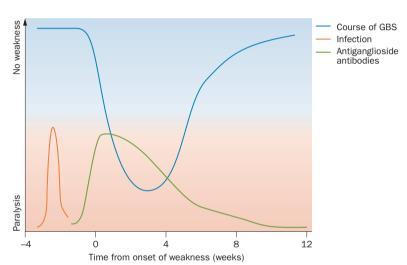


Figure 1 | The course of GBS. The majority of patients with GBS report an infection before the onset of weakness. Antiganglioside antibodies are often detected; their levels decrease over time. Different types of antibodies are related to the preceding infection and the GBS subtype. Progressive weakness reaches its maximum within 4 weeks (often within 2 weeks). The recovery phase may last many weeks, months or even years. Abbreviation: GBS, Guillain–Barré syndrome. Reprinted from *Lancet Neurology* 7, van Doorn, P. A., Ruts, L. & Jacobs, B. C. Clinical features, pathogenesis, and treatment of Guillain–Barré syndrome, 939–950 © (2008), with permission from Elsevier.

frequently in children (0.34–1.34 per 100,000 person-years) than in adults, ¹⁸ and its incidence increases with age. ^{16,18} The background incidence of GBS in most studies remains constant over time, although seasonal fluctuations have occasionally been found in studies from Curaçao, Bangladesh and China. ^{17,18,20,21}

The proportions of patients with GBS who have AIDP and AMAN vary greatly around the world. AIDP is the predominant subtype (60–80% of patients) in North America and Europe. 1,2,6 By contrast, the frequency of AMAN ranges from 6–7% in the UK and Spain to 30–65% in Asia, Central America and South America. 6,7,22–24 The geographical diversity is probably attributable to differences in exposure to certain types of

infection, possibly in combination with different genetic susceptibilities due to varying genetic polymorphisms between individuals or groups of people living in different areas of the world. These differences may be related not only to the development of a specific GBS subtype, but also to the course and severity of disease. Genetic studies with a high number of patients are required to investigate these relationships.

Pathogenesis

As indicated above, GBS is a postinfectious disorder. Two-thirds of patients report symptoms of a respiratory or gastrointestinal tract infection before the onset of GBS. In about half of patients with GBS, a specific type of preceding infection can be identified,²⁷ and C. jejuni is responsible for at least one-third of these infections.^{3,24,27} Other pathogens that cause antecedent infections related to GBS are cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumonia, Haemophilus influenzae, and influenza A virus. 3,27,28 Notably, a case-control study conducted in the Netherlands showed that 5% of patients with GBS had a hepatitis E virus infection before onset of GBS, compared with 0.5% of matched healthy controls.²⁹ Similarly, 10% of patients with GBS from Bangladesh had an antecedent hepatitis E virus infection, indicating that hepatitis E virus is a worldwide trigger of GBS.³⁰ However, despite the strong association between specific acute infections and GBS, the overall risk of developing this severe postinfectious complication is very small. Only one in 1,000-5,000 patients with Campylobacter enteritis will develop GBS in the subsequent 2 months.31,32 This fact explains why GBS is a sporadic disorder, although outbreaks of GBS after C. jejuni infection have occasionally been reported.³³

One of the critical steps in GBS pathogenesis after C. jejuni infection is the generation of antibodies that crossreact with specific gangliosides (Figure 2), which are not produced during uncomplicated C. jejuni gastroenteritis.34,35 However, the production of crossreactive antibodies is only induced in susceptible individuals. 35,36 Antibodies that crossreact with various gangliosides have been described in patients with GBS.3,37-39 However, only a subset of *C. jejuni* strains contain lipo-oligosaccharides that mimic the carbohydrate moiety of gangliosides that are present in human peripheral nerves (Figure 2).3 The synthesis of these ganglioside-mimicking carbohydrate structures depends on a set of polymorphic genes and enzymes that vary greatly between different C. jejuni strains. 40,41 The Thr51 variant of the C. jejuni cstII gene is associated with the occurrence of GBS, while the Asn51 variant is associated with MFS.42

Some antibody specificities are associated with particular GBS subtypes and related neurological deficits, reflecting the distribution of different gangliosides in human peripheral nerves (Table 1).^{3,43} *C. jejuni* infections are predominantly, but not exclusively, related to the AMAN or pure motor subtype of GBS.⁴⁴ Patients with AMAN frequently have serum antibodies against GM1a, GM1b, GD1a and GalNAc-GD1a gangliosides.^{3,7,37,45-47} Patients with MFS or MFS-GBS overlap syndrome

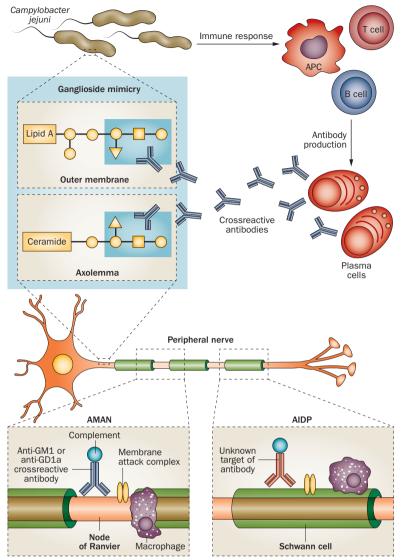


Figure 2 | Immunopathogenesis of GBS: molecular mimicry and antiganglioside antibodies. Infections with pathogens, such as Campylobacter jejuni, can trigger humoral immune and autoimmune responses that result in nerve dysfunction and the symptoms of GBS. Lipo-oligosaccharides on the C. jejuni outer membrane may elicit the production of antibodies that crossreact 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 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. Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; APC, antigen-presenting cell; GBS, Guillain-Barré syndrome; MAC, membrane attack complex.

(see below) frequently have antibodies against GD1b, GD3, GT1a and GQ1b gangliosides, which are related to ataxia and ophthalmoplegia.^{3,9,37,48,49} In a study from the Netherlands, 20% of patients with AIDP related to cytomegalovirus infection had anti-GM2 antibodies, although these antibodies are also found in patients

with uncomplicated cytomegalovirus infections. ^{27,50} Interestingly, as well as antibodies against single gangliosides, patients can also have antibodies against combinations of epitopes from ganglioside complexes. ^{38,51–53} Such complexes are located in specialized microdomains, or 'lipid rafts', in the cell membrane. ⁵⁴ Antibodies that target ganglioside complexes also crossreact with *C. jejuni* lipo-oligosaccharides, and are probably induced by a preceding infection with *C. jejuni*. ⁵⁵ Antibodies against various combinations or complexes of glycolipids have also been reported in patients with AIDP, although the role of these antibodies in its pathogenesis remains to be determined. ⁵³

In conjunction with the presence of antiganglioside antibodies, complement activation seems to contribute to nerve degeneration in GBS^{56,57}—a phenomenon that has been studied at the nodes of Ranvier and at the motor nerve terminal in a mouse model of AMAN.⁵⁸ Sodium channel clusters, as well as paranodal axoglial junctions, the nodal cytoskeleton, and Schwann cell microvilli, all of which stabilize the sodium channel clusters, were disrupted by complement activation in a GBS disease model.^{7,59,60} Additional studies in a GBS mouse model provided evidence that blockade of complement activation prevents emergence of the clinical signs of antiganglioside-mediated neuropathy.⁶¹

The development of GBS after a C. jejuni infection may also depend on patient-related factors that influence the susceptibility to produce crossreactive, carbohydratetargeted antibodies. This hypothesis is supported by the fact that GBS has a relapse rate of 5%, which is clearly higher than would be expected by chance.⁶² The initial pathogen-host interaction has a key role in the development of GBS. C. jejuni lipo-oligosaccharides bind to siglec-7 (sialic acid-binding immunoglobulin-like lectin 7) and activate dendritic cells via Toll-like receptor 4 and CD14. These dendritic cells produce type 1 interferon and tumour necrosis factor (TNF), which induce proliferation of B cells. 35,63,64 This immune activation could be influenced by genetic polymorphisms but, to date, genetic factors have only been studied in small cohorts of patients. Interestingly, a meta-analysis identified a moderate association between GBS and a particular TNF polymorphism.65 In addition, an association between polymorphisms in the MBL2 gene (encoding mannose-binding protein C) and the severity and outcome of GBS has been confirmed.²⁵ Future genomewide association studies in large, well-described and adequately controlled cohorts are required to establish the role of host factors in the pathogenesis of GBS.

The potential role of vaccination

A few patients develop GBS shortly after receiving a vaccination. Despite their rarity, such events cause considerable public concern. In the vaccination campaign against influenza A (H1N1) in the USA in 1976, the estimated attributable risk of vaccine-related GBS was about one in 100,000.⁶⁶ A similar association was suggested for the vaccination campaign against influenza A (H1N1) in 2009, but extensive national and international

Table 1 | GBS subtypes, clinical features and relevant antibodies 3,37,43

Table 1 GBS subtypes, clinical features and relevant antibodies			
GBS subtypes	Main clinical features	NCS findings	Antibodies*
Acute inflammatory demyelinating polyneuropathy (AIDP)	Sensorimotor GBS, often combined with cranial nerve deficits and frequent autonomic dysfunction	Demyelinating polyneuropathy	Various‡
Acute motor axonal neuropathy (AMAN)	Pure motor GBS; cranial nerves rarely affected	Axonal polyneuropathy, sensory action potential normal	GM1a, GM1b GD1a GalNAc-GD1a
Acute motor sensory axonal neuropathy (AMSAN)	Resembles severe AMAN, but sensory fibres are affected, leading to sensory deficits	Axonal polyneuropathy, sensory action potential reduced or absent	GM1, GD1a
Pharyngeal- cervical brachial variant	Prominent weakness of oropharyngeal, facial, neck and shoulder muscles	Normal in most patients, sometimes abnormalities in arms, mostly axonal pattern	GT1a>GQ1b >>GD1a
Miller Fisher syndrome	Ataxia, ophthalmoplegia, areflexia	Normal in most patients; discrete changes in sensory conduction or H-reflex may be present	GQ1b, GT1a

^{*}Antibodies are predominantly IgG, but IgM and IgA antibodies have also been demonstrated. ‡Association with GBS and role in its pathogenesis unknown. Abbreviations: GBS, Guillain–Barré syndrome; NCS, nerve conduction study.

studies found that vaccination was associated with only a small attributable risk of GBS: 1.6 excess cases of GBS per 1,000,000 vaccine recipients, a frequency similar to that for all seasonal vaccinations.⁶⁷ In fact, vaccination might even reduce the risk of acquiring GBS, as this condition can be caused by infections such as influenza. The risk of developing GBS after influenza infection is estimated to be 4–7 times higher than after influenza vaccination.⁶⁸ No relapses of GBS in patients with a history of this disease have been observed after influenza vaccination.^{68,69}

For these reasons, the following practical guideline regarding vaccination of patients with a history of GBS is currently used in the Netherlands: GBS as such is not an indication for influenza vaccination, and vaccination seems to be safe in patients who developed GBS >3 months ago and when onset of GBS was not shortly after vaccination.⁷⁰

Diagnosis

Diagnostic criteria

In 1978, the US National Institute of Neurological Disorders and Stroke (NINDS) developed case definitions for GBS in the course of investigating the suspected association between GBS and the swine flu vaccination campaign of 1976–1977. The initial diagnostic criteria published in 1981 were modified in 1990.^{4,71} Though primarily developed for research purposes, they are probably still the most widely used criteria in clinical practice.⁴ The criteria consist of features that are required for or strongly support the diagnosis of GBS, and features that cast doubt on the diagnosis (Box 1).

In 2011, the Brighton Collaboration published new case definitions for GBS while studying a possible association between GBS and the H1N1 swine flu vaccination

campaign of 2009–2010.72 These criteria were specifically developed for retrospective epidemiological and vaccine safety studies and, consequently, are likely to combine high specificity with limited sensitivity. The Brighton criteria identify GBS with four levels of diagnostic certainty, from level 1 (highest) to level 4 (lowest). Use of the Brighton criteria to classify patients with suspected GBS is highly dependent on completeness of the diagnostic data. A study from the Netherlands in 335 patients with GBS with complete sets of diagnostic data—which are required for level 1 certainty according to the Brighton criteria—classified 61% as level 1, 33% as level 2, none as level 3 and 6% as level 4. However, patients diagnosed at different levels of diagnostic certainty did not differ in disease severity or outcome.73 In studies from Korea and India in patients who had GBS, 24% and 14% of patients, respectively, were classified as level 4.74,75 The Brighton criteria are not, however, intended to be used for diagnostic purposes in clinical practice. Further research is needed to develop criteria that can be used to diagnose GBS and its less-frequent variants in the acute phase of the disease. However, in practice, the criteria published in 1990 still provide a good basis for clinicians worldwide to make a diagnosis of GBS.

Clinical symptoms and subtypes of GBS

GBS is characterized by a rapidly progressive, symmetrical weakness of the limbs in combination with hyporeflexia or areflexia.^{2,4,73} However, GBS is highly diverse with respect to the presence, distribution and extent of cranial nerve deficits, sensory symptoms, weakness, ataxia, pain, autonomic dysfunction, and the course of the disease. Many patients have sensory deficits, such as numbness and/or paraesthesias. About half of the patients have cranial nerve deficits, especially bilateral facial weakness, swallowing difficulties or (sometimes) extraocular motor dysfunction.4 A high proportion (54-89%) of patients with GBS experience pain, including painful paraesthesias, backache, muscle pain and meningism, which may even precede the onset of muscle weakness in about one-third of GBS cases. 2,4,76,77 Approximately 25% of patients develop respiratory insufficiency requiring artificial ventilation. 73,78-80 Autonomic dysfunction (predominantly cardiovascular dysregulation) is present in about two-thirds of patients, although its severity is highly variable.^{2,77,81} About one-third of patients remain able to walk throughout the course of the disease, and are often described as mildly affected.

GBS is a monophasic disease, usually reaching maximum severity (nadir) within 4 weeks.^{1,2,4} One study showed that 80% of patients with GBS reach the nadir within 2 weeks after onset of weakness, and 97% reach the nadir within 4 weeks.⁷³ A further subset of patients reach the nadir within 4–6 weeks of onset of weakness.^{73,82} The progressive phase is usually followed by a plateau phase ranging from 2 days to 6 months (median duration 7 days) before patients start to recover (Figure 1).⁷³

Various subtypes of GBS have been reported that differ in their clinical, electrophysiological and histological features (Table 1 and Box 1).^{1,3,6–8,23} The two

Box 1 | Diagnostic criteria for GBS^{2,4,6,7}

Features required for diagnosis of GBS*

- Progressive weakness in legs and arms (sometimes initially only in legs)
- Areflexia (or decreased tendon reflexes) in weak limbs

Acute inflammatory demyelinating polyneuropathy (AIDP)

Additional symptoms

- Progressive phase lasts 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)

Nerve conduction study findings

- Features of demyelination (only assessable if distal CMAP amplitude is >10% LLN)
- Prolonged distal motor latency
- Decreased motor nerve conduction velocity[‡]
- Increased F-wave latency, conduction blocks and temporal dispersion

Acute motor axonal neuropathy (AMAN)

Additional symptoms

- Progressive phase lasts days to 4 weeks
- Relative symmetry of symptoms
- No sensory symptoms or signs
- Cranial nerve involvement (rarely)
- Autonomic dysfunction
- Pain (sometimes)

Nerve conduction study findings

- No features of demyelination (or, one demyelinating feature in one nerve if distal CMAP amplitude is <10% LLN)
- Distal CMAP amplitude is <80% LLN in at least two nerves
- Transient motor nerve conduction block may be present (possibly caused by antiganglioside antibodies)

Features that should raise doubt about the diagnosis of GBS

- Increased number of mononuclear cells in cerebrospinal fluid (>50 cells per μl) or polymorphonuclear cells in cerebrospinal fluid
- 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 spinal cord sensory level
- Slow progression with limited weakness and without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or acute-onset chronic inflammatory demyelinating polyneuropathy)
- Marked persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- *Classification of GBS as either AIDP or AMAN is not required for diagnosis of GBS, and whether AIDP and AMAN require different treatments is unknown. [‡]The amount of conduction slowing required to define demyelination differs between classification systems. ^{6,23} Abbreviations: CMAP, compound muscle action potential; GBS, Guillain–Barré syndrome; LLN, lower limit of normal.

best-known GBS subtypes are AIDP and AMAN. AIDP is a sensorimotor form of GBS that is often accompanied by cranial nerve deficits, autonomic dysfunction, and pain. This condition is characterized by a demyelinating polyneuropathy at electrophysiological examination. By contrast, AMAN is a pure motor form of GBS, in which the axonal polyneuropathy is not accompanied by sensory deficits at clinical and electrophysiological examination (although 10% of patients with AMAN do have sensory symptoms). Cranial nerve deficits are less frequent than in AIDP, but patients with AMAN may have autonomic dysfunction and pain. AMAN than in AIDP, and recovery is often

prolonged, owing to axonal degeneration. However, some patients with AMAN recover quickly, even from severe weakness.⁸³ AMAN is frequently associated with an antecedent *C. jejuni* infection.^{7,8,46}

In some patients with axonal GBS, sensory as well as motor fibres are affected. This subtype, termed acute motor and sensory axonal neuropathy (AMSAN), can be considered a severe variant of AMAN. 1,3,7 MFS is an uncommon subtype of GBS characterized by the clinical triad of ophthalmoplegia, ataxia and areflexia. 9,10,49,84 In most patients, diplopia is the presenting symptom. 9,10,49 Patients with MFS usually have a good clinical outcome but some develop limb weakness and respiratory insufficiency (termed MFS-GBS overlap syndrome). A new electrophysiological technique called compound muscle action potential (CMAP) scanning has shown that some patients with MFS also have subclinical limb motor nerve dysfunction.85 Other local variants of GBS, such as the pharyngeal-cervical-brachial variant, have also been reported.3,84,86

Atypical GBS

About 8% of patients with GBS present with paraparesis, which often complicates the diagnosis and requires extensive diagnostic work-up. Paraparesis may persist in about 70% of these patients during follow-up.⁷³ Definite asymmetrical limb weakness, however, is very uncommon in patients with GBS.⁷³

Although the 1990 GBS criteria require hyporeflexia or areflexia for the diagnosis of GBS, in one cohort of patients with GBS, 9% had normal tendon reflexes in weak arms and 2% had normal tendon reflexes in weak legs at presentation.⁷³ During follow-up, all patients developed hyporeflexia or areflexia in their legs, but in some patients, normal reflexes persisted in the arms.⁷³ For an as yet unknown reason, a small proportion of patients with GBS, especially those with the AMAN subtype, have well-preserved or even exaggerated tendon reflexes.^{7,87}

Additional investigations

Lumbar puncture

A lumbar puncture is often performed in patients with suspected GBS. Importantly, this procedure especially should be done to exclude other diagnoses rather than to confirm GBS. A combination of elevated protein level and normal cell counts in the CSF (termed albuminocytological dissociation) is considered a hallmark of GBS. A frequent misconception, however, is that albuminocytological dissociation must always be present to confirm the diagnosis, ^{1–3,88} as only 64% of patients with GBS have this feature. Elevated CSF protein levels are found in approximately 50% of patients in the first 3 days after onset of weakness, which increases to 80% after the first week.⁷³

CSF cell counts >50 cells per μ l should cast doubt on the diagnosis of GBS, and other differential diagnoses should be considered, such as leptomeningeal malignancy, lymphoma, cytomegalovirus radiculitis, HIV polyneuropathy and poliomyelitis. ^{1-3,73,88} If the protein level in the CSF is normal, repeat lumbar punctures are

not usually recommended because albuminocytological dissociation is not necessary to diagnose GBS. In addition, treatment with high-dose IVIg can increase both protein levels and cell counts in the CSF, likely due to transudation or to aseptic meningitis, which can confuse the diagnostic picture in patients who undergo a repeat lumbar puncture.

Muscle and nerve electrophysiology

Nerve conduction studies (NCS) can help to support the clinical diagnosis of GBS and discriminate between axonal and demyelinating subtypes. Diagnosis of GBS can sometimes be difficult in the early phase of the disease, especially when reflexes are still present or the weakness is not distributed according to the classic pattern (for instance, in patients with paraparesis). NCS can demonstrate abnormalities in locations with subclinical disease, such as the arms. NCS findings of peripheral neuropathy or polyradiculopathy can also help to confirm the diagnosis of GBS.

Nerve conduction abnormalities tend to peak >2 weeks after the onset of weakness.⁶ However, if NCS are required to confirm a diagnosis of suspected GBS, a delay of 2 weeks is often too long. Although NCS can be performed earlier in the disease course, the results might still be normal at this stage. Often, the first-detected NCS abnormalities are prolonged or absent F-waves, although other conduction abnormalities become evident as the disease progresses. To increase the diagnostic yield of NCS, at least four motor nerves, three sensory nerves and F-waves should be investigated.

Abnormalities found on NCS depend on the GBS subtype (AIDP, AMAN or AMSAN). In patients with AIDP, NCS reveal features of demyelination, including prolonged distal motor latency, reduced nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion, and conduction block. The sural sensory potential is often preserved.89 Features of axonal GBS (AMAN or AMSAN) include decreased motor and/or sensory amplitudes, typically in the absence of demyelinating features. Sensory-nerve studies can help to differentiate between AMAN and AMSAN. In AMAN, neurophysiological findings can be very complex, as some patients with this condition have transient conduction block or slowing, which rapidly recovers during the course of the disease—a phenomenon called reversible conduction failure.7,90-93

Reversible conduction failure can mimic demyelination, and is probably caused by impaired conduction at the node of Ranvier caused by antiganglioside antibodies. Besides reversible conduction failure, other NCS features that suggest demyelination can sometimes be observed in the acute phase of axonal GBS. 4 Patients with reversible conduction failure may be falsely diagnosed as having AIDP instead of AMAN. Serial NCS might be needed to reliably distinguish these two subtypes of GBS; 5 for example, in an Italian study, 24% of patients initially classified as having AIDP were reclassified as having AMAN when serial NCS were performed. 52

Since no consensus exists on which neurophysiological criteria are best for confirming the diagnosis of GBS subtype, multiple classification systems are used. 6.23,95 At present, however, subtype classification does not seem to influence treatment choices, as patients with axonal and demyelinating forms of GBS currently receive similar treatment, at least in principle.

Testing for antiganglioside antibodies

Although antiganglioside antibodies are involved in the pathogenesis of GBS, their role in diagnosis has not been established. In general, the frequency of each specific antibody is low, implying that the negative predictive value of detection tests will also be low, and that the negative test findings cannot, therefore, exclude GBS as a diagnosis. In addition, tests for detecting these antibodies have a limited positive predictive value, as antiganglioside antibodies (especially those of the IgM class) also occur in other diseases. Possible exceptions to this rule might be anti-GQ1b antibodies, which are present in the serum of at least 90% of patients with MFS, and anti-GM1 and anti-GD1a IgG antibodies, which are frequently found in patients with AMAN. 7,9,37,46-49 Detection of these specific antibodies might be diagnostically helpful, provided that validated assays are used.⁹⁶ Moreover, research into antiganglioside antibody detection methods is rapidly progressing, and more-sensitive and more-specific tests may emerge in the near future.

Differential diagnosis

In patients with typical features of GBS, diagnosis is usually straightforward, but in patients with atypical features, GBS can sometimes be difficult to recognize. Even in patients with typical features, a lumbar puncture is recommended to rule out diagnoses other than GBS. The differential diagnosis of GBS includes infectious diseases, malignancy and disorders of the neuromuscular junction.^{1,2,97–99}

In patients with an elevated cell count in the CSF, differential diagnoses such as spinal root inflammation due to cytomegalovirus or HIV, transverse myelitis, Lyme disease, leptomeningeal malignancy, or poliomyelitis should be considered. Prop Laboratory investigations can also be helpful to reveal other causes of GBS-like symptoms, such as electrolyte disturbances (especially hypokalaemia) and vitamin B, deficiency.

In patients with pure motor symptoms, differential diagnoses of myasthenia gravis, polymyositis and dermatomyositis, poliomyelitis, hypermagnesaemia, porphyria, botulism, and lead or organophosphate poisoning should be considered. 97-99 NCS can be helpful in such individuals to differentiate between polyneuropathy, myopathy, anterior horn cell disease (poliomyelitis), and disorders of the neuromuscular junction.

When a diagnosis of GBS is considered in a patient with paraparesis or abnormal spinal sensory level at neurological examination, MRI of the spinal cord, and possibly also CSF examination, should be performed to exclude spinal cord compression or transverse myelitis. NCS can also be helpful in these patients, especially when

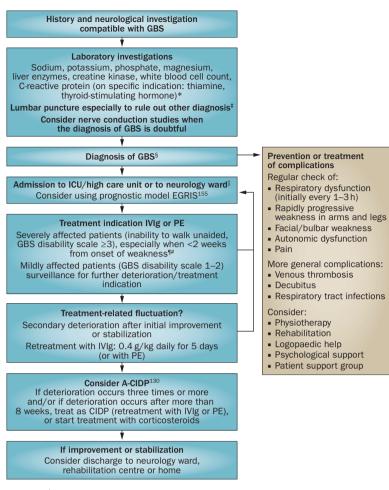


Figure 3 | Diagnosis and treatment of GBS. *If a non-GBS disorder is suspected, target laboratory investigations accordingly. ‡In case of cell count >50 cells per µl, consider spinal nerve root inflammation due to other causes. Normal cell counts and elevated cerebrospinal fluid protein level (albuminocytological dissociation) are indicative of GBS; however, protein level can be normal, especially in the first week.73 §When no other diagnosis could be confirmed by laboratory investigation, lumbar puncture or NCS. Consider performing NCS to subclassify GBS after 1-2 weeks. Indications for intensive care unit admission are rapidly progressive weakness with impaired respiration (vital capacity <20 ml/kg), need for artificial ventilation, insufficient swallowing (often with severe weakness), and severe autonomic dysfunction. ¶Or if the treating physician decides that there is an indication for treatment, for example, rapid progressive weakness, mild weakness with severe autonomic dysfunction, or severe swallowing problems. #IVIg: start within 2 weeks of onset: 0.4g/kg daily for 5 days. PE: start 5×PE with a total exchange volume of five plasma volumes in 2 weeks. Abbreviations: A-CIDP, acute-onset chronic inflammatory demyelinating polyneuropathy; EGRIS, Erasmus GBS Respiratory Insufficiency Score; GBS, Guillain-Barré syndrome; ICU, intensive care unit; IVIg, intravenous immunoglobulin; NCS, nerve conduction studies; PE, plasma exchange.

they reveal signs of demyelinating polyneuropathy or nerve conduction abnormalities in clinically unaffected arms, as both can be indicative of GBS. MRI findings of nerve root enhancement also support a diagnosis of GBS. ¹⁰⁰ For patients with bladder or bowel dysfunction at onset or who develop persistent bladder or bowel dysfunction, the differential diagnoses include spinal cord or caudal compression, and transverse myelitis.

If a patient has asymmetric weakness, differential diagnoses such as vasculitic neuropathy, multiple mononeuropathy, Lyme disease, diphtheria, poliomyelitis and leptomeningeal malignancy should be considered. 97-99 When the severity of respiratory failure is disproportionate to that of limb weakness, disorders such as myasthenia gravis, hypermagnesaemia, hypophosphataemia, high cervical intramedullary lesions, poliomyelitis and botulism should be excluded. 97-99

Diagnosis of GBS in children

The clinical presentation and outcome of GBS is different in children compared with adults, and diagnosis of childhood GBS can be challenging, especially in young children aged <6 years. ^{101–104} Pain, difficulty with walking, or refusing to walk are the most frequent presenting symptoms in children, and should raise suspicion of GBS. ^{101–104} However, only one-third of preschool children with GBS receive a correct diagnosis at admission. ¹⁰³ In young children, GBS may initially be diagnosed as meningitis, coxitis, or malaise caused by viral infections. Moreover, the diagnosis of GBS in children is often delayed. In preschool children (aged <6 years), the delay in diagnosis can be even more than 2 weeks. ¹⁰³ Insufficient monitoring of these children during this period may result in emergency intubation and even death. ¹⁰⁵

Assessment scales

Over the past few decades, the GBS Disability Scale has been used as an outcome scale in the majority of clinical trials in GBS. The GBS Disability Scale has six levels: 0 (healthy), 1 (minor symptoms and capable of running), 2 (able to walk 10 m without assistance but unable to run), 3 (able to walk 10 m across an open space with help), 4 (bedridden or wheelchair-bound), 5 (requiring assisted ventilation for at least part of the day), and 6 (dead). 106

GBS assessment scales must be valid, sensitive, reliable, and able to capture subtle clinical changes over time. The Peripheral Neuropathy Measures Outcome Study (PERINOMS) accordingly investigated a large number of assessment scales. ¹⁰⁷ In a European Neuromuscular Centre meeting, the PERINOMS study group reached a consensus about the use of a variety of measures for the follow-up of patients with GBS in future trials. ¹⁰⁷ They recommended using the GBS Disability Scale and the Rasch-built Overall Disability Scale to measure disability, and both the Medical Research Council (MRC) sum score (ranging from 0–60) and the new Rasch-built MRC score to measure muscle strength. ^{106–110}

Treatment

Treatment of GBS usually combines multidisciplinary supportive medical care and immunotherapy (Figure 3). Proven effective treatments for GBS are IVIg and plasma exchange. $^{11-13}$ Immunotherapy is usually started if patients are not able to walk 10 m unaided (GBS Disability Scale score ≥ 3). 2,11 Plasma exchange and IVIg have pleiotropic immunomodulatory effects, but we have yet to establish which effects explain their therapeutic efficacy in GBS, and whether the same effects are involved in all patients and all subtypes of GBS.

IVIg treatment may inhibit Fc-mediated activation of immune cells, binding of antiganglioside antibodies to

their neural targets or local complement activation. ^{12,111} Serum IgG Fc glycosylation in patients with GBS seems to be associated with disease severity and could influence the immunomodulatory effects of IVIg. ¹¹²

Plasma exchange is thought to remove neurotoxic antibodies, complement factors and other humoral mediators of inflammation. Plasma exchange is beneficial when performed within the first 4 weeks after onset of weakness in patients who are unable to walk unaided (GBS Disability Scale score ≥3), but the largest effect is seen when treatment is started within the first 2 weeks. Plasma exchange regimen consists of five treatments administered over 2 weeks, involving a total of about five plasma volumes. In mildly affected patients (still able to walk), however, two plasma exchange sessions induced more-rapid onset of motor recovery than did no plasma exchange. Plasma exchange.

IVIg is effective in patients who are unable to walk 10 m unaided (GBS Disability Scale score ≥3) and when started within 2 weeks of onset of weakness. 11,12 Randomized controlled trials showed that IVIg at a dose of 0.4 g/kg daily for 5 consecutive days (or 1 g/kg daily for 2 days) was as effective as a full course of five plasma exchange sessions applied over 2 weeks.80,116 Whether rapid IVIg treatment over 2 days is superior to treatment with the same total dose (2 g/kg) administered over 5 days has not been fully evaluated. However, one trial demonstrated that children receiving treatment over 2 days more frequently had treatment-related fluctuations than did children receiving treatment over 5 days.117 As IVIg therapy is widely available, does not require special equipment, and generally has only minor adverse effects, it has replaced plasma exchange as the preferred treatment for GBS in many hospitals.11,12 Immunoabsorption, as an alternative to plasma exchange, is occasionally used as a treatment for patients with GBS, and may be equally effective. However, no large-scale randomized controlled trials have shown that treatments other than IVIg or plasma exchange are effective.11,12

The choice of treatment depends on both patientrelated and socioeconomic factors. For instance, plasma exchange requires special equipment and is not always available in all hospitals. In addition, plasma exchange can be difficult to perform in young children, and care should be taken in patients with autonomic cardiovascular instability because of the large volume shifts involved in the plasma exchange procedure. However, the direct costs of IVIg treatment can be more than twice those of plasma exchange, making this treatment less attractive in low-income countries. 118,119 In this respect, it is important to remember that most clinical trials of these treatments were conducted in Western Europe or North America and, therefore, predominantly involved patients who fulfilled the most commonly used GBS diagnostic criteria.4 The results of these trials might be less applicable in other parts of the world, especially where AMAN is highly prevalent.

Whether patients with AMAN should receive the same treatment as those with AIDP remains uncertain.

Results from a small study, which unfortunately had some methodological flaws, suggested that patients with AMAN might have better outcomes after treatment with plasma exchange than after IVIg therapy, and that plasma exchange was also the most cost-effective option. 120 However, in countries where plasma exchange machines are not widely available or patients cannot afford this expensive procedure, small-volume plasma exchange or exchange transfusion can be a low-cost therapeutic option. 121-124 Controlled studies of these procedures are currently lacking.

The combination of plasma exchange followed by IVIg is not significantly better than either plasma exchange or IVIg alone. 11,80 Oral steroids and intravenous methylprednisolone are not beneficial in patients with GBS. 11,15,79 The 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. 79 Small randomized placebo-controlled trials of IFN- β 1a 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. 14,125

No randomized controlled trials have been performed in patients with MFS. 126 A retrospective analysis showed that recovery starts slightly earlier in patients with MFS treated with IVIg than in those who were treated with plasma exchange or received no immunotherapy. However, final outcomes were the same in all three groups. 126,127 Indeed, almost all patients with MFS recover fully, irrespective of whether they receive immunotherapy. 126,127 Owing to the lack of evidence of a beneficial effect of IVIg or plasma exchange in patients with MFS, combined with the good natural recovery seen in these patients, withholding of immunotherapy in patients with MFS seems currently justified. However, patients with MFS-GBS overlap syndrome can be severely affected, and treatment with IVIg or plasma exchange remains an option for these patients. Notably, no large-scale randomized controlled trials have been performed to determine the optimal treatment strategy in children with GBS and they are, therefore, usually treated in the same manner as adults with GBS. 104

Importance of supportive care in GBS

A patient in the progressive phase of GBS requires hospital admission. Important questions are how to monitor progression and how to avoid or treat complications related to weakness, immobility, respiratory insufficiency, autonomic dysfunction, and pain. Patients with GBS need multidisciplinary supportive care to prevent or to manage these diverse complications (Figure 3),¹²⁸ and to facilitate timely transfer to the intensive care unit (ICU) when indicated.

Care includes monitoring of respiratory function by frequent measurement of vital capacity and other clinical parameters, such as respiratory depth, respiratory frequency and cough strength. The optimal

Table 2 | Differentiating characteristics of GBS, GBS-TRF, A-CIDP and CIDP¹³⁰ Characteristic GBS **GBS-TRF** A-CIDP CIDE Time to nadir <2 weeks <2 weeks 4-8 weeks, followed >8 weeks (maximum by progression with (maximum 4 weeks) 4 weeks) deteriorations Disease >2 deteriorations or Progressive, Monophasic course deteriorations deterioration after stenwise or within 8 weeks 8 weeks fluctuating Severity Highly variable Highly variable Mostly moderate Mostly moderate hetween hetween patients. patients. distal and ranging from ranging from proximal mild symptoms mild symptoms weakness to paralysis to paralysis Ventilator 20-30% 20-30% Almost never Almost never dependence Cranial nerve Often Often Sometimes Sometimes deficits Response Good Good, with Variable Good to IVIg fluctuations EMG/NCS* Sometimes no Often demyelinating Demyelination Sometimes no classification classification polyneuropathy at first EMG/NCS possible at possible at first EMG/NCS first EMG/NCS IVIg or plasma Treatment IVIg or plasma Repeat IVIg IVIg, exchange or plasma exchange, on prednisolone confirmed diagnosis exchange or plasma of CIDP consider exchange also switch to prednisolone maintenance treatment

*AIDP or AMAN. Abbreviations: A-CIDP, acute-onset CIDP; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; EMG, electromyography; GBS, Guillain–Barré syndrome; GBS-TRF, Guillain–Barré syndrome with treatment-related fluctuation; IVIg, intravenous immunoglobulin; NCS, nerve conduction studies.

frequency to measure these vital functions has not been investigated, but is probably about once every 1–4 h depending on the rate of deterioration. The duration of ventilation may be shortened by selective digestive tract decontamination. 129

Other issues that require attention are prophylaxis against deep vein thrombosis, cardiac and haemodynamic monitoring, pain management, management of possible bladder and bowel dysfunction, physiotherapy, rehabilitation, and psychosocial support. ^{2,128} GBS can be a very challenging disorder for both patients and their relatives, who may benefit from contacting national or international GBS-related patient organizations.

Deterioration after initial improvement

About 10% of patients with GBS who have been treated with IVIg or plasma exchange deteriorate after initial improvement or stabilization—a phenomenon that is termed treatment-related fluctuation (TRF).^{130,131} These patients usually improve after retreatment with IVIg or plasma exchange, and although the efficacy of retreatment has never been demonstrated in a randomized controlled trial, this approach has become common practice. On the basis of clinical experience, we and others advise retreatment with IVIg (2 g/kg over 5 days)

in patients who develop TRF.² These patients may have a prolonged autoimmune response that causes ongoing nerve damage, or functional blockade that requires prolonged treatment.

GBS with extended progression phase

Some patients experience multiple periods of deterioration or have a progression phase that exceeds 4 weeks. In these patients, the question often arises of whether the patient really has GBS, or whether they have acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP).¹³⁰ A diagnosis of A-CIDP should be considered when patients who were initially diagnosed with GBS have three or more periods of clinical deterioration, or when new deterioration occurs >8 weeks after disease onset (Table 2).^{130,132} It is vitally important to recognize any late or additional deteriorations, because patients with GBS–TRF may improve after retreatment with IVIg, whereas those with A-CIDP often require chronic maintenance treatment with IVIg or a therapeutic switch to corticosteroids.

Residual deficits

Adult patients with GBS frequently have residual deficits that greatly impair their daily activities and quality of life. 133-139 For example, 6 months after disease onset, about 20% of patients with GBS are still not able to walk unaided. 1,2,11 Most improvement occurs within the first year after onset, but can continue after this period. 140,141 The most common residual deficits are reduced muscle strength, sensory signs, fatigue, and pain. 77,135,138,139 Many patients have to make changes to their lifestyle, work, and social activities. 133,135 However, even patients with a good functional outcome (GBS Disability Scale score ≤1) have a reduction in psychosocial health status. 134 Some evidence suggests that high-intensity, multidisciplinary rehabilitation reduces disability and improves quality of life in patients with GBS. 136,142,143 Children with GBS may have better outcomes than adults, although the longterm residual effects on daily life in children have not been established. 102,104

Long-lasting symptoms of fatigue are present in the majority of patients with GBS. ¹³⁸ Fatigue can be assessed using the fatigue severity scale, and the Rasch-built fatigue severity scale. ¹⁴⁴ The precise pathophysiological mechanisms leading to fatigue are not well understood, but axonal loss seems to be a contributory factor. ¹⁴⁵ A noncontrolled, nonblinded study showed that physical training is feasible and effective in patients who have, neurologically, recovered well from GBS, but who still have severe fatigue. ¹³⁶

Moderate to severe pain is very common in patients with GBS. A prospective follow-up study showed that two-thirds of patients report pain within the first 3 weeks after onset, and one-third still have pain after 1 year.⁷⁷ Up to 89% of patients experience pain at some point during their disease course,⁷⁶ and pain may even precede weakness in about one-third of patients.⁷⁷ The most common locations of pain are the extremities or the back; patients mainly report muscle pain, painful

paraesthesias, radicular pain, arthralgia or mening-ism. Attention must be paid to pain during the entire disease course because although pain can be very severe, it is often under-recognized. Pain can be treated with neuropathic analgesics, but not all patients have a good response to such treatment. A Cochrane review on the pharmacological treatment of pain in patients with GBS showed that evidence to support a pain-relieving effect of analgesics in this condition is scarce. ¹⁴⁶ The precise causes of pain in GBS are probably diverse, and may vary over the course of the disease. ¹⁴⁷ Notably, distal intraepidermal nerve fibre density is reduced in patients with GBS, and is associated with both incidence and severity of pain (but not with autonomic dysfunction, as discussed below). ^{148,149}

Autonomic dysfunction predominantly occurs in the acute phase of GBS but can also occur in the recovery phase. It can be a serious problem in patients with GBS and may cause sudden death. ^{150–152} Tachycardia (38%), hypertension (69%), gastrointestinal dysfunction (45%), and bladder dysfunction (19%) have been reported in a series of 156 GBS patients. ⁷⁷ Patients with severe cardiovascular dysfunction can have rapid changes in blood pressure and cardiac dysrhythmia that sometimes require a cardiac pacemaker. In children, autonomic dysfunction was present in half of the mildly affected patients and seemed not to be related to the severity of the disease, ⁸¹ which implies that autonomic disturbances are common and may occur throughout the spectrum of severity of GBS.

Autonomic dysfunction in patients with GBS reflects dysfunction of sympathic and/or parasympathic innervation, but the exact immunopathological mechanisms remain to be elucidated. Specifically, the relationship between specific antiganglioside antibodies and autonomic dysfunction needs to be investigated in more detail. We did not observe a correlation between reduction of intraepidermal nerve fibre density and autonomic failure. 149 The reason why some patients have severe autonomic dysfunction that can include light-fixed pupils and excessive sweating, whereas others have severe cardiac dysrhythmia, is currently unknown and, unfortunately, cannot be predicted from a clinical point of view. Careful monitoring for the presence of features of autonomic dysfunction is indicated also after a patient is discharged from the ICU.

Prognosis and outcome

As the clinical course and outcomes of GBS are highly variable, their accurate prediction is important to enable clinicians to tailor supportive care and treatment to the individual patient's needs and to inform patients and relatives about the expected clinical course.

Predictors of need for ventilation

Three large studies have been performed to predict the probability of respiratory insufficiency in patients with GBS. A French study including 722 patients found that time from onset to admission of <7 days, inability to cough, inability to stand, inability to lift the elbows or

head from the bed, and increased liver enzyme levels were predictors of an increased probability of need for artificial ventilation. ¹⁵³ A second French study found that peroneal nerve conduction block and low vital capacity correlated with a high risk of respiratory failure. ¹⁵⁴ The third study was conducted in the Netherlands, and used data from a derivation cohort of 397 patients with GBS to identify clinical predictors of mechanical ventilation, which were validated in an independent cohort of 191 patients with GBS. ¹⁵⁵

The results of the Dutch study led to development of the Erasmus GBS Respiratory Insufficiency Score (EGRIS). ¹⁵⁵ EGRIS is an accurate prediction model that can be used in the emergency room to predict the probability of respiratory insufficiency in the first week after admission for GBS. ^{155,156} The model incorporates the following parameters: severity of weakness (expressed as the MRC sum score), the number of days between onset of weakness and admission, and facial and/or bulbar weakness (Supplementary Figure 1 online). If a patient's predicted chance of developing respiratory insufficiency is high, it can be advisable to admit the patient to the ICU rather than to a general neurology ward.

Factors that are predictive of successful weaning from the ventilator are age <60 years, 157 lack of autonomic dysfunction, and vital capacity >20 ml/kg or an improvement in vital capacity of 4 ml/kg. 158 Autonomic dysfunction, advanced age and pulmonary comorbidity are associated with a long duration of mechanical ventilation and the need for tracheostomy. 158,159

Predictors of poor long-term outcomes

In almost all studies, poor outcome is defined as a GBS Disability Scale score ≥ 3 after either 6 months or 12 months. $^{160-163}$ Such a high grade on the GBS Disability Scale at neurological examination, diarrhoea preceding GBS onset, 28,160,163,164 and advanced age $^{28,78,140,141,154,160,162-165}$ are all predictors of poor outcome.

Validated prognostic models have been developed for use in clinical practice to predict long-term outcome in individual patients with GBS. An example is the Erasmus GBS Outcome Score (EGOS), which is based on three clinical characteristics: age, GBS Disability Scale score at 2 weeks after hospital admission, and preceding diarrhoea. ^{156,163} However, the 2-week delay before EGOS can be determined may be too long to adequately tailor treatment according to the patients' predicted outcome. By contrast, the modified EGOS can be used to predict outcomes early in the course of GBS, before irreversible damage occurs. ^{156,166} This model can be used at admission and at 1 week after admission, and is based on age, severity of weakness (expressed as MRC sum score), and preceding diarrhoea (Supplementary Figure 2 online).

Electrophysiological findings

In addition to their diagnostic role, electrophysiological findings might have prognostic relevance. In one NCS study, patients with features of demyelination more often required mechanical ventilation than did patients without this type of damage.¹⁵⁴ The most consistent

electrophysiological finding predictive of poor outcome is low CMAPs. 167 However, some studies demonstrated that an axonal neuropathy is not necessarily a predictor of poor outcome, since patients with AMAN can either improve very slowly and incompletely or recover rapidly. 22,168 These observations seem inconsistent, but rapid recovery might be caused by restoration of transient conduction block. Further studies are required to precisely delineate the relationships between conduction block, the presence of antiganglioside antibodies, the effects of treatment, and outcome.

Predictors of mortality

Mortality from GBS varies between 3% and 7%. 140,169,170 Predictors of an increased risk of death are advanced age, severe disease, increased comorbidity, pulmonary and cardiac complications, mechanical ventilation, and systemic infection. 140,160,169-171 Death can occur in all phases of the disease; however, in two studies, a large proportion of the deaths occurred >30 days from onset, and a subsequent study showed that the majority of patients who died were in the recovery phase. 160,170,171 Consequently, severely affected patients in the recovery phase of GBS and after discharge from the ICU still require good observation and supportive care. 170 The most common causes of death are respiratory insufficiency, pulmonary infection, autonomic dysfunction, and cardiac arrest. 78,160,170,171

Ongoing research

Nearly a century after it was first described, GBS is still a life-threatening disorder that results in a poor outcome in at least 20% of patients and has persistent residual effects in the majority. Further research is urgently required to improve this situation. From a clinical perspective, the following are the most challenging needs: to develop improved diagnostic criteria for use in daily clinical practice, trials and vaccine safety studies; to determine the burden of disease caused by GBS worldwide; to develop new and better GBS outcome measures; to establish the precipitating events and patient-related factors that lead to GBS; to define biological and clinical predictors of the clinical course and outcome in individual patients; and, most importantly, to develop moreeffective and specific treatments, as well as protocols for supportive care.

These aims can probably only be achieved by largescale international and multidisciplinary collaborations, such as the International GBS Outcome Study (IGOS), which was launched in 2012. Tissue samples and detailed, standardized clinical data are being collected during a follow-up period of 1-3 years with the intention of including at least 1,000 patients with GBS from all over the world. At present, centres from 17 countries— Argentina, Australia, Bangladesh, Belgium, Canada, Denmark, France, Germany, Italy, Japan, Malaysia, Netherlands, Spain, South Africa, Taiwan, UK and the USA—are recruiting patients. In addition, a randomized controlled trial, the SID-GBS study, is being conducted in the Netherlands. This trial is investigating the effect of a second course of IVIg given shortly after the first course in patients with GBS who have a poor prognosis (defined as a mEGOS score of 6-12 at 1 week after initiation of a standard 5 day course of IVIg). A related international study with an observational prospective design (I-SID-GBS) is investigating the same approach. This study is part of IGOS and is being performed by the Inflammatory Neuropathy Consortium.

In addition, a new randomized placebo-controlled trial of eculizumab in patients with early GBS who are unable to walk is about to start. 172 This study is partly based on findings in an animal model of GBS, in which antiganglioside antibodies induce complementdependent damage at the nodes of Ranvier, nerve terminals, and perisynaptic Schwann cells (Figure 2). 59,173 Notably, these deleterious effects of complement on nerve terminals in mice can be blocked by the administration of eculizumab, a humanized monoclonal antibody that binds with high affinity to complement factor C5 and prevents its cleavage to C5a and the proinflammatory, cytolytic C5b-9 complex.61 Many other studies, such as those investigating pain treatment, nerve regeneration, and other factors that may improve the outcomes of patients with GBS, are eagerly awaited.

Conclusions

GBS is a heterogeneous and often severe disorder. Although nonspecific immunotherapy is available and effective in most patients, a need remains for improved treatment and patient care throughout the disease course. Optimal supportive medical care is also essential to prevent or treat disease-related complications. Novel prognostic models have been developed and might enable treatment to be tailored to each patient's requirements.

Although a large amount of information on the immunopathogenesis of the various subtypes of GBS has been collected, further research is still needed. In the past few years, new large-scale clinical studies based on worldwide collaborations have been started and will help us to further define this syndrome and to optimize the care of affected patients.

Review criteria

PubMed was searched for articles published between January 1990 and March 2014. MeSH search terms were "Guillain-Barré syndrome" alone and in combination with "epidemiology", "immunology", "genetics", "therapy", "drug therapy" or "mortality". Non-MeSH search terms were "Guillain-Barré syndrome", "acute inflammatory demyelinating polyneuropathy", "acute motor axonal polyneuropathy" and "Guillain-Barré syndrome" combined with "epidemiology", "diagnosis", "diagnostic criteria", "infection", "antibodies", "immunology", "nerve conduction studies", "electrophysiology", "treatment", "genetics", "vaccination", "autonomic dysfunction" or "pain". Only papers in English were reviewed. Articles were selected for their relevance, with a preference for new papers. Some other relevant papers known by the authors were also included.

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Author contributions

B.v.d.B. and P.v.D. researched data for the article; B.v.d.B., B.J. and P.v.D. made substantial contributions to discussion of content. All authors made substantial contributions to writing, review and/or editing of the manuscript before submission.

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