Predicting and Improving Outcome in GBS

Christa Walgaard

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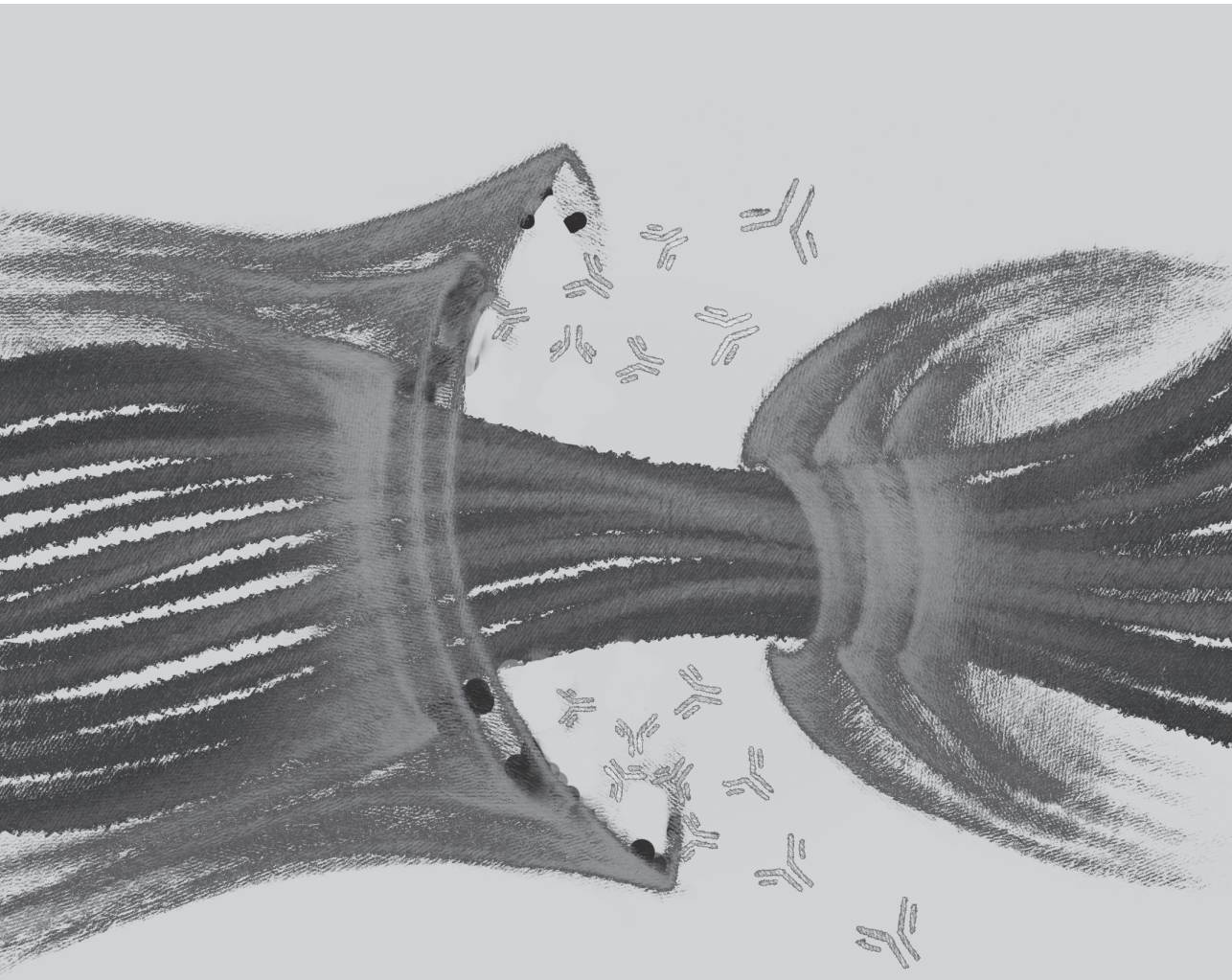

1

Introduction

1.1

General Introduction

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy, characterized by progressive bilateral muscle weakness with reduced or absent tendon reflexes in arms and legs.[1] Usually GBS runs a monophasic disease course, with rapid deterioration in days to weeks, until a plateau is reached, which can last for weeks to months after which patients start to recover. Unfortunately not all patients recover completely and many patients have residual symptoms, such as fatigue and neuropathic pain. GBS results from immune-mediated damage of the peripheral nerves and nerve roots, often precipitated by a recent preceding infection, but the exact pathogenesis of GBS has not been fully elucidated.[2] GBS is a heterogeneous disease regarding clinical symptoms, severity, course and outcome. Some patients develop only mild and transient limb paresis from which they recover spontaneously, whereas others develop oculomotor, bulbar, respiratory muscle and limb paralysis and remain bedbound for several months with severe residual disability despite appropriate treatment. Although GBS is a rare disease, with an incidence rate of 0.81–1.89 (median 1.11) per 100,000 person–years, the syndrome is likely known by every neurologist. This is due to the dramatic clinical presentation when previously healthy people suddenly become paralyzed with preserved consciousness and remain hospitalized for weeks to months.[3] General medical care with regular checks of respiratory and autonomic (dys)function is of utmost important in patients with GBS.[4] In 1985 for the first time a causative treatment for GBS was proved to be effective for patients who are unable to walk and still within the first 4 weeks from onset of weakness.[5] Plasma exchange (PE) hastens recovery and results in a better outcome at 4 weeks and 6 months after onset of GBS.[5] In 1992, The Dutch GBS Study Group showed in a randomized clinical trial (RCT) that a 5 day course of IVIg was at least as effective as PE, when initiated within 2 weeks after onset of weakness in patients unable to walk.[6] Treatment trials with corticosteroids never proved its benefit in GBS patients, and oral corticosteroids may even induce worsening, which is quite remarkable considering the immune-mediated destruction of the peripheral nerves.[7-9] Later, the combination of methylprednisolone and IVIg was compared with IVIg alone, but a positive effect of adding corticosteroids was not proven.[10] Nowadays IVIg in a dosage of 0.4g/kg for 5 consecutive days is the first choice treatment.[2] In **Chapter 1.2** the pathogenesis, diagnosis, treatment and prognosis of GBS is described in further detail.

Historical perspective on prognosis and GBS

More than 100 years ago (in 1916) Georges Guillain, Jean Alexandre Barré, and André Strohl described two French soldiers with acute flaccid limb paresis who recovered fully.[11] This was a remarkable clinical course as most patients in those days with acute flaccid limb paresis suffer from poliomyelitis (acute anterior) and other infections, in which full recovery is rare. The authors applied the recently developed technique of lumbar puncture to examine the cerebrospinal fluid.[11] They showed that these two patients had a high protein level, but a normal number of leucocytes, which distinguishes this syndrome from poliomyelitis and other infections.[11]

In the first decades after the report of Guillain, Barré and Strohl, outcome of GBS was considered to be good, presumably because it was compared with poliomyelitis. Illustrative of this conviction in a good outcome was that one of the 12 proposed diagnostic criteria for GBS in the New England Journal of Medicine in 1960 was: "there is complete functional recovery, without residua, in six months".[12] Patients with a poor outcome or otherwise not meeting the criteria were labelled as having 'atypical polyneuritis' instead of GBS.[12] This conviction in the good outcome of GBS changed in 1968, when a cohort of 49 patients with acute flaccid limb paresis was divided in two groups according to the 12 NEJM criteria except for the outcome criterion. Outcome was comparable in both groups and the authors concluded that this criterion of good outcome cannot be justified.[13] This change in paradigm did not only influence the diagnosis of GBS, but also the search for a medical treatment for GBS patients with poor outcome. The acknowledgement that patients with GBS may have either a good or poor outcome, also resulted in the search for factors influencing and predicting the clinical course and outcome in individual patients. In the next paragraph those predictive factors are further described.

Treatment dilemmas and prognosis in GBS

Due to the large variability in disease severity, course and outcome, and the limited treatment trials that have been conducted in GBS, physicians in clinical practice are confronted with uncertainties and dilemmas (Figure 1), as illustrated in this case description.

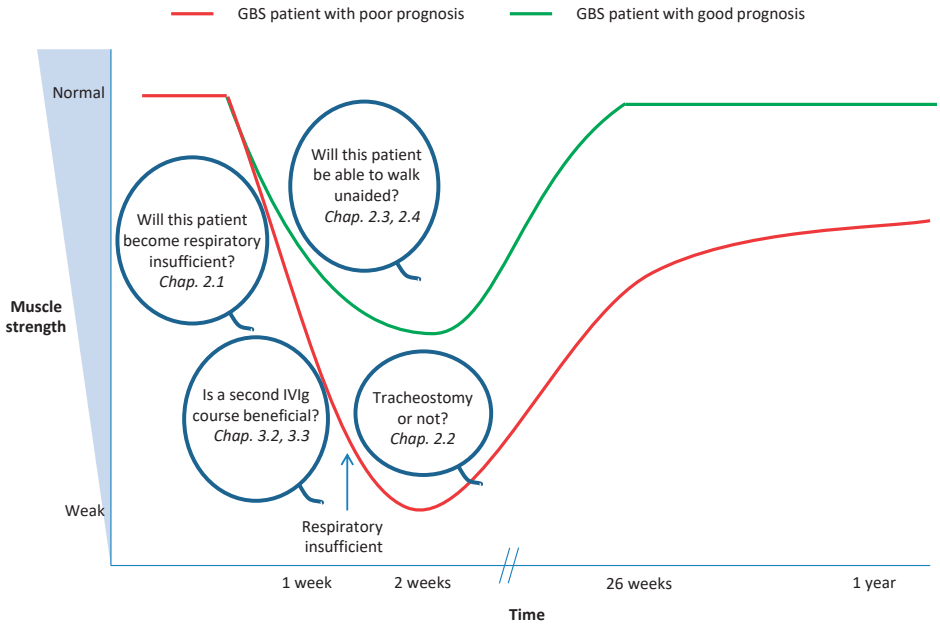

Figure 1 | Clinical dilemmas in GBS treatment

A 38-year old previously healthy man presents at the emergency department because of progressive weakness in his legs since one day. At the day of admission, he was unable to walk unaided and also in his arms weakness became apparent. Neurological examination revealed a tetraparesis and areflexia, sock-shaped sensory deficits and no increased cell count or elevated protein was found in the cerebrospinal fluid. GBS was diagnosed and IVIg was started.

➢ *Dilemma 1: Should this patient be admitted to the ICU?*

Respiratory insufficiency may emerge rapidly and requires immediate airway management, but ICU beds are scarce and expensive.

Our patient became respiratory insufficient and was intubated on day 2 and ventilated. In the following days his weakness progressed. The ICU specialist suggests to perform a tracheostomy.

➢ *Dilemma 2: Should a tracheostomy be performed?*

Tracheostomy is usually indicated when mechanical ventilation is required for more than two weeks, but it requires surgery and leaves a prominent scar for life.

One week later, the progression stabilized but no signs of recovery are seen yet. The family asks how the future will look like. Will he ever be able to walk again?

➢ *Dilemma 3: What will be the long-term outcome?*

Previous studies have shown that about 20% of patients with GBS are unable to walk after 6 months, but of course the patient and family want to know for sure if in this specific case the patient can walk or not.

The ICU specialist asks if the patient requires a second course of IVIg.

➢ *Dilemma 4: May this patient benefit from a second course of IVIg?*

IVIg is usually considered to have relatively mild side effects and small uncontrolled studies show a possible positive effect of a second course. However, IVIg is expensive and safety of very high dosages of IVIg (when a second IVIg course is administered shortly after the first IVIg treatment) has not been investigated in an randomized controlled trial yet.

The patient remained dependent on mechanical ventilation for 2 months, was discharged to a rehabilitation center, and was able to walk independently 5 months after admission.

➢ ***Dilemma 1: Prediction of respiratory insufficiency***

Respiratory insufficiency is a life-threatening manifestation of GBS that occurs in 20-30% of patients in clinical trials and is associated with poor outcome.[14-16] The respiratory problems in GBS often develop insidiously but may rapidly progress and if not monitored appropriately may result in respiratory failure and emergency intubation. Prediction of respiratory insufficiency is important to avoid respiratory distress and emergency intubation, which frequently occur during the night. Accurate prediction can guide decision-making about admittance to the ICU or the general neurology ward, in case of low risk of respiratory insufficiency, which saves costs and resources. In addition, it provides important information for the patient and relatives.

In 2006, a model was developed and validated which uses electrophysiological testing of the common peroneal nerve and vital capacity to predict the chance of respiratory insufficiency.[17] In this study, electrophysiological testing was usually done within 6 days after admission.[17] However, the majority of the patients develop respiratory insufficiency within the first days of admission, so the chance of respiratory insufficiency is preferably predicted already at hospital admission. In addition, electrophysiological testing required expertise and the facilities and quality may vary between hospitals. For clinical practice a model for predicting respiratory failure would be available at hospital admission and based only on clinical information that is easily available for every clinician already in the emergency room. In **Chapter 2.1** we describe a clinical prediction model which accurately predicts the chance of respiratory insufficiency. This Erasmus GBS Respiratory Insufficiency Score (EGRIS) was developed in a Dutch cohort of patients participating in previous treatment trials. As clinical course and outcome of GBS varies worldwide[18], validation in an international cohort of GBS patients is required. A validation was performed in the International GBS Outcome Study cohort in **Chapter 2.2**.

➢ ***Dilemma 2: Prediction of duration of mechanical ventilation***

The duration of mechanical ventilation varies widely between patients with GBS, ranging from a few days to several months. This variation complicates the decision about tracheostomy which is considered in patients who need endotracheal ventilation for more than 2 weeks. When patients are expected to need mechanical ventilation for a prolonged duration, early tracheostomy can prevent damage of the vocal cords, laryngeal mucosa, and recurrent laryngeal nerves due to decubitus or local pressure from the endotracheal tube.[19] On the other hand, early tracheostomy may be unnecessary because of clinical improvement and exposes patients to the risk of perioperative bleeding, infection, esophageal perforation, pneumothorax, and tracheal stenosis and, in all cases, leaves a permanent scar.[20] In **Chapter 2.3** we searched for predictors for prolonged mechanical ventilation, which aids the decision to perform a tracheostomy or not.

➢ *Dilemma 3: Early prediction of functional outcome*

Functional outcome in our studies was defined using the GBS disability scale (Table 1). This score is often used as functional outcome measure in clinical trials and other research in GBS, and makes our results comparable with previous studies.[5,8] An important step in the clinical recovery is the ability to regain the ability to walk independently (GBS disability scale grade 2). Poor outcome is usually defined as a grade 3 or higher on the GBS disability scale.[5,8]

Table 1 | The GBS disability scale[5,8]

Grade	Label	Dichotomization
0	Healthy	Favorable outcome
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	Unfavorable outcome
4	Bedridden or wheelchair-bound	
5	Requiring assisted ventilation for at least part of the day	
6	Dead	

A shortcoming of the GBS disability scale is that it focuses on ambulation; arm function, swallowing difficulty or autonomic dysfunction are not taken into account.

Preceding infection, age, rapid progression, disability at nadir, and electrophysiological characteristics were associated with long-term outcome in earlier studies.[21-26] The first prediction model applicable for the individual patient was published in 2007 and predicts the ability to walk independently (GBS disability grade 0-2) after 6 months.[27] This Erasmus GBS Outcome Score (EGOS) model uses age, preceding diarrhea and GBS disability score at 2 weeks after admission (Table 2 and Figure 2).[27]

The model was developed in Dutch patients with GBS and externally validated in an English cohort of GBS patients. The model uses clinical available predictors and is therefore easy to use and can assist clinicians to inform individual patients with GBS and their relatives about the prognosis. A limitation of the EGOS however is that it is based on clinical information not sooner available than 2 weeks after admission. These first 2 weeks are crucial for the treatment of GBS since the inflammation is then still active and possibly cause further nerve damage. Selection of patients with poor outcome for treatment trials would require a prognostic model that can be used in an earlier stage, since early treatment may prevent further deterioration ('time is nerve').[28] In **Chapter 2.5** we describe a modified model (mEGOS) which enables to predict outcome early (at admission and one week after admission) in the course of the disease. This prediction model is able to select patients with a poor prognosis for participation in selective treatment trials.

Table 2 | The Erasmus GBS Outcome Scale (EGOS)[27]

Prognostic factor	Categories	Score
Age at onset (years)	>60	1
	41 – 60	0.5
	≤40	0
Diarrhea (≤4 weeks)	Absence	0
	Presence	1
GBS disability score (at two weeks after entry)	0 or 1	1
	2	2
	3	3
	4	4
	5	5
Erasmus GBS Outcome Score		1-7

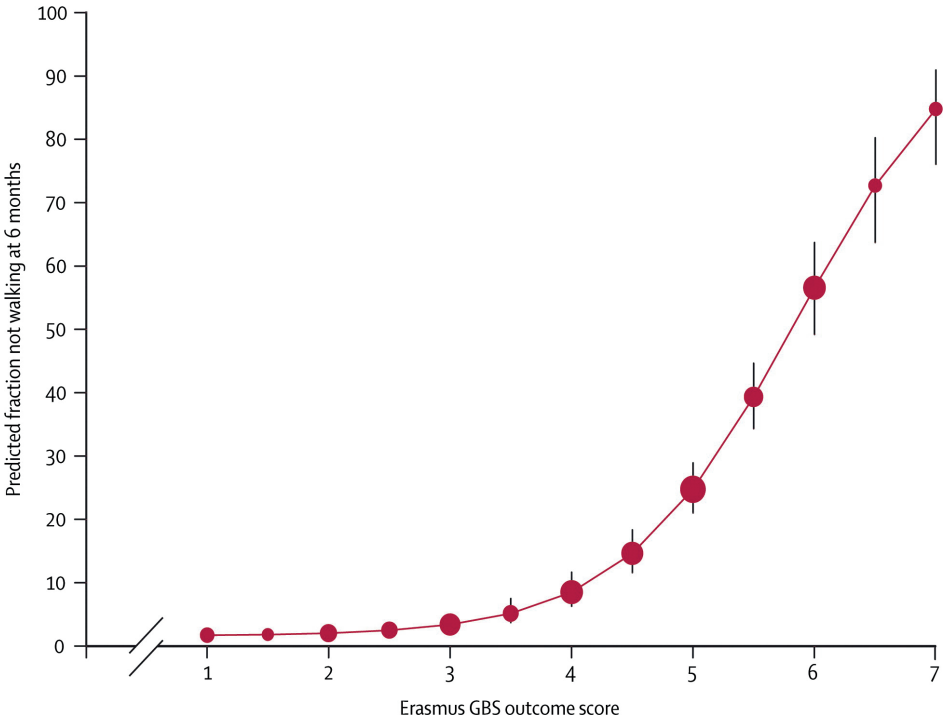

Figure 2 | The Erasmus GBS Outcome Score (EGOS)[27]

➢ *Dilemma 4: Second IVIg course to improve outcome*

Considering the proven efficacy of IVIg in GBS, the question is if patients with poor predicted outcome may benefit from a second course of IVIg. Data from a large prospective international observational study (International GBS Outcome Study; IGOS) show that nowadays about 25% of the patients who do not respond to a first standard IVIg course are retreated with a

second IVIg course, while evidence for this strategy is lacking.[29] The RCT's which established the current standard treatment with 0.4 g/kg for 5 days likely chose this dosage and regimen as it was initially used in hematological disorders.[30] However, it is questionable if this standard regimen is sufficient for each individual GBS patient.[28] In 2001 a phase II trial suggested that the time to regain independent walking was significantly shorter in mechanically ventilated GBS patients who were treated with 6 days of 0.4 g/kg IVIg compared to 3 days of 0.4 g/kg IVIg.[31] Further dose finding studies in GBS were never done. Especially patients with a poor predicted outcome may benefit from a second IVIg course. To investigate this, it is crucial to accurately select patients with a predicted poor outcome. Furthermore, it is important to select and treat those patients early in the disease course, before severe or possibly irreversible nerve damage has occurred. The model described in **Chapter 2.4** was used in a double-blind RCT to study the added effect of a second IVIg course in GBS patients with poor prognosis. A selective trial design conducted only in patients with poor prognosis was chosen because IVIg is relatively scarce, costly and can have side effects. Patients with a good prognosis after a standard IVIg course, likely will not benefit from an additional IVIg course.

The following studies substantiate the need of an RCT to investigate the added effect of a second IVIg course.

1) In 2009 it was shown that patients with a small increase in serum IgG level after a standard course of IVIg treatment (2g/kg) had a significantly poorer outcome than patients who have a large serum IgG increase (Figure 3).[32] This may indicate that a subgroup of patients need a higher dosage of IVIg to further improve.
2) About 10% of IVIg treated patients have a secondary clinical deterioration after initial stabilization of improvement after treatment, which usually responds well to a second IVIg course.[33] This also suggests that at least those patients require a repeated course of IVIg.
3) In addition, two small case series of severely affected GBS patients seemed to benefit from a second IVIg course.[34,35]

In this thesis the protocol (**Chapter 3.2**) and the results (**Chapter 3.3**) of a multicenter double-blind randomized controlled trial to investigate the additional effect of a second IVIg course (SID-GBS trial) are described.

Aims and scope of this thesis

The clinical course and outcome of GBS is highly diverse, whereas current treatment is limited to a single standard course of IVIg for all patients unable to walk unaided. This 'one size fits all' treatment results in insufficient recovery in a substantial proportion of patients. Patients with a poor prognosis may profit from a more intensive treatment, provided there are early applicable and accurate prognostic models and additional effective treatments.

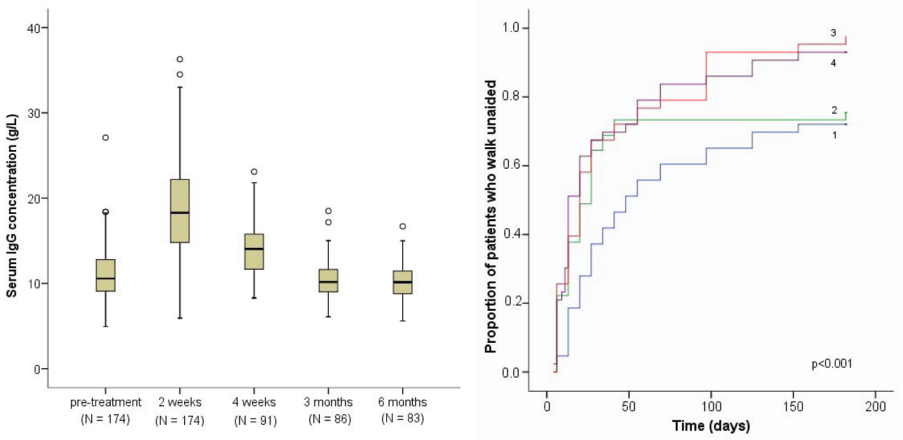

Figure 3 | A: Variability of serum immunoglobulin (Ig)G levels in GBS patients before and at 4 time points after treatment with a standard high dose of intravenous Ig (2g per kg body weight). Boxes indicate interquartile range (IQR), horizontal bars within boxes indicate medians, and whiskers indicate range without outliers. Observations more than 1.5 times IQR from the box are indicated as open dots. **B: Proportion of patients who regained the ability to walk unaided in quartiles based on increase in serum immunoglobulin (Ig)G 2 weeks after treatment with a standard high dose of intravenous Ig**. The Kaplan-Meier curves show the cumulative fractions of patients walking unaided along time grouped according to the quartiles (1– 4) of increase in serum IgG (ΔIgG). Cutoff values of ΔIgG for quartile 1: <3.99g/L (n = 43); quartile 2: 3.99 –7.30g/L (n = 45); quartile 3: 7.31–10.92g/L (n = 43); and quartile 4: >10.92g/L (n =43). p Value is based on the log-rank test for trend.

There were two general aims of the studies in this thesis:

1. To develop prognostic models that can be used to predict the clinical course and outcome in individual patients with GBS (**Chapter 2**)
2. To improve treatment for GBS patients with a poor prognosis (**Chapter 3**).

In **Chapter 2.1** we describe a model which predicts the chance of respiratory insufficiency (EGRIS). This aids the clinician to admit the patient to the appropriate department (general ward or ICU), and can thereby lower the risk of emergency intubation, saliva aspiration, pneumonia and sepsis. In **Chapter 2.2** the EGRIS model is validated in an international cohort. In **Chapter 2.3** we identified predictors for prolonged mechanical ventilation, to aid decision-making about performing tracheostomy in individual patients. In **Chapter 2.4** the prognostic ability of serum albumin was studied. Serum albumin may be an ideal biomarker, because it is easily to determine and routinely available. **Chapter 2.5** describes a model for prediction of functional outcome (the ability to walk unaided) for individual patient use. This model (mEGOS) is a modification of the EGOS model[27] and adapted to be applicable early in the disease course, to enable selection of patients with poor prognosis for early treatment in selective clinical trials.

Conducting randomized controlled trials in GBS is challenging because GBS is a rare and heterogeneous disease both in severity, course and outcome. In **Chapter 3.1** treatment trial data from the Dutch GBS Study Group were used to identify covariate adjustment and proportional odds analysis as the most efficiently use of the available data. This analytical approach was used in the Second IVIg Dose in GBS patients with poor prognosis (SID-GBS) trial, of which the protocol is described in **Chapter 3.2**. In this randomized, double-blind, multicenter trial the added effect of a second IVIg course administered shortly after the first standard course was investigated in GBS patients with a poor prognosis. The results of this trial conducted by the Dutch GBS Study Group are described in **Chapter 3.3**.

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1.2

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

Bianca van den Berg
Christa Walgaard
Judith Drenthen
Christiaan Fokke
Bart C. Jacobs
Pieter A. van Doorn

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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.

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).[2,4-8] 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.

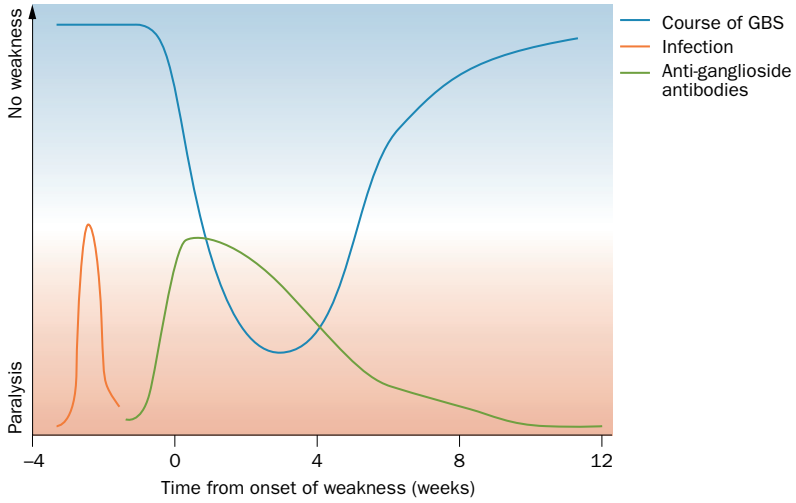

Figure 1 | The course of GBS. The majority of patients with GBS report an infection before the onset of weakness. Antiganglioside antibodies are often detected; their levels decrease over time. Different types of antibodies are related to the preceding infection and the GBS subtype. Progressive weakness 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.

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 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.

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

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).[2,16] 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 Curaçao and Bangladesh.[16-20] GBS seems to occur less 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.[2,3,6] 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.[25,26] 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.[4,24,27] Other pathogens that cause antecedent infections related to GBS are cytomegalovirus, Epstein– Barr virus, Mycoplasma pneumonia, Haemophilus influenzae, and influenza A virus.[4,27,28] 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.[4,37-39] 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).[4] 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]

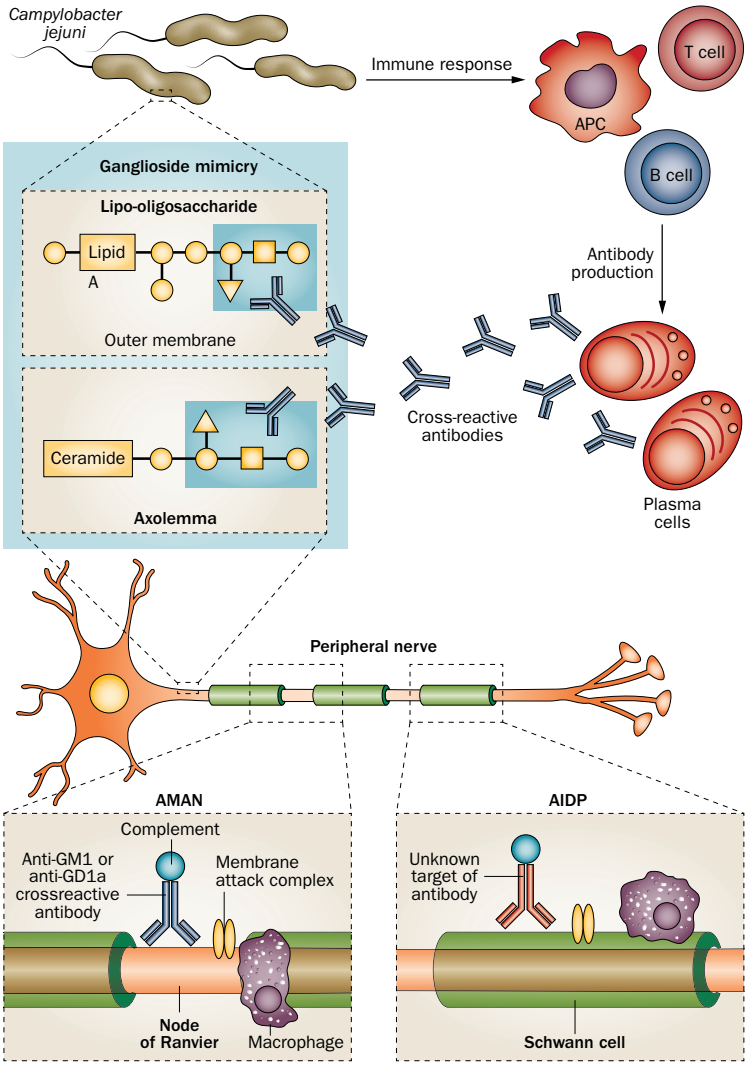

Figure 2 | Immunopathogenesis of GBS: molecular mimicry and antiganglioside antibodies. Infections with pathogens, such as *Campylobacter jejuni*, can trigger humoral immune and autoimmune responses that result in nerve dysfunction and the symptoms of GBS. Lipo-oligosaccharides on the *C. jejuni* outer 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.

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).[4,43] 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. [4,7,37,45-47]

Table 1 | GBS subtypes, clinical features and relevant antibodies[4,37,43]

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	GM1 1a, 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, ophtalmoplegia, 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.

Patients with MFS or MFS–GBS overlap syndrome (see below) frequently have antibodies against GD1b, GD3, GT1a and GQ1b gangliosides, which are related to ataxia and ophthalmoplegia.[4,9,37,48,49] 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.[39,51-53] 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, carbohydrate-targeted 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 I 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 genome-wide 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 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.[1,71] Though primarily developed for research purposes, they are probably still the most widely used criteria in clinical practice.[1] 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.[1,3,73] 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.[1] About half of the patients have cranial nerve deficits, especially bilateral facial weakness, swallowing difficulties or (sometimes) extraocular motor dysfunction.[1] 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

Box 1 | Diagnostic criteria for GBS[1,3,6,7]

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.

muscle weakness in about one-third of GBS cases.[1,3,76,77] 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.[3,77,81] 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.[1-3] 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).[2,4,6-8,23] The two 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.[2,4,8] 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).[6-8,46] Cranial nerve deficits are less frequent than in AIDP, but patients with AMAN may have autonomic dysfunction and pain.[4,7,77] Usually, disease progresses more rapidly in 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.[2,4,7] 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.[4,84,86]

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,[2-4,88] 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 µl 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.[2-4,73,88] 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.[94] 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;[95] for example, in an Italian study, 24% of patients initially classified as having AIDP were reclassified as having AMAN when serial NCS were performed.[92]

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.[2,3,97-99]

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.[97-99] Laboratory investigations can also be helpful to reveal other causes of GBS-like symptoms, such as electrolyte disturbances (especially hypokalaemia) and vitamin B1 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 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.[12,13,15] Immunotherapy is usually started if patients are not able to walk 10 m unaided (GBS Disability Scale score ≥3).[3,12] 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.[13,111] 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.[12,15] 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.[12,15,113,114] The usual 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.[115]

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.[12,13] 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.[78,116] 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.[12,13] 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.[12,13]

The choice of treatment depends on both patient-related 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.[1] 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.[12,78] Oral steroids and intravenous methylprednisolone are not beneficial in patients with GBS.[12,14,79] 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-β1a and brain-derived neurotrophic factor, and one trial studying a 6 week course of mycophenolate mofetil combined with standard IVIg versus IVIg alone, did not indicate beneficial effects of these treatments.[11,125]

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.

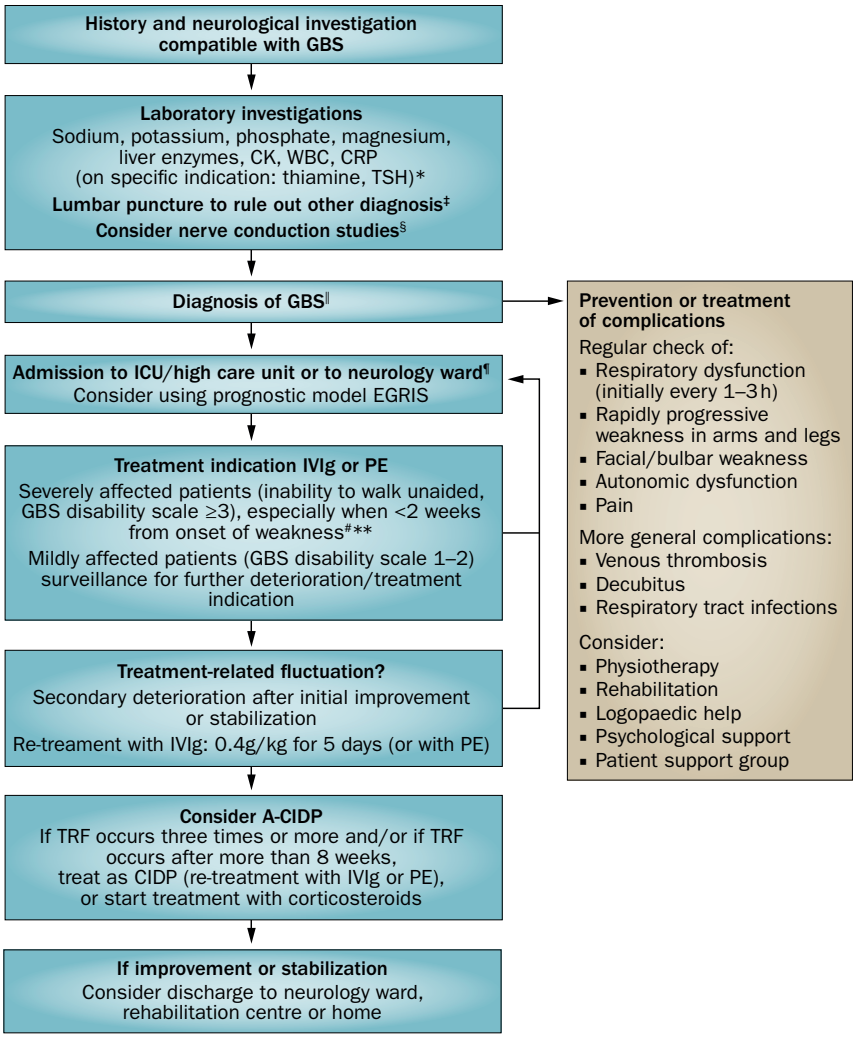

Figure 3 | Diagnosis and treatment of GBS. *If a non-GBS disorder is suspected, target laboratory investigations accordingly. ‡In case of cell count >50 cells per µl, consider spinal nerve root inflammation due to other causes. Normal cell counts and elevated cerebrospinal fluid protein level (albuminocytological 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: 0.4 g/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.

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 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.[3,128] 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.[3] 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.[2,3,12] 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.[77,135,137,139] 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 long-term residual effects on daily life in children have not been established.[102,104]

Table 2 | Differentiating characteristics of GBS, GBS-TRF, A-CIDP and CIDP[130]

Characteristic	GBS	GBS-TRF	A-CIDP	CIDP
Time to nadir	<2 weeks (maximum 4 weeks)	<2 weeks (maximum 4 weeks)	4–8 weeks, followed by progression with deteriorations	>8 weeks
Disease course	Monophasic	1–2 deteriorations within 8 weeks	>2 deteriorations or deterioration after 8 weeks	Progressive, stepwise or fluctuating
Severity	Highly variable between patients, ranging from mild symptoms to paralysis	Highly variable between patients, ranging from mild symptoms to paralysis	Mostly moderate	Mostly moderate, distal and proximal weakness
Ventilator dependence	20–30%	20–30%	Almost never	Almost never
Cranial nerve deficits	Often	Often	Sometimes	Sometimes
Response to IVIg	Good	Good, with fluctuations	Variable	Good
EMG/NCS*	Sometimes no classification possible at first EMG/NCS	Sometimes no classification possible at first EMG/NCS	Often demyelinating polyneuropathy at first EMG/NCS	Demyelination
Treatment	IVIg or plasma exchange	Repeat IVIg or plasma exchange	IVIg or plasma exchange, on confirmed diagnosis of CIDP consider also switch to prednisolone maintenance treatment	IVIg, prednisolone or plasma exchange

*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.

Long-lasting symptoms of fatigue are present in the majority of patients with GBS.[139] 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 meningism.[77] 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). 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[28,80,140,141,154,160,162-165] 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).

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.[80,160,170,171]

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 more-effective and specific treatments, as well as protocols for supportive care.

These aims can probably only be achieved by large-scale 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 complement-dependent damage at the nodes of Ranvier, nerve terminals, and perisynaptic Schwann cells (Figure 2).[60,173] 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.

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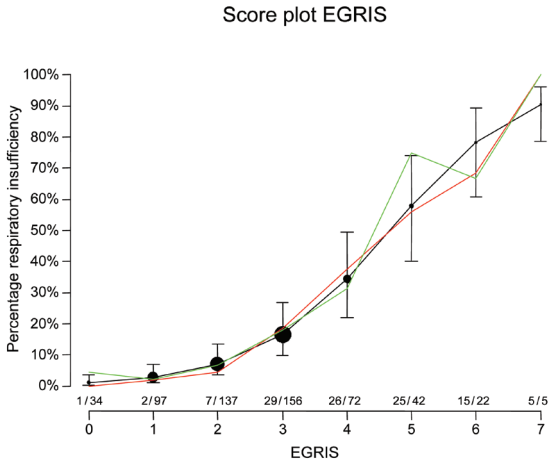
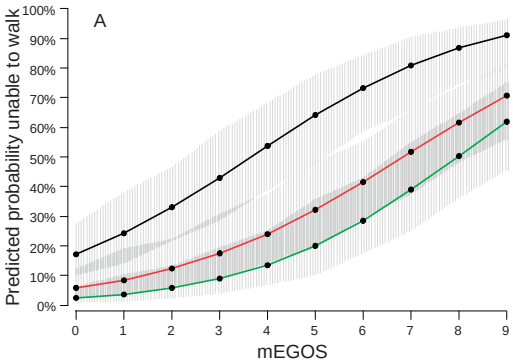


Supplementary figure 1 | Predicted probability of respiratory insufficiency and observed percentage of mechanical ventilation (MV) in derivation and validation cohorts according to the Erasmus GBS Respiratory Insufficiency Score (EGRIS). The black line reflects the predicted probability of respiratory insufficiency derived from the combined cohorts. The size of bullets in the graph reflects the size of the patient group with a corresponding EGRIS score in the combined cohorts (n = 565). The red line reflects the observed percentage of MV in the derivation cohort (n = 377), and the green line reflects this percentage in the validation cohort (n = 188). Above the x-axis are the numbers of patients requiring MV of patients with a defined EGRIS in the derivation and validation cohorts. Adapted from Walgaard, C. et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. Ann Neurol 67, 781-787 (2010).

Supplementary table | EGRIS scoring system[5]

Predictor	Categories	Score
Time from onset of weakness to	>7 days	0
hospital admission (days)	4-7 days	1
	≤3 days	2
Facial and/or bulbar weakness at	Absent	0
hospital admission	Present	1
MRC sum score at hospital admission	51-60	0
	41-50	1
	31-40	2
	21-30	3
	≤20	4
EGRIS total score		**0-7**

EGRIS = Erasmus GBS Respiratory Insufficiency Score; MRC = Medical Research Council.

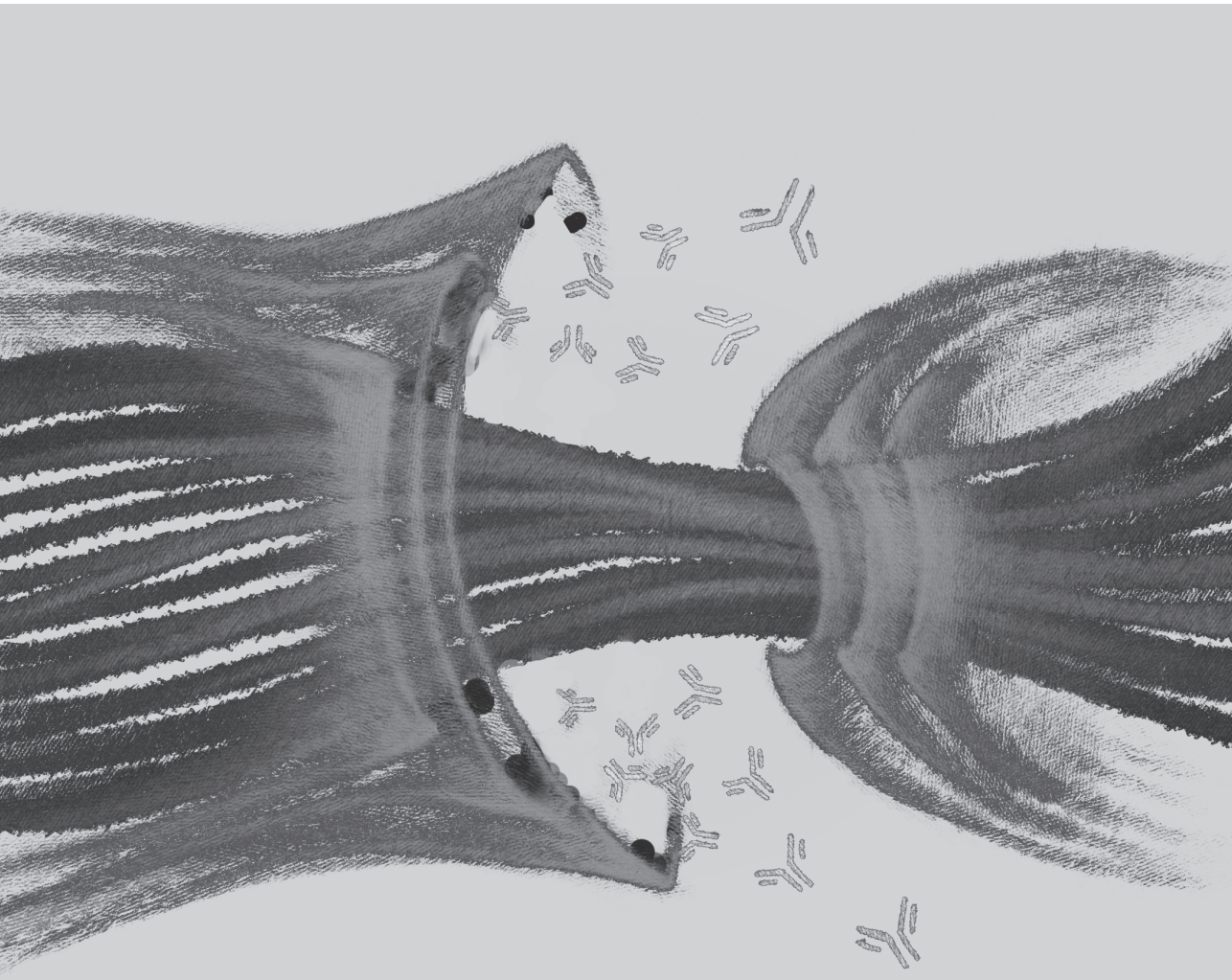


Supplementary figure 2 | Predicted fraction of patients unable to walk independently at 4 weeks (black lines), 3 months (red lines), and 6 months (green lines) on the basis of the mEGOS at hospital admission (A)and at day 7 of admission.(B) The gray areas around the colored lines represent 90% confidence intervals. MRC sum score = sum of the MRC score of 6 bilateral muscles: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsal flexors. Range: 0 (tetraparalytic) to 60 (normal strength)).
Adapted from Walgaard, C. et al. Early recognition of poor prognosis in Guillain-Barré syndrome. Neurology 76, 968-975 (2011).

Supplementary table | Modified Erasmus GBS Outcome Scores

Prognostic factors	Categories	Score	Prognostic factors	Categories	Score
Age at onset (years)	≤ 40	0	Age at onset (years)	≤ 40	0
	41– 60	1		41– 60	1
	> 60	2		> 60	2
Preceding diarrhea[a]	Absent	0	Preceding diarrhea[a]	Absent	0
	Present	1		Present	1
MRC sum score	51– 60	0	MRC sum score	51– 60	0
(at hospital admission)	41– 50	2	(at day 7 of admission)	41– 50	3
	31– 40	4		31– 40	6
	0 – 30	6		0 – 30	9
mEGOS		0 – 9	mEGOS		0 – 12

Abbreviations: mEGOS = modified Erasmus GBS Outcome Score; MRC = Medical Research Council.
[a] Diarrhea in the 4 weeks preceding the onset of weakness.



2

Predicting outcome in GBS

2.1

Prediction of Respiratory Insufficiency in Guillain-Barré Syndrome

Christa Walgaard
Hester F. Lingsma
Liselotte Ruts
Judith Drenthen
Rinske van Koningsveld
Marcel J.P. Garssen
Pieter A. van Doorn
Ewout W. Steyerberg
Bart C. Jacobs

Ann. Neurol. 2010; 67:781-787

ABSTRACT

Objective

Respiratory insufficiency is a frequent and serious complication of the Guillain-Barré syndrome (GBS). We aimed to develop a simple but accurate model to predict the chance of respiratory insufficiency in the acute stage of the disease based on clinical characteristics available at hospital admission.

Methods

Mechanical ventilation (MV) in the first week of admission was used as an indicator of acute stage respiratory insufficiency. Prospectively collected data from a derivation cohort of 397 GBS patients were used to identify predictors of MV. A multivariate logistic regression model was validated in a separate cohort of 191 GBS patients. Model performance criteria comprised discrimination (area under receiver operating curve [AUC]) and calibration (graphically). A scoring system for clinical practice was constructed from the regression coefficients of the model in the combined cohorts.

Results

In the derivation cohort, 22% needed MV in the first week of admission. Days between onset of weakness and admission, Medical Research Council sum score, and presence of facial and/or bulbar weakness were the main predictors of MV. The prognostic model had a good discriminative ability (AUC, 0.84). In the validation cohort, 14% needed MV in the first week of admission, and both calibration and discriminative ability of the model were good (AUC, 0.82). The scoring system ranged from 0 to 7, with corresponding chances of respiratory insufficiency from 1 to 91%.

Interpretation

This model accurately predicts development of respiratory insufficiency within 1 week in patients with GBS, using clinical characteristics available at admission. After further validation, the model may assist in clinical decision making, for example, on patient transfer to an intensive care unit.

INTRODUCTION

Respiratory insufficiency is a life-threatening manifestation of the Guillain-Barré syndrome (GBS) that occurs in 20 to 30% of patients and is associated with poor functional outcome.[1-4] Respiratory insufficiency often develops insidiously in GBS. This may explain the relatively high frequency of nocturnal and emergency intubations.[5,6] Moreover, 60% of intubated patients develop major complications, including pneumonia, sepsis, and pulmonary embolism.[7] Delaying intubation may increase the risk of pneumonia due to aspiration and worsens outcome.[8,9] Specific treatments for GBS may not have reduced mortality and length of hospital stay among ventilated GBS patients.[10] Prediction of respiratory insufficiency is important to triage patients to the appropriate unit (general ward or intensive care unit [ICU]) and to avoid respiratory distress.

Previous studies identified various risk factors for respiratory insufficiency in GBS, including cranial nerve deficits,[5,11-13] disability grade on admission,[8,11,14] rapid progressive motor weakness,[5,14] areflexia,[8] descending weakness,[15] dysautonomia,[5] electromyographic features of nerve conduction block,[11,16] positive cytomegalovirus (CMV) serology,[17] anti-GQ1b antibodies,[12] and increased liver enzymes.[11,14] Only 1 validated model for the prediction of respiratory insufficiency in clinical practice is available, based on information about the vital capacity and the ratio of the proximal to distal peroneal nerve compound muscular amplitude potential.[11] In this study, electrophysiological testing generally was done within 6 days after admission, whereas most intubations in GBS occur in the first week of admission. Prediction models for respiratory insufficiency should be available as early as possible, preferably at hospital admission, and based on readily available information. Previous studies showed that clinical parameters in the progressive phase are highly predictive of the clinical course of GBS.[18,19]

The aim of the current study was to develop a simple and accurate model using clinical features available at hospital admission to predict the occurrence of respiratory insufficiency in the acute stage of GBS. Model performance was validated in an independent cohort of patients with GBS.

PATIENTS AND METHODS

Patients

Prospectively collected data from a cohort of 397 patients with GBS were used to identify risk factors for respiratory insufficiency in the acute stage. This derivation cohort consisted of patients included in 2 treatment trials and 1 pilot study. The first study was a multicenter, double-blind, randomized controlled trial that compared plasma exchange with intravenous immunoglobulin (IVIg) for which 147 patients were included between 1985 and 1991.[20] The second

study was a pilot study in 25 Dutch patients to determine the additional therapeutic effect of methylprednisolone with IVIg.[21] In the third study, this combination was tested in a multicenter, double-blind, randomized controlled trial including 225 patients between 1994 and 2000.[22] Most patients were randomized in Dutch hospitals, the others in 2 German and 2 Belgian hospitals. The same inclusion and exclusion criteria were used in these 3 studies. Inclusion criteria were fulfillment of the National Institute of Neurological Diseases and Stroke diagnostic criteria for GBS,[23] being unable to walk unaided 10m across an open space (GBS disability score ≥3), and onset of weakness within 2 weeks before randomization. Exclusion criteria were age <6 years, previous GBS, known severe allergic reaction to properly matched blood products, pregnancy, known selective IgA deficiency, previous steroid therapy, severe concurrent disease, inability to attend follow-up, or contraindications for corticosteroid treatment (not in first trial).

To validate the model, we used prospectively collected data from a cohort of 191 patients enrolled in 1 pilot study[24] and 1 observational study. The pilot study determined the additional therapeutic effect of mycophenolate mofetil with IVIg and methylprednisolone, and for this study 27 patients were included between 2002 and 2005. The same inclusion and exclusion criteria were used as in the derivation cohort. Regarding the observational study, 168 GBS patients were included between 2005 and 2008 to assess pain and autonomic dysfunction. This study also included patients with a milder course (able to walk throughout the course of the disease) (n = 33) or Miller Fisher syndrome (n = 18). Patients with additional central nervous system involvement (n = 4) were excluded. All patients in the validation cohort were included in Dutch hospitals. Patients who were intubated before the day of admission in the participating hospital were excluded from the derivation and validation set.

Data Collection

Baseline characteristics (age, gender, pre-existing chronic pulmonary disease), preceding diarrhea or symptoms of an upper respiratory tract infection, day of onset of weakness, cranial nerve dysfunction, Medical Research Council (MRC) sum score, GBS disability score, and sensory deficit at study entry were collected prospectively. Most patients entered the study within 1 day of hospital admission (interquartile range, 0–1 days). The MRC sum score is defined as the sum of MRC scores of 6 different muscles measured bilaterally, resulting in a score ranging from 0 (tetraplegic) to 60 (normal; Supplementary Text).[25] The GBS disability score is a widely accepted scale to assess functional status of GBS patients, ranging from 0 (normal) to 6 (death; Supplementary Text).[26] Additional serological screening was performed to determine recent infections with *Campylobacter jejuni*, CMV, Epstein-Barr virus, and Mycoplasma pneumonia and antibodies to the gangliosides GM1, GD1a, and GQ1b. The serum samples used were obtained within 4 weeks from onset of weakness and before start of treatment. Liver enzymes (aspartate aminotransferase, alanine aminotransferase) were considered abnormal when the ratio between measured values and the upper limit of normal was >1.5.

Endpoint

The main endpoint in our study was mechanical ventilation (MV) in the first week of hospital admission, as an indicator of acute stage respiratory insufficiency. The decision to intubate was based on the discretion of the treating physician.

Statistical analysis

Potential predictors of MV within 1 week were first considered in logistic regression models in the derivation cohort. Predictors that were statistically significant in univariate analysis and available at admission were further analyzed in a multivariate logistic regression model. A backward stepwise selection procedure was done with a p value of 0.1 as selection criterion. Variables with >15% missing data were omitted from analysis. Missing values in other variables were imputed using a multiple imputation method.[27] Odds ratios of univariate analysis were compared between the imputed dataset and the unimputed dataset. Model performance was quantified with respect to discrimination (area under the receiver operating curve [AUC]). The AUC ranges from 0.5 to 1.0 for sensible models. Internal validity of the model was assessed using bootstrapping techniques, and included the selection of predictors. The model was applied to the validation dataset for external validation. Model performance in the validation set was quantified with respect to discrimination (AUC) and calibration. Calibration was assessed graphically by plotting observed frequencies against predicted probabilities. A final scoring system was constructed based on the regression coefficients of the multivariate model in a dataset where the derivation and validation sets were combined for larger reliability. Statistical analyses were done with SPSS for Windows (SPSS Inc., Chicago, Ill), and R statistical software.

RESULTS

In the derivation cohort, 20 (5%) of the 397 patients were intubated before referral to 1 of the participating hospitals and excluded from the current study. Eighty-three (22%) of the remaining 377 patients required MV in the first week of hospital admission and 16 (4%) after the first week. In the validation cohort, 3 (2%) of the 191 GBS patients were excluded because of intubation before referral to a trial hospital. Twenty-seven (14%) of the remaining 188 patients required MV in the first week of hospital admission and 2 (1%) after the first week.

Strong associations with MV in the first week after admission were found for the following clinical parameters available at hospital admission: MRC sum score, GBS disability score, rate of initial disease progression (indicated by the number of days between onset of weakness and hospital entry), facial weakness, bulbar weakness, and areflexia of arms and legs (Table 1).

Table 1 | Characteristics of the derivation set of 377 patients with GBS in relation to MV in the first week of hospital admission.

Characteristic	No.	MVwithin 1 week	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
Demographic features						
Total	377	83 (22%)				
Age (years)				0.3		
≤ 40	131 / 377	24 (18%)	1			
40 - 60	109 / 377	29 (27%)	1.6 (0.9 - 3.0)			
> 60	137 / 377	30 (22%)	1.3 (0.7 - 2.3)			
Gender (male)	209 / 377	49 (23%)	1.2 (0.7 - 2.0)	0.5		
Chronic pulmonary disease	11 / 243	1 (9%)	0.5 (0.1 - 4.1)	0.5		
Neurological deficits at entry						
Onset weakness – entry (days)				<0.001		<0.001
> 7	96 / 376	7 (7%)	1		1	
4 - 7	147 / 376	28 (19%)	3.0 (1.3 - 7.2)		3.5 (1.3 - 9.3)	
≤ 3	133 / 376	47 (35%)	6.9 (3.0 - 16)		9.2 (3.4 - 25)	
Cranial nerve involvement						
Facial and/or bulbar weakness	119 / 377	39 (33%)	2.4 (1.4 - 3.9)	0.001	3.9 (2.1 - 7.3)	<0.001
Bulbar weakness	37 / 377	18 (49%)	4.0 (2.0 - 8.1)	<0.001		
Facial weakness	112 / 377	8 (32%)	1.7 (0.7 - 4.2)	0.002		
Ophthalmoplegia	25 / 377	36 (32%)	2.2 (1.3 - 3.6)	0.2		
MRC sumscore				<0.001		<0.001
60 - 51	48 / 375	1 (2%)	1		1	
50 - 41	180 / 375	26 (14%)	8.1 (1.1 - 61)		6.3 (0.8 - 50)	
40 - 31	77 / 375	16 (21%)	12 (1.6 - 97)		9.8 (1.2 - 81)	
30 - 21	46 / 375	22 (48%)	44(5.6 - 346)		29 (3.4 - 246)	
≤ 20	24 / 375	18 (75%)	144 (16 - 1281)		87 (9.1 - 830)	

Table 1 | Characteristics of the derivation set of 377 patients with GBS in relation to MV in the first week of hospital admission. *(continued)*

Characteristic	No.	MVwithin 1 week	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
GBS disability score				<0.001		0.2
3	92 / 377	6 (7%)	1		1	
4 or 5	285 / 377	77 (27%)	5.3 (2.2 - 13)		1.9 (0.7 - 5)	
Sensory deficits	244 / 371	53 (22%)	1.1 (0.6 - 1.8)	0.8		
Pain	181 / 375	37 (20%)	0.8 (0.5 - 1.4)	0.5		
Areflexia (both arms and legs)	149 / 265	47 (32%)	2.9 (1.5 - 5.4)	0.001		
Infection and serology						
Symptoms of preceding infection[a]						
Diarrhea	85 / 375	18 (21%)	0.9 (0.5 - 1.7)	0.8		
Upper respiratory tract infection	137 / 369	28 (20%)	0.9 (0.5 - 1.5)	0.5		
Infection serology[b]						
Campylobacter jejuni	97 / 333	24 (25%)	1.3 (0.7 - 2.2)	0.4		
Cytomegalovirus	42 / 332	14 (33%)	2.0 (1.0 - 4.0)	0.06		
Epstein-Barr virus	42 / 332	10 (24%)	1.1 (0.5 - 2.4)	0.8		
Mycoplasma pneumoniae	17 / 332	3 (18%)	0.8 (0.2 - 2.7)	0.7		
Anti-ganglioside IgM/IgG antibodies[b]						
GM1	72 / 333	11 (15%)	0.6 (0.3 - 1.2)	0.1		
GD1a	16 / 333	6 (38%)	2.2 (0.8 - 6.4)	0.1		
GQ1b	21 / 333	6 (29%)	1.5 (0.6 - 3.9)	0.5		
Liver dysfunction[b]						
ALAT	55 / 357	17 (31%)	1.7 (0.9 - 3.1)	0.1		
ASAT	37 / 357	12 (32%)	1.7 (0.8 - 3.7)	0.1		

[a]Symptoms of infection in the 4 weeks preceding the onset of weakness. [b]Using pretreatment serum samples obtained at entry. GBS = Guillain-Barré Syndrome; MV = mechanical ventilation in the first week after hospital admission; OR = odds ratio; CI = confidence interval; MRC = Medical Research Counsel; Ig = immunoglobulin; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase.

Facial weakness and bulbar weakness elaborately overlapped in these GBS patients and were combined as a single predictor for multivariate analysis. Areflexia was left out of the multivariate logistic regression analysis because data were missing in 30% of patients. For the remaining parameters, data were missing in <3% and were imputed using multiple imputation. In multivariate logistic regression analysis, strong predictors of MV in the first week of hospital admission were MRC sum score at admission ($p < 0.001$), days between onset of weakness and admission ($p < 0.001$), and facial and/or bulbar weakness at admission ($p < 0.001$). GBS disability score was not associated with respiratory insufficiency in multivariate analysis. A model to predict respiratory insufficiency was constructed using these 3 statistically significant clinical parameters and showed a very good discriminative ability (AUC = 0.84). After excluding the 18 patients intubated within 24 hours after hospital admission, the discriminative ability remains very good (AUC = 0.83).

The model developed in the derivation cohort was further tested in the independent validation cohort and showed an equally good discriminative ability (AUC = 0.82) and calibration (Supplementary Fig). The Erasmus GBS Respiratory Insufficiency Score (EGRIS) was based on the regression coefficients of the 3 predictors in the multivariate model in the combined cohorts (n = 565). Scores ranged from 0 to 7, with 5 categories for the MRC sum score at admission, 3 categories for days between onset of weakness and hospital entry, and 2 categories for facial and/or bulbar weakness at admission, with corresponding chances for respiratory insufficiency within 1 week ranging from 1 to 91% (Table 2 and Fig). Median duration of MV was 27 days (interquartile range, 12–53 days). The duration of MV was not associated with the EGRIS (data not shown).

Table 2 | EGRIS.

Measure	Categories	Score
Days between onset of weakness and hospital admission	> 7 days	0
	4 – 7 days	1
	≤ 3 days	2
Facial and/or bulbar weakness at hospital admission	Absence	0
	Presence	1
MRC sum score at hospital admission	60 – 51	0
	50 – 41	1
	40 – 31	2
	30 – 21	3
	≤ 20	4
EGRIS		0 – 7

EGRIS = Erasmus GBS Respiratory Insufficiency Score; MRC = Medical Research Counsel

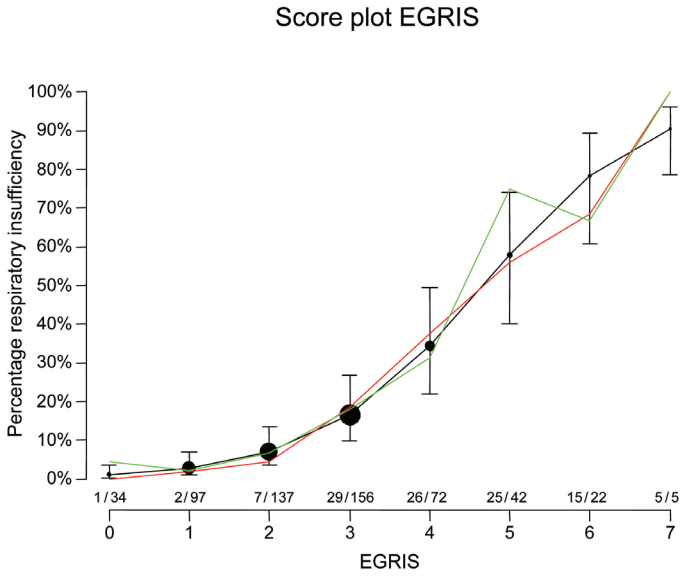


Figure | Predicted probability of respiratory insufficiency and observed percentage of mechanical ventilation (MV) in derivation and validation cohorts according to the Erasmus GBS Respiratory Insufficiency Score (EGRIS). The black line reflects the predicted probability of respiratory insufficiency derived from the combined cohorts. The size of bullets in the graph reflects the size of the patient group with a corresponding EGRIS score in the combined cohorts (n = 565). The red line reflects the observed percentage of MV in the derivation cohort (n = 377), and the green line reflects this percentage in the validation cohort (n = 188). Above the x-axis are the numbers of patients requiring MV of patients with a defined EGRIS in the derivation and validation cohorts.

As an example, we consider 2 hypothetical patients at the emergency department with a MRC sum score of 25 (3 points). The first patient had weakness since day 1 (2 points) and facial weakness (1 point), whereas the second patient had weakness since day 10 (0 points) and no facial or bulbar weakness (0 points). The EGRIS for the first patient is 6 points, corresponding to a risk of respiratory insufficiency in the first week of admission of 77% (95% confidence interval [CI], 61–89%; see Fig). The EGRIS for the second patient is 3 points, corresponding to a much lower risk of respiratory insufficiency of 17% (95% CI, 10–27%; see Fig). For further illustration, patients were divided into 3 clinically relevant risk groups (Table 3). Only 10 (4%) of 268 patients with a low EGRIS (0 –2) had respiratory insufficiency in the first week, compared with 45 (65%) of 69 patients with a high EGRIS (5–7).

DISCUSSION

In the current study, a prognostic model was developed that accurately predicts respiratory insufficiency in the early stage of GBS using 3 clinical characteristics readily available at hospital

Table 3 | Risk categories for respiratory insufficiency according to EGRIS.

Category	Derivation set	Validation set	Combined sets
Low risk (EGRIS 0-2)	5/152 (3%)	5/116 (4%)	10/268 (4%; 95% CI, 1-6%)
Intermediate risk (EGRIS 3-4)	42/168 (25%)	13/60 (22%)	55/228 (24%; 95% CI, 19-30%)
High risk (EGRIS 5-7)	36/57 (63%)	9/12 (75%)	45/69 (65%; 95% CI, 54-76%)
Total	83/377 (22%)	27/188 (14%)	110/565 (19%; 95% CI, 16-23%)

Probability of respiratory insufficiency in the first week of hospital admission in the derivation, validation, and combined sets stratified for EGRIS and expressed as number of mechanically ventilated patients/total number of patients (%). EGRIS = Erasmus GBS Respiratory Insufficiency Score; CI = confidence interval for combined sets.

admission. The most important predictors of MV in the first week of admission were the rate of disease progression, indicated by the number of days between onset of weakness and hospital admission, the MRC sum score, and the presence of facial or bulbar weakness. A multivariate prediction model proved valid in an independent cohort of GBS patients. The proposed 8-point EGRIS accurately predicts the probability of respiratory insufficiency in the first week of hospital admission in individual GBS patients, ranging from 1 to almost 90%.

Our study confirms findings by others that respiratory insufficiency in GBS is associated with a high GBS disability score at hospital admission,[8,11,14] rapid disease progression,[5,14] presence of cranial nerve deficit,[5,11-13] and areflexia.[8] In our cohort, no data were available on dysautonomia[5] or descending weakness,[15] both previously reported to be predictors of respiratory insufficiency. Also, very limited information was available regarding vital capacity or electrophysiology at admission, so we were unable to validate the model of Durand et al.11 Vital capacity and electrophysiological measurements at hospital admission may further improve the EGRIS. Measurement of vital capacity may be confounded by bilateral facial weakness, occurring in more than half of GBS patients, and a low vital capacity may reflect impending or established respiratory insufficiency rather than an increased risk of future respiratory insufficiency. Moreover, electrophysiology may not be available at admission, and the results may be highly variable in the first week of GBS.[28]

The clinical risk factors for acute stage respiratory insufficiency partly differ from those for a poor long-term outcome. In a previous study, using the same derivation cohort of patients, the ability to walk unaided after 6 months depended on age, presence of preceding diarrhea, and GBS disability score at 2 weeks after admission.[19] A low GBS disability score was associated with respiratory insufficiency, but lost significance in the multivariate regression analysis together with MRC sum score. In addition, MV is incorporated in the GBS disability score, rendering this score less suitable to predict respiratory insufficiency. Age and preceding diarrhea were not associated with respiratory insufficiency in the current and previous studies. Probably, age influences the capacity to recover more than the disease severity in the acute phase. Preceding diarrhea in GBS is frequently caused by infections with C. jejuni, and associated with a severe,

pure motor, and axonal variant.[29,30] In this form of GBS, the proximal muscles and cranial nerves are relatively spared, which may explain why this phenotype does not predispose to respiratory insufficiency. The frequency of respiratory insufficiency in GBS patients may be lower in Japan, where the C. jejuni or axonal form of GBS is predominant,[31] in contrast to Western countries, where the demyelinating forms are predominant. In a Japanese cohort of patients with severe GBS, only 10% needed MV,[15] compared with 19% in the combined cohorts from the current study. This may support the hypothesis that in GBS, severe demyelination is associated with respiratory insufficiency.[11,16]

The EGRIS has some limitations. First, the derivation and validation cohorts differed with respect to the proportion of patients requiring MV (22% vs 14%). The lower frequency of MV in the validation cohort is explained by different inclusion criteria that allowed inclusion of patients with mild forms of GBS. However, the EGRIS model developed in the derivation cohort performed equally well in the validation cohort, demonstrating its wide clinical applicability. Second, the endpoint in our study was MV, which is only an indirect indicator of respiratory insufficiency. In fact, the decision to intubate is relatively arbitrary and based on the discretion of the treating physician, supported by previously published general criteria for intubation in GBS.[32] Our results could be biased by the long time span of data acquisition, during which the practice of intubation may have changed. However, no trend was found in our dataset regarding the frequency of MV and the performance of EGRIS. More detailed information is required in future studies regarding respiratory parameters, especially at the time of intubation. Third, model development focused on the prediction of MV in the first week after admission. The first week of the disease reflects probably the most unpredictable period of GBS, with the highest frequency of acute respiratory insufficiency. In our cohorts, 3% of the patients were intubated after the first week of admission. The EGRIS predicted the need of MV, irrespective of the time point during clinical course, accurately with an AUC of 0.80. Fourth, time from onset of weakness to hospital admission is probably influenced by social factors. The time from onset of weakness to loss of ambulation is possibly less arbitrary but was not documented in our cohorts. Because most patients were included in the trials shortly after losing ambulation, the moment of study entry usually equals that of losing ambulation. Lastly, most patients included in our studies were Dutch Caucasians, and the EGRIS may not be applicable to patients from other geographical areas or ethnic origin. Prospective studies in more diverse populations of patients are required to determine the general validity of the EGRIS.

How to apply the EGRIS in clinical practice? Based on the model, respiratory insufficiency in the first week of admission cannot be excluded in an individual patient ith GBS. Even in the low-risk subgroup, with an EGRIS score of ≤2, 4% (95% CI, 1–6%) of the patients developed respiratory insufficiency, which required MV. This underlines that the clinical course in individual GBS patients can by highly variable and stresses the importance of regular pulmonary function

monitoring (vital capacity, respiratory frequency), initially every 2 to 6 hours in the progressive phase and every 6 to 12 hours in the plateau phase.[30] Nonetheless, the EGRIS model holds great promise as a practical tool to inform patients and their families and assist physicians in decision making. For examples, patients with an increased risk of respiratory insufficiency may be transferred to an ICU, or be considered for early elective intubation.

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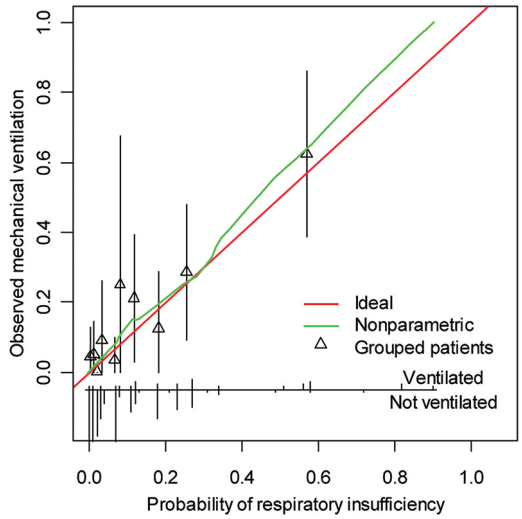
SUPPLEMENTARY MATERIAL



Supplementary Figure 1

External validity of the EGRIS for prediction of respiratory insufficiency in the validation cohort. The red line from (0,0) to (1,1) indicates perfect calibration. Triangles indicate the probabilities in grouped patients with similar predicted risks. A non-parametric, smoothed, green curve indicates the relation between predicted probability and observed frequency of mechanical ventilation. The distribution of predicted probabilities of respiratory insufficiency is shown at the bottom of the graph.

2.2

International validation of the Erasmus GBS Respiratory Insufficiency Score

Alex Y. Doets
Christa Walgaard
Hester F. Lingsma
Badrul Islam
Nowshin Papri
Yuko Yamagishi
Susumu Kusunoki
Mazen M. Dimachkie
Waqar Waheed
Noah Kolb
Kenneth C. Gorson
Bart C. Jacobs
the IGOS Consortium*

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ABSTRACT

Objective

This study aimed to validate the Erasmus Guillain-Barré syndrome Respiratory Insufficiency Score in the International Guillain-Barré Syndrome Outcome Study cohort, and to improve its performance and region-specificity.

Methods

We examined data from the first 1500 included patients, aged ≥6 years and not ventilated prior to study entry. Patients with a clinical variant or mild symptoms were also included. Outcome was mechanical ventilation within the first week from study entry. Model performance was assessed regarding the discriminative ability (area under the receiver operating characteristic curve) and the calibration (observed versus predicted probability of mechanical ventilation), in the full cohort and in Europe/North America and Asia separately. We recalibrated the model to improve its performance and region-specificity.

Results

In the group of 1023 eligible patients (Europe/North America n=842, Asia n=104, other n=77), 104 (10%) required mechanical ventilation within the first week from study entry. Area under the curve values were ≥0.80 for all validation subgroups. Mean observed proportions of mechanical ventilation were lower than predicted risks: full cohort 10% vs. 21%, Europe/North America 9% vs. 21% and Asia 17% vs. 23%. After recalibration, predicted risks for the full cohort and Europe/North America corresponded to observed proportions.

Interpretation

This prospective, international, cohort study validated the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score, and showed that the model can be used in the full spectrum of Guillain-Barré syndrome patients. In addition, a more accurate, region-specific version of the model was developed for patients from Europe/North America.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a postinfectious inflammatory disease of the peripheral nervous system that is frequently complicated by respiratory insufficiency. About 10-30% of all patients with GBS require mechanical ventilation during the disease course [1]. Respiratory failure in GBS often develops insidiously, without traditional signs of respiratory compromise. Delayed intubation may lead to aspiration and a subsequent increased risk of pneumonia, which is associated with a worse outcome[2, 3]. Early prediction of respiratory insufficiency in GBS patients is important to correctly triage patients to the appropriate level of care (i.e. general ward, high or intensive care unit (ICU)) and to prevent complications associated with delayed intubation. Previous studies identified various risk factors for respiratory insufficiency in GBS, including factors related to the disease progression rate, severity of muscle weakness, nerve conduction study parameters, respiratory function tests, infection serology, liver enzymes, and anti-ganglioside antibodies[2, 4-12]. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) is a prediction model that estimates the risk of respiratory failure – defined by the need for mechanical ventilation within the first week from hospital admission – in individual patients with GBS[5]. EGRIS predictions are based on three clinical factors that are determined at hospital admission: the time from onset of weakness to admission, presence of facial and/or bulbar weakness and the severity of muscle weakness defined by the Medical Research Council (MRC) sum score (Table 1). The EGRIS total score ranges from 0 to 7, which corresponds to an estimated risk of respiratory failure within the first week ranging from 1% to 90%. Results from previous single country studies already showed differences in the clinical presentation, disease course, subtypes and outcome of GBS among countries [13-17]. This regional variation was recently confirmed by our study describing the first 1000 patients included in the International GBS Outcome Study (IGOS)[18]. The EGRIS has been developed with data from a Dutch GBS cohort, but is currently used in GBS patients from all around the world[5]. Until now validation only has been performed in two smaller Asian cohorts[19, 20]. Therefore this study aimed to validate the EGRIS in the IGOS cohort to define its performance in an international GBS population. The second aim was to further improve model performance by applying region-specific adjustments to the EGRIS.

MATERIALS AND METHODS

Dataset for external validation

For this external validation study we used data from the first 1500 patients included in IGOS, an ongoing prospective multicentre cohort study on GBS, in which all variants and subtypes of GBS are represented[21]. Patients were enrolled between May 2012 and April 2017 in 155 hospitals from 19 countries: Argentina, Australia, Bangladesh, Belgium, Canada, China, Denmark, France,

Germany, Greece, Italy, Japan, Malaysia, The Netherlands, South Africa, Spain, Taiwan, UK, USA. IGOS was approved by the review board of the Erasmus University Medical Centre, Rotterdam, The Netherlands (MEC-2011-477), and the local institutional review boards of participating hospitals or universities. Written informed consent was obtained from all patients or their legal representatives.

Table 1 | EGRIS scoring system[5]

Predictor	Categories	Score
Time from onset of weakness to hospital admission (days)	>7 days	0
	4-7 days	1
	≤3 days	2
Facial and/or bulbar weakness at hospital admission	Absent	0
	Present	1
MRC sum score at hospital admission	51-60	0
	41-50	1
	31-40	2
	21-30	3
	≤20	4
EGRIS total score		**0-7**

EGRIS = Erasmus GBS Respiratory Insufficiency Score; MRC = Medical Research Council.

For validation of the EGRIS we included all patients with GBS or its variants, who had been enrolled in IGOS within two weeks from the onset of weakness[22, 23]. Patients in whom the diagnosis was altered during the 1-3 years follow up were excluded. We also excluded patients under 6 years, because the MRC scores cannot be assessed reliably in young children, and patients from Bangladesh as most of these patients do not receive specific immunotherapy and facilities for supportive care (including ventilatory support) are limited in Bangladesh. Finally, we excluded patients who were admitted to the hospital before the onset of weakness and patients who were ventilated prior to study entry. Patients in whom mechanical ventilation was started at the same day as the entry assessment were retained in the analysis.

Statistical analysis

Predictive performance

Because study entry is the first data collection time point in IGOS, we used the 'MRC sum score at entry' and 'facial and/or bulbar weakness at entry' to calculate the EGRIS score, and defined outcome as 'the need for mechanical ventilation within the first week from study entry'. Some patients were first admitted to another hospital before they were transferred to an IGOS-participating centre. For these patients we used the date of the first hospital admission to define the time from onset of weakness to admission.

We assessed model performance by determining the discrimination and calibration. Discrimination is the ability of the model to distinguish between patients who need and do not need mechanical ventilation and is quantified by the area under the receiver operating characteristic (ROC) curve. The ROC curve provides the sensitivity (i.e. true positive rate) of a model at different probability thresholds plotted against (1-specificity) (i.e. false positive rate). The area under the ROC curve (AUC) ranges from 0.5 (discriminative ability equal to flipping a coin) to 1 (perfect discrimination), and represents the probability that in a random pair of patients, one who was ventilated and one who was not ventilated, the EGRIS is higher in the patient who was ventilated. We calculated two types of AUC-values: the "external validation AUC" and the "refitted AUC". The external validation AUC defines the discriminative ability of the original EGRIS model (with its original regression coefficients) in the IGOS cohort. This external validation AUC was compared with the AUC value in the EGRIS development cohort. A similar AUC value, or a minimal change as compared to the development AUC, would indicate that the original EGRIS model can also be applied to a more diverse cohort of GBS patients. The refitted AUC provides the discriminative ability of the EGRIS model with re-estimated odds ratios based on the IGOS data. This measure provides the optimum discriminative ability that can be obtained with a model with these three clinical factors in the IGOS cohort. Calibration defines the accuracy of the model predictions by comparing the predicted probabilities with the observed frequencies of mechanical ventilation. Calibration curves were generated to graphically delineate the correspondence between the observed and predicted risks. In case of perfect calibration, the curve would rest on the 45° diagonal, indicating that observed frequencies of mechanical ventilation are equal to predicted risks[24, 25].

We determined model performance in the total group and in regional subgroups: Europe/North America (including the UK; Eu/NA) and Asia, and compared this with model performance in the EGRIS development cohort. The subdivision into different regions was based on previously identified differences in the clinical presentation, disease course and subtypes of GBS between various regions[18]. We compared the study design and patient characteristics of the development and validation cohort, to explain potential differences in model performance. For external validation we used the original regression formulas with the EGRIS total score as a single predictor. We also assessed the predictive ability of the individual factors included in the EGRIS model and compared these between the development and regional validation cohorts.

Model recalibration

To improve the accuracy of the model predictions (i.e., the correspondence between the predicted values and those observed in the validation cohorts) we recalibrated the EGRIS model. With recalibration systematic errors in model predictions can be corrected. For example, if predicted probabilities are systematically too low in the validation cohort then recalibration increases all predicted probabilities. We used the "closed testing procedure" described in the

paper by Vergouwe et al[26] to define the extent of updating that was required for the EGRIS model. This procedure compares four levels of updating, ranging from (1) no updating (i.e. keeping the original model) to (4) full model revision (i.e. re-estimating all model coefficients), to identify the optimal updating method for the validation sample. The closed testing procedure was applied to the first imputation set, and showed that full revision of the model with re-estimation of all regression coefficients did not significantly improve model performance. For recalibration of the EGRIS in this study, we applied correction factors to the original regression formula (intercept and coefficients), which is used to calculate the predicted probabilities. We corrected the regression formula that contained the EGRIS total score as single predictor. As per the closed testing procedure, we did not separately correct the coefficients of the individual factors included in the EGRIS total score, so their relative contribution to the score has remained the same. Therefore, this recalibration method only corrects the overall predicted probabilities, but does not change the discriminative ability. Average correction factors from the 10 imputation sets were used to recalibrate the model[24, 27]. We used bootstrapping (with n=500 bootstrap samples) to internally validate the recalibrated EGRIS model, using the *validate*-function from the *rms-package* in R. This bootstrapping procedure re-derives the recalibrated EGRIS in each of the bootstrap samples and calculates the AUC-value in the original dataset. The average AUC-value from the models derived in the n=500 bootstrap samples is compared to the AUC-value of our recalibrated model to define the level of overfitting.

Missing values

We used multiple imputation (n=10) to impute missing values for the EGRIS predictors (R function: *areglmpute*). Calibration curves were based on data from the first imputation set. Data were analysed using SPSS Statistics version 24 and R Studio version 3.6.1. (*R packages: Hmisc, rms, devtools, CalibrationCurves*).

RESULTS

From the IGOS-1500 cohort we excluded patients with an alternative diagnosis (n=85, 6%; of whom 53 had CIDP), a protocol violation (n=34, 2%) and patients for whom no data was entered at all (n=7, 0.5%). From the remaining cohort of 1374 patients we excluded the Bangladeshi patients (n=203, 15%) and patients aged under 6 years or with missing age (n=44, 3%). Of the remaining 1133 patients, 52 patients (5%) were ventilated prior to study entry, 52 (5%) patients were admitted to the hospital before the onset of weakness, 7 patients (0.6%) had missing values for the date of onset of weakness or the date of hospital admission, and 5 patients (0.4%) had a missing start date of mechanical ventilation. All of these patients were also excluded.

For validation of the EGRIS 1023 patients remained in the analysis (Fig 1), of whom 121 (12%) required mechanical ventilation at some point during follow up (Table 2). Patients were included in the following countries: Argentina (n=40), Australia (n=9), Belgium (n=19), Canada (n=22), China (n=12), Denmark (n=104), France (n=29), Germany (n=50), Greece (n=12), Italy (n=114), Japan (n=62), Malaysia (n=25), The Netherlands (n=112), South Africa (n=28), Spain (n=96), Taiwan (n=5), United Kingdom (n=139) and United States of America (n=145). In total, 0.6% of the data points (126/20610) were missing for the EGRIS predictors, which were imputed by multiple imputation.

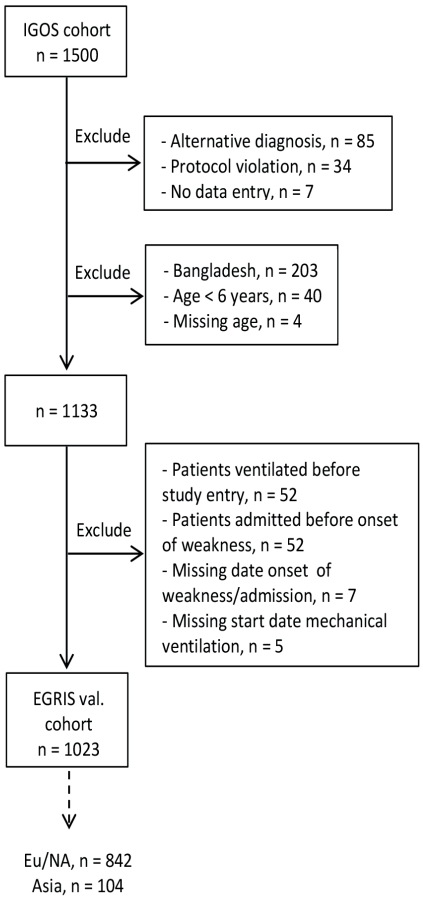

Figure 1 | **Study population** Eu/NA = Europe/North America;
The sum of the exclusions in the second and third box is higher than the total number of exclusions at the corresponding step because of overlap in patient characteristics, i.e. 6 patients with age <6 years were included in Bangladesh, 5 patients who were ventilated prior to study entry were also admitted before the onset of weakness, and 1 patient with missing start date of mechanical ventilation was also admitted before the onset of weakness.

Table 2 | Characteristics of the patients in the EGRIS development and IGOS validation cohort

Predictors and outcome		IGOS validation Full (n = 1023)	Development cohort[5] (n = 565)
Age, years		53 (39-66)	*NA*[a]
Time onset weakness to hospital admission	7 days	107 (11%)	157 (28%)
	4-7 days	280 (27%)	219 (39%)
	≤ 3 days	636 (62%)	189 (34%)
MRC sum score at entry	51-60	454/1017 (45%)	127 (23%)
	41-50	329/1017 (32%)	250 (44%)
	31-40	126/1017 (12%)	106 (19%)
	21-30	57/1017 (6%)	53 (9%)
	≤ 20	51/1017 (5%)	29 (5%)
Facial and/or bulbar weakness at entry		379/1022 (37%)	170 (30%)
GBS disability score at entry	≤2	301/1016 (30%)	33 (6%)
	>2	715/1016 (70%)	532 (94%)
GBS variant	Sensorimotor	641/973 (66%)[b]	*NA*
	Pure motor	146/973 (15%)[b]	*NA*
	MFS	81/973 (8%)[b]	18 (3%)
	MFS-GBS overlap	57/973 (6%)[b]	*NA*
	Other	48/973 (5%)[b]	*NA*
MV during follow up		121 (12%)	128 (23%)
MV within the first week of admission		104 (10%)	110 (20%)
IVIg/PE		931 (91%)	95%[c]

This table provides an overview of the characteristics of the patients in the EGRIS development cohort and the IGOS validation dataset. Numbers are provided as median (IQR) or n (%), unless stated otherwise. MRC = Medical Research Council. GBS = Guillain-Barré syndrome. NA = not applicable/available. MFS = Miller Fisher syndrome. MV = mechanical ventilation. [a] The EGRIS development cohort contained data from 5 different studies. The median age of the patients was derived from the separate manuscripts describing these studies: (1) study 1-3, median age (IQR) in years: 52 (33-66),[27, 28, 30] (2) study 4: median age (95% CI) in years: 46 (23-76),[29] (3) study 5: median age (IQR) in years: 50 (35-63).[31] [b] For the IGOS validation cohort we used GBS variants at visit week 2 as classified by the local treating neurologist. If the week 2 variant was missing we used the variant at week 1 or study entry. Other GBS variants include the pharyngeal-cervical-brachial variant, pure sensory GBS, ataxic variant, Bickerstaff Brainstem encephalitis. [c] This proportion was deduced from the separate manuscripts describing the 5 studies that were included in the EGRIS development cohort. This number provides an approximation of the proportion of patients who were treated in the development cohort, as the exact numbers could not be retrieved.

Characteristics of the EGRIS development cohort and IGOS validation cohorts

The characteristics of the EGRIS development cohort and the IGOS validation cohorts are provided in Table 2 and Supplementary Table 1 and 2. The EGRIS development cohort contained data from 5 different studies, including 2 randomized controlled trials (RCT)[28, 29], two pilot studies[30, 31], and one observational study[32]. Most of the patients in the development cohort were included in Dutch centres, although a minority was included in Germany or Belgium. Two-thirds of the IGOS patients were admitted to the hospital within three days from the onset of weakness, as compared to one-third in the EGRIS development cohort. The proportion of severely

affected patients (as indicated by the inability to walk unaided at study entry) was 94% in the in the EGRIS development cohort and 70% in the IGOS validation cohort. The IGOS validation cohort included data on the full spectrum of GBS clinical variants, while variants were excluded from the EGRIS development cohort, except for 18 patients with Miller Fisher syndrome (MFS). In the IGOS cohort, 121 (12%) patients required mechanical ventilation at some point during follow-up, and the time to start of ventilation ranged from 0 to 33 days. Ten percent of the IGOS patients already required mechanical ventilation within the first week from study entry, versus 20% in the EGRIS development cohort (Table 2, Supplementary Table 1).

Discriminative ability

Validation of the original EGRIS model in the IGOS cohort showed an AUC-value (95% confidence interval (CI)) of 0.86 (0.80-0.91) in the full IGOS cohort, 0.86 (0.80-0.93) in the Eu/NA subgroup and 0.80 (0.62-0.91) in Asia. The external validation AUC-values were comparable to the development AUC of 0.84 (Fig 2). Refitted AUC-values for the full cohort and Eu/NA subgroup were similar to the AUC values that were derived upon external validation of the original model. For the Asian cohort the refitted AUC value (95% CI) was slightly higher than the external validation AUC: 0.86 (0.72-0.93) versus 0.80 (0.62-0.91)(Fig 2).

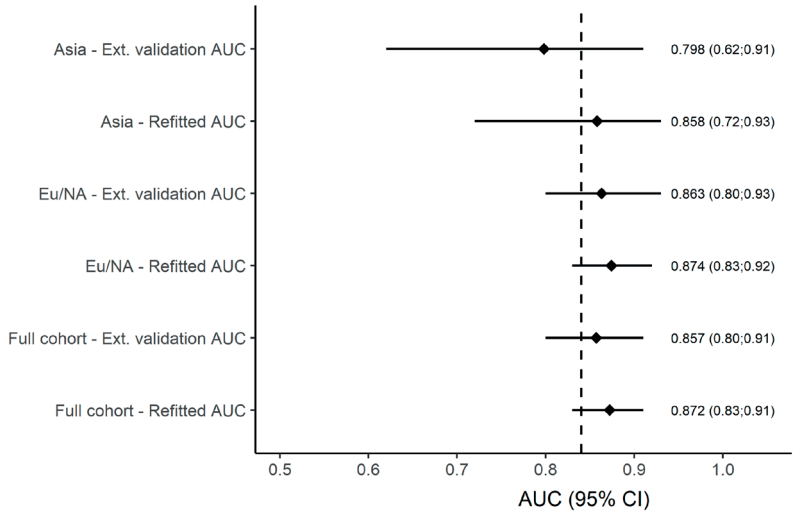

Figure 2 | Discrimination upon external validation. The AUC value is a measure for the discriminative ability of a prediction model, ranging from 0.5 (flipping a coin) to 1.0 (perfect discrimination). For the EGRIS this represents the ability of the model to distinguish patients who need and do not need mechanical ventilation. The external validation AUC = the discriminative ability of the original EGRIS model in the IGOS cohort. Refitted AUC = the discriminative ability of the model after refitting, e.g. re-estimation of the odds ratio based on the IGOS data. The refitted AUC provides the optimum discriminative ability that can be obtained with these three clinical factors in the IGOS dataset. The dotted line represents the AUC value in the EGRIS development cohort. Ext. = External; AUC = area under the receiver operating characteristic curve; Eu/NA = Europe/North America; 95% CI = 95% confidence interval.

We also assessed the predictive ability of each of the individual factors included in the EGRIS model (Table 3). The predictive ability of the MRC sum score and facial and/or bulbar weakness was similar between the EGRIS development and IGOS validation cohorts. Disease progression rate (i.e., the time in days between the onset of weakness and hospital admission) was a strong predictor in the EGRIS development cohort, but odds ratios were not significant for the full IGOS cohort and Eu/NA subgroup (Table 3). Because of the small sample size of the Asian cohort (especially the small number of events: only 18 patients needed mechanical ventilation within the first week), we could not determine the predictive ability of the individual factors in this subgroup.

Table 3 | Effects of the individual predictors included in the EGRIS model *Values at study entry in the IGOS validation cohorts. Eu/NA = Europe/North America.

		Validation		Development
		Full cohort	Eu/NA	
Predictors		OR (95% CI)	OR (95% CI)	OR (95% CI)
Time from onset of weakness	>7	**Ref**	**Ref**	**Ref**
to hospital admission (days)	4-7	0.5 (0.1; 1.9)	0.3 (0.1; 1.6)	2.6 (1.2; 5.7)
	≤3	2.8 (0.9; 8.1)	2.3 (0.7; 8.0)	7.6 (3.5; 16.6)
Facial and/or bulbar weakness at admission*	Absent	**Ref**	**Ref**	**Ref**
	Present	4.6 (2.8; 7.4)	3.5 (2.0; 6.0)	3.5 (2.1; 6.0)
MRC sum score at admission*	51-60	**Ref**	**Ref**	**Ref**
	41-50	3.9 (1.9; 8.4)	5.0 (2.0; 12.7)	3.8 (1.4; 10.4)
	31-40	9.1 (4.0; 20.8)	12.7 (4.6; 34.7)	8.0 (2.8; 22.6)
	21-30	22.3 (9.4; 53.0)	32.7 (11.5; 93.1)	27.1 (9.0; 81.6)
	≤20	30.9 (12.8; 74.4)	35.9 (12.5; 102.8)	40.5 (11.7; 139.4)

Calibration

In all three validation cohorts the observed proportion of patients who needed mechanical ventilation within the first week from study entry was lower than the predicted risk based on the EGRIS model (Fig 3 and 4). After adjustment of the original regression formula (intercept and coefficient) – the updating approach that was most appropriate based on the closed testing procedure – the correspondence between the predicted probabilities and observed frequencies improved for the full cohort and Eu/NA subgroup (Fig 4). Due to the small sample size and wide 95% confidence interval around the calibration curve for the Asian cohort, it was not possible to recalibrate the model for this subgroup. Internal validation of the recalibrated EGRIS for European and North American patients (EGRIS-Eu/NA) by bootstrapping, showed an AUC of 0.862, indicating that there was no overfitting.

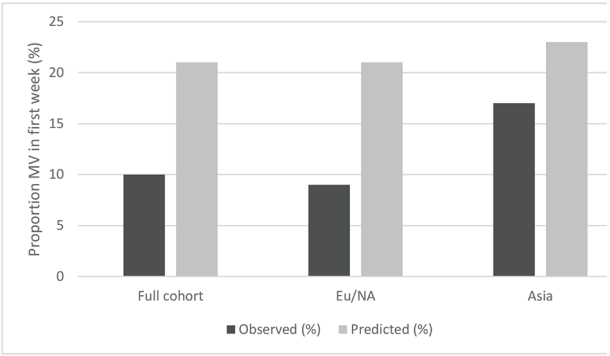

Figure 3 | Observed probabilities versus predicted risks. Mean observed proportions of mechanical ventilation within 1 week in the IGOS validation cohorts versus predicted risks based on the EGRIS model.

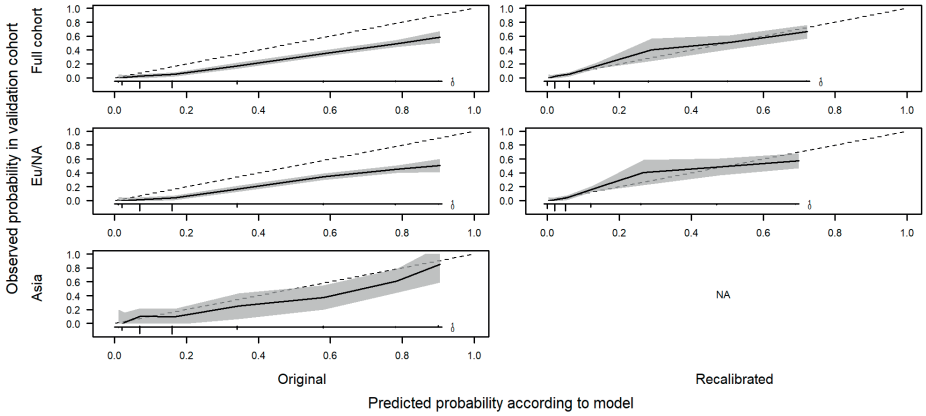

Figure 4 | Calibration curves: original and after recalibration. This figure provides the calibration curves for the original (left) and recalibrated (right) EGRIS model, for the full IGOS cohort, Europe/North America and Asia. Observed probabilities of mechanical ventilation (y-axis) are plotted against predicted risks based on the EGRIS model (x-axis). The dotted line represents perfect calibration (i.e. predicted risks are equal to observed frequencies). The grey-shaded areas are 95% confidence intervals around the calibration curves.
Eu/NA = Europe/North America; NA = not applicable.

DISCUSSION

This study validated the EGRIS in a GBS cohort with patients from 18 countries, including all disease severities and GBS clinical variants. The model was able to distinguish between patients at high and low risk for mechanical ventilation as indicated by the high AUC-values (≥0.8). In all regions, the risk of mechanical ventilation was overestimated by the EGRIS, i.e. the predicted probabilities were higher than the observed proportions of mechanical ventilation. Recalibration improved the correspondence between the predicted and observed risks, and enabled us to develop a more accurate, region-specific version for patients from Europe and North America (EGRIS-Eu/NA).

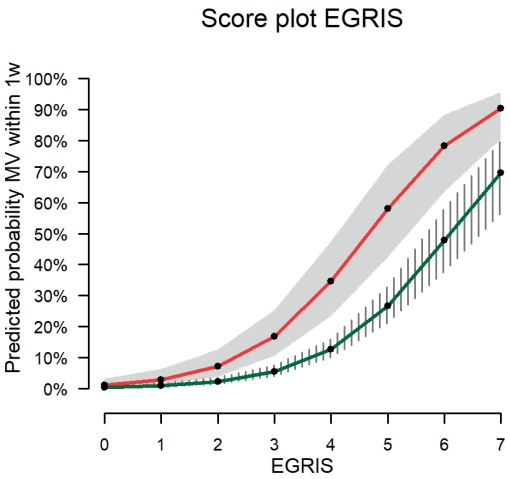

Figure 5 | Predicted probabilities of mechanical ventilation within one week according to the recalibrated EGRIS-Eu/NA model. This figure provides the predicted probabilities of the need for mechanical ventilation within the first week from hospital admission based on the EGRIS (scores 0-7). Probability graphs are based on the original EGRIS model (red line) and the recalibrated model for the Europe/North America subgroup (EGRIS-Eu/NA; green line). Dashed and grey areas around the curves represent the 95% confidence intervals. The EGRIS model can be applied to all patients with GBS, including mild cases (GBS disability score ≤2) and GBS variants. The EGRIS total score can be calculated based on the scoring system provided in Table 1. With the EGRIS total score and the probability graphs provided above, one can deduce the predicted probability of the need for mechanical ventilation for an individual patient with GBS. To predict the need for mechanical ventilation within the first week in European and North American GBS patients the probability graph based on the recalibrated model can be used: EGRIS-Eu/NA (green line). For predictions in GBS patients from countries outside Europe and North America the probability graph based on the original validated EGRIS model can be used (red line). EGRIS = Erasmus GBS Respiratory Insufficiency Score; MV = mechanical ventilation.

Our findings are in line with previous studies that validated the EGRIS in Japan and Malaysia[19, 20]. Both studies assessed the discriminative ability of the model by comparing EGRIS scores between patients who did and did not require mechanical ventilation within the first week of admission. EGRIS scores were significantly higher for patients who required mechanical ventilation. The study by Tan et al also provided an AUC-value for the group of severely affected (GBS disability score ≥3) GBS patients (without MFS), which was similar to the AUC-value in our Asian cohort (0.786)[19, 20]. Model calibration was not described in these studies but could be deduced from the reported results. In both studies the risk of mechanical ventilation was underestimated by the EGRIS model (Yamagishi et al: predicted probability 13%, observed 17%; Tan et al: predicted probability 23%, observed 44%). These results confirm that the EGRIS can be used in Asia to identify GBS patients at high risk for developing respiratory failure, as indicated by the high AUC-values. Model calibration in Asia varies between studies, which may be explained by differences in the clinical settings and selection of patients. Assessment of model performance in a larger Asian cohort may provide a better estimate of model calibration in Asian GBS patients,

and will enable the development of a region-specific version. Until that time, we recommend using the original, validated EGRIS in Asia, but want to emphasize that attention should be paid to differences between predicted and observed outcomes when the EGRIS is applied in clinical practice, especially in situations where specific cut-offs for predicted probabilities are used to guide decision making.

In the current study, only 10% of the patients required mechanical ventilation within the first week (and 12% during overall follow up), which is lower than reported in most previous studies. This low frequency is in part explained by the selection of a specific subgroup of GBS patients for this validation study, as in the cohort including the Bangladeshi patients and patients ventilated prior to study entry (n=1034) the proportion requiring ventilation was 16% within the first week (and 18% overall). Another possible explanation is the study design of IGOS which allowed the inclusion of all patients with GBS, including milder or variant forms, in contrast to previous studies investigating cohorts from trials or admitted to the ICU. This also was illustrated by a recent meta-analysis of 34 studies on respiratory insufficiency in GBS, which included data from both observational studies and trials in severely affected patients, and showed that the prevalence of mechanical ventilation varied from 7% to 65%.[1]. In addition, when we focused on the IGOS patients who were admitted to the ICU (n=222, 22%), we found that 101 (45%) of these patients required ventilation within the first week.

The EGRIS model systematically overestimated the risk of respiratory insufficiency, which may be explained by various factors. First, the EGRIS was developed in a cohort of patients with mostly severe forms of GBS and high risks of respiratory failure as compared to the validation cohort. The original EGRIS was probably influenced by this higher a priori risk of respiratory failure in the development cohort, even though the model includes predictors related to disease severity. Second, most patients in the EGRIS development cohort participated in trials and probably have been monitored and treated more strictly than the patients in the validation cohort, which was based on observational data. In addition, the guidelines for monitoring and start of ventilation may differ between countries. These difference in monitoring and treatment protocols also may have influenced the decision to start ventilation. Third, there is a marked regional variation of GBS. Several factors previously have been associated with the risk of respiratory failure in GBS, and their occurrence may differ between the development and validation cohort. Examples include the type of preceding infection, NCS subtype and the target of the immune response[8, 10-12]. Because these factors were not tested in both the development and validation cohort, their prognostic value will need to be defined in future studies.

When we assessed the effect of the individual predictors included in the EGRIS model, we found that the time from onset of weakness to hospital admission was not significantly associated with the risk of mechanical ventilation in the IGOS cohort. This finding is explained by the categories

that were used for this variable (≤3 days, 4-7 days, >7 days), because when we included time to admission as a continuous variable (instead of a categorical variable), in a regression model with the same three predictors, we did find a significant effect in the IGOS cohort. Nonetheless, the discriminative ability of the model in the IGOS cohort did not change by either including time to admission as a continuous or a categorical variable, and therefore we kept the categories as originally specified for the EGRIS model.

How can these results be applied in clinical practice? The validated EGRIS can be applied in all adult patients with GBS, including mild cases and clinical variants. At hospital admission, the EGRIS scoring system (Table 1) can be used to calculate the EGRIS based on the time from onset of weakness to hospital admission, the presence of facial and/or bulbar weakness and the severity of limb weakness as defined by the MRC sum score. The predicted probability of mechanical ventilation for an individual patient with GBS can be determined based on the calculated EGRIS and Fig 5. To predict the risk of respiratory insufficiency for GBS patients from Europe and North America we recommend using the recalibrated EGRIS (EGRIS-Eu/NA). For patients from other regions (including Asia) we recommend using the original EGRIS that was validated in the current study. The EGRIS is also available as an online tool that can be accessed via: https://gbstools.erasmusmc.nl/prognosis-tool/0/0. The predicted probabilities of respiratory failure that are provided by this online tool are now based on the original EGRIS, but we will update this tool based on the results of this study. In practice, clinicians can use the EGRIS to early identify GBS patients at highest risk of developing respiratory insufficiency within the first week of admission, to provide them with the appropriate level of care and prevent complications from delayed or emergency intubation. Without the EGRIS model, clinicians only would be able to provide general information on the risk of respiratory insufficiency based on reported prevalences from large population studies. In contrast, by using the EGRIS the risk of respiratory insufficiency can be further stratified for individual patients based on clinical information that can be easily obtained at hospital admission.

This study has several limitations. First, part of the IGOS-1500 cohort had to be excluded for this validation study because we could not calculate the EGRIS (i.e. children <6 years, patients admitted before the onset of weakness or patients with missing data for the EGRIS predictors) or because patients were already ventilated before study entry. As MRC scores are difficult to determine in young children additional studies should be performed to identify alternative predictors that can be used instead of the MRC sum score to predict the risk of respiratory failure in children with GBS. Furthermore, in clinical practice routine examination does not always include assessment of all individual muscles included in the MRC sum score. Several previous studies have shown an association between weakness in selected proximal muscles and respiratory failure in GBS[4, 6, 33], and further studies should be performed to determine if the EGRIS could be simplified by the inclusion of individual muscles scores instead of the MRC

sum score. Second, when the EGRIS model is applied in practice it is important to realize that neither the original model nor the recalibrated EGRIS-Eu/NA provide the "gold standard" for the prediction of respiratory failure in GBS, but model performance may differ depending on the clinical setting and patient population. Therefore, especially in settings where specific cut-off values for predicted probabilities are used to drive decision making, it will remain important to pay attention to differences between predicted and observed risks. Validation is a continuous process, and additional studies should be performed to validate the original, but also the recalibrated EGRIS-Eu/NA in new GBS cohorts.

In conclusion, this study validated the EGRIS in an international GBS cohort, and showed that the model can be applied to the full spectrum of GBS patients. In addition, a region-specific version was developed for patients from European and North American countries.

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2.3

Tracheostomy or Not: Prediction of Prolonged Mechanical Ventilation in Guillain-Barré Syndrome

Christa Walgaard
Hester F. Lingsma
Pieter A. van Doorn
Mathieu van der Jagt
Ewout W. Steyerberg
Bart C. Jacobs

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ABSTRACT

Background

Respiratory insufficiency occurs in 20% of Guillain–Barré syndrome (GBS) patients, and the duration of mechanical ventilation (MV) ranges widely. We identified predictors of prolonged MV to guide clinical decision-making on tracheostomy.

Methods

We analyzed prospectively collected data from 552 patients with GBS in the context of two clinical trials and three cohort studies in The Netherlands. Potential predictors for prolonged MV, defined as duration of ≥14 days, were considered using crosstabs. Selected predictors were analyzed using Cox regression analysis.

Results

On a total of 150 (27%) patients requiring MV, 106 (71%) patients needed prolonged MV. The median duration of MV was 28 days (Interquartile Range [IQR] 12–60 days). The strongest observed predictors of prolonged MV were muscle weakness and axonal degeneration or unexcitable nerves on nerve conduction studies. Patients who are unable to lift the arms from the bed (bilateral Medical Research Council [MRC] of deltoid muscles of 0–2) at 1 week after intubation have an 87% chance to require prolonged MV versus 69% in patients who are able to lift the arms from the bed (bilateral MRC of deltoid muscles of 3–10). Patients in this last group who had axonal degeneration or unexcitable nerves on nerve conduction studies also have a 90% chance to require prolonged MV.

Conclusions

Ventilated GBS patients who are unable to lift the arms from the bed and patients who have axonal degeneration or unexcitable nerves at 1 week are at high risk of prolonged MV, and tracheostomy should be considered in these patients.

INTRODUCTION

Respiratory failure is a life-threatening manifestation of the Guillain–Barré syndrome (GBS) that occurs in 20–30% of patients with GBS.[1-4] Immunomodulatory treatment reduces the proportion of patients who require mechanical ventilation (MV) as well as the duration of MV.[5,6] The duration of the required MV varies widely in GBS, ranging from a few days to several months and even longer than 1 year. In general, tracheostomy should be considered when the expected ventilation duration is more than 14 days.[7,8] The uncertainty about the duration of required MV in individual patients may complicate this decision in clinical practice. Delayed tracheostomy in ventilated patients may result in avoidable damage of the vocal cords, laryngeal mucosa, and recurrent laryngeal nerves due to decubitus or local pressure from the endotracheal tube.[7] On the other hand, early tracheostomy may be unnecessary because of clinical improvement and exposes patients to the risk of perioperative bleeding, infection, esophageal perforation, pneumothorax, and tracheal stenosis and, in all cases, leaves a permanent scar.[9]

Previous studies showed that the clinical course of GBS in individual patients can be predicted with reasonable accuracy.[10-14] In the current study, we described the variability in duration of MV and characteristics of GBS patients with prolonged MV and aimed to identify predictors of prolonged MV. These predictors may support individual clinical decision-making about indication and timing of tracheostomy in patients with GBS early in the course of their disease.

PATIENTS AND METHODS

Patients

Prospectively collected data were used from 552 patients who fulfilled the diagnostic criteria for GBS, were treated with either plasma exchange or intravenous immunoglobulins, and did not die in the first week of hospital admission. These patients previously participated in a treatment trial,[15,16] an observational study,[17] or a pilot study [18,19] conducted by the Dutch GBS Study Group. The ethical review board of Erasmus MC approved all studies, and all patients gave written informed consent to use their data for further research.

Data Collection

Data collected prospectively for all patients were age, gender, preceding infections, number of days from onset of weakness to hospital admission, date of intubation and extubation, and neurological examination (cranial nerve testing, sensory and motor testing; using the Medical Research Council [MRC] sumscore) at predefined time points (at admission and at 3, 7, 14, 28, 90, and 181 days after admission). The MRC sumscore is defined as the sum of MRC scores of six different muscles measured bilaterally, which results in a sumscore ranging from 0 (tetraplegic)

to 60 (normal). For this study, we recorded neurological examination at 1 week after intubation. Nerve conduction studies were performed in the first 2 weeks after inclusion, and the data were used to classify GBS as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), equivocal, or unresponsive according to the Hadden criteria.[20] Serological screening was performed to determine recent infections with *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, and Mycoplasma pneumonia and antibodies to the gangliosides GM1, GD1a, and GQ1b. The serum samples used were obtained within 4 weeks from onset of weakness and before start of treatment and were stored at -80 °C until use.

Endpoints

The primary endpoint in our study is the occurrence of prolonged MV, defined as MV of more than 14 days, as an established criterion to consider tracheostomy.[7,8] In addition, we determined the risk of requiring MV for more than 21 and 28 days. We defined liberation from MV as either successful extubation or spontaneous breathing off the ventilator in tracheotomized patients for more than 24 h. Predictors of prolonged MV were sought at day 7 after start of ventilation, as a clinical decision point for considering early tracheostomy. Also, we determined the time to reach the ability to walk unaided in different patient groups.

Statistical Analysis

A Kaplan–Meier curve with log-rank test was used to compare time to reach the ability to walk unaided during a follow-up period of 6 months between patients with prolonged MV, patients with MV for <14 days, and patients not requiring MV. Potential predictors for prolonged MV were considered in crosstabs, and univariate logistic regression models and odds ratios (ORs) indicated relative effects of predictors. Cox regression analysis was used to further analyze selected predictors and calculate the estimated risk percentages for prolonged MV duration (≥14, ≥21, and ≥28 days). A Cox regression model was used since our cohort was relatively small. Using specific cutoffs of long versus short MV duration would result in low numbers of patients in specific categories and unstable models. Cox regression accounts for the total duration of ventilation and thus uses the data more efficient than logistic regression with a binary outcome (long vs. short MV). Missing values were imputed based on relevant covariates and outcome. A two-sided p value <0.05 was considered to be statistically significant. Statistical analyses were conducted with SPSS for Windows and R statistical software (version 2.7, using the design library).

RESULTS

Mechanical Ventilation in GBS

In the cohort of 552 patients with GBS, 150 (27%) required MV at some time during the follow-up of 6 months. The median duration of the MV was 28 days (Interquartile Range IQR 12–60 days; absolute range 1 to >181 days; Fig. 1). Patients were intubated at a median of 1 day after admission (IQR 0–4). The timing of intubation was not correlated with the MV duration (Table 1). Eight patients in the MV group (5%) died during the follow-up period of 6 months. Mortality was not significantly different between the patients who needed prolonged MV (6%) and those who did not (5%). The indication for intubation was not systematically documented, but the percentage of bulbar weakness was not significantly different between the two groups.

MV was associated with poor outcome, as 57 % in the ventilated group regained the ability to walk in the first 6 months, in comparison with 87 % in the unventilated group (OR 5.0 [3.2–7.7], $p < 0.001$). Patients with prolonged MV also needed more time to regain the ability to walk than the patients with MV <14 days (log-rank test, $p < 0.001$) (Fig. 2). Forty-four patients who required MV <14 days had a comparable recovery as the 402 unventilated patients (log-rank test, $p = 0.2$) (Fig. 2).

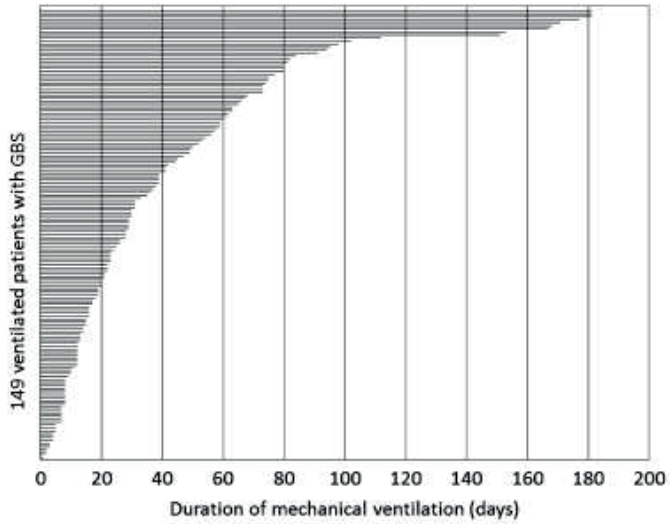

Figure 1 | The figure indicates the duration of mechanical ventilation in 149 patients with Guillain–Barré syndrome. One patient of the original cohort of 150 ventilated patients was excluded because the patient was lost to follow-up after 3 months of ventilation. Median duration of mechanical ventilation was 28 days, interquartile range of 12–60 days, absolute range 1 to >181 days (follow-up of the studies ended at 181 days)

Table 1 | Characteristics of the cohort of 132 GBS patients on the ventilator for at least 7 days in relation to prolonged mechanical ventilation MV mechanical ventilation, IQR interquartile range, OR odds ratio, CI confidence interval, MRC Medical Research Council, AIDP acute inflammatory demyelinating polyradiculoneuropathy, AMAN acute motor axonal neuropathy. Q Because of 100% values, it was impossible to calculate ORs and p values for AMAN, unexcitable nerves, and anti-GQ1b antibodies [a] At 1 week after intubation, [b] Sum of MRC grades for bilateral muscle groups, [c] Symptoms of infection in the 4 weeks preceding the onset of weakness, [d] Using pretreatment serum samples obtained at entry.

Characteristic	Total	N (%) prolonged MV (≥ 14 days)	Median (IQR) days on ventilator	OR (95% CI) for prolonged MV	p value
Total	132	106 (80%)	31 (16 - 63)		
Demographic features					
Age (in years)					NS
≤40	41	32 (78%)	23 (16 - 57)	ref	
41 – 60	41	34 (83%)	40 (21 - 77)	1.4 (0.5 - 4.1)	
>60	50	40 (80%)	30 (16 - 60)	1.1 (0.4 - 3.1)	
Gender (male)	71	57 (80%)	30 (16 - 63)	1.0 (0.4 - 2.4)	NS
Clinical severity#					
Days from onset weakness to MV				1.0 (0.9 - 1.0)	NS
Bulbar weakness	28	22 (79%)	52 (15 - 78)	0.9 (0.3 - 2.4)	NS
Facial weakness	56	46 (82%)	41 (17 - 67)	1.2 (0.5 - 3.0)	NS
MRC sumscore					<0.001
41 – 60	18	7 (39%)	11 (8 - 20)	0.2 (0.04 - 0.5)	
21 – 40	43	35 (81%)	28 (15 - 44)	ref	
0 – 20	71	64 (90%)	49 (25 - 80)	2.1 (0.7 - 6.3)	
M. deltoideus*				0.7 (0.6 - 0.8)	<0.001
M. deltoideus dichotomized					0.001
MRC 0 – 2	61	58 (95%)	53 (27 - 82)	9.3 (2.6 - 32.7)	
MRC 3 – 10	71	48 (68%)	21 (12 - 40)	ref	
M. biceps*				0.7 (0.6 - 0.9)	<0.001
M. extensor carpi radialis*				0.8 (0.6 - 0.9)	0.001
M. iliopsoas*				0.7 (0.6 - 0.9)	<0.001
M. quadriceps*				0.7 (0.6 - 0.9)	<0.001
M. tibialis anterior*				0.8 (0.7 - 0.9)	0.002
Nerve Conduction Studies					
AIDP	64	48 (75%)	29 (14 - 54)	Q	
AMAN	4	4 (100%)	131 (69 - 178)		
Equivocal	26	20 (77%)	23 (15 - 49)		
Inexcitable	15	15 (100%)	82 (62 - 171)		
Infection and serology					
Symptoms of preceding infection[a]					
Diarrhea	32	27 (84%)	45 (21 - 112)	1.44 (0.5 - 4.2)	NS
Upper respiratory tract infection	47	33 (70%)	24 (13 - 66)	0.4 (0.2 - 0.9)	0.03

Table 1 | Characteristics of the cohort of 132 GBS patients on the ventilator for at least 7 days in relation to prolonged mechanical ventilation MV mechanical ventilation, IQR interquartile range, OR odds ratio, CI confidence interval, MRC Medical Research Council, AIDP acute inflammatory demyelinating polyradiculoneuropathy, AMAN acute motor axonal neuropathy. Q Because of 100% values, it was impossible to calculate ORs and p values for AMAN, unexcitable nerves, and anti-GQ1b antibodies [a] At 1 week after intubation, [b] Sum of MRC grades for bilateral muscle groups, [c] Symptoms of infection in the 4 weeks preceding the onset of weakness, [d] Using pretreatment serum samples obtained at entry. (continued)

Characteristic	Total	N (%) prolonged MV (≥ 14 days)	Median (IQR) days on ventilator	OR (95% CI) for prolonged MV	p value
Infection serology[b]					
Campylobacter jejuni	43	37 (86%)	44 (20 - 87)	1.8 (0.7 - 5.0)	NS
Cytomegalovirus	20	18 (90%)	52 (26 - 63)	2.7 (0.6 - 12.6)	NS
Epstein-Barr virus	13	12 (92%)	29 (23 - 73)	3.5 (0.4 - 28.1)	NS
Mycoplasma pneumoniea	6	5 (83%)	20 (17 - 26)	1.3 (0.2 - 11.8)	NS
Anti-ganglioside IgM/IgG antibodies					
GM1	14	12 (86%)	91 (18 - 176)	1.6 (0.3 - 7.6)	NS
GD1a	9	8 (89%)	23 (16 - 60)	2.2 (0.3 - 18.4)	NS
GQ1b	10	10 (100%)	49 (16 - 60)	Q	Q

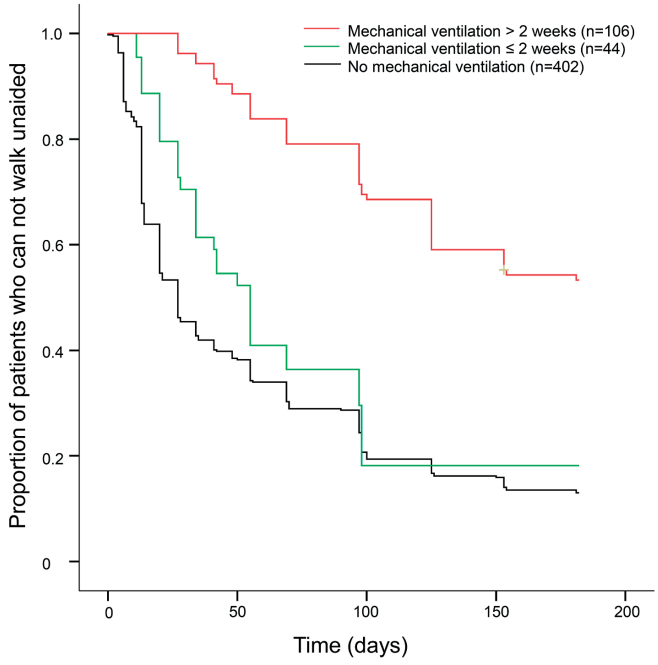

Figure 2 | Outcome of GBS in relation to duration of mechanical ventilation. Relation between mechanical ventilation, its duration, and the time (in days) to recover to independent walking in a cohort of 552 patients with Guillain–Barré syndrome. Kaplan–Meier curves show the proportion of patients who regained the ability to walk unaided during a follow-up of 181 days

Prediction of MV duration

Predictors of prolonged MV were determined at day 7 after start of ventilation, which was considered a critical time point in clinical practice to make a decision about tracheostomy. Patients requiring MV for 7 days or less (N = 18) were excluded from this analysis (Fig. 3). In the remaining 132 patients, 106 (80%) needed prolonged MV (Fig. 3). In Table 1, the observed frequencies of potential predictors and crude associations with prolonged MV are shown. The strongest predictor of prolonged MV was severe limb weakness defined by the MRC sumscore 1 week after intubation ($p < 0.001$; Table 1). Further analysis showed that the MRC scores of the bilateral deltoid muscles alone also were a strong predictor of prolonged ventilation ($p < 0.001$; Table 1). Furthermore, a total of 61 patients were unable to lift the upper arms (bilateral MRC score ≤2), and 58 (95%) of those needed prolonged MV (OR 9.3 [2.6–32.7], $p = 0.001$; Table 1). Also, regression (OR 3.7, 95% CI, 0.4–3.0) or improvement (OR 0.2, 95% CI, 0.06–0.7) of muscle strength of the bilateral deltoid muscles was predictive of prolonged ventilation ($p = 0.007$). Patients with AMAN (N = 4) or unexcitable nerves (N = 15) all required prolonged MV (Table 1); and therefore, it was not possible to calculate an OR or p value in univariate analysis. Because of the small patient numbers in the nerve conduction study (NCS) subgroups, we divided the patients for the multivariate analysis into two groups: AMAN or unexcitable versus AIDP or equivocal. In addition, all patients with serum anti-GQ1b antibodies (N = 10) required MV. We used Cox regression analysis to predict chances to require MV for more than 14, 21, and 28 days in the different groups based on the condition of the patient after 1 week of mechanical ventilation (Table 2). Based on this model, patients who were unable to lift the arms from the bed had an estimated chance of prolonged MV for more than 14 days of 87% (Table 2). NCS results significantly contribute to the prediction and can be taken into consideration.

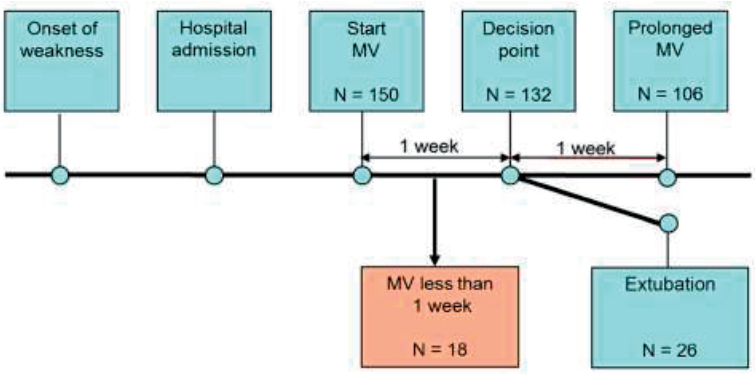

Figure 3 | Flowchart of patient subgroups in relation to mechanical ventilation. MV mechanical ventilation, N number of patients.

Table 2 | Predicted chances (Cox regression analysis) of a total mechanical ventilation duration of ≥14, ≥21, and ≥28 days. AIDP acute inflammatory demyelinating polyneuropathy, CI confidence interval, MV mechanical ventilation, N number, NCS nerve conduction study.

		Chance (%, 95% CI) of a total MV duration of		
Condition at one 1 week after intubation	**N**	**≥14 days**	**≥21 days**	**≥28 days**
Mechanical ventilation (observed)	131	80	66	55
Mechanical ventilation *and* unable to lift arms	61	87 (81-92)	77 (70-85)	68 (60-78)
Mechanical ventilation *and* unable to lift arms *and* axonal NCS/inexcitable NCS	16	96 (93 - 98)	93 (87 - 97)	89 (82 - 95)
Mechanical ventilation *but* able to lift arms *and* axonal NCS/inexcitable NCS	5	90 (84 - 96)	83 (73 - 93)	75 (63 - 89)
Mechanical ventilation *but* able to lift arms *and* AIDP or equivocal NCS	65	67 (58 - 78)	48 (38 - 60)	34 (24 - 46)

DISCUSSION

The decision for tracheostomy in patients with GBS depends on the expected duration of respiratory failure, which may range from a few days to more than 6 months. In the current study, MV was required in 27% of patients and 71% of these patients required MV for more than 14 days. Eighty percent of the patients who were still intubated after 1 week required prolonged MV. The chance of prolonged MV was further increased in the subgroup of patients with severe paresis of the deltoid muscles, defined as being unable to lift the arms from the bed (MRC grade 0 or 1 bilaterally), and the patients with an axonal or unresponsive polyneuropathy in the NCS. In these patients, it may be considered to perform an early tracheostomy.

Our study confirms previous findings by others that the duration of MV in GBS is associated with the extent of limb muscle weakness. Fourrier et al.[10] reported that the lack of foot flexion at the end of immunotherapy was a predictor for prolonged MV in a group of 40 ventilated GBS patients in a retrospective, single-center study. They did not report on the predictive value of paresis of other limb muscles. In the current study, we confirmed the association between prolonged MV and paresis of the anterior tibial muscle; but stronger associations were found for paresis of the deltoid, biceps, iliopsoas, and quadriceps muscles. These results provide further support for the hypothesis that patients with prolonged MV have a severe diffuse neuropathy, which affects both the respiratory and limb muscles. We preferred to use the deltoid muscle for the prognostic model because of the strong association with prolonged MV, its common C5 innervation with the phrenic nerve, and relatively easy accessibility for physical examination in bed-bound patients. However, when the examination of the deltoid muscles is not possible in an individual patient, substitution of other preferably proximal muscle groups, such as the iliopsoas muscles, seems plausible.

In the current study, all ventilated patients with AMAN (N = 4) and unexcitable nerves (N = 15) required prolonged MV. This finding is in line with previous findings.[1,21] One study indicated that the presence of AIDP was associated with a higher chance of respiratory failure,[22] but we were unable to confirm that finding. The electrophysiology results are influenced by the applied classification criteria and the timing of the NCS. In Western countries, the axonal forms of GBS are relatively rare compared to AIDP and are found in 5–10% of GBS patients. In addition, NCS performed at 1 week is less accurate for identifying axonal GBS, as the axonal pattern may appear only after 2–4 weeks. At 1 week of admission, patients more frequently show unexcitable nerves in NCS. These patients may have either AIDP or axonal forms, but in all cases this is a sign of severe diffuse neuropathy. As such, unexcitable nerves may be a more frequent indication than AMAN for early tracheostomy.

Remarkably, our study showed that all 10 ventilated patients with serum anti-GQ1b antibodies required prolonged MV. Antibodies to GQ1b in patients with GBS are strongly associated with the occurrence of ophthalmoplegia and swallowing disorders. Some studies indicated that these patients are prone to develop respiratory failure,[23] but this was not found by others.[13,24] As far as we know, the current study is the first to demonstrate the relation between GQ1b antibodies and the duration of MV in ventilated patients with GBS. Some of these patients also had severe weakness of arms and legs or unexcitable nerves, indicating that the presence of anti-GQ1b antibodies is probably not an independent prognostic factor. A further limitation of this biomarker for supporting the decision of tracheostomy in current clinical practice is the delay and quality of the test results, which are influenced by the used assay protocol. Because of these limitations, we have not used the test in the current prognostic models.

We were unable to confirm the finding from a previous retrospective, single-center study in 60 ventilated GBS patients that age is an independent predictor for prolonged MV.[21] In most studies, older age is a predominant prognostic factor for poor outcome in GBS, including those of our own group. In the current study, we found no association between age and prolonged MV (OR 1.1 for age >60 years), neither did other previous studies. Also the presence of a preceding *C. jejuni* infection, which is a general poor prognostic factor in GBS, was not predictive for prolonged MV. Previously, we showed that selective gut decontamination may shorten the time of MV and admission to ICU but does not shorten the time to reach the ability to walk.[25] Apparently, the recovery from respiratory failure depends on other factors than the recovery of limb weakness.

The current study has several limitations that need to be addressed. First, the group of ventilated patients was too small to be able to develop and validate a prognostic model, as was done previously for predicting respiratory failure in the first week in GBS[13]. To overcome this limitation in part, we used Cox regression analysis that also takes the total duration of MV

into account. This resulted in slightly lower, but presumably more realistic, predictions of MV duration. For example, we observed that all patients with the axonal subtype or unexcitable nerves (100%) needed prolonged MV. Model-based prediction in this subgroup resulted in a 93% chance of prolonged MV (univariate; data not shown). Hence, some predictors of prolonged MV were present in even smaller subgroups, such as the axonal subtype and anti-GQ1b antibodies, although all these patients had prolonged MV. Second, the patient population investigated was biased toward adult patients and patients with AIDP, which is the predominant GBS subtype in The Netherlands. The observed finding at present cannot be extrapolated to pediatric GBS or countries where axonal forms predominate. Third, in this multicenter study, differences in the duration of MV may reflect variation in local clinical management; intubation or extubation criteria were not used in our patient group. Also, usage and timing of tracheostomy was not recorded in our cohort, and this probably influenced the duration of MV. All patients were included in previous trials, which have the advantage of protocoled, repeated clinical assessments, but could have influenced the standard clinical care. Fourth, in the current study we have used data collected in various previous studies conducted in the last 25 years. We cannot exclude that the criteria for extubation and supportive care have changed over time. In the future, international prospective validation studies in larger cohorts of GBS patients, including children and patients from other regions and with clear definitions regarding extubation criteria, will be needed to substantiate our findings.

Debate is still ongoing about the optimal timing of tracheostomy. A consensus report on MV indicated that the translaryngeal route is preferred when the expected duration is not exceeding 10 days, while tracheostomy is preferred for expected durations longer than 21 days.[26] Prolonged MV via the translaryngeal route carries significant risks, while tracheostomy has its own complications and leaves permanent disfigurement. Nowadays prospective trials show that early tracheostomy was associated with less sedative and analgesic administration, less frequent prescriptions of haloperidol to treat agitation or delirium, earlier oral nutrition, and out-of-bed mobilization. Early tracheostomy does not seem to shorten the duration of MV, length of hospital stay, mortality, or frequency of infectious complications.[8,27-30]

CONCLUSION

Most GBS patients on MV after 1 week will require prolonged MV, and the chances are further increased in patients with severe deltoid muscle weakness and axonal/unexcitable NCS. These patients are candidates for early tracheostomy.

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2.4

Association of albumin levels with outcome in intravenous immunoglobulin-treated Guillain-Barré syndrome.

Willem-Jan R. Fokkink
Christa Walgaard
Krista Kuitwaard
Anne P. Tio-Gillen
Pieter A. van Doorn
Bart C. Jacobs

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ABSTRACT

Importance

There is an urgent need for biomarkers to monitor treatment efficacy and anticipate outcome in patients with Guillain-Barré syndrome (GBS).

Objective

To assess whether there is an association between serum albumin levels, a widely used and relatively easily measurable biomarker of health and inflammation, and the clinical course and outcome of GBS in patients treated with intravenous immunoglobulin (IVIG).

Design, setting, and participants

We used serum samples derived from a cohort of patients with GBS admitted to hospitals across the Netherlands participating in national GBS studies from May 5, 1986, through August 2, 2000. Serum albumin was measured from January 13 to 20, 2011. Analysis was performed from February 25, 2013, to September 6, 2016. All patients fulfilled the criteria for GBS and had severe disease (defined as not being able to walk unaided >10 m). Patients misdiagnosed as having GBS were retrospectively excluded from the study. Serum samples were obtained before and after IVIG treatment at 4 standardized time points from 174 patients. Albumin levels were determined by routine diagnostic turbidimetry and related to demographics and clinical course during a follow-up of 6 months.

Main outcomes and measures

Serum albumin concentration was determined before and after treatment with IVIG and related to clinical outcome: muscle weakness (measured by Medical Research Council sum score), respiratory failure (measured by requirement and duration of mechanical ventilation), and ability to walk (measured by GBS disability score).

Results

Serum albumin levels were determined in 174 patients with GBS (mean [SD] age, 49.6 [20.1] years; 99 males [56.9%]). Before treatment, the median serum albumin level was 4.2 g/dL (interquartile range, 3.8-4.5 g/dL), with hypoalbuminemia (albumin, <3.5 g/dL) in 20 (12.8%) of 156 patients. Two weeks after commencing treatment with IVIG (2 g/kg), the median serum albumin level decreased to 3.7 g/dL (interquartile range, 3.2-4.1 g/dL) ($P < .001$), and the number with hypoalbuminemia increased to 60 (34.5%) of 174 ($P < .001$). Hypoalbuminemia was associated with an increased chance of respiratory failure before (16 [36.4%] of 44, $P = .001$) or after (29 [54.7%] of 53, $P < .001$) IVIG treatment, inability to walk unaided (21 [35.0%] of 60 vs 6 [5.3%] of 114, $P < .001$), and severe muscle weakness at 4 weeks (Medical Research Council sum score,

31.8 vs 52.9, P < .001) and 6 months (Medical Research Council sum score, 49.4 vs 58.4, P < .001).

Conclusions and relevance

Patients with GBS may develop hypoalbuminemia after treatment with IVIG, which is related to a more severe clinical course and a poorer outcome. Further studies are required to confirm that serum albumin can be used as a biomarker to monitor disease activity and treatment response to IVIG in patients with GBS.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a polyradiculoneuropathy characterized by a rapidly progressive bilateral paresis of the limbs. Nadir is typically reached within a number of days or weeks, followed by a recovery that is generally much slower and often incomplete.[1] For more than 2 decades, intravenous immunoglobulin (IVIG) has been the treatment of choice, and all patients still receive the same high dose of IVIG (2 g/kg over 5 days).[2] Despite the proven efficacy of this high-dose regimen in GBS, recovery and outcome still vary greatly among patients.[3] Some of the more severely affected patients might benefit from an additional IVIG course, which is currently being studied in an ongoing randomized clinical trial (Second IVIG Dose in GBS Patients With Poor Prognosis).[3] Still, the reasons why some patients respond poorly to IVIG therapy are unknown, and there is an urgent need to find a biomarker that, preferably, can be determined within the first 2 weeks of onset. Such a biomarker would allow a more personalized approach to monitor treatment efficacy and anticipate outcome.[4,5] Existing prognostic models are based on clinical features, including the extent of muscle weakness and demographic factors, but previous studies[3] failed to identify a serologic biomarker to enhance these models.

To further improve prognosis and assessment of treatment response, biomarkers reflecting IVIG efficacy are needed. For purposes of clinical practice, the measurement of such biomarkers Should preferably be straightforward and accurate and align with routine diagnostic procedures. Although the change in serum level of IgG after IVIG treatment has been identified as a candidate biomarker, no distinction could be made between exogenous, IVIG-derived IgG and endogenous IgG.[6] Whereas the IgG level after IVIG logically increases, the serum albumin level is reduced after high-dose IVIG therapy in diseases other than GBS.[7,8] Like IgG, albumin binds to the neonatal Fc receptor (FcRn), which transports it back into the circulation.[9,10] Furthermore, serum albumin is identified as an independent factor associated with outcome in amyotrophic lateral sclerosis and failure of IVIG therapy in Kawasaki disease.[11,12] Therefore, serum albumin is an interesting alternative to IgG as a biomarker for GBS, fitting the profile of a routinely measured protein already established as a prognostic marker in numerous pathologic conditions.[13]

In this study, we aimed to determine whether serum albumin levels can serve as a prognostic marker in patients with GBS treated with IVIG. We determined the variation in serum albumin levels over time and assessed the serum albumin levels in response to IVIG after treatment. Finally, we analyzed whether circulatory albumin levels were related to disease severity and clinical outcome.

Key Points

Question Do serum albumin levels correlate with the clinical course and outcome of Guillain-Barré syndrome in patients treated with intravenous immunoglobulin?

Findings In this cohort study of 174 patients with Guillain-Barré syndrome, the serum albumin level at 2 weeks after treatment correlated with clinical recovery, independent of other clinical prognostic factors. More than one-third of the patients were hypoalbuminemic, but even low-normal albumin levels were associated with poor outcome.

Meaning Albumin is an easily accessible and strong prognostic biomarker for Guillain-Barré syndrome in patients treated with intravenous immunoglobulin.

METHODS

Patients

The patients were included in 2 clinical trials previously conducted from May 5, 1986, through August 2, 2000, in which clinical data and serum samples were prospectively collected according to a predefined standard protocol.[14,15] Serum albumin was measured from January 13 to 20, 2011. Analysis was performed from February 25, 2013, to September 6, 2016. All patients provided written informed consent after approval by the institutional review board of Erasmus University Medical Center Rotterdam. The database, including all participants, was de-identified before analyzing.

All 174 patients in the current study received the same dosage of IVIG (2 g/kg over 5 days of Gammagard or Gammagard S/D [Baxter International]) and were previously used to appraise the pharmacokinetics of IgG (Table 1).[6] For 18 patients (10.3%), stored pretreatment serum was of insufficient quantity to determine the albumin level. In one of the previous trials, intravenous methylprednisolone (500 mg/d for 5 consecutive days) was administered in addition to IVIG (concerning 60 patients [34.5%] included in the current study). Samples were taken at standardized time points and were stored at -80°C until use. Clinical condition of the patients during the trials was monitored using the Medical Research Council (MRC) sum score, ranging from 0 (tetraparalysis) to 60 (normal strength), and by the GBS disability scale, ranging from 0 (healthy) to 6 (deceased). Not being able to walk 10 m independently (GBS disability score >2) at 6 months was regarded as a poor outcome, as defined previously.[6,16-18] Serum was collected before treatment (at randomization) and after treatment at 2, 4, 14, and 24 weeks (end of follow-up).[14,15]

Albumin Measurement

Serum albumin concentrations were determined by routine automated diagnostic turbidimetry using a clinical chemistry analyzer (Hitachi 917; Hitachi Ltd). Because the serum samples (-80°C) were stored for a long period, a number of samples wherein the albumin level was previously determined were reanalyzed to exclude the possible influence of long-term storage on the measurement.

Table 1 | Demographic and Clinical Characteristics of 174 Patients With GBS Treated With Intravenous Immunoglobulin[a]. Abbreviations: GBS, Guillain-Barré syndrome; MRC, Medical Research Council; URTI, upper respiratory tract infection.[a] Data are presented as number (percentage) of patients unless otherwise indicated. All patients were treated with the same standard regimen of intravenous immunoglobulin (2 g/kg over 5 consecutive days). All items are shown for the whole group of 174 patients unless otherwise specified.

Characteristic	Finding
Age, mean (SD), y	49.6 (20.1)
Age group, y	
<40	60 (34.5)
40 - 60	50 (28.7)
>60	64 (36.8)
Male	99 (56.9)
Diarrhea (n = 173)	41 (23.7)
URTI (n = 173)	60 (34.7)
Facial and/or bulbar weakness (n = 167)	56 (33.5)
Mechanical ventilation needed	
In 6 mo (n = 162)	41 (25.3)
In the first week (n = 167)	29 (17.4)
GBS disability score, mean (SD)	
Nadir	4.1 (0.7)
At inclusion	3.8 (0.5)
1 wk	3.7 (0.9)
2 wk	3.3 (1.2)
4 wk	2.8 (1.4)
26 wk	1.4 (1.3)
MRC sum score, mean (SD)	
Nadir	33.2 (16.9)
At inclusion	40.3 (11.5)
1 wk (n = 173)	38.8 (16.3)
2 wk	41.3 (17.7)
4 wk (n = 167)	44.7 (18.1)
26 wk	54.6 (9.5)

Statistical Analysis

To compare the albumin levels at different time points, the Friedman analysis of variance with the Dunn post hoc test was used. Spearman ρ was used to assess correlation between the change in IgG (ΔIgG) and the change in serum albumin (Δalbumin) 2 weeks after IVIG treatment. The ΔIgG and Δalbumin were calculated by subtracting the pretreatment level from the 2-week posttreatment level of the respective serum protein. To assess the possible influence of serum albumin on disease severity, 2 strategies were used. In the first analysis, patients were stratified in tertiles based on the serum albumin level before or 2 weeks after commencing IVIG therapy. In the second analysis, patients were divided into 2 groups: those with hypoalbuminemia

(albumin, <3.5 g/dL [to convert to grams per liter, multiply by 10]) and those within the reference range of serum albumin levels (3.5-5.5 g/dL).[19] Because the serum albumin level decreases with advanced age, analysis of covariance (ANCOVA) and Cox proportional hazards regression analyses were corrected for age.[20] The groups were compared by ANCOVA with respect to various outcome measures, including the requirement and duration of mechanical ventilation and the clinical severity at nadir at 4 weeks after initiating treatment and at the end of follow-up of 6 months. Kaplan-Meier analysis, stratified for the GBS disability score at entry or stratified for age groups (Table 1), was used to assess the ability to walk unaided at the end of follow-up. Subsequent Cox proportional hazards regression analysis was used to correct for a possible age effect. Logistic regression analysis was performed to assess the effect on disease severity and clinical outcome. The syntax of previously developed prognostic models was used to assess the contribution of albumin. These models were correlated with the need of respiratory support in the first week (Erasmus GBS Respiratory Insufficiency Score [EGRIS]) and the outcome during follow-up and at 6 months (Erasmus GBS Outcome Score or modified Erasmus GBS Outcome Score [EGOS/mEGOS]).[16-18] Statistical analysis was performed using GraphPad Prism, version 6.0 for Windows (Graph- Pad Software) and SPSS, version 21.0 for Windows (SPSS Inc). Statistical significance was defined as a 2-sided $P < .05$.

RESULTS

Serum albumin in patients with GBS

Serum albumin levels were determined in 174patientswithGBS (mean [SD] age, 49.6 [20.1] years; 99 males [56.9%]) at several standardized, predefined time points (Figure 1A). In the acute phase of GBS before treatment, circulatory albumin levels were within the reference range in most patients (median, 4.2 g/dL; interquartile range [IQR], 3.8-4.5 g/dL), and only 20 (12.8%)of 156 presented with hypoalbuminemia (albumin,<3.5 g/dL). Two weeks after treatment with IVIG was started, serum albumin levels decreased compared with levels before treatment (median, 3.7 g/dL; IQR, 3.2-4.1 g/dL; $P < .001$), and a larger number of patients were hypoalbuminemic (60[34.5%] of 174; $P < .001$). After 3 months, serum albumin levels returned to reference range values in all patients except in 2 (2.0%) of 101 patients with persistent hypoalbuminemia and 2 (2.0%) of 101 patients with hyperalbuminemia. At 6 months after treatment, the albumin levels were higher when compared with the pretreatment level (median serum albumin, 4.5 g/dL; IQR,43-48g/dL;$P < .001$). There was no influence of concomitant methylprednisolone treatment on serum albumin levels (median albumin, 3.7 g/dL in the IVIG-only group vs 3.65 g/dL in the IVIG and methylprednisolone group; $P = .82$, Mann-Whitney test).

Association Between Serum Albumin and IgG Level

After IVIG, the IgG level increased,6 but the serum albumin level decreased (Figure 1AandB). This ΔIgG correlated, albeit weakly, with Δalbumin (Figure 1C). Rather than a negative correlation, in which increasing levels of IgG reduce the serum albumin concentration, a positive correlation was observed. This somewhat unexpected result also became apparent from the correlation between the IgG and albumin serum levels at 2 weeks (Figure 1D). Pretreatment levels of serum albumin or IgG do not seem to profoundly influence posttreatment levels (eg, pretreatment serum albumin correlated weakly with ΔIgG: $\rho = 0.23$, P = .003; pretreatment IgG with Δalbumin: $\rho = -0.11$, P = .18). Other immunoglobulins (IgA and IgM) in a subgroup of 46 patients did not change significantly 2 weeks after IVIG compared with levels before treatment (mean pretreatment and 2-week post-treatment IgA, 310 and 320 mg/dL, respectively; P = .17, paired-samples t-test; mean pretreatment and 2-week post-treatment IgM, 230 and 250mg/dL, respectively, P = .07, paired-samples t-test [to convert IgA and IgM to grams per liter, multiply by 0.01]).

Association of Serum Albumin and Clinical Severity and Outcome

To assess the potential of albumin as a biomarker for disease severity and outcome, patients were grouped according to their serum albumin levels. Patients were allocated to 1 of 2 groups (clinical hypoalbuminemia present or absent) or divided into tertiles (of approximately equal number) based on the raw data to maximize the value of information (also within the reference range values of albumin). This categorization based on serum albumin levels was performed both before and 2 weeks after IVIG. The groups based on pre-treatment serum albumin levels significantly differed in respiratory failure and the MRC sum score at nadir (Table 2). Patients with low serum albumin levels after treatment also required respiratory support more frequently and had a poorer GBS disability score and MRC sum score throughout and at the end of follow-up (all P < .001). Dividing the patients based on hypoalbuminemia vs normoalbuminemia yielded comparable results (ie, a higher serum albumin level was associated with a better clinical course and reduced disease severity at the end of follow-up [defined by the same clinical grading factors given in Table 2]). Intensive care unit (ICU) admission and mechanical ventilation could potentially influence the serum albumin levels. Therefore, we also analyzed the MRC sum score and GBS disability score at the end of follow-up, including mechanical ventilation and GBS disability score at nadir as covariates(mean [SD] GBS disability scores, 2.01 [1.5] for the <3.5-g/dL group, 1.2 [1.1] for the 3.5- to 4.0-g/dL group, and0.7 [0.6] for the >4.0-g/dL group, P = .004;mean [SD] MRC sumscores, 48.7 [13.2] for the <3.5-g/dL group, 56.5 [6.1] for the 3.5- to 4.0-g/dL group, and 58.3 [4.3] for the >4.0-g/dL group, P = .01, ANCOVA). In addition, patients not requiring ICU admission or mechanical ventilation also had poor outcomes on the basis of serum albumin levels 2 weeks after starting IVIG treatment (mean [SD] GBS disability scores, 2.1 [1.7] for the <3.5-g/dL group, 1.1 [1.1] for the 3.5- to 4.0-g/dL group, and 0.6 [0.6] for the >4.0-g/dL group, P < .001; mean [SD] MRC sum score, 51.0 [11.2] for the <3.5-g/dL

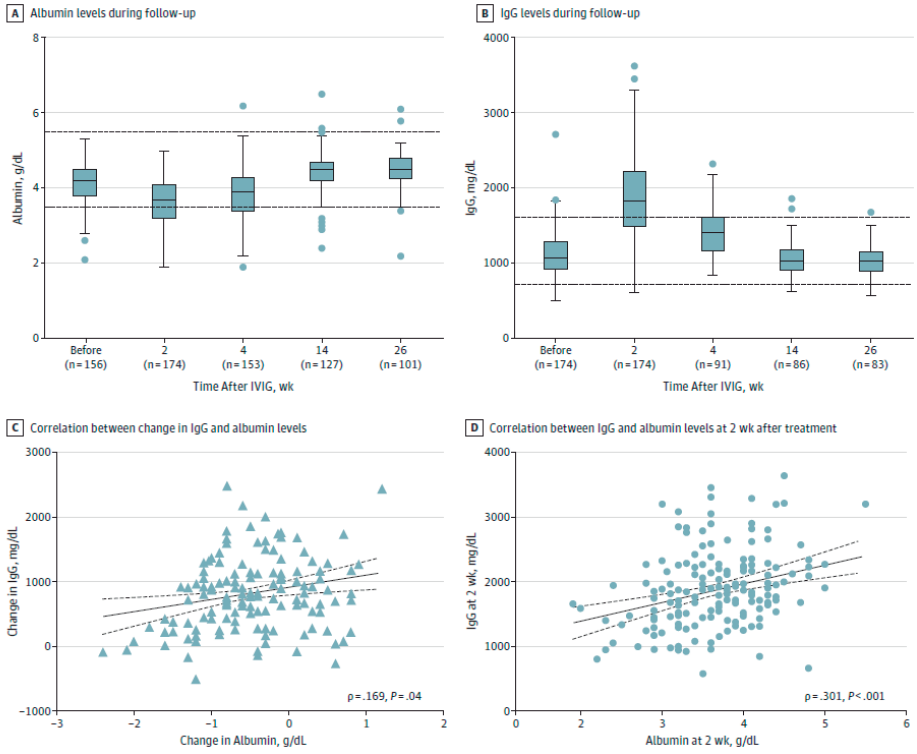

Figure 1 | Serum Albumin Levels in Patients With Guillain-Barré Syndrome (GBS) Before and After Treatment With Intravenous Immunoglobulin (IVIG). A, Serum albumin levels during a follow-up of 26 weeks in patients with GBS treated with IVIG. Dotted lines represent reference range values of albumin (3.5-5.5 g/dL [to convert to grams per liter, multiply by 10]). B, For comparison, the serum IgG levels in the same cohort of patients are shown (reprinted with permission from Wiley[6]) (to convert to grams per liter, multiply by 0.01). Boxes indicate medians with interquartile ranges (IQRs); whiskers (according to the Tukey test), 1.5 × IQR; and dots outside whiskers, outliers. C, Scatterplot showing the correlation between the change in albumin and IgG levels. D, Scatterplot showing the correlation between the albumin and IgG levels at 2 weeks after treatment. Solid line indicates regression (ρ); dotted lines, 95% CI of the regression.

group, 57.5 [5.6] for the 3.5- to 4.0-g/dL group, and 58.3 [4.4] for the >4.0 g/dL group, P = .002, ANCOVA). Survival analysis (Kaplan-Meier) with respect to the time required to improve 1 point on the GBS disability scale or the achievement of walking more than 10 m unaided during the trial follow-up (6 months) was not significantly different for patients based on their pretreatment albumin levels (eFigure 1 in the Supplement). Patients who maintained a serum albumin level within low-normal or high-normal range after treatment recuperated faster than hypoalbuminemic patients (6 of 114 patients [5.3%] vs 21 of 60 [35.0%] were unable to walk unaided; log-rank test for trend, P < .001) (Figure 2). Serum albumin levels decreased with age, as denoted by the negative correlation between post-treatment level and age (ρ = –0.406, P < .001) and the higher age in the hypoalbuminemic group (Table 2). Stratifying for age (group

Table 2 | Clinical Outcome Scores in Patients With GBS When Divided on the Basis of Serum Albumin Levels 2 Weeks After Intravenous Immunoglobulin Treatment[a]

	Serum Albumin Levels							
	Pretreatment				Posttreatment			
Group	Low (<4.0 g/dL) (n = 49)	Medium (4.0-4.5 g/dL) (n = 54)	High (>4.5 g/dL) (n = 53)	*P* Value[b]	Low (<3.5 g/dL) (n = 60)	Medium (3.5-4.0 g/dL) (n = 53)	High (>4.0 g/dL) (n = 61)	*P* Value[b]
Age, mean (SD), y	55.6 (19.1)	55.4 (17.3)	41.5 (19.9)	<.001	57.8 (17.1)	53.7 (17.5)	37.9 (19.8)	<0.001
Male	33 (67.3)	27 (50.0)	32 (60.4)	.20	31 (51.7)	30 (56.6)	38 (62.3)	.50
Diarrhea	12 (24.5)	11/53 (20.8)	12 (22.6)	.90	12 (20.0)	14 (26.4)	15/60 (25.0)	.70
URTI	15 (30.6)	23 (42.6)	15 (28.3)	.21	18 (30.0)	21 (39.6)	21/60 (35.0)	.56
Facial and/or bulbar weakness	16/45 (35.6)	19/52 (36.5)	17 (32.1)	.88	20/57 (37.0)	13/52 (25.0)	23 (37.7)	.29
Mechanical ventilation	16/44 (36.4)	11/49 (22.4)	5/51 (9.8)	.001	29/53 (54.7)	9/51 (17.6)	3/58 (5.2)	<.001
Duration, mean (SD), d	12.2 (23.0)	7.1 (20.5)	3.9 (12.8)	.04	23.1 (34.4)	3.3 (10.6)	1.1 (8.4)	<.001
GBS-disability score, mean (SD)								
Nadir	4.3 (0.8)	4.1 (0.7)	3.9 (0.6)	.06	4.6 (0.7)	4.0 (0.6)	3.8 (0.5)	<.001
1 wk	3.9 (0.9)	3.7 (0.9)	3.5 (1.0)	.08	4.4 (0.7)	3.6 (0.9)	3.2 (0.9)	<.001
2 wk	3.5 (1.2)	3.3 (1.2)	3.1 (1.2)	.31	4.2 (0.9)	3.2 (1.1)	2.7 (1.0)	<.001
4 wk	3 (1.4)	2.6 (1.4)	2.6 (1.3)	.36	3.8 (1.2)	2.5 (1.2)	2.0 (1.0)	<.001
26 wk	1.7 (1.5)	1.2 (1.3)	1.2 (1.0)	.17	2.2 (1.6)	1.3 (1.1)	0.7 (0.7)	<.001
MRC sum score, mean (SD)								
Nadir	29.1 (17.6)	35.02 (16.7)	38.0 (14.4)	.01	21.4 (17.5)	36.8 (14.2)	41.8 (11.1)	<.001
1 wk	36.7 (16.4)	39.6 (16.9)	43.3 (13.5)	.09	27.7 (17.5)	42.1 (14.2)	46.7 (10.0)	<.001
2 wk	38.7 (18.6)	42.6 (17.3)	45.5 (15.7)	.16	28.8 (19.6)	45.5 (15.2)	50.0 (90)	<.001
4 wk	41.3 (19.7)	46.9 (16.8)	48.4 (15.5)	.12	31.8 (21.4)	49.2 (14.6)	52.9 (8.2)	<.001
26 wk	53.8 (9.9)	55.3 (8.3)	56.2 (7.5)	.62	49.4 (12.8)	56.2 (6.8)	58.4 (4.1)	<.001

Abbreviations: GBS, Guillain-Barré syndrome; MRC, Medical Research Council; URTI, upper respiratory tract infection. [a]Data are presented as number (percentage) of patients unless otherwise indicated. Analyses were performed by analysis of covariance. Tests for clinical outcome were adjusted for age. [b]P value denotes difference over all groups.

wise as given in Table 1) revealed similar results, although the negative effect on improvement of a low serum albumin concentration is more pronounced in elderly populations (>60 years of age) (eFigure 2 in the Supplement). When adjusted for age (Cox proportional hazards regression), posttreatment serum albumin levels remained a highly significant factor associated with regaining the ability to walk unaided ($P < .001$). Multivariate analysis with clinical predictive factors (Table 2) in prognostic models for GBS identified pretreatment and posttreatment serum albumin as independent factors. The addition of serum albumin to the 3 models improved the predictive capability in this cohort of patients, as expressed in the area under the curve when compared with models without the incorporation of serum albumin levels. The area under the curve increased from 0.83 to 0.85 for the EGRIS, from 0.91 to 0.92 for the mEGOS at 4 weeks, and from 0.83 to 0.85 for the mEGOS at 6 months.

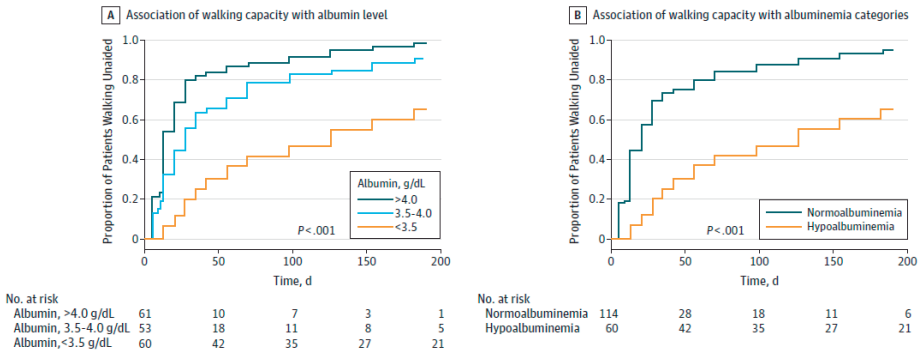

Figure 2 | Clinical Recovery of Patients With Guillain-Barré Syndrome (GBS) in Relation to Serum Albumin Levels. Kaplan-Meier analysis of patients with GBS regaining the capacity to walk unaided for more than 10m (GBS disability score of 2) in relation to tertiles of serum albumin levels at 2 weeks after start of intravenous immunoglobulin treatment (A) and hypoalbuminemia (albumin, <3.5 g/dL) (n = 60) vs normoalbuminemia (albumin,3.5 g/dL) (n = 114) (B) at the same time point. To convert albumin to grams per liter, multiply by 10.

DISCUSSION

We correlated the serum levels of albumin in 174 patients with GBS before and after standard high-dose IVIG therapy to clinical recovery. Before, but more evidently 2 weeks after, the start of IVIG treatment, serum albumin levels were significantly decreased, and low serum albumin levels were associated with a poorer clinical outcome. Subsequent logistic regression analysis identified albumin as an independent factor associated with outcome. Clinical prognostic models have been developed previously to estimate the chance of respiratory failure (EGRIS) and disability at 1, 3, and 6 months (EGOS/mEGOS).[16-18] Given the acute onset of GBS, biomarkers should ideally give an indication of outcome as early as possible to provide optimal medical care. Low albumin levels in serum obtained before treatment revealed a limited but potentially

relevant association with poor outcome, especially with respect to the chance of respiratory failure. The pretreatment albumin levels were associated with respiratory failure independent of the clinical factors in the EGRIS model. Two weeks after IVIG was started, the variability of the serum albumin levels was most pronounced, with one-third of the patients having developed hypoalbuminemia (albumin level, <3.5 g/dL). These patients had a poor clinical outcome compared with patients with normal albumin levels. In addition, in the normoalbuminemic group, patients with low-normal levels (defined as 3.5-4.0 g/dL) had worse outcomes compared with patients with high-normal values (defined as >4.0 g/dL). Multiple regression analysis revealed that serum albumin levels at 2 weeks after treatment were an independent factor associated with respiratory failure and inability to walk at 3 and 6 months, improving the capability of the EGRIS and mEGOS for anticipating these outcomes. In a healthy individual, serum albumin levels are kept within a well-defined reference range. The main causes of a reduction in serum albumin are increased catabolism, decreased production, and extravasation attributable to increased capillary permeability in the setting of inflammation or severe disease.[13,21,22] All 3 causes may contribute to the observed reduced serum albumin levels in GBS. In addition, high dose IVIG treatment in disorders other than GBS is related to a reduction of the serum albumin level.[7,8,23] This effect may be caused by exhaustion of the albumin and IgG recycling pathway via FcRn that binds both proteins. In the present study, however, no association was found between an increase in serum IgG levels after IVIG and a decrease in albumin levels. This finding may indicate that there is no direct competition for binding to the FcRn, and previous studies[24-26] found that human FcRn has distinct binding sites for IgG and albumin. Even in the absence of direct competition, serum albumin levels might reflect an individual's recycling capacity (eg, expression levels of FcRn) and be an indicator of IVIG pharmacokinetics, as has been speculated before.[8,27,28] Aside from a potential association with IVIG pharmacokinetics, albumin has been explored as a marker for prognosis in numerous other diseases and is a well-known indicator of general health.[13,29] Moreover, a low serum albumin level is a strong marker of poor outcome in the setting of acute illness.[30,31] Studies[32-34] focusing on ICU and critically ill patients identified serum albumin as a biomarker for survival and the need for mechanical ventilation. In a previous study[11] on biomarkers in amyotrophic lateral sclerosis, patients' survival increased with higher serum albumin levels, even within the reference range.

Limitations

Serum albumin levels before treatment and 2 weeks after IVIG treatment may be an additional prognostic factor in GBS. Our findings should now be validated in prospective studies, preferably with greater numbers of patients. This study did not seek to compare the prognostic capabilities of serum albumin vs the previously identified ΔIgG.[6] Nonetheless, determining the serum albumin concentration once is more efficient than calculating the change in IgG over time. We also assessed Δalbumin, which gave comparable results. Hence, only the pre-treatment or post-treatment levels were required for final analysis. The latter limits, of course, the practi-

cal use in GBS given the often rapid disease development that calls for early intervention. In our analyses regarding the prognostic models, we did not address the potential problem of overfitting, and no independent cohort of patients was available to validate our findings. Admission to the ICU could be an important factor in the reduction of serum albumin levels (eg, fluid therapy or mechanical ventilation), but patients who have not been admitted to the ICU also had reduced serum albumin levels of prognostic value to clinical outcome. Finally, we cannot rule out potential bias caused by the recumbence of patients, which is known to expand the plasma volume and thereby lower serum protein levels. However, this effect seems unlikely because levels of other serum proteins (IgA and IgM) did not decrease.

Conclusions

This study found that serum albumin, often already in use as a routine diagnostic indicator of overall health (eg, comprehensive metabolic panel), is an independent factor associated with the short- and long-term prognosis of patients with GBS treated with IVIG. The most auspicious finding is the prognostic value of pretreatment levels for the need for mechanical ventilation. Prospective studies should verify these findings to confirm the benefit of serum albumin as a biomarker for prognosis of GBS in clinical practice.

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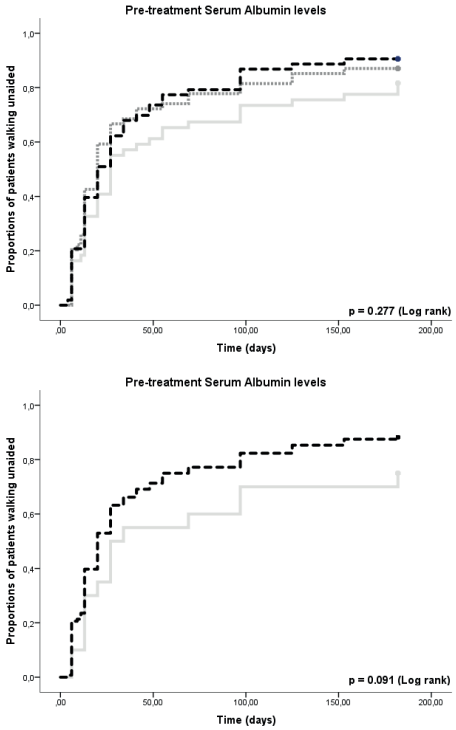
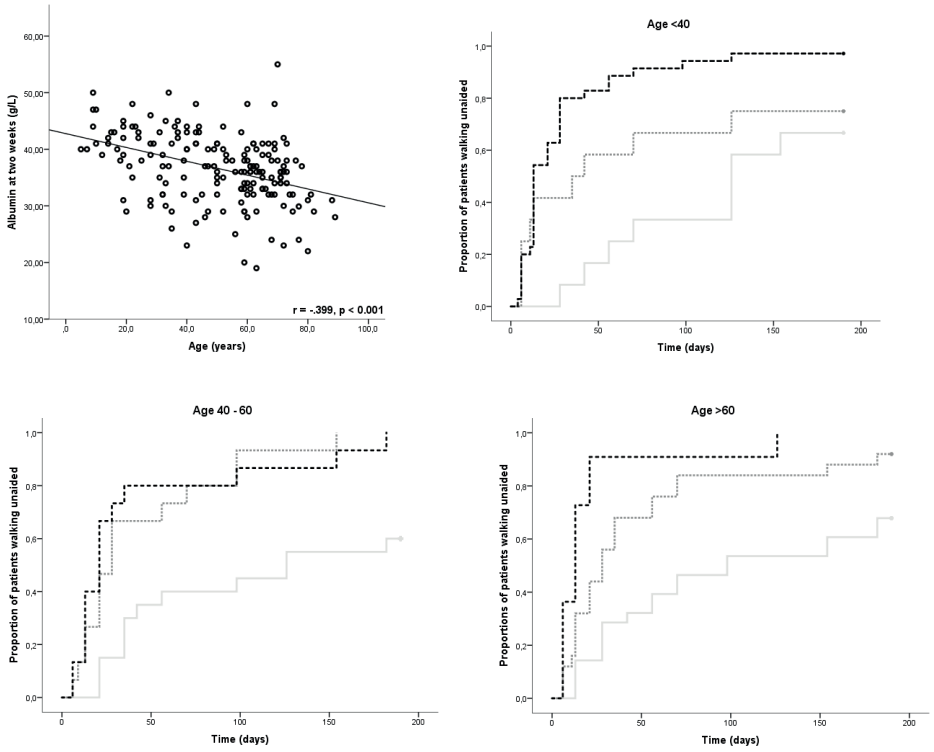
Supplementary Online Content

Fokkink W-JR, Walgaard C, Kuitwaard K, Tio-Gillen AP, van Doorn PA, Jacobs BC. Association of albumin levels with outcome in intravenous immunoglobulin–treated Guillain-Barré syndrome. *JAMA Neurol.* Published online December 27, 2016. doi:10.1001/jamaneurol.2016.4480

This supplementary material has been provided by the authors to give readers additional information about their work.



eFigure 1 | Recovery Based on Pretreatment Serum Albumin Levels. No significant difference in the time to regain independent walking with pre-treatment serum albumin levels. The upper KM-Meier curve is based on tertiles (see table 2), bold dashed line denotes a serum albumin level >45 g/L, dark grey dotted line 40 – 45 g/L, light grey continuous line <40 g/L. Lower KM-Meier curve based on hypoalbuminemia, light grey continuous line (n= 20) and normoalbuminemia, bold dashed line (n= 136).



eFigure 2 | Age Influences Serum Albumin Levels. The upper left panel shows the correlation between age and albumin. The KM-Meier curves are stratified on age groups. The bold dashed line denotes a serum albumin level >40 g/L, dark grey dotted line 35 – 40 g/L, light grey continuous line <35 g/L. Log-rank p-value when stratified for age is significant across all groups based on the serum albumin level 2 weeks after IVIg (P < 0.001).

2.5

Early recognition of poor prognosis in Guillain-Barré syndrome

Christa Walgaard
Hester F. Lingsma
Liselotte Ruts
Pieter A. van Doorn
Ewout W. Steyerberg
Bart C. Jacobs

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ABSTRACT

Background

Guillain-Barré syndrome (GBS) has a highly diverse clinical course and outcome, yet patients are treated with a standard therapy. Patients with poor prognosis may benefit from additional treatment, provided they can be identified early, when nerve degeneration is potentially reversible and treatment is most effective. We developed a clinical prognostic model for early prediction of outcome in GBS, applicable for clinical practice and future therapeutic trials.

Methods

Data collected prospectively from a derivation cohort of 397 patients with GBS were used to identify risk factors of being unable to walk at 4 weeks, 3 months, and 6 months. Potential predictors of poor outcome (unable to walk unaided) were considered in univariable and multivariable logistic regression models. The clinical model was based on the multivariable logistic regression coefficients of selected predictors and externally validated in an independent cohort of 158 patients with GBS.

Results

High age, preceding diarrhea, and low Medical Research Council sumscore at hospital admission and at 1 week were independently associated with being unable to walk at 4 weeks, 3 months, and 6 months (all p 0.05–0.001). The model can be used at hospital admission and at day 7 of admission, the latter having a better predictive ability for the 3 endpoints; the area under the receiver operating characteristic curve (AUC) is 0.84–0.87 and at admission the AUC is 0.73–0.77. The model proved to be valid in the validation cohort.

Conclusions

A clinical prediction model applicable early in the course of disease accurately predicts the first 6 months outcome in GBS.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a monophasic polyradiculoneuropathy with a highly variable clinical severity and outcome. IV immunoglobulin (IVIg) and plasma exchange (PE) are beneficial in patients who are severely affected, although one-third recover incompletely.[1] These patients require more effective treatment, but the clinical diversity and the rarity of the disease hamper good and well-powered randomized controlled trials in this patient group. To identify early patients with a poor outcome, who are eligible for additional treatment, prognostic models are needed. Prognostic models can also increase the power of therapeutic studies by adjusting for prognostic factors.[2] Ultimately, such prediction models can be used to individualize therapy in accordance with the expected outcome.

Previous studies have identified patient characteristics associated with poor outcome in GBS.[3-10] The Erasmus GBS Outcome Score (EGOS) is a prognostic model based on age, diarrhea, and GBS disability score at 2 weeks after hospital admission that accurately predicts the chance of being able to walk independently at 6 months.[8] However, prognostic models to optimize treatment in GBS should be applicable in the earliest phase of the disease, when treatment is considered to be most effective. Such models should also be designed to predict the primary endpoints used in most treatment trials in GBS; i.e., the clinical recovery on the GBS disability score at 4 weeks.[11-15] The aim of the current study was to develop a readily applicable prognostic model for accurate selection of patients with a poor prognosis, based on clinical information available in the first week of hospital admission.

METHODS

Patients

Data collected prospectively from a cohort of 397 patients with GBS were used to identify predictors for outcome. This derivation cohort consisted of patients who had been included in 2 treatment trials and one pilot study. The first study was a multicenter double-blind randomized controlled trial; this included 147 patients between 1985 and 1991 and compared PE with IVIg.[14] The second study was a pilot study in 25 Dutch patients to determine the additional therapeutic effect of methylprednisolone (MP) to IVIg.[16] This combination was tested in the third study: a multicenter double-blind randomized controlled trial in 225 patients included between 1994 and 2000.[15] Most patients were included in Dutch hospitals, the others in 2 German and 2 Belgian hospitals. All 3 studies used the same inclusion and exclusion criteria. Inclusion criteria were fulfillment of the National Institute of Neurological Disorders and Stroke diagnostic criteria for GBS,[17] inability to walk unaided 10 meters across an open space (GBS disability score 3 or more), and onset of weakness within 2 weeks before randomization. Exclu-

sion criteria were age below 6 years, pregnancy, previous GBS, known severe allergic reaction to properly matched blood products, known selective IgA deficiency, previous steroid therapy, severe concurrent disease, inability to attend follow-up, or contraindications for corticosteroid treatment (not in first trial).

To validate the model, we used data collected prospectively from a cohort of 191 patients enrolled in a pilot study[18] and an observational study[19] in patients with GBS, both performed in the Netherlands. The pilot study evaluated the additional therapeutic effect of mycophenolate mofetil to IVIg and MP in 27 patients included between 2002 and 2005. The same inclusion and exclusion criteria were used as in the derivation cohort. Between 2005 and 2008, 164 patients with GBS were included in the observational study, which assessed pain and autonomic dysfunction (GRAPH study).[19] Patients with a mild form of GBS (able to walk throughout the course of the disease) (n = 33) were also included in this study, but not used for validation. Patient characteristics were described in more detail in the trial and survey reports.[14-16,18,19]

Standard protocol approvals, registrations, and patient consents.

Approval was received by an ethical standards committee on human experimentation for each of the studies mentioned above. Written informed consent was received from all patients.

Data collection.

All data were collected prospectively. At hospital admission, information was obtained regarding age, gender, diarrhea, or symptoms of an upper respiratory tract infection in the 4 weeks preceding onset of weakness, day of onset of weakness, cranial nerve dysfunction, Medical Research Counsel (MRC) sumscore,[20] GBS disability score,[21] and sensory deficits. In addition, data on the MRC sumscore and GBS disability score were collected at day 7 of hospital admission. The MRC sumscore is defined as the sum of MRC scores of 6 different muscles measured bilaterally, which results in a sumscore ranging from 0 (tetraplegic) to 60 (normal; appendix e-1 on the Neurology® Web site at www.neurology.org).[20] The GBS disability score is a widely accepted scale for assessing the functional status of patients with GBS, ranging from 0 (normal) to 6 (death; appendix e-1).[21] Pretreatment serum samples obtained within 4 weeks of onset of weakness were used for serologic screening to identify recent infections with Campylobacter jejuni and cytomegalovirus (CMV). Age and MRC sumscore were categorized to facilitate the applicability in clinical practice. Categories were based on even group sizes and predictive ability.

Outcome measures.

This study used walking ability as outcome measure. Poor outcome was defined as the inability to walk unaided 10 meters across an open space (GBS disability score of 3 or higher). Outcome was assessed at 4 weeks, 3 months, and 6 months after inclusion in one of the studies. An additional outcome measure in this study was the improvement of one or more points on

the GBS disability score in the first 4 weeks after inclusion. No improvement was considered as poor outcome. Both outcome measures have been used as primary endpoint in previous treatment trials in GBS.[11-15]

Model development.

Potential prognostic factors of outcome at 4 weeks, 3 months, and 6 months after inclusion were first analyzed in the derivation cohort by univariable logistic regression analysis. Statistically significant predictors for poor outcome at all time points were further analyzed for their independent predictive value using multivariable logistic modeling. Missing values were imputed using a multiple imputation method.[22] Odds ratios (OR) were used to express the strength of prognostic effects and were compared between the imputed and the complete case analyses. Predictive value was also measured using the likelihood ratio χ^2 test (LR chi2), to account for the prevalence of the predictor. Variables that added significant predictive information were selected for use in a multivariable model. A p value <0.05 was considered to be significant. The model was fitted using the ability to walk unaided at 4 weeks after hospital admission as outcome measure. The model was constructed based on the multivariable logistic regression coefficients in the derivation dataset. Predictive performance of the model was quantified with respect to discrimination (area under the receiver operating characteristic curve [AUC]). The AUC ranges from 0.5 to 1.0 for sensible models. The internal validity of the model was assessed by bootstrapping techniques, including both the selection of predictors and estimation of the coefficients.22 The model was externally validated in an independent validation cohort of patients with GBS. Model performance in the validation set was quantified with respect to discrimination (AUC) and calibration. Calibration was assessed graphically by plotting observed frequencies against predicted probabilities. Statistical analyses used SPSS version 15.0 for Windows, Stata version 11, and R statistical software (version 2.7, using the Design library).

RESULTS

Three (<1%) of the 397 patients in the derivation cohort died in the first week after hospital admission and were excluded from the current study. In this cohort, the primary endpoint was missing at 3 months for 3 (<1%) patients and at 6 months for 12 (3%) patients. Fifty-five percent had a poor outcome at 4 weeks, 30% at 3 months, and 19% at 6 months after hospital admission. In the validation cohort, none of the patients died in the first week of follow-up. Due to the slightly different follow-up structure of the observational study, outcome was unavailable for 38 (24%) patients at 4 weeks, 14 (9%) patients at 3 months, and 7 (4%) patients at 6 months after hospital admission. These patients were excluded from the study. Of the remaining patients in the validation cohort, 54% had poor outcome at 4 weeks, 29% at 3 months, and 15% at 6 months after hospital admission.

Table 1 | Risk of poor outcome, defined as inability to walk unaided at 4 weeks, 3 months, and 6 months after entry to the hospital, according to potential predictors in the derivation set of 394 patients with GBS based on univariable regression analysis.

		Inability to walk unaided					
		4 wk, OR		3 mo, OR		6 mo, OR	
	No.	(95% CI)	*P*	(95% CI)	*P*	(95% CI)	*P*
Total	394						
Age, y			0.003		0.01		<0.001
≤ 40	138	1 (ref)		1 (ref)		1 (ref)	
40-60	114	1.9 (1.2-3.2)		1.6 (0.9-2.8)		2.2 (1.0-4.6)	
> 60	142	2.2 (1.4-3.5)		2.3 (1.3-3.9)		4.0 (2.1-7.9)	
Days onset weakness until admission[a]		0.9 (0.9-1.0)	0.02	0.9 (0.8-1.0)	0.003	0.9 (0.8-1.0)	0.006
Clinical severity at admission							
MRC sum score			<0.001		<0.001		<0.001
60-51	47	1 (ref)		1 (ref)		1 (ref)	
50-41	180	2.8 (1.3-5.8)		5.9 (1.4-25)		6.1 (0.8-46)	
40-31	83	6.8 (3.0-15)		14 (3.3-64)		19 (2.4-144)	
≤ 30	83	14 (5.8-32)		23 (5.2-101)		26 (3.4-198)	
GBS disability score			<0.001		<0.001		0.002
0,1 or 2	0	0		0		0	
3	91	1 (ref)		1 (ref)		1 (ref)	
4	265	3.6 (2.1-6)		3.9 (1.9-7.9)		2.7 (1.2-5.8)	
5	38	10.5 (4.1-27)		7.3 (2.9-18)		6.1 (2.3-16)	
Clinical severity at day 7 of admission							
MRC sum score			<0.001		<0.001		<0.001
60-51	95	1 (ref)		1 (ref)		1 (ref)	
50-41	119	5.0 (2.5-10)		3.6 (1.2-11)		2.5 (0.7-9.5)	
40-31	76	19 (8.8-43)		11 (3.5-32)		6.3 (1.7-23)	
≤ 30	104	137 (46-405)		47 (16-139)		30 (8.8-99)	
GBS disability score			<0.001		<0.001		<0.001
0,1 or 2	33	0		0		0	
3	79	1 (ref)		1 (ref)		1 (ref)	
4	186	10.6 (5.4-21)		8.5 (3.0-24)		8.6 (2.0-37)	
5	96	36 (15-83)		21.3 (7.2-63)		25 (5.8-109)	
Infection and serology							
Symptoms of preceding infection[b]							
Diarrhea	89	1.6 (1.0-2.6)	0.05	1.8 (1.1-3.0)	0.02	2.3 (1.3-3.9)	0.003
URTI	147	0.5 (0.4-0.8)	0.003	0.7 (0.5-1.2)	NS	0.5 (0.3-0.8)	0.006
Infection serology[c]							
Campylobacter jejuni	114	1.7 (1.1-2.6)	0.02	2.2 (1.4-3.4)	0.001	2.6 (1.5-4.3)	<0.001
Cytomegalovirus	45	2.2 (1.1-4.3)	0.02	2.4 (1.3-4.6)	0.006	0.9 (0.4-2.0)	NS

Abbreviations: CI = confidence interval; GBS = Guillain-Barré syndrome; MRC = Medical Research Council; NS = nonsignificant; OR = odds ratio; URTI = upper respiratory tract infection.

[a] Time between onset of weakness and admission in days, odds ratio per extra day.

[b] Symptoms of an infection in the 4 weeks preceding the onset of weakness.

[c] Using pretreatment serum samples obtained at entry.

Gender, bulbar and facial weakness, sensory deficit, and pain were not significantly correlated with outcome (table e-1). In univariate analysis, 6 predictors of outcome—at 4 weeks, 3 months, and 6 months—were identified: age, disease progression (expressed as number of days between onset of weakness and hospital entry), MRC sumscore and GBS disability score, diarrhea in the 4 weeks preceding GBS, and C jejuni serology (all p = 0.05– 0.001) (table 1 and table e-1). C jejuni serology was excluded for multivariable analysis because in clinical practice serology results will be difficult to obtain shortly after hospital admission. For further modeling, the MRC sumscore was selected over the GBS disability score, because the model using the MRC sumscore had a substantially better performance (LR statistic 69.75 vs 46.49 at admission and 195.27 vs 154.35 at 1 week). Disease progression lost its predictive ability when analyzed in a multivariable model with age, diarrhea, and MRC sumscore. The results of the multivariable analyses of the remaining prognostic factors are shown in table 2.

Table 2 | Multivariable analysis of main predictors of poor outcome, defined as being unable to walk at 4 weeks after hospital admission and as no improvement on the GBS disability score in the first 4 weeks after admission.

	Outcome measure at 4 weeks after admission					
	Unable to walk unaided			No improvement on GBS disability score		
	OR (95% CI)	*P*	AUC	OR (95% CI)	*P*	AUC
At admission			0.73			0.71
Age (years)		0.006			0.001	
≤ 40	1 (ref)			1 (ref)		
40-60	1.9 (1.1-3.3)			1.9 (1.1-3.3)		
> 60	2.3 (1.3-3.8)			2.7 (1.6-4.5)		
MRC sum score		<0.001			<0.001	
60-51	1 (ref)			1 (ref)		
50-41	2.8 (1.3-6.2)			5.0 (2.0-13)		
40-31	6.1 (2.5-14)			11 (4.0-29)		
≤ 30	9.6 (3.8-24)			13 (4.7-34)		
Preceding diarrhea[a]	1.7 (1.0-2.9)	0.07		1.8 (1.1-3.1)	0.02	
At day 7 of admission			0.87			0.87
Age (years)		0.008			0.001	
≤ 40	1 (ref)			1 (ref)		
40-60	2.1 (1.0-4.2)			2.0 (1.0-3.8)		
> 60	2.8 (1.4-5.4)			3.2 (1.7-5.9)		
MRC sum score		<0.001			<0.001	
60-51	1 (ref)			1 (ref)		
50-41	3.8 (1.7-8.4)			8.0 (2.9-22)		
40-31	10 (4.2-26)			35 (12-99)		
≤ 30	58 (18-188)			110 (38-320)		
Preceding diarrhea[a]	2.1 (1.0-4.4)	0.04		1.9 (1.0-3.5)	0.05	

Abbreviations: AUC = area under the receiver operating characteristic curve; CI = confidence interval; MRC = Medical Research Council; OR = odds ratio. [a] Diarrhea in the 4 weeks preceding the onset of weakness.

Age, diarrhea, and MRC sumscore were used to develop the model for clinical practice. This model was a modification of the previously developed EGOS.[8] In contrast to the EGOS, this modified EGOS (mEGOS) can be applied already at hospital admission and at day 7 of hospital admission. When used at admission, the mEGOS scores ranged from 0 to 9 with 4 categories for the MRC sumscore, 3 categories for age, and 2 categories for preceding diarrhea (table 3 and figure 1A). The predictive ability of the model was better when used at day 7 of admission, because the MRC sumscore at this time point predicts outcome more accurately. Therefore, the MRC sumscore was weighted stronger in the mEGOS when used at 1 week and the scores range from 0 to 12 (table 3 and figure 1B).

Table 3 | Modified Erasmus GBS Outcome Scores

Prognostic factors	Categories	Score	Prognostic factors	Categories	Score
Age at onset (years)	≤ 40	0	Age at onset (years)	≤ 40	0
	41– 60	1		41– 60	1
	> 60	2		> 60	2
Preceding diarrhea[a]	Absent	0	Preceding diarrhea[a]	Absent	0
	Present	1		Present	1
MRC sum score (at hospital admission)	51– 60	0	MRC sum score (at day 7 of admission)	51– 60	0
	41– 50	2		41– 50	3
	31– 40	4		31– 40	6
	0 – 30	6		0 – 30	9
mEGOS		0 – 9	mEGOS		0 – 12

Abbreviations: mEGOS = modified Erasmus GBS Outcome Score; MRC = Medical Research Council.
[a] Diarrhea in the 4 weeks preceding the onset of weakness.

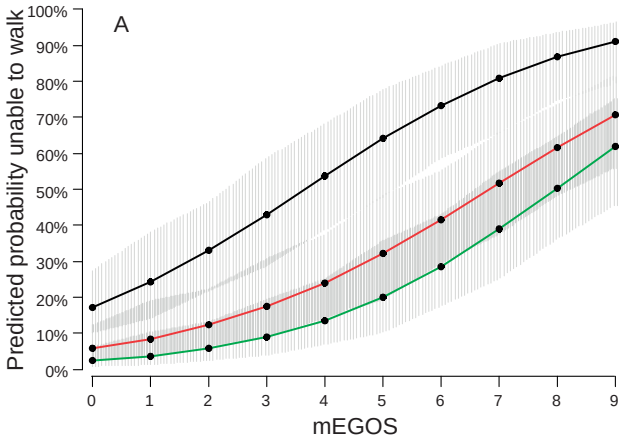

Figure 1 | Predicted fraction of patients unable to walk independently according to modified Erasmus GBS Outcome Score (mEGOS)
Predicted fraction of patients unable to walk independently at 4 weeks (black lines), 3 months (red lines), and 6 months (green lines) on the basis of the mEGOS at hospital admission (A) and at day 7 of admission (B). The gray areas around the colored lines represent 90% confidence intervals.

The performance of mEGOS when used at admission was good for prediction of outcome at 4 weeks (AUC 0.73), at 3 months (AUC 0.73), and at 6 months (AUC 0.77) and was excellent when used at day 7 of admission, with AUCs for predicting outcome at these 3 time points of 0.87, 0.84, and 0.84, respectively. The mEGOS was validated in an independent cohort and showed a good calibration (figure e-1) and a good discriminative ability for predicting outcome at all 3 time points (admission: AUC = 0.75, 0.73, and 0.75; 1 week: AUC = 0.81, 0.70, and 0.77). Age, preceding diarrhea, and MRC sumscore in multivariable analysis were also independently associated with another endpoint that is frequently used in therapeutic trials in GBS: the improvement of one or more points on the GBS disability score at 4 weeks after hospital admission (table 2). In addition, the mEGOS model predicted the failure to improve on the GBS disability score at 4 weeks with high accuracy (AUC of 0.71 and 0.87).

The current model can also be used to compare populations of patients included in various therapeutic trials and for covariate adjustment. To illustrate this, we compared 3 study populations[14,15,19] with respect to the distribution of the patients over the mEGOS categories (figure 2). The figure illustrates the ability of mEGOS to make a distinction between different GBS populations with respect to prognosis. The patients included in the observational study had an overall better prognosis, as was expected because of the different inclusion criteria, which allowed the inclusion of mildly affected patients.

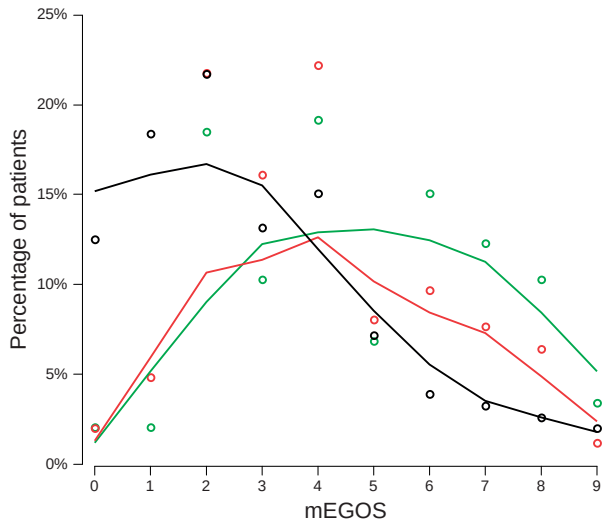

Figure 2 | Comparing 3 therapeutic study populations with respect to prognostic factors at hospital admission using modified Erasmus GBS Outcome Score (mEGOS). Points represent the percentages of patients with a specific mEGOS in a therapeutic trial comparing plasma exchange vs IV immunoglobulin (IVIg) (green), a therapeutic trial comparing IVIg/placebo vs IVIg/methylprednisolone (red), and an observational study (black). Smoothed lines represent the distribution of the study population over the total mEGOS.

DISCUSSION

The variation in clinical severity and outcome between patients with GBS hampers optimizing of treatment, because heterogeneous study populations will reduce the statistical power of treatment trials. New therapies and treatment modalities for GBS may not further improve outcome in patients who already recover sufficiently after standard treatment. Therefore, selective treatment trials should focus on a more homogeneous subgroup of patients with poor recovery despite current standard treatment. In this study a prognostic model is presented which early identifies patients with poor outcome and can be used for future therapeutic trials. The main predictors of being unable to walk independently at 4 weeks, 3 months, and 6 months were MRC sumscore, age, and preceding diarrhea in our study. Based on these predictors, a model was constructed which proved to be valid in an independent cohort of patients with GBS. The model is applicable at hospital admission as well as at day 7 of hospital admission and is therefore suitable to study treatments which should be started immediately as well as after standard treatment in patients with poor prognosis. The model may provide a first step toward individualized treatment in GBS.

This mEGOS originates from the EGOS, which can be applied in clinical practice at 2 weeks after hospital admission to predict outcome at 6 months and is based on the predictors age, preceding diarrhea, and GBS disability score.[8] The EGOS is a simple, accurate, and validated prognostic model, but less suited for treatment development because of the delay of 2 weeks and the predicted outcome measure. The mEGOS was primarily designed for future treatment studies in GBS and for this application has important advantages. First, the mEGOS model can be applied already in the first week of admission, when treatment is considered to be most effective. Second, the mEGOS predicts reaching independent walking or improving on the GBS disability score at 4 weeks, which are the 2 primary endpoints most frequently used in therapeutic trials in GBS. Third, the mEGOS also accurately predicts long-term GBS disability scores, which were important secondary endpoints in previous trials. Because of these features, the mEGOS model can be used for early identification of patients with poor prognosis for future selective therapeutic studies. In addition, this model can be used for covariate adjustment, which is a powerful tool in heterogeneous patient populations to estimate the effect of treatment in individuals and to increase the statistical power of therapeutic trials.[2,23,24] For example, adjustment for the effect of age on outcome results in an estimated treatment effect for a patient of a given age instead of an average age. When the results of these selective trials in patients with poor prognosis are positive, the mEGOS may also be used to individualize treatment of patients with GBS in routine clinical practice.

Our study confirms that poor outcome is associated with older age,[4,5,7,8,10] rapid disease progression, [7,10] severe disease indicated by GBS disability score or MRC sumscore, [3,4,7,8] preceding

diarrhea, positive C jejuni serology, [3,5,8] positive CMV serology, [9] and no symptoms of a preceding respiratory tract infection.[3,4] Two of these studies used partly the same data as in this study.[8,9] For the purpose of this study, we selected age, preceding diarrhea, and MRC sumscore, which are readily available at hospital admission of the patient. Prognostic biomarkers may further improve those models in the future. Promising candidates are infection serology, antiganglioside antibodies, and serum IgG level increase after IVIg treatment, which were all related to outcome.[3,5,6,8,9] The need for accurate prediction models for outcome has also been acknowledged for traumatic brain injury[25] and for stroke.[26,27] These neurologic conditions resemble GBS in the sense that they are acute and monophasic and have a highly variable clinical course.

Our study had several limitations. First, the prognostic model was derived from cohorts of Dutch Caucasians, which may restrict the application to those patients. Second, information on outcome at 4 weeks was not available in 24% of patients from the validation cohort. For this cohort data were used from an observational study, in which 4 weeks was not a standardized evaluation time point. However, percentages of patients with a poor outcome at 4 weeks in the derivation and validation cohort were comparable (55% and 54%), so it is unlikely that this caused bias. A third limitation is that the model only predicts the ability to walk independently, and not the full ordinal GBS disability scores, as this would have provided maximum statistical power.[28] However, this specific outcome measure we used is highly relevant for patients and was previously used by most therapeutic trials in GBS. Finally, EMG may have prognostic relevance in GBS, as indicated by several studies[3-5,7,10]; unfortunately, EMG was not performed systematically in the current study. Future studies are needed to define if EMG has additional value for predicting outcome already at the day of hospital admission.

The mEGOS is an accurate and validated model for prediction of outcome at several time points in the first 6 months after onset of GBS. An important advantage above existing models is that the mEGOS can be used in the early phase of disease when the process of nerve damage is ongoing and possibly reversible. This model predicts commonly used trial endpoints in GBS and can be used to conduct new trials selectively in patients with poor outcome. In addition, the model can be used to compare patient populations with respect to prognostic factors and expected outcome. This model may assist clinicians in optimizing treatment for individual patients with GBS.

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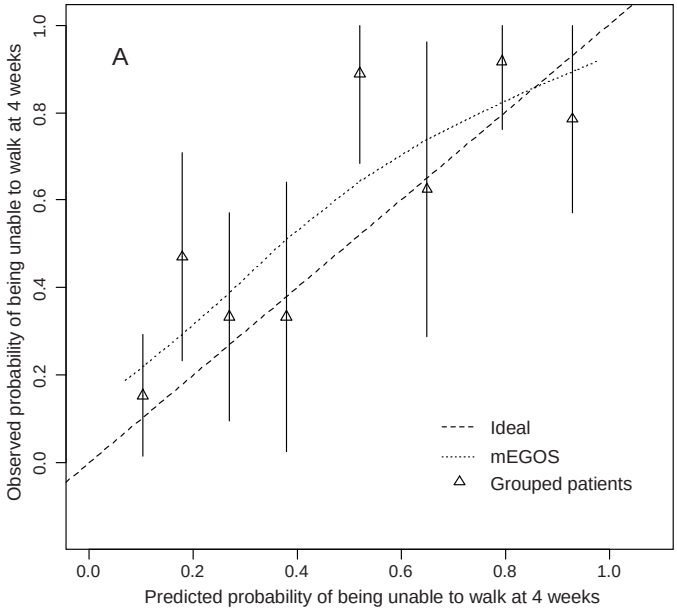
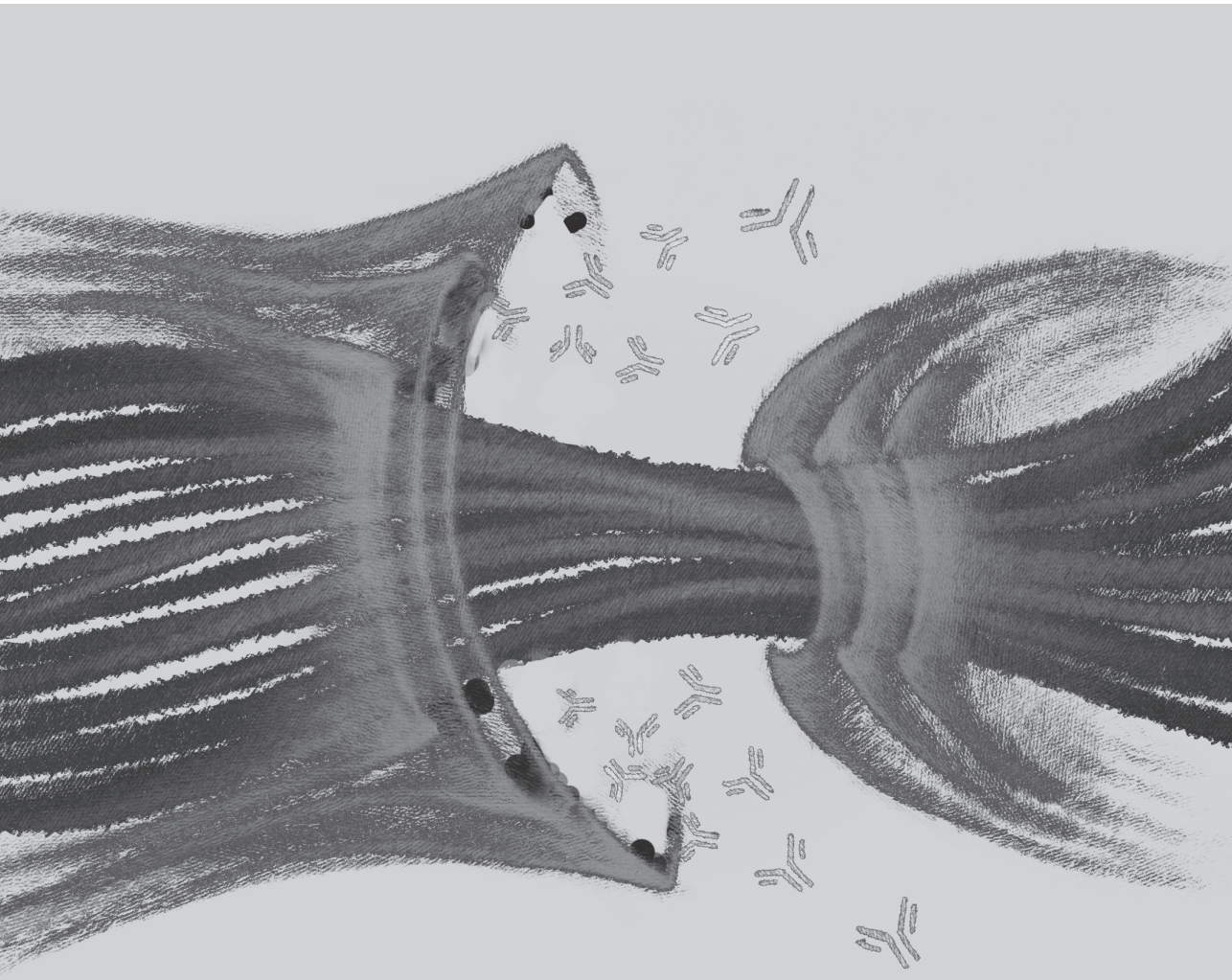


Figure e-1 | Calibration of the mEGOS in the validation cohort.

Calibration of mEGOS in the validation cohort when applied at admission (A) and at day 7 of admission (B). The striped lines from (0,0) to (1,0) indicate perfect calibration. Triangles indicate the probabilities in grouped patients with similar predicted risks. Non-parametric, smoothed curves indicate the relation between predicted probability and observed frequency of inability to walk at 4 weeks.



3

Improving outcome in GBS

3.1

Efficient design and analysis of randomized controlled trials in rare neurological diseases: An example in Guillain-Barré syndrome.

Nikki van Leeuwen
Christa Walgaard
Pieter A. van Doorn
Bart C. Jacobs
Ewout W. Steyerberg
Hester F. Lingsma

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ABSTRACT

Background

Randomized controlled trials (RCTs) pose specific challenges in rare and heterogeneous neurological diseases due to the small numbers of patients and heterogeneity in disease course. Two analytical approaches have been proposed to optimally handle these issues in RCTs: covariate adjustment and ordinal analysis. We investigated the potential gain in efficiency of these approaches in rare and heterogeneous neurological diseases, using Guillain-Barré syndrome (GBS) as an example.

Methods

We analyzed two published GBS trials with primary outcome 'at least one grade improvement' on the GBS disability scale. We estimated the treatment effect using logistic regression models with and without adjustment for prognostic factors. The difference between the unadjusted and adjusted estimates was disentangled in imbalance (random differences in baseline covariates between treatment arms) and stratification (change of the estimate due to covariate adjustment). Second, we applied proportional odds regression, which exploits the ordinal nature of the GBS disability score. The standard error of the estimated treatment effect indicated the statistical efficiency.

Results

Both trials were slightly imbalanced with respect to baseline characteristics, which was corrected in the adjusted analysis. Covariate adjustment increased the estimated treatment effect in the two trials by 8% and 18% respectively. Proportional odds analysis resulted in lower standard errors indicating more statistical power.

Conclusion

Covariate adjustment and proportional odds analysis most efficiently use the available data and ensure balance between the treatment arms to obtain reliable and valid treatment effect estimates. These approaches merit application in future trials in rare and heterogeneous neurological diseases like GBS.

INTRODUCTION

RCTs are the standard to investigate the effectiveness of medical interventions. However, RCTs are challenging in rare heterogeneous diseases. The randomization process in RCTs ensures that observed and unobserved patient characteristics on average are similar between treatment arms.[1] However, it does not ensure full balance.[1] Different baseline risks for outcome can arise between treatment arms, simply due to chance.[1] In diseases with large between-patient differences in natural disease course, severity and outcome, small imbalances in covariates between the treatment arms may, positively or negatively, affect the estimated treatment effect.

Sample sizes in RCTs in rare diseases are usually small. Small trials are a subject to a greater chance of imbalance than large trials.[1] Moreover, small RCTs can easily fail to detect treatment benefits, due to lack of statistical power. In rare neurological disorders, such as inflammatory neuropathies like Guillain-Barré syndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN), this heterogeneity and rarity is a major challenge for conducting RCTs.

Two approaches to optimize RCT design and analysis that have been successfully applied in other acute neurological diseases such as stroke and traumatic brain injury are covariate adjustment and ordinal analysis.[2-4] (Table 1) Covariate adjustment is a statistical method that adjusts the treatment effect for baseline risk on poor outcome in the treatment arms. When the treatment arms are imbalanced, an unadjusted analysis is suboptimal to estimate the treatment effect. In addition, previous studies found that covariate adjustment could increase statistical power.[1,5-9] Ordinal analysis is an approach to analyze a full ordinal outcome scale instead of a dichotomized version. Although these techniques already have been successfully applied in stroke and traumatic brain injury, it is still relevant to study this in other diseases like GBS, since the effect of the different approaches can work out differently in different study settings. The most commonly used outcome in GBS is the ordinal GBS disability score, consisting of seven categories. Usually the scale is dichotomized into favorable or unfavorable outcome, or the improvement on the GBS disability score from admission calculated and dichotomized as minimal one grade improvement. In ordinal analysis the outcome is not dichotomized but analyzed as the full ordinal scale with proportional odds analysis, preventing loss of information.[10] Simulation studies and empirical validation studies in other fields have demonstrated that proportional odds analysis increases statistical power in RCTs.[10-13]

To test the applicability and value of these approaches in rare and heterogeneous neurological diseases, we use Guillain-Barré syndrome (GBS) as an example. GBS is a life-threatening acute immune-mediated polyradiculoneuropathy,[14,15] which requires early diagnosis and hospital admission for accurate monitoring, treatment and supportive care. Some patients may show

Table 1 | Distribution of baseline predictors and outcome distribution in two randomized controlled trials in GBS.

	PE vs IVIg trial			**IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial**		
	Total (n = 146)	Control (PE) (n =73)	Treatment (IVIg) (n = 73)	Total (n = 22)	Control (IVIg) (n = 111)	Treatment (IVIg+MP) (n = 110)
Age (Median, Interquartile Range 25th-75th Percentile)	49 (32 – 63)	51 (33 – 66)	47 (32 – 61)	55 (35 – 67)	52 (35 – 67)	57 (34 – 68)
Preceding diarrhea	27 (19%)	16 (22%)	11 (15%)	60 (27%)	30 (27%)	30 (27%)
GBS disability score at admission						
Able to walk over 10m open space with help	29 (20%)	16 (22%)	13 (18%)	58 (26%)	32 (30%)	26 (24%)
Bedridden or chair bound	92 (63%)	44 (60%)	48 (66%)	153 (49%)	78 (70%)	75 (68%)
Needs ventilation for at least a part of the day	25 (17%)	13 (18%)	12 (16%)	10 (5%)	1 (1%)	9 (8%)
Predicted probability of one or more grades improvement on the GBS disability score after 4 weeks	0.43	0.41	0.45	0.62	0.64	0.60
One or more grades improvement on the GBS disability score after 4 weeks	63 (43%)	25 (34%)	38 (52%)	137 (62%)	63 (57%)	74 (67%)
GBS disability score after 4 weeks						
0 = Healthy	0 (0%)	0 (0%)	0 (0%)	5 (2%)	0 (0%)	5 (5%)
1 = Minor symptoms	16 (11%)	6 (8%)	10 (14%)	37 (17%)	24 (22%)	13 (12%)
2 = Able to walk 10m unassisted but not able to run	30 (21%)	12 (16%)	18 (25%)	74 (34%)	31 (28%)	43 (39%)
3 = Able to walk over 10m open space with help	19 (13%)	9 (12%)	10 (14%)	22 (10%)	10 (9%)	12 (11%)
4 = Bedridden or chair bound	48 (33%)	27 (37%)	21 (29%)	54 (24%)	31 (28%)	23 (21%)
5 = Needs ventilation for at least a part of the day	31 (21%)	17 (23%)	14 (19%)	26 (12%)	14 (13%)	12 (11%)
6 = Dead	2 (1%)	2 (3%)	0 (0%)	3 (1%)	1 (1%)	2 (2%)

spontaneous and full recovery, while others require ventilation at an ICU for months and remain severely disabled. Several RCTs have successfully been conducted in GBS.[16-18]

We aimed to explore the potential benefit of covariate adjustment and proportional odds analysis in rare and heterogeneous neurological diseases, compared to the conventional statistical approaches. We hereto re-analyzed two RCTs in GBS.

METHODS

Patient population

We analyzed data from two RCTs in GBS, the Plasma Exchange (PE) vs Intravenous Immunoglobulin (IVIg) (PE vs IVIg) trial[17] and the IVIg and placebo versus IVIg and Methyl-Prednisolone (MP) (IVIg vs MP) trial,[18] conducted between 1986 and 2000. In the PE vs IVIg trial, the control group received IVIg and the treatment group received PE. In the IVIg vs MP trial, the patients receiving IVIg and placebo were considered as control patients and the patients receiving IVIg and MP were considered as treated patients. The primary outcome in both trials was improvement (corresponding to lower GBS disability scores) by one or more grades on the GBS disability score after 4 weeks. The GBS disability score is an ordinal scale ranging from 0 = healthy to 6 = dead. However, in order to estimate treatment effects for a positive outcome for all the analyses, we used the reversed GBS disability score at 4 weeks, to keep the estimates easy to compare. For all the regression models used in this paper, higher numbers (in outcome) mean better health outcomes.

Statistical analysis

The predicted probabilities for one grade improvement on the GBS disability score were calculated and used as a measure for baseline risk to indicate potential unbalance between the treatment arms in baseline characteristics.

To estimate treatment effects, we used two commonly used primary (dichotomous) outcomes in GBS trials as reference; (1) favorable outcome (0–2) on the GBS disability scale at 4 weeks as outcome and (2) minimal one grade improvement on the GBS disability score between the moment of randomization and 4 weeks as outcome, both analyzed with binary logistic regression without covariate adjustment. Consequently, these references were compared with the two approaches under study: covariate adjustment and ordinal analysis.

Covariate adjustment

With covariate adjustment, conditional treatment effects are estimated with regression models. Adjusting for GBS disability score at admission results in an estimated treatment effect for

a patient with a given GBS disability score, while unadjusted analysis results in an average estimated treatment effect over all patients, irrespective of the GBS disability score. Unadjusted analysis is expressed by the following formula:

log odds (improvement) = α + β * *treatment*

, where improvement is by one or more grades on the GBS disability score, and treatment is an indicator for the randomization arm. The coefficients α and β indicate the intercept and regression coefficient for treatment. In logistic regression, exp(β) indicates the odds ratio (OR).

For adjusted analysis, we used three well-known predictors of outcome[19,20]: age, preceding diarrhea and GBS disability score at admission. The covariate adjusted model is expressed by the following formula:

log odds (improvement) = α + β * *treatment* + β*1* * *age* + β*2* * *preceding diarrhea*
+ β*3* * *GBS disability score at admission*

This results in an adjusted regression coefficient β for the estimated treatment effect. In the trial analysis, the observed difference of the unadjusted and adjusted regression coefficient for the treatment variable is a result of imbalance and stratification.[8] We hereto calculated the linear predictor based on age, diarrhea and GBS disability score at admission. We then calculated the difference in treatment effect that was attributable to imbalance as the difference between the mean value of the linear predictor between the treatment arms.[8] The remaining part of the difference between the unadjusted and the adjusted treatment effect was attributed to stratified estimation, i.e. conditioning on covariates.[8]

Proportional odds analysis

For ordinal analysis we used proportional odds logistic regression to exploit the ordinal nature of the GBS disability score. A proportional odds logistic regression model was fitted with the GBS disability score collapsed to a 5-point scale. We combined both healthy (0) and minor symptoms (1), as well as needs ventilation at least a part of the day (5) and dead (6) because of small numbers in these extreme categories. We used the reversed GBS disability scale to estimate treatment effects on a positive outcome, and to keep these estimates comparable to the estimates of the other logistic regression models on positive dichotomous outcomes (improvement and favorable outcome). The proportional odds model uses an ordinal outcome variable with more than two possible categories. It estimates a common OR over all possible cut-offs of the outcome scale. Next, we used the difference between the GBS disability score at admission and the GBS disability score at four weeks as outcome. A proportional odds logistic regression model was used to analyze the difference in GBS disability score.

Treatment effect estimates

The coefficient β of the treatment effect and the corresponding standard error (SE) were calculated for the four approaches to analyze outcome, with and without covariate adjustment. The SE of the treatment effect indicates the precision of the calculated treatment effect. The SEs in the proportional odds regression models are expected to be smaller than those in the logistic models. Both trials were analyzed with complete case analysis, ignoring 1 and 4 patients with incomplete baseline data. Statistical analyses were performed in R Statistical Software version 2.15.3 using the *rms* package (R Foundation for Statistical Computation, Vienna, Austria).

RESULTS

Patient population and reference strategies

We analyzed data from 146 patients in the PE vs IVIg trial and 221 patients in the IVIg vs IVIg + MP trial. Both trials were slightly imbalanced with regard to the baseline characteristics. In the IVIg vs IVIg + MP trial the treatment group (with MP) had a probability of 0.60 to improve at least one grade on the GBS disability score compared to a predicted probability of 0.64 in the control group (without MP). So without any treatment, the prognosis of the treatment arm was slightly better. An opposite distribution of baseline covariates between treatment arms is shown in the PE vs IVIg trial. The treatment group (PE) has a higher predicted probability (0.45) to improve at least one grade on the GBS disability score compared to the control group (IVIg; predicted probability 0.41, Table 1).

Regarding the actual outcome, 63 (57%) control patients treated with IVIg and placebo and 74 (67%) patients treated with IVIg and methylprednisolone improved minimal one grade on the GBS disability score after 4 weeks. In the other trial, 25 (34%) control patients treated with PE and 38 (52%) patients receiving IVIg improved minimal one grade on the GBS disability score after 4 weeks.

The treatment under study in both trials had a positive effect on health outcomes. With the reference strategy of logistic regression on a favorable GBS disability scale (0–2) at 4 weeks as outcome, the estimated treatment OR was 1.80 (95% confidence interval (CI) 0.84–3.85, SE 0.39, $p = 0.13$) in the PE vs IVIg trial and 1.69 (95% CI 0.93–3.08, SE 0.31, $p = 0.09$) in the IVIg vs IVIg + MP trial. The treatment effect estimates on one grade improvement were slightly larger (Table 2).

Covariate adjustment

With covariate adjustment, the estimated treatment effect was larger in the IVIg vs IVIg + MP trial, partly as a result of adjustment, which makes the estimates more extreme, and partly

Table 2 | Treatment effect analysis: Unadjusted and adjusted binary and proportional odds logistic regression

		PE vs IVIg trial (n = 146)		IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (n = 221)	
		Unadjusted	Adjusted*	Unadjusted	Adjusted*
Binary logistic regression – GBS disability 3-6 vs 0-2 §	OR (95% CI)	1.90 (0.93 – 3.87)	1.80 (0.84 – 3.85)	1.27 (0.75 – 2.15)	1.69 (0.93 – 3.08)
	SE	0.36	0.39	0.27	0.31
	P-value	0.08	0.13	0.38	0.09
Binary logistic regression – improvement on GBS disability score	OR (95% CI)	2.08 (1.07 – 4.06)	1.95 (0.96 – 4.00)	1.57 (0.91 – 2.71)	1.96 (1.08 – 3.56)
	SE	0.34	0.36	0.28	0.31
	P-value	0.03	0.06	0.11	0.03
Proportional odds logistic regression – reversed GBS disability score at 4 weeks ^	OR (95% CI)	1.76 (0.98 – 3.19)	1.76 (0.98 – 3.19)	1.12 (0.70 – 1.80)	1.41 (0.87 – 2.28)
	SE	0.30	0.30	0.24	0.25
	P-value	0.06	0.06	0.63	0.17
Proportional odds logistic regression – Δ GBS disability score (grades improvement between admission and 4 weeks)	OR (95% CI)	1.93 (1.07 – 3.49)	1.80 (0.99 – 3.27)	1.43 (0.89 – 2.30)	1.34 (0.89 – 2.32)
	SE	0.30	0.30	0.24	0.25
	P-value	0.03	0.05	0.14	0.14

.*Adjustment for age, preceding diarrhea and GBS disability score at admission. § 0 = Healthy / 1 = Minor symptoms / 2 = Able to walk 10m unassisted but not able to run / 3 = Able to walk over 10m open space with help / 4 = Bedridden or chair bound / 5 = Needs ventilation for at least a part of the day / 6 = Dead ^ In order to estimate the treatment effect for a positive outcome, we used the reversed GBS disability score at 4 weeks

because of the imbalance at baseline. Poorer prognosis at baseline for the intervention (IVIg + MP) group implied a +31% increase in the adjusted treatment effect (Table 3). The stratification effect of adjustment was an additional 18% increase in the treatment effect (OR = 1.96). In contrast, the treatment effect was smaller with adjustment for baseline characteristics in the PE vs IVIg trial. The stratification effect increased the treatment effect with 8%, but the better prognosis in the intervention (IVIg) group at baseline reduced the estimated treatment effect by -24%. The net effect was a difference in treatment effect of -16%. These results were similar for all binary and ordinal outcome analyses (Table 2).

Proportional odds analysis

For illustration of the proportional odds analyses we calculated the treatment effect estimates (ORs) for each cut-off of the reversed ordinal scale. The common OR can be interpreted as the pooled estimate of these binary ORs. The treatment under study in both trials had a positive effect on health outcomes in all the ordinal analyses. In the PE vs IVIg trial the ORs over each cut-off were relatively similar (Fig 1C and 1D). The common OR was similar as well, but the SE and CI were smaller. In the IVIg vs IVIg + MP trial, the ORs were more variable (Fig 1A and 1B). The common OR was less extreme compared to ORs for the cut-off used in the reference

Table 3 | Results of unadjusted and adjusted binary logistic regression analysis of the effect of treatment versus control on GBS disability score at four weeks in both PE vs IVIg trial (n = 146) and the IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (n = 221).

	OR	Coefficient	Absolute difference in treatment effect between adjusted and unadjusted	Imbalance between treatment arms	Relative difference in treatment effect between adjusted and unadjusted due to imbalance	Relative difference in treatment effect between adjusted and unadjusted due to stratification
	PE vs IVIg trial					
Unadjusted	2.08	0.73				
Adjusted for age, preceding diarrhea and GBS disability score at admission	1.95	0.67	- 0.06^	-0.12	-16%*	8%#
	IVIg vs IVIg + MP trial					
Unadjusted	1.57	0.45				
Adjusted for age, preceding diarrhea and GBS disability score at admission	1.96	0.67	0.22^	0.14	31%*	18%#

^ Adjusted coefficient–Unadjusted coefficient * Imbalance between treatment arms / Unadjusted coefficient
# (Absolute difference in treatment effect between adjusted and unadjusted—Imbalance between treatment arms) / Unadjusted coefficient.

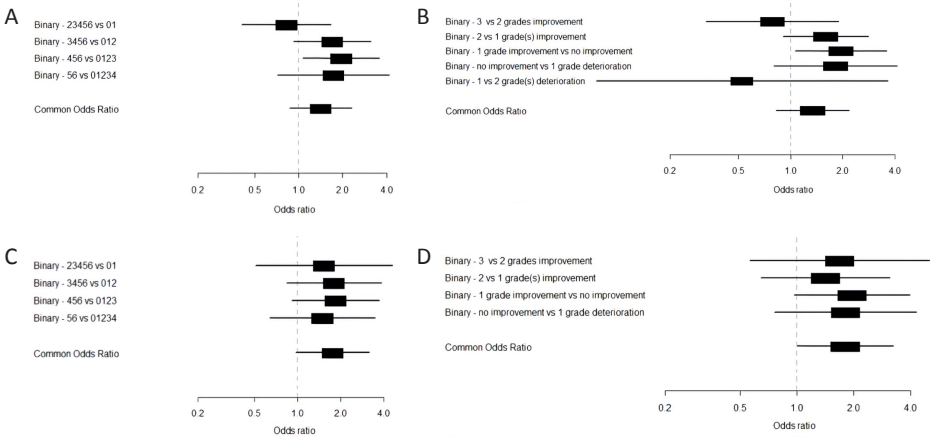

Figure 1 | Treatment effect analysis: forest plots of the adjusted binary and proportional odds logistic regression in the IVIg + placebo vs IVIg + Methylprednisolon (IVIg vs MP) trial (a and b) and PE vs IVIg trial (c and d) show smaller confidence intervals for the common odds ratio compared to the binary estimates

approach (0–2 vs. 3–6 and minimal one grade improvement vs. no improvement). But again, the SE and CI were smaller. This can also be seen in Table 2; in all analyses, the proportional odds

analysis on the GBS disability score after four weeks and on the improvement on the GBS disability score resulted in lower SEs of the treatment effect compared to the binary approaches.

DISCUSSION

In this study we assessed the potential benefit of the use of covariate adjustment and proportional odds analysis in RCTs compared to the conventional method, by reanalyzing two GBS trials. We found that covariate adjustment increased the estimated treatment effect in one trial, and decreased the estimated treatment effect in the other trial, due to imbalances in baseline characteristics between the treatment arms. Although such imbalances are fully due to chance if a proper randomization procedure is followed, our results illustrate that their impact on interpretability of treatment effect estimates can be substantial and can be different in several study settings. We found that the proportional odds analysis resulted in lower standard errors and thus smaller confidence intervals of the treatment effect estimate compared to the conventional method of logistic regression on dichotomized outcome measures. Thus, dichotomization of ordinal outcome measures does not merit application. In future trials in rare and heterogeneous neurological diseases like GBS both covariate adjustment and proportional odds analysis are advised.

Covariate adjustment

On expectation, covariate adjustment leads to more extreme treatment effect estimates and larger standard errors for non-linear regression models.[21] The p values are a function of the treatment effect estimates and standard error. With covariate adjustment the increase in treatment effect estimate will outweigh increased in standard error and the p values will be lower compared to unadjusted analysis.[21]

Indeed, we found increased standard errors in all adjusted analyses compared to the unadjusted analyses. The better prognosis in the treatment group decreased the treatment effect estimate β after covariate adjustment in the PE vs IVIg trial. In the IVIg vs MP trial, the treatment group had a lower probability of favorable outcome. Therefore, in the IVIg vs MP trial covariate adjustment led to a larger β and a smaller p value.

Covariate adjustment increases statistical power, despite the larger standard error.[1,7] When there are no baseline imbalances, the adjusted conditional estimates will be more extreme than the unadjusted marginal estimates.[22] However, the size and the direction of the difference between the unadjusted and adjusted estimates are dependent on the strength of the prognostic factors and the imbalance in baseline risk between the treatment- and control group in the specific trial and this is shown in our study. When investigating the effectiveness of a medical

intervention in rare and heterogeneous neurological diseases, such as GBS, one has to deal with small sample sizes. We therefore recommend performing covariate adjustment in future trials in rare and heterogeneous neurological diseases. For GBS this covariate adjustment should be applied with known predictors for (functional) outcome, specifically age, preceding diarrhea, GBS disability score and MRC sum score.[18,20]

The outcome 'minimal one grade improvement' implicitly involves a form of covariate adjustment. The baseline disease severity of the patient is taken into account in the analysis by estimating improvement for each patient from his or her own starting position at admission (Table 4). This principle of a measure of change between baseline and follow up seems attractive to control for baseline imbalance. However, analyzing change does not control for baseline imbalance because of regression to the mean[23,24]; baseline values are negatively correlated with change because patients with high scores at baseline generally improve more than those with low scores.[25] Therefore covariate adjustment with the absolute baseline value is still preferable over implicitly taking into account baseline severity in the outcome measure 'improvement'. Moreover, disease severity at baseline is not the only covariate we could adjust for. Especially, the age of the patient will be an important covariate in most neurological diseases.

Table 4 | Characteristics of four methods of treatment effect analysis in GBS trials. Approach in bold is the recommended approach. *Only baseline GBS disability score, no other covariates.

	Takes into account baseline imbalance	Takes into account ordinal nature of the outcome measure
Unadjusted binary logistic regression on cutoff for GBS disability score	NO	NO
Adjusted binary logistic regression on cutoff for GBS disability score	YES	NO
Unadjusted binary logistic regression on ≥ 1 grade improvement on GBS disability score	PARTLY*	NO
Adjusted binary logistic regression on ≥ 1 grade improvement on GBS disability score	YES	NO
Unadjusted proportional odds logistic regression on GBS disability score	NO	YES
Adjusted proportional odds logistic regression on GBS disability score	**YES**	**YES**
Unadjusted proportional odds logistic regression on Δ GBS disability score	PARTLY*	YES
Adjusted proportional odds logistic regression on Δ GBS disability score	YES	YES

Thus, in general, ignoring baseline imbalance between treatment arms in trials may cause invalid conclusions on both the magnitude and significance of the treatment effect estimate compared

to analysis using covariate adjustment. The impact on interpretability of treatment effect estimates can be substantial and can be different in several study settings. When designing a trial, the analysis plan should be precisely pre-specified. Also, the covariates that will be used for adjustment should be pre-specified. Previous studies have shown that the stronger the relation of the covariates with outcome, the larger the increase in statistical power with covariate adjustment will be.[5,26,27] In GBS, predictors of outcome are relatively well known[19,20] and therefore pre-specifying important baseline variables for covariate adjustment is possible in GBS trials.

Proportional odds analysis

It is evident that the GBS disability scale is not a linear scale. For example, improvement from "needs ventilation for at least a part of the day" to "bedridden or chair bound" is not the same improvement as the improvement from "able to walk over 10m open space with help" to "able to walk 10m unassisted but not able to run". However, whether or not the ordinal outcome under study is a linear scale is not relevant for the validity of the proportional odds analysis. Proportional odds analysis merely requires ordering of outcomes. The proportional odds analysis estimates the treatment effect on each cut-off of the scale, instead of estimating the treatment effect on the difference between the averages scores in the treatment arms, as linear regression. The proportional odds model results in a common OR, which is interpretable as a pooled OR over all ORs for the different cut-offs. The common OR is formally valid if the ORs for each cut-off are the same (the proportional odds assumption). We can, however, interpret the common OR as a summary measure of the treatment effect, even if the ORs differs slightly per cut-off.[12,28] The common OR can also be interpreted as the average shift over the total ordinal outcome scale caused by the treatment under study.[10-13] Moreover, simulation studies have shown that ordinal analysis is more efficient than binary analysis, even if the proportional odds assumption is violated.[11] Because the ordinal analysis uses the full ordinal outcome scale instead of one dichotomy, the variability will be smaller compared to binary analysis. This was confirmed in our study, where the proportional odds resulted in lower standard errors compared to the binary approaches. Although the importance of applying proportional odds analysis already has been assessed in other diseases, it is still relevant to study this for specific cases like GBS. For example it is important to have more insight in the effect of treatment on the different cut-offs for the specific ordinal outcome measure, in this case the GBS disability score, and see if the proportional odds assumption holds.

In the PE vs IVIg trial, the ORs for each cut-off were very similar and as a result the common OR was also similar. Thus, with the smaller SE, the p value was lower. In contrast, in the IVIg vs IVIg + MP trial, the ORs were more scattered. One explanation is chance: the ORs for the different cut-offs are uncertain, especially at the tails of the outcome scale where numbers are usually small. However, almost all binary ORs have confidence intervals that overlap. Another explanation is that the effect is truly different for different cut-offs, although this is clinically unlikely.

The cut-off chosen in the reference approach in the analysis of improvement appeared to be the most optimal cut-off from a statistical perspective, since it was the only cut-off resulting in a significant treatment effect.

However, if we assume a relatively constant treatment effect across the different cut-offs of an ordinal outcome scale, it is unpredictable which cut-off will show the strongest effect. Therefore, the ordinal analysis is a 'safe' choice and the common OR is a fair representation of the effect of treatment on the ordinal outcome compared to the binary approach, because it takes into account improvement over all levels of the GBS disability score. Since it is also more efficient, we recommend the use of the full ordinal outcome scale in future trials in rare and heterogeneous neurological diseases. In observational studies, ordinal analyses could be combined with propensity score methods to maximize statistical power.

Limitations

Patients with missing covariate data were excluded from the analyses. Data from 367 patients were analyzed rather than 372 patients in the original analyses. We did not assess heterogeneous treatment effects according to baseline risk, which could influence the ability of covariate adjustment to improve the statistical power in an RCT. In this study we only investigated GBS which may not fully be representative for other neurological disorders, although covariate adjustment and proportional odds analysis have shown advantages in other fields, such as stroke and traumatic brain injury.[3,4,7,12]

Conclusion and implications

Covariate adjustment corrects for baseline imbalance and increases power. Proportional odds analysis optimally exploits the ordinal nature of outcome scales. A combined approach is advised for reliable and efficient estimation of treatment effects in small RCTs in rare and heterogeneous diseases like GBS.

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3.2

Second IVIg course in Guillain-Barré syndrome patients with poor prognosis (SID-GBS trial): protocol for a double-blind randomized, placebo-controlled clinical trial.

Christa Walgaard
Bart C. Jacobs
Hester F. Lingsma
Ewout W. Steyerberg
David R. Cornblath
Pieter A. van Doorn
For the Dutch GBS Studygroup

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ABSTRACT

One course of intravenous immunoglobulins (IVIg) of 2 g/kg is standard treatment in Guillain-Barré syndrome (GBS) patients unable to walk independently. Despite treatment some patients recover poorly, in part related to rapid consumption of IVIg, indicating that they may benefit from a second course of IVIg. The aim of the study is to determine whether a second course of IVIg, administered 1 week after start of the first course in patients with GBS and predicted poor outcome improves functional outcome on the GBS disability scale after 4 weeks. Secondary outcome measures include adverse events (AEs), Medical Research Council sumscore and GBS disability score after 8, 12, and 26 weeks, length of hospital and ICU admission, mortality, and changes in serum IgG levels. GBS patients of 12 years and older with a poor prognosis, based on the modified Erasmus GBS outcome score (mEGOS) at 1 week after start of the first IVIg course are eligible for randomization in this double-blind, placebo-controlled (IVIg or albumin) clinical trial. This study will determine if a second course of IVIg administered in the acute phase of the disease is safe, feasible, and effective in patients with GBS and a poor prognosis. This Dutch trial is registered prospectively as NTR 2224 in the Netherlands National Trial Register (NTR) which is the Primary Registry in the WHO Registry Network for the Netherlands.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy, and the most frequent cause of acute neuromuscular weakness affecting 0.81 to 1.89 persons per 100 000 per year worldwide.[1,2] GBS is characterized by rapidly progressive flaccid paresis with a highly variable clinical course and outcome. Patients may develop mild limb paresis only, whereas others develop oculomotor, facial, and bulbar weakness, respiratory failure, and tetraparalysis and remain bedbound for months.[2] Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are proven effective treatments for GBS.[3,4] Currently, IVIg in a dosage of 2 g/kg in 2 to 5 days, has become first choice treatment for patients with GBS who are unable to walk unaided or worse and who are still within the first 2 weeks from onset of weakness.[2] The outcome of GBS after 6 or 12 months however has not, or only marginally been improved since the introduction of PE and IVIg.[5-8] Despite these therapies, 25% progress during treatment, 20% require mechanical ventilation, 20% remain unable to walk after 6 months, and 3% to 10% die of GBS. Patients with severe GBS and a poor prognosis may potentially benefit from additional or more aggressive therapy.

There are several arguments suggesting that GBS patients with a poor prognosis after the first course of IVIg may benefit from a second course:

1. About 10% have a "treatment-related clinical fluctuation" that usually respond to a second course of IVIg.[9]
2. A second course of IVIg is suggested to be effective in two small uncontrolled series of severe unresponsive GBS patients.[10,11]
3. A smaller increase in serum IgG level after IVIg treatment is related with poor recovery after 6 months.[12]

We hypothesized that GBS patients with a poor prognosis after a first course of IVIg may benefit from a second course of IVIg when administered within the first weeks after onset of disease, when nerve damage is most likely still reversible.

METHODS

Patients

The annual incidence of GBS in the Netherlands is 1.2 per 100.000 persons,[13] so it is estimated that around 200 persons will develop GBS yearly. Neurologists in all hospitals in the Netherlands (91 hospitals in 2008) were contacted and asked to participate in this trial. All GBS patients of 12 years or older, within 2 weeks from onset of weakness and in need of IVIg treatment, according to the treating neurologist, in a standard dosage of 2 g/kg in 2 to 5 consecutive days are

potentially eligible for this study after obtaining informed consent. The inclusion and exclusion criteria are shown in Table 1.[14]

Table 1 | Inclusion and exclusion criteria.

Inclusion criteria
A. To be included in this GBS study
• Patients are diagnosed with GBS.[14]
• There is an indication to start IVIg (irrespective of co-treatment with MP therapy):
1. Patient is unable to walk unaided for >10 m (grade 3-5 of the GBS disability scale)
or
2. There is otherwise an indication to start IVIg (with or without MP) treatment according to the treating neurologist.
• Onset of weakness due to GBS is less than 2 wks ago.
• Signed informed consent.
B. To be randomized in the second IVIg course phase (RCT), patients must fulfill the following criteria:
• First IVIg (with or without MP) treatment with (in principal) Nanogam started within 2 weeks from onset of weakness.
• IVIg treatment has been 2 g/kg administered in 2-5 d.
• Poor prognosis based upon the modified EGOS (mEGOS 6-12) at day 7 (range to 8-9 d) after start of first IVIg treatment.
Exclusion criteria
A. To enter this GBS study
Age less than 12 y.
• Patient known to have a severe allergic reaction to properly matched blood products or plasma products.
• Pregnancy or breastfeeding.
• Patient known to have a selective IgA deficiency.
• Patient shows clear clinical evidence of a polyneuropathy caused by for example, diabetes mellitus (except mild sensory), alcoholism, severe vitamin deficiency, porphyria.
• Patient received immunosuppressive treatment (eg, azathioprine, cyclosporine, mycofenolaat mofetil, tacrolimus, sirolimus, or >20 mg prednisolone daily) during the last month.
• Patient known to have a severe concurrent disease, like malignancy, severe cardiovascular disease, AIDS, and severe COPD.
• Inability to attend follow-up during 6 mo.
B. Relative contra-indications for second IVIg course[a]:
• Patients known to have severe kidney dysfunction (GFR below 40 mL/min).
• Pre-existing risk factors of thrombo-embolic complications or severe ischemic heart disease.

Abbreviations: AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; mEGOS, modified Erasmus GBS outcome score; MP, methylprednisolon; RCT, randomized clinical trial. [a] These patient groups run a greater risk (although they are still rare) to develop serious complications like acute tubular necrosis and thrombo-embolic events. To prevent this, the patient should be pre-treated with fluids and infusion rate of the trial medication must be adjusted.

Modified Erasmus GBS outcome score (EGOS)

In the study we used the modified EGOS to select patients with poor prognosis (Table 2 and Figure 1).[15] Modified Erasmus GBS outcome score (mEGOS) was used at 1 week after start of the first IVIg course. The model uses age, preceding diarrhea, and the Medical Research Council sumscore (a score often used in GBS research) as predictors for outcome. The model predicts outcome at 4 weeks and 6 months. The mEGOS has very good predictive power (Area Under the Receiver Operating Characteristic [ROC] Curve [AUC] = 0.87) for prediction of outcome after 4 weeks, indicating very good discriminative ability. The mEGOS was recently validated in a Japanese cohort and performed equally good in this cohort, underlining the validity of the model.[16] In the Second IVIg Dose-Guillain-Barré syndrome (SID-GBS) trial an mEGOS score of at least 6 was used as a cutoff for poor prognosis. Of the patients with an mEGOS of ≥6 in the Erasmus GBS databank cohort (n = 394), 85% were unable to walk unaided after 4 weeks and 35% were unable to walk unaided after 6 months.

Table 2 | Modified Erasmus GBS outcome score (mEGOS).

Factor	Category	Score
Age (years)	≤40	0
	41-60	1
	>60	2
Diarrhea	No	0
	Yes	1
MRC sumscore[a] (1 wk after inclusion)	51-60	0
	41-50	3
	31-40	6
	0-30	9
mEGOS		0-12

Abbreviation: GBS, Guillain-Barré syndrome; MRC, Medical Research Council. [a] Bilateral m.deltoideus, m.biceps, wrist extensors, m.iliopsoas, m.quadriceps, m.tibialis anterior (range 0-60).

Study design

A double-blind randomized placebo-controlled trial design was used in selected patients with a poor prognosis (mEGOS 6-12). In patients with a good prognosis (mEGOS 0-5) the study has an observational design. The prognosis (mEGOS) must preferentially be assessed 7 days after start of the first IVIg course, with a range to 8 or 9 days. Trial medication needs then to be started within 24 hours when indicated according to the mEGOS score (Figure 2). The IVIg treated GBS patients with a good prognosis (mEGOS 0-5) at day 7 are not randomized. These patients were also followed prospectively. This allows us to compare outcomes between patients with a good prognosis and those with a poor prognosis randomized to the treatment or control arm, and to further improve mEGOS with contemporary data.

Treatment

Patients with the poorest prognosis based upon the mEGOS (score 6-12) after the first (standard) IVIg course are randomized to get a second course of IVIg (Nanogam) in a dosage of 0.4 g/kg (=8 mL/kg) for 5 days or placebo (Albumin 4%, GPO) in a dosage of 8 mL/kg for 5 days. Patients with a good prognosis at day 7, with a range to 8 or 9 days, receive no additional treatment in the context of the trial (Figure 1). The local principal investigators use a web-based randomization procedure (Clinical Trial Center Maastricht; CTCM). The randomization is performed with randomization blocks (six patients per block) into two groups. Randomization is stratified according to medical center. Randomization is double-blind. The pharmacist in each center has a randomization list and allocations are sent to the pharmacies after randomization. This study is executed exclusively in the Netherlands, mainly because Sanquin blood supply, one of the subsidizing institutions of this study, supplies their IVIg (Nanogam) only in the Netherlands. The Netherlands seems suited to perform such a trial because of the short distances; according to treatment allocation Sanquin sends IVIg or albumin to the local pharmacy, who prepares the trial medication in a blinded fashion using a standardized protocol. This process should take place on the same day.

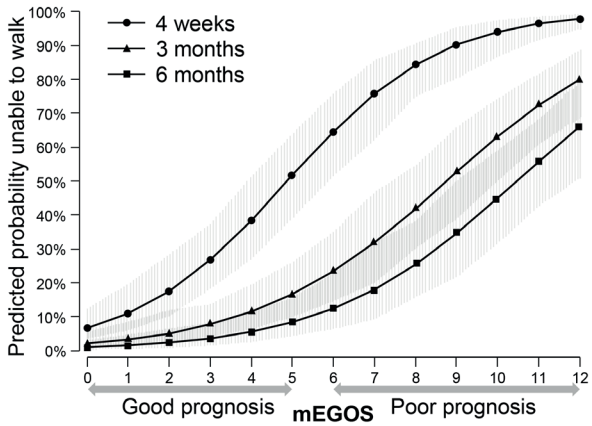

Figure 1 | Predicted probability being able to walk at 4 weeks, 3 months and 6 months according to modified Erasmus GBS outcome score (mEGOS). Patients with mEGOS 6 to 12 will be selected for randomization.

Study endpoints

The primary endpoint for evaluating the efficacy of treatments in GBS in most trials was based on the GBS disability at 4 weeks after start of treatment.[8,17-19] Therefore, we will also use the GBS disability scale at 4 weeks as primary outcome in this trial. The primary analysis will be proportional odds model comparing the GBS disability score at 4 weeks between the treatment groups, with adjustment for the mEGOS at randomization. Secondary study endpoints are functional outcome and muscle strength after 8, 12, and 26 weeks, the percentage of patients

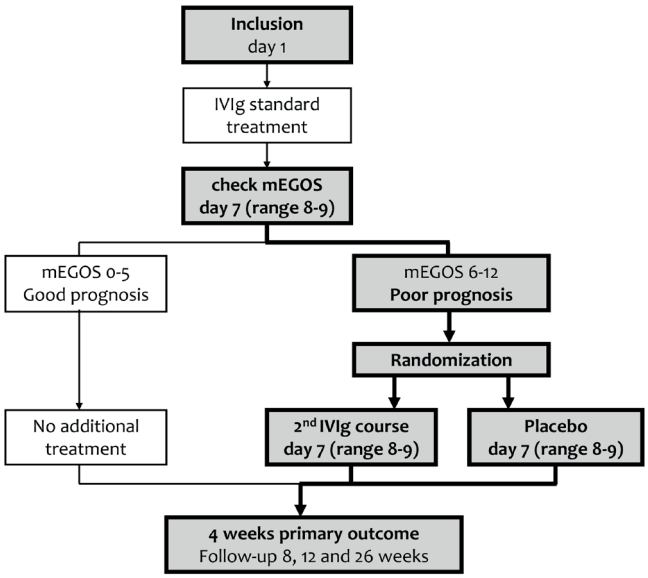

Figure 2 | Trial flowchart

needing artificial ventilation, number of days on respirator, number of days in an intensive care unit, mortality, number of days to hospital discharge, percentage of patients with secondary deterioration due to treatment-related fluctuations (TRF), adverse events (AEs), and serum IgG levels at different time points. Furthermore, all AEs reported spontaneously by the patient or observed by the investigators will be recorded, and all serious adverse events (SAEs) will be reported to the accredited Independent Review Board that approved the protocol. Both AEs and SAEs will be compared between the randomized groups (placebo vs second IVIg course) using descriptive statistics.

Study procedures

When patients are included in the study they will undergo the following extra procedures;

- Throat swaps

To identify evidence of Mycoplasma pneumoniae, because a relation is described between M. pneumoniae infection and GBS.[20]

- Blood collection

Blood collection will take place before start of standard IVIg treatment (visit 1), after standard IVIg treatment (visit 2), after 2 weeks (visit 3), after 4 weeks (visit 4) and after 3 months (visit 6).

- Cerebrospinal fluid (CSF) collection

At admission virtually all patients undergo a lumbar puncture as part of the standard medical workup; extra CSF will be collected for the SID-GBS study.

- Nerve conduction studies

Nerve conduction studies were not mandatory for this study but are performed when needed in the standard work-up according to local standard protocols. The participating neurologists were asked to perform nerve conduction studies according to an electrophysiology guideline, which was developed in a way that a minimum set of nerves is tested to enable classification of electrophysiological data according to Hadden et al.[21]

Hemolysis

In 2015 an amendment to the protocol was made due to a publication in which hemolytic anemia is described in three out of five GBS patients who received two courses of IVIg within a short sequence.[22] It was suggested that this may be caused by the presence of anti-A and anti-B blood type IgG antibodies present in IVIg derived from 0-type blood donors. Since this amendment, extra laboratory measurements on blood samples (in randomized patients only) were asked to conduct to trace possible hemolysis; Hb, Ht, haptoglobine, lactate dehydrogenase, reticulocytes, bilirubin, and direct Coombs test. Blood group will also be determined. Retrospectively we collected information about already included and randomized patients and no evidence for hemolytic anemia was found so far in our cohort.

Study monitoring

Sanquin Plasma Products has developed monitoring and auditing procedures. Monitors or delegates of Sanquin Plasma Products monitor the site, in order to comply with Good Clinical Practice (GCP) guidelines. All records from randomized patients are monitored. The expected average monitoring frequency is 6 months, or more frequent, if necessary, by personal visit. The pharmacy will be visited once a year or more frequent, if necessary. The hospital laboratory will be visited when required. Checking of the case report forms for completeness and clarity, and cross-checking with source documents in the presence of the investigator—giving due consideration to data protection and medical confidentiality—will be required.

Statistical analysis

All patients who were randomized and trial medication was actually started will be included in an intention-to-treat analysis. Additionally there will be a separate analysis on all the randomized patients, irrespective of trial medication was started. Outcomes will be compared between patients who received a second IVIg course and patients who received placebo. The primary analysis will be a proportional odds regression model with the full GBS disability scale as outcome. Scores on this ordinal scale will be compared between groups, with adjustment for

the mEGOS after the first IVIg course. The treatment effect will be expressed as an adjusted proportional odds ratio with 95% confidence interval.

- ***Proportional odds model***

The primary endpoint is the full GBS disability scale at 4 weeks as an ordinal outcome, instead of a dichotomization of the GBS disability scale (eg, GBS disability score of ≤2 vs >2). Analysis will be with a proportional odds regression model.23 The proportional odds model provides a more sensitive analysis than would be possible by arbitrarily dichotomizing the outcome variable and does so without imposing unverifiable assumptions regarding the structure of the data.[23] The disadvantage is that we have to make the assumption of proportional odds, that is, that the treatment effect (as an odds ratio) is similar across all possible cut-offs for the GBS disability scale. This assumption will be assessed by a test for heterogeneity of effect across cut-offs.

- ***Covariate adjustment***

We will use covariate adjustment, which is an established approach to deal with variation between patients in baseline risk and to increase statistical power in clinical phase III trials.[24] Using covariate adjustment we can also compare outcomes from the patients who receive a second IVIg course with the other included patients with good and poor prognosis. Unadjusted analysis can be expressed by the following formula, in which α indicates the intercept and β represents the regression coefficient for the treatment:

Log odds (GBS disability scale) = $\alpha + \beta \times$ treatment

The covariate-adjusted model uses mEGOS after first IVIg treatment as well as the treatment variable:

Log odds (GBS disability scale) = $\alpha + \beta \times$ treatment + $\beta 1 \times$mEGOS

The increase in statistical power of covariate adjustment depends on the predictive strength of the baseline characteristics; this is difficult to quantify a priori, but the modified EGOS has a very good predictive power (AUC = 0.87).

- ***Sample size calculation***

For the power calculation, we start from a crude comparison of the proportion of patients being able to walk unaided between the two treatment groups. If we assume a 20% difference in the proportion of patients being able to walk unaided between the patients with and without treatment we would need to randomize 145 patients with a poor prognosis (α = 0.05 and power = 0.80). We expected that covariate adjustment and the use of the ordinal outcome result in a reduction in required sample size of 40% to 50%.[25] This leads to a required sample size of 60% of 145 patients, which is a total of 88 patients

with a poor prognosis who will be randomized to receive a second course of IVIg (n = 44) or placebo (n = 44). Given the observed percentage of patients with poor prognosis in a historical cohort derived from previous trials, we initially expected that 50% of the included patients would have a poor prognosis and could be randomized in the SID-GBS trial. However, due to the inclusion of GBS patients with a broader range of severity, and the current day to day clinical practice to start IVIg also in some patients still being still able to walk without assistance, the percentage of all GBS patients treated with IVIg and having a poor prognosis at day 7 is lower (about 30%). This led to a longer period of inclusion.

CONCLUSION

In the SID-GBS trial the effects and safety of a second IVIg course, administered in the acute phase of the disease in a selected patient group with a poor predicted outcome based on the mEGOS prognostic model will be studied. If a second IVIg course is beneficial, this will result in an improvement of the outcome of this disease for the first time since the introduction of PE as the first treatment in 1985[26,27] and the introduction of a standard course of IVIg for treatment of GBS.[19] The first patient was included and randomized in the SID-GBS trial in February 2010, in June 2018 inclusion was stopped after 99 randomizations. It is expected that the first results of the SID-GBS randomized clinical trial will be available early 2019.

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3.3

Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial

Christa Walgaard, Bart C. Jacobs, Hester F. Lingsma, Ewout W. Steyerberg, Bianca van den Berg, Alex Y. Doets, Sonja E. Leonhard, Christine Verboon, Ruth Huizinga, Judith Drenthen, Samuel Arends, Ilona Kleine Budde, Ruud P. Kleyweg, Krista Kuitwaard, Marjon F.G. van der Meulen, Johnny P.A. Samijn, Frederique H. Vermeij, Jan B.M. Kuks, Gert W. van Dijk, Paul W. Wirtz, Filip Eftimov, Anneke J. van der Kooi, Marcel P.J. Garssen, Cees J. Gijsbers, Maarten C. de Rijk, Leo H. Visser, Roderik J. Blom, Wim H.J.P. Linssen, Elly L. van der Kooi, Jan J.G.M. Verschuuren, Rinske van Koningsveld, Rita J.G. Dieks, H. Job Gilhuis, Korné Jellema, Taco C. van der Ree, Henriette M.E. Bienfait, Catharina G. Faber, Harry Lovenich, Baziel G.M. van Engelen, Rutger J. Groen, Ingemar S.J. Merkies, Bob W. van Oosten, W. Ludo van der Pol, Willem D.M. van der Meulen, Umesh A. Badrising, Martijn Stevens, Albert-Jan J. Breukelman, Casper P. Zwetsloot, Maaike M. van der Graaff, Marielle Wohlgemuth, Richard A.C. Hughes, David R. Cornblath, Pieter A. van Doorn, on behalf of the Dutch GBS Study Group

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SUMMARY

Background

Treatment with one standard dose (2 g/kg) of intravenous immunoglobulin is insufficient in a proportion of patients with severe Guillain-Barré syndrome. Worldwide, around 25% of patients severely affected with the syndrome are given a second intravenous immunoglobulin dose (SID), although it has not been proven effective. We aimed to investigate whether a SID is effective in patients with Guillain-Barré syndrome with a predicted poor outcome.

Methods

In this randomised, double-blind, placebo-controlled trial (SID-GBS), we included patients (≥12 years) with Guillain-Barré syndrome admitted to one of 59 participating hospitals in the Netherlands. Patients were included on the first day of standard intravenous immunoglobulin treatment (2 g/kg over 5 days). Only patients with a poor prognosis (score of ≥6) according to the modified Erasmus Guillain-Barré syndrome Outcome Score were randomly assigned, via block randomisation stratified by centre, to SID (2 g/kg over 5 days) or to placebo, 7–9 days after inclusion. Patients, outcome adjudicators, monitors, and the steering committee were masked to treatment allocation. The primary outcome measure was the Guillain-Barré syndrome disability score 4 weeks after inclusion. All patients in whom allocated trial medication was started were included in the modified intention-to-treat analysis. This study is registered with the Netherlands Trial Register, NTR 2224/NL2107.

Findings

Between Feb 16, 2010, and June 5, 2018, 327 of 339 patients assessed for eligibility were included. 112 had a poor prognosis. Of those, 93 patients with a poor prognosis were included in the modified intention-to-treat analysis: 49 (53%) received SID and 44 (47%) received placebo. The adjusted common odds ratio for improvement on the Guillain-Barré syndrome disability score at 4 weeks was 1·4 (95% CI 0·6–3·3; p=0·45). Patients given SID had more serious adverse events (35% vs 16% in the first 30 days), including thromboembolic events, than those in the placebo group. Four patients died in the intervention group (13–24 weeks after randomisation).

Interpretation

Our study does not provide evidence that patients with Guillain-Barré syndrome with a poor prognosis benefit from a second intravenous immunoglobulin course; moreover, it entails a risk of serious adverse events. Therefore, a second intravenous immunoglobulin course should not be considered for treatment of Guillain-Barré syndrome because of a poor prognosis. The results indicate the need for treatment trials with other immune modulators in patients severely affected by Guillain-Barré syndrome.

Funding

Prinses Beatrix Spierfonds and Sanquin Plasma Products.

INTRODUCTION

Guillain-Barré syndrome is an immune-mediated polyradiculoneuropathy, which affects 0·81–1·89 per 100 000 people annually worldwide.[1] Guillain-Barré syndrome is usually a monophasic disease with rapidly progressive limb weakness.[2] The clinical severity, course, and outcome are variable.[1] Intravenous immunoglobulin and plasma exchange are proven effective treatments.[3,4] Even with standard intravenous immunoglobulin treatment, about 20% of patients remain unable to walk after months. In 20–30% of patients, mechanical ventilation is needed, 3–7% die, and many have persistent residual complaints such as fatigue and pain.[5] Patients with a poor prognosis early in their disease course might gain particular benefit from additional treatment. A second intravenous immunoglobulin dose (SID), administered early in the course of disease, before severe or irreversible nerve damage has occurred, might be beneficial, although there is scant evidence to support this approach.[6,7]

In current practice, about a quarter of patients with Guillain-Barré syndrome given intravenous immunoglobulin who show no clinical improvement are re-treated with intravenous immunoglobulin.[6] This practice could be based on results from a small uncontrolled case series of patients with severe Guillain-Barré syndrome and a phase 2 trial suggesting that a higher dose of intravenous immunoglobulin was more beneficial than a lower dose.[8-10] Another argument that repeated intravenous immunoglobulin doses might be effective comes from the observation that about 10% of patients with Guillain-Barré syndrome have a so-called treatment-related fluctuation, which seems to respond to a SID.[11] Additionally, patients have a variable increase in serum IgG concentration after a standard dose of intravenous immunoglobulin, and a low IgG increase is associated with poor outcome, indicating that these patients might benefit from additional intravenous immunoglobulin treatment.[12] However, intravenous immunoglobulin is costly; moreover uncommon severe side-effects might be more frequent when administered repeatedly. We aimed to evaluate the effect of SID in patients with Guillain-Barré syndrome with poor prognosis.

METHODS

Study design and participants

We did a double-blind, randomised, placebo-controlled phase 3 trial (SID-GBS) in patients with Guillain-Barré syndrome with a poor prognosis. The protocol of this trial has been published.[13] Patients were included from 59 hospitals in the Netherlands (a list of participating centres and number of inclusions per centre is available in the appendix (p 17). Patients aged 12 years or older, diagnosed with Guillain-Barré syndrome, and with an indication for intravenous immunoglobulin treatment according to the treating neurologist, were potentially eligible for inclusion in the trial.[2] Full eligibility criteria are available in the appendix (p 18).

Research in context

Evidence before this study

A PubMed search for articles in English, published from database inception up until May 22, 2020, for "[Guillain-Barré syndrome], and [second IVIg course]", "[Guillain-Barré syndrome], and [repeated intravenous immunoglobulin]", and "[Guillain-Barré syndrome], and [second cycle immunoglobulin]" identified four case reports, two case series, and one observational study in which additional intravenous immunoglobulin treatment was investigated in patients with Guillain-Barré syndrome with a severe disease course. The case reports and case series (n=11) suggested additional benefit from a second intravenous immunoglobulin course. The observational study based on patients with Guillain-Barré syndrome enrolled in the international Guillain-Barré syndrome outcome study selected patients with a poor predicted outcome according to the modified Erasmus GBS Outcome Scale prognostic model. No difference in outcome was found between patients given one intravenous immunoglobulin course (n=199) or two intravenous immunoglobulin courses (n=38). None of these studies reported complications possibly attributable to the additional intravenous immunoglobulin treatment. Not all patients in these studies received an early second intravenous immunoglobulin course and publication bias could have played an important role in the positive findings.

Added value of this study

The SID-GBS trial is the first randomised, placebo-controlled, double-blind trial investigating the added value of a second intravenous immunoglobulin course in patients with Guillain-Barré syndrome with a poor predicted outcome, to our knowledge. The study showed that a second intravenous immunoglobulin course in these patients does not have a clinically meaningful benefit for recovery. All secondary endpoints did not differ between treatment groups. This trial was the first controlled study to show a possible harmful effect of a second intravenous immunoglobulin course.

Implications of all the available evidence

A second intravenous immunoglobulin course in patients with Guillain-Barré syndrome with a poor prognosis is not recommended. The results are based on the absence of evidence for a better outcome and on the higher frequency of serious adverse events, including severe thromboembolic complications. Although the absence of evidence does not equate to evidence of ineffectiveness, it is very unlikely that a second intravenous immunoglobulin course will have a clinically relevant positive effect.

Patients were randomly allocated (1:1) to receive SID or placebo for 5 days, which was administered at 7–9 days after the start of the first standard intravenous immunoglobulin treatment (2 g/kg administered over 5 consecutive days). Interim monitoring was done after 36 randomisations.

All patients (poor and good prognosis) were included on the first day of their standard intravenous immunoglobulin treatment. We used the modified Erasmus GBS Outcome Scale (mEGOS) 7–9 days after start of the standard intravenous immunoglobulin dose to select patients with a poor prognosis.[7] Only patients with a poor prognosis were randomly assigned to SID or placebo. The mEGOS prognostic model ranges from 0 (best prognosis) to 12 (worst prognosis) and uses age, preceding diarrhoea, and the Medical Research Council (MRC) sumscore[14] as clinical predictors of outcome (appendix pp 9, 19).[7] In this trial, an mEGOS of six or more was used as the cutoff for poor prognosis. Using this cutoff, we expected to select about 50% of the included patients for random assignment.

The trial was approved by the ethics committee of all participating centres, and all patients provided written informed consent before random assignment.

Randomisation and masking

A web-based computerised random number generator from an external party (Clinical Trial Centre Maastricht) allocated treatment in a 1:1 ratio by block randomization (six patients per block with the block size unknown to local sites), stratified according to participating centre. Placebo (albumin) was matched to the study drug by volume (8 mL/kg) and fluid aspect (due to proteins in intravenous immunoglobulin and albumin, both are slightly foaming liquids). As the colour of intravenous immunoglobulin can differ between batches, the bag (ethylene vinyl acetate) containing the trial medication was concealed using aluminum foil and opaque connecting lines were used to mask study staff. Patients, outcome adjudicators, monitors, and the steering committee were masked to treatment allocation.

Procedures

Patients with a poor prognosis were randomly assigned to receive either SID (Nanogam 50 mg/mL, Sanquin Plasma Products, Amsterdam, Netherlands) or placebo (albumin 4%, pasteurised plasma protein solution until June, 2012, and Albuman 40 g/L from June, 2012, onwards, Sanquin Plasma Products) in a dose of 8 mL/kg, both for 5 days. Patients with a good prognosis (mEGOS 0–5) were not randomly assigned, but had otherwise the same follow-up and outcome parameters assessment as the randomly assigned participants. All patients underwent clinical assessments at the start of standard intravenous immunoglobulin treatment; at week 1 (randomisation); weeks 2 and 4 (primary endpoint); and weeks 8, 12, and 26 after start of standard intravenous immunoglobulin treatment. Adverse events were assessed at every study visit. At study entry, blood was collected and serum was stored for detection of antiganglioside antibodies, antibodies to cytomegalovirus, Epstein-Barr virus, hepatitis E, and *Campylobacter jejuni* using routine diagnostic assays.[15-18] Also IgG and albumin concentrations were measured in serial serum samples (baseline, 1, 2, 4, and 13 weeks). Nerve conduction studies were reviewed in the coordinating centre by two masked trial electrophysiologists (JD and SA) and classified according to the Hadden criteria.[19] All patients were given standard supportive care as recommended by guidelines, including low molecular weight heparin.[20]

Outcomes

The primary outcome was Guillain-Barré syndrome disability scale21 score at 4 weeks after the start of standard intravenous immunoglobulin treatment. This disability scale is the most frequently used clinical outcome measure in Guillain-Barré syndrome trials. It is a seven-point scale ranging from 0 (no symptoms) to 6 (death).[4] Prespecified secondary outcomes were assessed at weeks 4, 8, 12, and 26, and comprised the Guillain-Barré syndrome disability scale,[21] improvement of at least one grade on the Guillain-Barré syndrome disability scale,[21] the MRC

sumscore,[14] the Overall Neuropathy Limitations Scale,[22] the percentage of patients needing artificial ventilation, duration of artificial ventilation, intensive care admission and hospital admission, mortality, percentage of treatment-related fluctuations, and serum IgG concentrations at subsequent timepoints. Adverse events and serious adverse events were collected by treating physicians, according to the International Conference on Harmonization Good Clinical Practice guidelines, and compared between the randomised groups using descriptive statistics.

Statistical analysis

We assumed that a 20% difference in the proportion of patients improving at least one grade on the Guillain-Barré syndrome disability scale between the patients with and without SID treatment 4 weeks after the start of standard intravenous immunoglobulin treatment would be clinically relevant. Without covariate adjustment and ordinal outcome analysis, we needed to randomly assign 145 patients with a poor prognosis (α=0·05, power 0·80) to detect this difference. We expected covariate adjustment and ordinal outcome analysis to result in a reduction in required sample size of 40–50%.[23] This expectation reduced the required sample size to between 73 and 88 patients.[13]

The primary analysis was modified intention to treat, in which all randomly assigned patients in whom allocated trial medication was started were included. The primary efficacy outcome was estimated with a proportional odds regression analysis.[24,25] For both primary and secondary endpoints, prespecified covariate adjustment was done to adjust for variation in baseline prognostic risk between patients. We adjusted for age, preceding diarrhoea, and MRC sumscore at randomisation.[13,26] This adjustment resulted in an adjusted common odds ratio for the effect of treatment with a 95% CI and corresponding p value. A two-tailed p value of less than 0·05 was considered statistically significant. Multiple imputation was applied to account for missing values in covariates and secondary endpoints; the primary endpoint was not imputed. There was no adjustment for multiple comparisons of secondary outcomes and these are presented as point estimates with unadjusted 95% CIs, from which no inferences can be made. Treatment-effect modification was explored in prespecified subgroups of patients as defined in the appendix (p 7). A trial data safety and monitoring board overlooked the trial and interim monitoring was done after 36 randomisations. This study is registered with the Netherlands Trial Register, NTR 2224/NL2107 and the statistical analysis plan was published here before unblinding the trial data. Analyses were done using R Studio version 3.6.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Between Feb 16, 2010, and June 5, 2018, 327 of 339 patients assessed for eligibility with Guillain-Barré syndrome were included (figure 1). 12 were excluded before mEGOS could be determined at days 7–9 (figure 1). 215 had a good prognosis (mEGOS <6), and 112 had a poor prognosis (mEGOS ≥6). 13 (12%) of the 112 patients with a poor prognosis were excluded before random assignment (mainly because of withdrawal of consent). Of the 99 randomly assigned patients, 53 (54%) were assigned to the SID group and 46 (46%) to the placebo group. Six patients were excluded after random assignment: two declined to participate before the start of allocated treatment, two patients did not receive the allocated treatment, and two patients were lost to follow-up shortly after randomisation when it became clear that they had an alternative diagnosis (one case of eosinophilic vasculitis in the placebo group and one case of myelopathy in the SID group). Of these patients, four had been assigned to SID and two had been assigned to placebo (figure 1). In the modified intention-to-treat analysis, 49 (53%) patients received SID and 44 (47%) received placebo.

Almost all patients who had been randomly assigned had severe weakness (as assessed with the MRC sumscore and Guillain-Barré syndrome disability score) and 85% were still deteriorating at 1 week according to the MRC sumscore, despite a standard intravenous immunoglobulin course (appendix pp 14–16).

Predictors of poor outcome were not evenly distributed between the two groups. Typically, patients in the SID group were older and had preceding diarrhoea more commonly than those in the placebo group (table 1, appendix p 12). Prespecified covariate adjustment was done for known prognostic factors.

Data for the primary outcome were complete (table 2). The adjusted common odds ratio for improvement on the Guillain-Barré syndrome disability score at 4 weeks was 1·4 (95% CI 0·6–3·3; p=0·45; figure 2, table 2). The unadjusted common odds ratio was 1·3 (95% CI 0·6–3·3). There was no evidence of a difference between treatment groups for any of the secondary outcomes. Guillain-Barré syndrome disability scores at weeks 8, 12, and 26 did not differ between groups (appendix p 16). Additionally, the probability of improving one grade or more on the Guillain-Barré syndrome disability scale at four different timepoints did not differ between groups. The MRC sumscore and Overall Neuropathy Limitations Scale were not different between groups at weeks 4, 8, 12, and 26 (appendix pp 14–15). Duration of hospital admission, intensive care unit admission, and mechanical ventilation were not different between groups (table 2, appendix p 11). Outcomes in the prespecified subgroups did not differ between treatment groups (figure 3). Patients with a good prognosis (n=208, seven excluded) had a

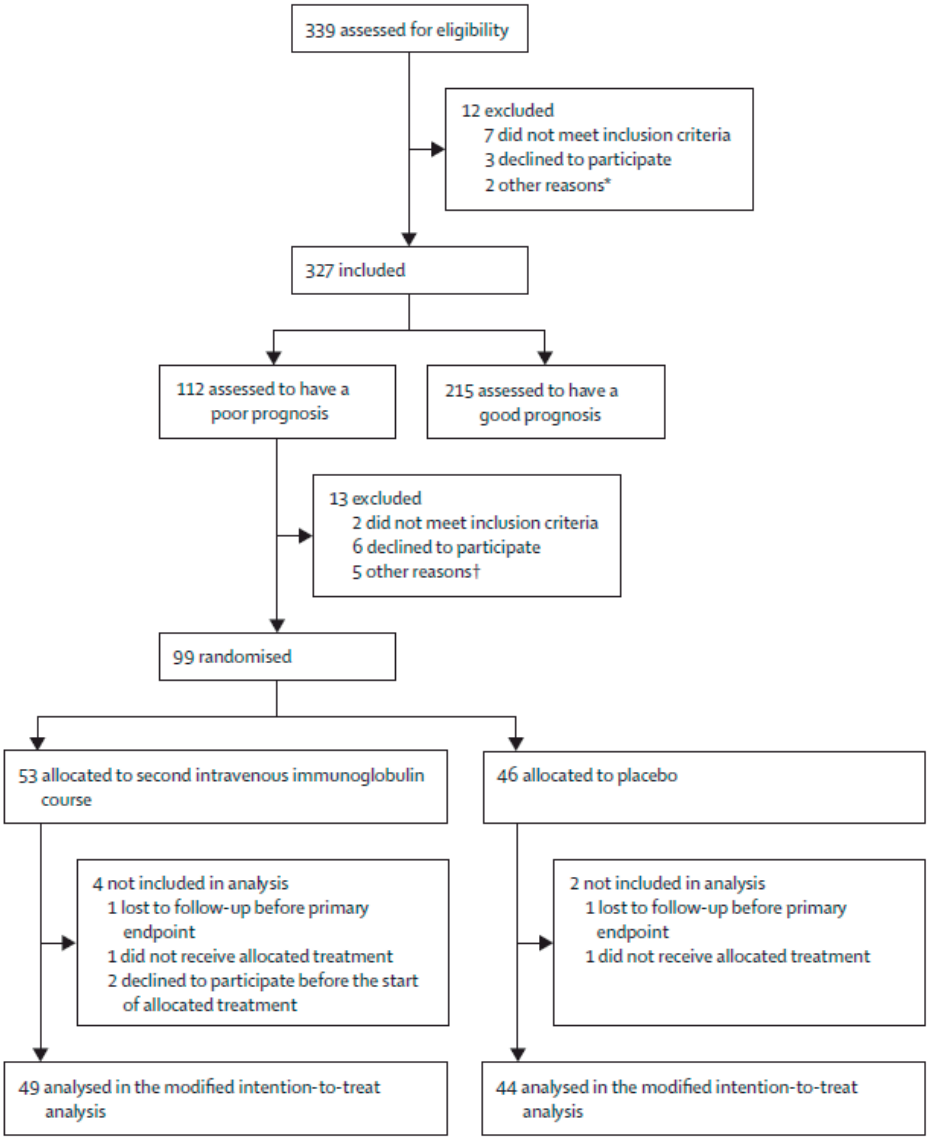

Figure 1 | Trial profile

*Other refers to transfer to hospital abroad or pharmacy not prepared to deliver allocated treatment. †Other refers to receiving open second intravenous immunoglobulin dose before random assignment, erroneously marked as good prognosis (n=3), or case report files lost in participating hospital.

median Guillain-Barré syndrome disability score of 2 (IQR 2–3) at 4 weeks, 1 (1–2) at 12 weeks, and 1 (0–2) at 26 weeks, indicating a generally good outcome in this group.

Table 1 | Baseline characteristics.

	SID (n=49)	Placebo (n=44)
Age, years	66·0 (59·5 – 74·0)	59·0 (42·5 – 70·0)
Sex		
Women	18 (37%)	10 (23%)
Men	31 (63%)	34 (77%)
Preceding diarrhoea*	24 (49%)	14 (32%)
Disability score at randomisation		
3	1 (2%)	1 (2%)
4	28 (57%)	23 (52%)
5	20 (41%)	20 (45%)
MRC sumscore at randomisation, 0-60	23 (6-38)	26 (12-35)
Nerve conduction studies†		
Demyelinating	31 (63%)	29 (66%)
Axonal	2 (4%)	2 (5%)
Equivocal	7 (14%)	4 (9%)
Inexcitable	7 (14%)	4 (9%)
Not performed or unjudgable	2 (4%)	5 (11%)
Positive *Campylobacter jejuni* serology‡	16 (33%)	10/42 (24%)
Antiganglioside IgM or IgG antibodies		
GM1	15/48 (31%)	11/42 (26%)
GD1a	5/48 (10%)	4/42 (10%)
Mean serum delta IgG concentration, g/L§	16·1 (95% CI 13·6-18·5)	18·4 (95% CI 15·7-21·1)
Mean serum albumin concentration after intravenous immunoglobulin, g/dL¶	32·5 (95% CI 30·7-34·3)	35·1 (95% CI 33·5-36·7)

Data are median (IQR), n (%), or n/N (%), unless specified. SID=second intravenous immunoglobulin dose. MRC=Medical Research Council. *Diarrhoea in the 4 weeks preceding the onset of weakness. †According to the Hadden criteria.19 ‡Data were missing for two patients in the placebo group. §Value 1 week after start of the first standard intravenous immunoglobulin dose: baseline (pre-treatment) or, when missing, 3 months after intravenous immunoglobulin treatment. ¶Data were missing for five patients in the intervention group and five patients in the control group.

Four patients died during the trial, all of whom were assigned to SID. The deaths included a 59-year-old man who was previously healthy before developing Guillain-Barré syndrome, who died 16 weeks after random assignment due to asystole that was deemed possibly related to a serious adverse event (acute coronary syndrome), which occurred 4 days after administration of SID. An 82-year-old woman died 13 weeks after randomization due to discontinuation of artificial ventilation at the request of the patient, after no signs of improvement, multiple complications, and severe pain. A 72-year-old woman died 21 weeks after randomisation from a cardiac cause in a nursing home. An 81-year-old woman died 24 weeks after randomisation, because of discontinuation of artificial ventilation at the request of the patient after no signs of improvement, and multiple complications. Serious adverse events, including thromboembolic events, occurred more often in the SID group than the placebo group (51% vs 23%, table

Table 2 | Primary and secondary endpoints.

	SID (n=49)	Placebo (n=44)	Adjusted common odds ratio (95% CI)
Primary outcome			
Disability score at 4 weeks	4 (4-5)	4 (4-5)	1·4 (0·6 to 3·3)
Secondary outcome			
Disability score at 8 weeks	4 (3-4)	4 (2-4)	1·5 (0·7 to 3·3)
Disability score at 12 weeks	3 (2-3)	3 (2-3)	2·1 (0·9 to 4·6)
Disability score at 26 weeks	2 (1-4)	2 (1-3)	1·0 (0·5 to 2·2)
Disability score improvement (≥1 point)			
4 weeks	18 (37%)	12 (27%)	1·8 (0·6 to 5·3)
8 weeks	27 (55%)	26 (59%)	1·0 (0·4 to 2·5)
12 weeks	36 (73%)	34 (77%)	1·7 (0·5 to 5·4)
26 weeks	40 (82%)	41 (93%)	0·4 (0·1 to 2·6)
ONLS score			
4 weeks	10 (8-12)	10 (7-12)	1·2 (0·5 to 2·6)
8 weeks	8 (6-10)	9 (4-11)	0·9 (0·4 to 1·9)
12 weeks	6 (3-9)	7 (2-10)	1·8 (0·8 to 3·7)
26 weeks	3 (1-7)	3 (1-5)	0·9 (0·4 to 1·9)
Mechanical ventilation	30 (61%)	25 (57%)	1·3 (0·5 to 3·3)
Treatment related fluctuation	3 (6%)	5 (11%)	0·6 (0·1 to 2·7)
Mean MRC sumscore			
4 weeks	32 (26-37)	30 (25-36)	1·3 (-1·6 to 4·1)*
8 weeks	37 (32-43)	37 (32-42)	1·2 (-1·9 to 4·3)*
12 weeks	40 (35-46)	43 (38-48)	-0·1 (-3·2 to 3·0)*
26 weeks	46 (41-52)	51 (47-55)	-2·0 (-4·8 to 0·8)*
Duration of mechanical ventilation, days	26 (12-58)	43 (9-80)	NA
Duration of intensive care unit admission, days	23 (8-55)	25 (4-77)	NA
Duration of hospital admission, days	39 (21-67)	30 (21-73)	NA

Data are median (IQR), n (%), or mean (95% CI) unless specified. SID=second intravenous immunoglobulin dose. NA=not analysed as the assumptions of the linear regression model were not met due to non-normal distributions of the outcome. ONLS=Overall Neuropathy Limitations Scale. MRC=Medical Research Council. *β coefficient from linear regression presented here.

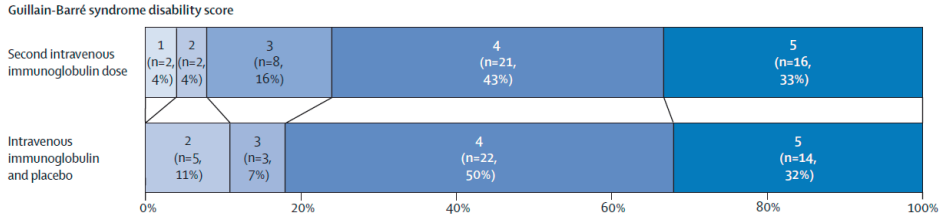

Figure 2 | Guillain-Barré syndrome disability score at 4 weeks in the modified intention-to-treat population

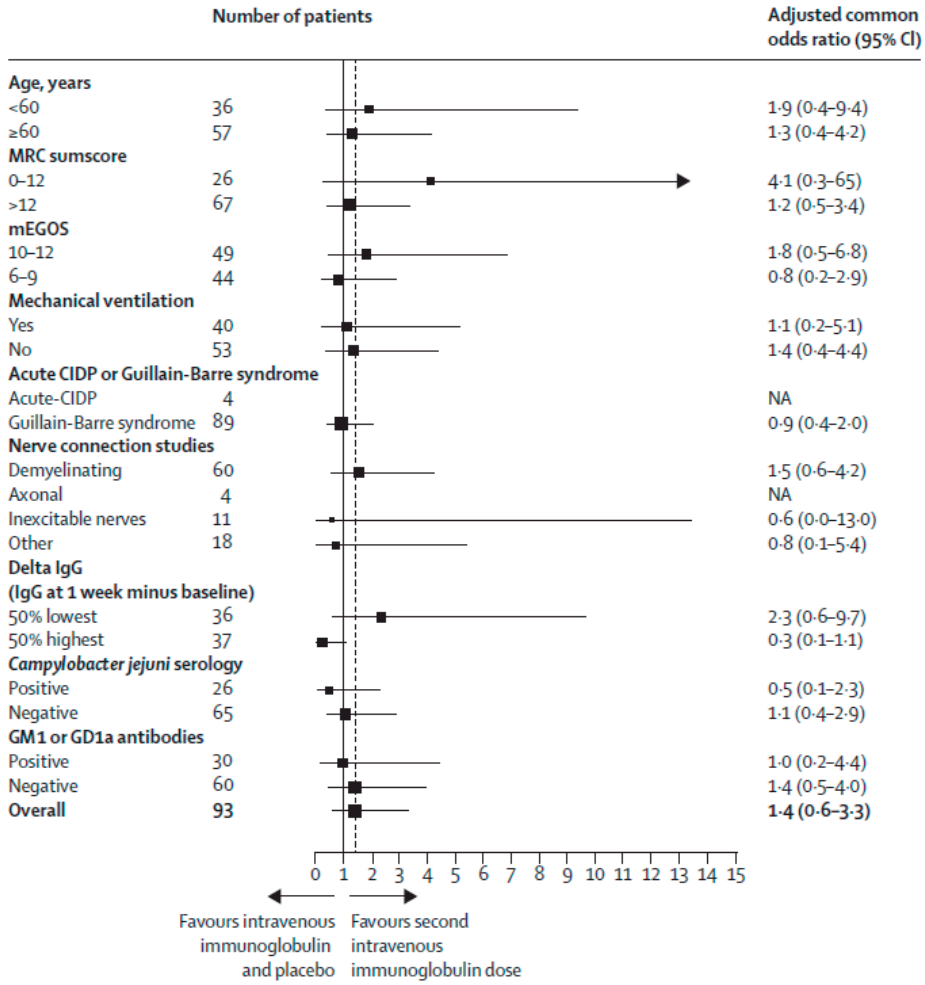

Figure 3 | Subgroup analyses. Treatment effect in prespecified subgroup analyses. The outcome is improvement on the Guillain-Barré syndrome disability score at 4 weeks after inclusion (using proportional odds analysis, after covariate adjustment for mEGOS at 1 week). Each dot represents the adjusted common odds ratio, the size of the dot represents the number of patients in each subgroup, and the line represents the 95% CI. mEGOS=modified Erasmus GBS Outcome Scale. NA=not applicable. CIDP=chronic inflammatory demyelinating polyneuropathy. MRC=Medical Research Council.

3, appendix p 12). Trial medication was not completed in two cases due to adverse events (ophthalmoplegia due to pituitary adenoma after placebo and severe skin rash after SID). From 2015 onward, randomly assigned patients (24 [26%] of 93) were tested for haemolytic anaemia after a protocol amendment based on a report about this possible adverse event in high-dose intravenous immunoglobulin treatment, but this adverse event was not seen in our trial.[27]

Table 3 | Safety measures and serious adverse events.

	SID (n=49)	Placebo (n=44)
Serious adverse events*		
Any serious adverse event during study (excluding deaths)†	25 (51%)	10 (23%)
Any serious adverse event in the first 30 days (excluding deaths)	17 (35%)	7 (16%)
Coronary ischaemia	1 (2%)	1 (2%)
Asystole	2 (4%)	0
Transient ischaemic attack (multiple)	1 (2%)	0
Pulmonary embolism	2 (4%)	0
Radial artery thrombosis	1 (2%)	0
Renal insufficiency	1 (2%)	1 (2%)
Pneumonia	12 (24%)	7 (16%)
Other infection	2 (4%)	1 (2%)
Other serious complications‡	8 (16%)	3 (7%)
Other possible related complications§		
Haemolytic anaemia	0	0
Blood transfusion¶	3 (6%)	0

Data are n (%). SID=second intravenous immunoglobulin dose. *Only first events of a certain type are listed. Patients having multiple events of one type were counted once. †Odds ratio 3·54 (95% CI 1·44–8·72); p=0·0050. ‡See appendix (p 21). §Prospectively collected from 2015 onward (24 of 93 patients). ¶For various reasons other than haemolytic anaemia.

In the SID group, serum IgG was maintained at a high concentration longer than in the placebo group (median 34 g/L [IQR 30–43] vs 17 g/L [16–20] at 2 weeks after start of the standard intravenous immunoglobulin dose; appendix p 13). Median serum IgG at 4 weeks was still higher in the SID group than in the placebo group (median 19 g/L [IQR 16–22] vs 15 g/L [12–18]), but serum IgG concentrations were similar in both groups after 12 weeks.

We compared IgG concentrations in association with thromboembolic events, and found that patients with thromboembolic events did not have higher IgG concentrations after one standard course of intravenous immunoglobulin (mean IgG 26 g/L compared with 30 g/L in patients without thromboembolic events) or after SID (mean IgG 29 g/L compared with 37 g/L in patients without thromboembolic events).

DISCUSSION

This randomised trial did not show a significant clinical benefit of SID in selected patients with Guillain-Barré syndrome who had a predicted poor outcome after a first course of intravenous immunoglobulin. These patients almost all continued to deteriorate at 1 week after the first intravenous immunoglobulin course, and were in a poor neurological condition based on the MRC sumscore and Guillain-Barré syndrome disability score. Our results complement earlier studies,

which found that additional immunotherapy (ie, either intravenous immunoglobulin after plasma exchange, six instead of four cycles of plasma exchange, or intravenous methylprednisolone with intravenous immunoglobulin) in the general Guillain-Barré syndrome population was not beneficial.[28-31] We believe our results can be generalised to the entire Guillain-Barré syndrome population even though we studied SID only in those with a poor prognosis.

One of the arguments that suggests a second series of intravenous immunoglobulin might be effective was the observation that a larger increase in serum IgG concentration after intravenous immunoglobulin treatment was related to a more substantial recovery.[12,13]

Our trial showed that SID is able to increase the serum IgG concentration further and for a prolonged period of time than controls (appendix p 13), but this effect did not improve outcome. It might be that a relatively small rise in serum IgG after standard intravenous immunoglobulin treatment is an indicator for disease severity or more rapid intravenous immunoglobulin catabolism, rather than a target for therapy. It seems probable that intravenous immunoglobulin in Guillain-Barré syndrome is predominantly effective very early in the course of disease and that prolonging a high serum IgG concentration provides no additional benefit. This hypothesis could explain both the results of the previous study, in which a higher delta IgG was related to a better outcome than a lower delta IgG,[12] and the results of the current trial. Further research into the mechanisms of the treatment-modifying effect of IgG in Guillain-Barré syndrome is needed. Another possible reason for not finding a positive effect of a SID could be that the included patients had too severe disease. Too much axonal damage might have already occurred at the time of SID administration to find a difference between the groups. However, there was no suggestion of a positive effect of a SID in the subgroup of patients predicted to have a less severe outcome. Instead of repeating the standard dose, doubling the initial intravenous immunoglobulin dose could have resulted in better outcomes, but even more serious adverse events might have occurred as a consequence.

Patients who were given SID had more serious adverse events than those who were given a single intravenous immunoglobulin dose and placebo. Thromboembolic events were reported more often in patients who were given SID than in those who were given placebo. Thromboembolic events are a well-known, rare, side-effect of intravenous immunoglobulin, and their mechanism is thought to be due to a dose-dependent increase of plasma viscosity.[32] For this reason, known pre-existing vascular risk factors were a contraindication for randomization in this trial (appendix p 18). However, other factors such as immobility, dehydration, leucocytosis, and coexisting inflammation can also cause a critical increase of plasma viscosity causing this serious adverse event. Patients with thromboembolic events did not have higher IgG concentrations after one standard course of intravenous immunoglobulin or after SID when compared with patients without these events, and therefore the administration of a second intravenous

immunoglobulin course rather than the serum IgG concentration only might be related to these serious adverse events.

Our trial has several limitations. First, the sample size was relatively small, and the estimated odds ratio of 1·45 had wide CIs. However, we believe that our results are valid as the main trial result is the same using modified intention-to-treat or full intention-to-treat analyses; covariate adjustment as prespecified in the statistical analysis plan and protocol did not change the interpretation of the trial; there were no differences between treatment groups for any of the secondary endpoints; and we did not find differences in the subgroup analysis. Although a larger sample size would have increased the statistical power, the trial was powered to find a large treatment effect to improve treatment for this group of severely affected patients, considering that smaller effects would not be clinically meaningful.

Second, some of the baseline variables were unbalanced between groups even though the patients were randomly assigned, which could have affected the outcome. Both age and preceding diarrhoea are known prognostic factors, and correction for these factors (together with baseline MRC sumscore) using covariate adjustment was prespecified in the protocol. Covariate adjustment did not change the interpretation of the trial, as the unadjusted and adjusted common odds ratios were similar.[25,26]

Third, acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP) was diagnosed in four patients during follow-up (two in each group), which is consistent with the frequency reported in the literature in general in trials for the syndrome.[11] Patients with acute-onset CIDP or with a treatment related fluctuation were given additional intravenous immunoglobulin in the trial (according to established guidelines).[11] These patients were retained in the main analysis; their exclusion did not affect the results of the trial in a prespecified subgroup analysis. The results of the trial should not change treatment practice of patients with acute-onset CIDP or with treatment related fluctuations.

Fourth, in two patients, the diagnosis was changed (eosinophilic vasculitis in the placebo group and myelopathy in the SID group) shortly after random assignment and initiation of trial medication. Once the alternative diagnosis was made, follow-up stopped, and primary endpoint analysis was not possible. A full intention-to-treat analysis (n=96, three missing endpoints) resulted in an adjusted common odds ratio of 1·3 (95% CI 0·6–3·1), which was not different from the modified intention-to-treat analysis.

Lastly, our trial had an inclusion period of more than 8 years. This long inclusion period was largely due to the rarity of Guillain-Barré syndrome, and only patients with a poor prognosis were randomly assigned. However, immune treatment of Guillain-Barré syndrome in the Neth-

erlands has not changed over the past 8 years, so we expect that the population recruited in this trial was given the same treatments, despite the long recruitment period.

In conclusion, we found no significant clinical benefit of a second intravenous immunoglobulin course administered shortly after the first standard intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis. Additionally, the group given a second series of intravenous immunoglobulin had more serious adverse events than those given placebo. When looking for better treatments for Guillain-Barré syndrome, we should consider agents acting through a different mechanism than intravenous immunoglobulin, including complement inhibitors (NCT04035135) and IgG degrading enzymes (NCT03943589).

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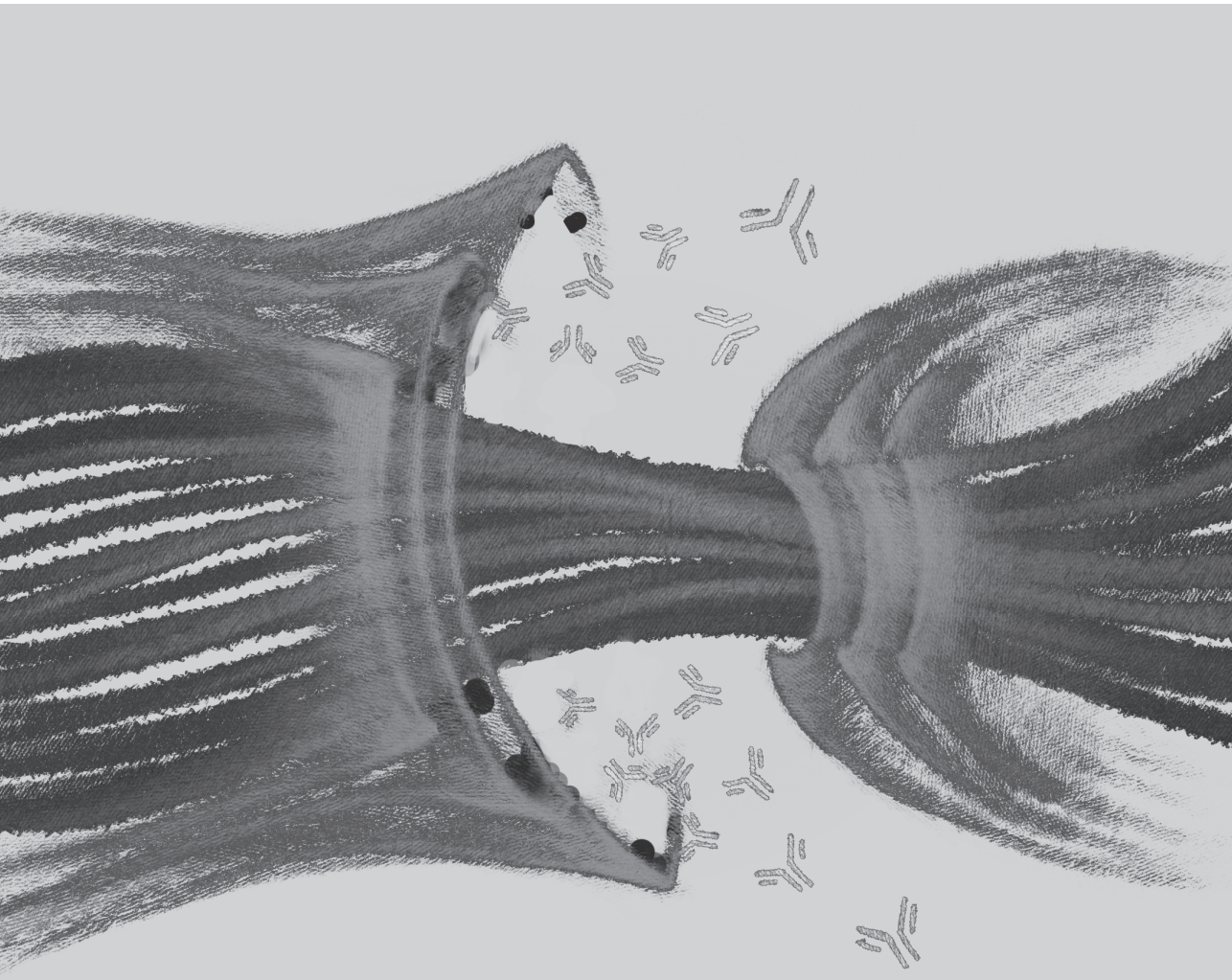

4

General discussion

The overall aim of the studies described in the thesis are to predict and improve the outcome of GBS. The first aim of this thesis is the identification of prognostic factors to predict the clinical course and outcome of individual patients with GBS. These factors were used to construct prediction models for three important outcomes in individual GBS patients: (1) a model to predict the chance of respiratory insufficiency in the first week of hospital admission, (2) a model to predict the duration of mechanical ventilation, especially if this is longer than 2 weeks when tracheostomy is indicated (3) a model to predict the chance to achieve the ability to walk after 4, 12 and 26 weeks.

The second overall aim of this thesis was to improve the clinical outcome for GBS patients with a predicted poor prognosis. A conditional randomized placebo-controlled double-blind trial was conducted to study the added effect of a second IVIg course in GBS patients with a poor prognosis.

In this chapter the main results of the studies described in chapter 2 and 3 are discussed in relation to the available literature. Based on these results, recommendations for clinical practice and suggestions for further research will be given.

PREDICTING OUTCOME IN GUILLAIN-BARRÉ SYNDROME

The usefulness of prognostic models in clinical practice.

One of the most critical parts of practicing medicine is clinical decision making. Clinical decision making is concerned with making choices for individual patients about the diagnosis and treatment with the final aim to improve the outcome of the patient. Prognostic models are a tool to assist clinicians in predicting the clinical course and outcome in individual patients. Without prognostic models, a clinician likely makes decisions based on knowledge of the literature and clinical experience with earlier patients, but without quantified information on the risks and benefits for a specific patient. Prognostic models are usually based on large databases with information on early clinical characteristics, disease course and outcome. When using prognostic models, the clinician make use of all these previous patients in a quantitative way.[1] Prognosis refers to all clinical outcomes that may occur during the disease course, for example respiratory insufficiency, the ability to walk after 6 months or resumption of work after 6 months. A prognostic model is based on a set of predictors that in combination are most effective in predicting clinical outcome in individual patients. To be useful for clinical practice it is essential that a prognostic model is based on easily accessible information that can be used at the bedside of the patients. Especially for GBS patients, who have a heterogeneous disease course, prognostic models are very useful for assisting in clinical decision making and

for providing specific information to patients and their relatives about the expected clinical course and outcome. In research, prediction models can assist in the selection of patients for trials, in the analysis of trials and for comparing different patient/trial cohorts.[1] Using prediction models, the disease course of GBS is surprisingly predictable, when compared to for example multiple sclerosis.[2] Although this other immune-mediated demyelinating neurological disorder is much more prevalent, no prediction model was accurate and valid enough for use in routine clinical practice.[2] In general, statistical models should have an assisting role but never take over the responsibility of the treating physician. The physician should always keep in mind that a prediction model is based on risk probabilities that will never be fully accurate.

Prediction of respiratory dysfunction in GBS

Supportive care is key in the management of GBS and aims to prevent and to treat complications adequately and timely.[3] Very useful for clinical practice is the recently published international consensus guideline for the management of GBS.[4] Dutch GBS patients can seek support via the patient organization Spierziekten Nederland, which is very active in peer support already when patients are still admitted to the ICU. Respiratory failure is a common and serious manifestation of GBS, that occurs in about 20% of the patients and is associated with poor outcome.[5,6] However, these patients can also make an excellent recovery with meticulous supportive care. Careful monitoring and timely recognition of imminent respiratory insufficiency is important to prevent delayed or emergency intubation and lowers the risk of pneumonia and sepsis due to aspiration (aspiration risk is higher because it concerns non-fasted patients who are critically ill). Therefore, early and accurate prediction of respiratory insufficiency is needed.

In 2006, a model was published which accurately predicts respiratory insufficiency, using vital capacity and the proximal/distal compound muscular amplitude potential (p/dCMAP) ratio of the common peroneal nerve as predictors.[7] The p/dCMAP ratio is a prognostic marker for demyelination, which is in accordance with the previous finding that patients with demyelinating disease are at higher risk for developing respiratory failure than patients with axonal disease.[8] However, the incorporation of an electrophysiological parameter in a prediction model may make the model more accurate, but complicates the prognostication at the emergency department. In addition, the quality and facilities to conduct early electrophysiology in these patients varies between hospitals. Knowing that most patients with GBS develop respiratory failure in the first week of admission we developed a model based only on the clinical information available at the emergency department. In **chapter 2.1** it is described how we constructed and validated a prediction model (Erasmus GBS Respiratory Insufficiency Score; EGRIS) which uses three predictors: (1) disease progression in days, (2) facial and/or bulbar weakness, and (3) MRC sum score at admission. The EGRIS model accurately predicts the probability of respiratory insufficiency (the need for invasive mechanical ventilation) in the first week after hospital admission.[9] The prognostic model is also used in the Dutch national guideline on GBS and will

be incorporated in the new European Academy of Neurology / Peripheral Nerve Society (EAN/PNS) guideline on GBS.

The EGRIS was developed and validated in a Dutch cohort of GBS patients. Marked differences exists in the clinical presentation, disease course, subtypes and outcome of GBS between geographical regions, which may depend on the variation in preceding infections, genetic background and immune status.[10] To use the EGRIS for patients outside the Netherlands, it was important to externally validate the model in patients from other countries. Moreover, an independent validation in Dutch patients was required as well. In **chapter 2.2** we describe a large cooperative study using data of 1027 GBS patients included in the International GBS Outcome Study (IGOS) to validate and re-calibrate the EGRIS model for specific regions. The IGOS is a collaborative study in which currently 22 countries, from 5 continents, are participating.[11] The EGRIS model showed good discriminative ability when applied to this international GBS cohort. Assessment of calibration showed an overestimation of the need for mechanical ventilation by the EGRIS model; mean observed proportions vs. predicted risks were 10% vs. 21% in the full cohort. This difference may be caused by differences in patient characteristics or disease management between RCTs and observational studies. Recalibration further improved model accuracy and a region-specific version of the EGRIS for Europe/North America was created. Recalibration did not change de relative contribution of the 3 predictors in the model, but changed only the formula to convert the total EGRIS score into a probability of mechanical ventilation by adapting the intercept and coefficient of the total EGRIS in the regression formula. Because of the small sample size of Asian patients, we were not able to reliably validate and recalibrate the EGRIS for Asian patients. However, studies that were conducted in Pakistan and India identified the same predictors for mechanical ventilation and, validation studies in a Japanese and a Malaysian cohort concluded that EGRIS was also a reliable prediction tool in those patients.[12-15] In conclusion, the EGRIS model is an easy applicable, reliable, and valid prognostic tool for patients with GBS provided they receive accurate monitoring and treatment. For patients in low-income countries in which monitoring and treatment is not evident, the EGRIS needs to be validated and probably requires adjustments.

A prediction model for mechanical ventilation, published in 2014, also uses clinical predictors only; neck weakness, single breath count, and bulbar palsy (NSB score).[16] A simple model, even more easy to assess than the EGRIS score, as it uses neck weakness only instead of a sum score of 12 muscle scores in EGRIS. This study however has generalizability problems, because it was conducted in patients with GBS yet admitted at the neuro-intensive care unit in a tertiary hospital. This study population is probably biased towards patients with more severe GBS, co-morbidity or complications, compared to the general population of patients that may present at the emergency department of a general hospital or University Medical Center. Also those patients were screened later in the course of the disease, when already admitted to the ICU,

and therefore this model is not directly applicable to patients admitted to the emergency department.

Important to mention is that the decision to intubate a GBS patient is in part arbitrary and may be influenced by other factors than clinical characteristics, for example the ICU capacity or the experience of the ICU specialist. Also in our databases, no uniform criteria or respiratory parameters were used to initiate mechanical ventilation, instead the decision was left to the ICU specialist. This can result in unpredictable differences between regions, hospitals or even physicians and also in time. This may partly explain why the observed proportion of patients who needed mechanical ventilation was substantially lower in the international validation cohort than the predicted risk based on the EGRIS model. At the moment, efforts are undertaken to further simplify the EGRIS model using the IGOS database, also including neck flexion, and to search for prognostic biomarkers which may improve the accurateness of the model.

Prediction of duration of mechanical ventilation in GBS

In the cohort used for the development of the EGRIS (n=565), patients were mechanically ventilated for a median of 28 days with a broad range of 1 to more than 181 days (the maximum follow-up duration in those studies). A longer duration of mechanical ventilation is associated with poor long-term functional outcome.[17] Prediction of the duration of mechanical ventilation is important for counselling patients and family and for decision-making regarding tracheostomy. This is important because prolonged endotracheal intubation can result in damage to vocal cords, laryngeal mucosa, and recurrent laryngeal nerves due to decubitus or local pressure from the tube. When patients in need of prolonged mechanical ventilation can be recognized early, a tracheostomy can be performed early.[18] To avoid post-intubation tracheal injury and stenosis, tracheostomy is strongly encouraged to be performed after 2 weeks intubation at the most.[19] On the other hand, tracheostomy can be complicated by hemorrhage, infection or pneumothorax, and leaves a permanent scar. Therefore, tracheostomy needs to be avoided in patients needing only short-term mechanical ventilation, but early tracheostomy has clear advantages when needed anyway. For clinicians it is important to have a tool which can aid in the clinical dilemma to perform a tracheostomy that can be used in individual GBS patients to predict the chance of prolonged ventilation (>2 weeks). In **Chapter 2.3** we concluded that ventilated GBS patients unable to lift the arms from the bed and having axonal degeneration or inexcitable nerves with nerve conduction studies 1 week after intubation, are at high risk of prolonged mechanical ventilation (>2 weeks) and early tracheostomy should be considered in these patients.[20] Respiratory muscle weakness, but also severe bulbar dysfunction or pneumonia can play a role in the need of intubation or tracheostomy in GBS patients. A recent study found that the main reason for intubation was respiratory muscle weakness, however, severe dysphagia was the main reason preventing direct decannulation after successful weaning.[21] Flexible Endoscopic Evaluation of Swallowing (FEES) can be used to evaluate the ability to

swallow. Combining FEES with the prognostic factors described in **Chapter 2.3** will probably result in a good tool to select patients for early tracheostomy. We were not able to validate the prediction tool like for the prediction of respiratory insufficiency (EGRIS) because of the much smaller available patient cohort (only the 150 patients who need mechanical ventilation). Scarce literature is available about the management of ventilation in GBS patients and our study describes the largest cohort of mechanically ventilated patients until today. Only with very large cohorts of GBS patients it may be possible to construct a prediction model which accurately predicts the chance of prolonged mechanical ventilation in GBS patients. Using data from IGOS it may be possible to predict the duration of the mechanical ventilation in individual patients and to develop more accurate models.[11]

Outcome measures in GBS

At present it is debatable what the best clinical outcome measure is to indicate the long-term outcome (3 months to years) in GBS. Ambulation at 6 months, expressed as the GBS disability scale (table 1), is often used in GBS research. The GBS disability score is a functional outcome scale, ranging from zero (healthy) to six (death).[22] This score is most used in clinical trials in GBS and is often dichotomized according to the ability to walk unaided (GBS disability score of ≤2 vs >2). However, ambulation is merely one of the multiple factors that influences the quality of life.[23] Other important factors that are not covered with this scale include cranial nerve palsy, arm dysfunction, sensory dysfunction, autonomic dysfunction, neuropathic pain and fatigue. A second limitation of this ordinal, 7-point GBS disability scale is that the intervals between grades are not equal. Extensive research is ongoing to construct outcome measures for inflammatory neuropathies which are simple, communicable, valid, reliable, and responsive.[23]

Table 1 | Guillain-Barré syndrome (GBS) disability scale. Adapted from Hughes *et al*, and PSGBS group[22,24]

Grade	
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 chair bound
5	Requiring assisted ventilation for at least part of the day
6	Dead

Prediction of long-term outcome (disability) in GBS

In **chapter 2.5** the modified Erasmus GBS Outcome Scale (mEGOS), a prognostic model that predicts the ability to walk unaided at 4 weeks, 3 and 6 months is described. Predictors in this model are the MRC sum score (at admission or at one week after admission), preceding diar-

rhea and age of the patient (table 2). This mEGOS is a modification of the previously published Erasmus GBS Outcome Scale (EGOS).[25] The model was modified on two main points. First, the MRC sum score instead of the GBS disability score was used as predictor (table 2). Both scores are a reflection of the clinical severity, but the MRC sum score showed a better predictive ability early in the disease course than the GBS disability score. Second, in part because of this more accurate predictive value of the MRC sum score, the mEGOS can be used already at hospital admission or one week after admission (after standard IVIg treatment), whereas the EGOS cannot be used until 2 weeks after admission. Because we intended to use the model for selecting patients with poor prognosis for treatment trials, the model should be applicable yet early in the disease course, when nerve damage might be still reversible and maximal effect of additional treatment may be expected. Therefore, mEGOS is better suitable as a tool for selection of patients with poor prognosis for treatment trials. The predictive power of the validated mEGOS model (AUC = 0.87) was sufficient to use the model for the selection of patients with a poor prognosis for the Dutch SID-GBS trial, in which patients with a poor prognosis were selected for randomization to a second IVIg course or placebo at one week after inclusion in the trial.

Table 2 | EGOS (long-term), mEGOS (long-term) and EGRIS (short-term) compared.

Model	Predictors	When applicable	Predicted outcome measure	Timing of outcome
EGOS	Age	Two weeks after diagnosis	Ability to walk unaided	6 months
	Preceding diarrhea			
	GBS disability scale			
mEGOS	Age	At diagnosis	Ability to walk unaided	4 weeks
	Preceding diarrhea	One week after diagnosis		3 months
	MRC sum score			6 months
EGRIS	Cranial nerve involvement	At diagnosis	Respiratory insufficiency	1 week
	Time between onset of weakness and hospital admission			
	MRC sum score			

A shortcoming of the mEGOS model is that the model was derived from and validated in a Dutch cohort of GBS patients, just as the EGRIS model (**Chapter 2.1**). The mEGOS was recently validated in a Japanese cohort and this study concluded that mEGOS can be used in this population as well.[12] The original EGOS model was validated in a Brazilian cohort, but the conclusion of that study was that EGOS does not suit the Brazilian GBS patients.[26] Possibly because of the marked differences in baseline variables; the patients in the Brazilian cohort were

younger (64% <40 years) en more severely affected at two weeks from disease onset. This may also be the case for other countries where the general population and GBS patients tend to be younger, and experience other preceding infections such as (at that time) Zika virus or Chikungunya virus. Therefore, the mEGOS model was validated in an international cohort of 809 GBS patients from the IGOS consortium[11] and it was shown that the model is a clinically useful tool to predict the inability to walk unaided in GBS, also in patients from countries outside The Netherlands.[27] However, mEGOS may probably be less suitable in low income countries, like Bangladesh, in which most patients cannot afford treatment with IVIg or plasma exchange.

In **Chapter 2.1 and 2.3** prognostic models were presented that predict outcomes in the acute phase of the disease and are used to assist in clinical decision making at that stage. Prediction of long-term outcome includes the recovery phase as well. In the acute phase outcome is dependent mostly on factors of the acute illness itself, whereas in predicting outcome at the long-term other factors also play a role, like age, co-morbidity and accessibility of rehabilitation facilities. In comparison with the EGRIS model, described in **Chapter 2.1**, mEGOS has different predictors, accept for the MRC sum score (table 2). Age is associated with long-term outcome but not with respiratory insufficiency (that usually occurs within the first 2 weeks). Age seems associated with the capacity to recover from nerve damage more than that it is associated with disease severity. Young adult patients may also have severe GBS and a need for mechanical ventilation just as often as older patients, but younger patients have the capacity to recover faster and better from nerve damage in comparison with older patients. Preceding diarrhea was associated with the ability to walk at 6 months (long-term outcome), but not associated with the chance of mechanical ventilation. This can be explained by the fact that the predominant cause of preceding diarrhea in GBS is an infection with *Campylobacter jejuni*, which is associated with a pure motor, distal, axonal form of GBS with more severe muscle weakness.[28] Respiratory insufficiency is less frequent in these patients and probably explained by the fact that this is caused by weakness of proximal muscles (diaphragm, bulbar muscles), but the ability to walk is also dependent on strong distal muscles.

Biomarkers and outcome

In **Chapter 2.1, 2.3 and 2.5** we searched for clinical predictors of outcome to develop a prognostic model that can easily be applied in clinical practice. However, biomarkers may have an additional prognostic value independent of the clinical predictors and may be used to further improve the existing prognostic models for GBS. In previous studies the following biomarkers are linked to prognosis in GBS; soluble interleukin-2 receptor, anti-GM1 (subclasses), serum neurofilament light chain, CSF tau protein and CSF neurofilament.[29-34]

Both serum albumin and serum immunoglobulin G (IgG) were investigated as biomarkers of IVIg treatment efficacy and outcome in GBS.[35-37] Hallmark of both proteins is their long half-life

under physiological concentrations (half-lives of both approximately 3 weeks) and increased catabolism at higher serum concentrations.[38] These phenomena are explained by the presence of an intracellular endothelial receptor (neonatal Fc-receptor; FcRn) that protects both IgG and albumin from intracellular catabolism in lysosomes and shuttles IgG and albumin back to the circulation.[38] Protection of degradation is a pH dependent cellular mechanism. IgG, albumin and other plasma proteins are ingested via pinocytosis. The endosome is more acidic than outside the cell and IgG and albumin bind to FcRn, retaining it in the endosome and protecting them from transport to the lysosome for degradation. The FcRn bound proteins are than shuttled back to the plasma membrane, where the content of the endosome is released into the circulation.[38]

Albumin was identified as an independent marker of poor outcome in other diseases[39], can be measured routinely in every hospital and is thereby an ideal candidate for an easily applicable biomarker. In **chapter 2.4** we describe that the serum albumin level after IVIg treatment can drop to hypoalbuminemia and this was independently correlated with poor clinical outcome.[36] One could speculate about the causality of this correlation and the presumed underlying pathophysiology of this finding. A low serum albumin can be a reflection of inflammation solely. More inflammation may result in more nerve damage and a poor prognosis. On the other hand, it can also be a result of the IVIg treatment. The FcRn recycle pathway serves both IgG and albumin. When the FcRn recycle pathway is saturated by IgG from IVIg treatment, recycling of albumin is reduced, which results in a lower serum albumin. To rule out the IVIg effect, it is interesting to look at serial albumin levels in GBS patients who were not treated with IVIg. Our findings that low serum albumin was independently correlated with poor outcome in GBS, were later confirmed in a cohort of 36 adult GBS patients from Turkey. However, this was not found for 32 pediatric GBS patients from the same study.[35] This difference between adult and pediatric GBS patients may be explained by the fact that these were small groups and that poor outcome in the pediatric group occurred infrequently. Another potential prognostic biomarker for IVIg treatment efficacy and outcome of GBS are the IgG levels measured in serum after start of the treatment, as it likely plays a central role in the pathogenesis of GBS and is the main component of IVIg. After a standard single course of IVIg (2 g/kg in 5 days) a large interpatient variation in pharmacokinetics of IgG exists, and a low delta IgG after two weeks was independently associated with a poor outcome.[37] Also in multifocal motor neuropathy (MMN) patients treated with IVIg this same large interpatient variability was shown.[40] Both in MMN and in GBS, genetic polymorphisms in the promotor region of FcRn that influences the expression of the FcRn was not correlated to the variation in IgG levels and outcome.[40,41] If IVIg has a dose-dependent effect, the correlation between delta IgG (serum IgG pre-treatment compared with serum IgG 2 weeks post-treatment) and outcome can be explained. For example, a severely affected GBS patient may need more IVIg to recover (dose-dependent). When this patient receives a standard IVIg dosage (in this particular case too less IVIg), this patient would have a poor prognosis

(because of suboptimal treatment) and a low delta IgG (received not enough IVIg to result in a detectable serum IgG rise). Comparable with treatment of anemia with packed cells, when the anemia is severe, a patient needs more packed cells. A low delta IgG may result in suboptimal immune modulation, more extensive or prolonged damage of peripheral nerves, and worse outcome. This could indicate that patients with a low delta IgG may benefit from an additional course of IVIg. The relation between low delta IgG levels and poor outcome was one of the rationales for starting the SID-GBS trial, in which the added effect of a second IVIg course in GBS patients with a poor prognosis was studied, which will be discussed later on in this chapter.

IMPROVING OUTCOME IN GUILLAIN-BARRÉ SYNDROME

Intravenous immunoglobulins (IVIg)

In GBS, both plasma exchange and IVIg are proven effective treatments for patients who are unable to walk and still within two weeks of onset of weakness.[42,43] Nowadays IVIg is first choice treatment in the Western world because it is readily available and has a better side effect profile than plasma exchange. IVIg is an expensive treatment (around €12.500 for a standard treatment course of 2g/kg for a patient of 75 kg bodyweight), which makes it less affordable in low- or middle income economies. The exact working mechanism of IVIg in non-immune deficiency is unknown, but is thought to be pluripotent.[43,44] It has pleotropic modulatory effects on the immune system, including inhibition of B- and T-cell and macrophage activation, saturation of FcRn receptors, neutralization of autoantibodies and cytokines, and inhibition of complement activation. Proper IVIg dose finding studies have not been done in GBS and in principle all GBS patients unable to walk are treated with the same arbitrary dose of 2 g IVIg per kg bodyweight usually divided over a five day course. This IVIg dosage is based mainly on the clinical experience of treating patients with idiopathic thrombocytopenic purpura. In general, patients treated with IVIg or plasma exchange improve faster and require a significantly shorter period of mechanical ventilation in comparison with supportive treatment alone.[45] The response to IVIg treatment is highly variable, and it is currently unknown why some GBS patients improve following IVIg treatment, where as other deteriorate further. This is illustrated by the fact that despite IVIg treatment, 20% needs mechanical ventilation during the course of the disease, 1-5% dies, 20% is still unable to walk unaided at 6 months after the disease and many patients (70%) have pain or remain severely fatigued for a long period of time. This underlines the importance of new treatment trials, especially in the group of GBS patients with a poor prognosis. Additional treatment entails a risk of complications, lengthens hospital stay (in case of intravenous treatment) and is costly. Additional medical treatment therefore is likely not indicated for patients who recover well after current standard treatment. Accurate prognostic models are vital to conduct a conditional trial in specific subgroups of GBS patients with a poor prognosis. Immune treatment is likely most effective early in the disease course, when nerve damage might be still

reversible. In the second IVIg course trial in GBS patients with poor prognosis (predicted by an mEGOS score ≥6), patients were treated with an additional IVIg course (or placebo), which was administered already one week after initiation of the first standard IVIg course.

The Second IVIg Course (SID) in GBS patients with a poor prognosis trial – trial design

The following arguments were the basis for the SID-GBS trial, in which the added effect of a second IVIg course was studied:

1. About 10% have a "treatment-related fluctuation" that usually respond to a second course of IVIg.[46] A treatment-related fluctuation is a secondary deterioration after initial improvement or stabilization after a standard IVIg course.[46]
2. A second course of IVIg is suggested to be effective in two small uncontrolled series of severe unresponsive GBS patients.[47,48]
3. A smaller increase in serum IgG level 2 weeks after start of IVIg treatment is related with poor recovery after 6 months.[37]

In **Chapter 3.1** the protocol of the SID-GBS trial is described. Both the rarity and heterogeneity of GBS challenges performing randomized controlled trials in GBS. In contrast with for example stroke and traumatic brain injury trials, small sample sizes are the rule in GBS trials. When sample sizes in trials are very large, stratification in randomization can be used to minimize imbalance in baseline risk. In GBS stratification for multiple factors is not possible because of the small sample size and despite adequate randomization imbalance in baseline risk will often occur simply by chance. In the presence of such imbalance the comparability of the treatment groups may be questioned, especially with regards to any known important prognostic factors (e.g., severity of disease or age).[49] In **Chapter 3.2** we report on two statistical approaches to improve the trial design in GBS.[50] We analyzed covariate adjustment (1), which takes known baseline prognostic factors into account and proportional odds analysis (2) which makes full use of the ordinal outcome scale.[50] Both techniques were incorporated in the design of the SID-GBS trial.[50,51]

Covariate adjustment

Covariate adjustment is an established approach to correct for variation between patients in baseline risk and to increase statistical power in clinical phase III trials.[52] In RCTs, covariate adjustment leads to adjusted estimates of treatment effects, in contrast to unadjusted estimates. For example, adjusting for age results in an estimated treatment effect for a patient of a given age, while unadjusted analysis results in an estimated treatment effect for a patient of average age in the same sample. In the SID-GBS trial the effect of treatment was adjusted for the total

mEGOS score (combining age, MRC sum score and preceding diarrhea as predictors) after the first IVIg treatment.

Proportional odds model

The primary endpoint in the SID-GBS trial is the (full) GBS disability scale (Table 1) at 4 weeks as an ordinal outcome, instead of a dichotomization of the GBS disability scale (eg, GBS disability score of ≤2 vs >2). Analysis took place with a proportional odds regression model, such a model makes use of the full ordinal scale (Figure 1).[53] The proportional odds model provides a more sensitive analysis than would be possible by arbitrarily dichotomizing the outcome variable.[53] The disadvantage is that we have to make the assumption of proportional odds, that is, that the treatment effect (as an odds ratio) is similar across all possible cut-offs for the GBS disability scale. This assumption turned out to hold according to assessment afterwards by a test for heterogeneity of effect across cut-offs.

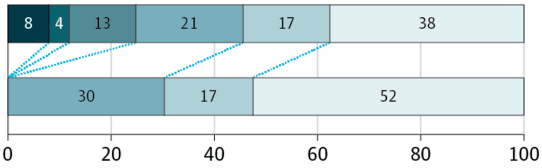

Figure 1 | Example of presentation of ordinal outcome

For the power calculations, we assumed a minimal 20% difference in the proportion of patients being able to walk unaided between the patients treated with and without a second IVIg course as a relevant outcome measure. This is quite a large difference, but we found that a small difference would not be clinically relevant in this group of severely affected GBS patients with poor prognosis. Also, in order to detect a small significant difference between treatment groups, the number of patients needed to randomize had to be much larger.

The SID-GBS trial – trial results

In the SID-GBS trial an mEGOS score of at least 6 (6-12) was used as a cutoff for poor prognosis. Of the patients with an mEGOS of ≥6 in the Erasmus GBS databank cohort (total n = 394), 85% were unable to walk unaided after 4 weeks and 35% were unable to walk unaided after 6 months. Patients were included from 59 hospitals in the Netherlands. It took 8 years to randomize the minimal amount of 87 GBS patients with a poor prognosis. This took longer than expected because we calculated that about 50% of the included patients would have a poor prognosis and would be randomized, this number was calculated in the historical Erasmus GBS databank cohort of treatment trial patients which was used to develop the mEGOS model in. In the end, it turned out that only 30% in the SID-GBS trial population had a poor prognosis.

Reason for this difference may be that the indication to start IVIg treatment in daily clinical practice had become wider over time. In former treatment trials one of the inclusion criteria for starting IVIg (or plasma exchange) was that a patient should not be able to walk unaided for 10 meters across an open space (GBS disability score ≥3). In the SID-GBS trial this was replaced by the criterion for inclusion that the treating physician must see an indication to start IVIg. This change was made because daily clinical practice was followed as much as possible and to be able to include patients who were started on IVIg treatment because they have a rapidly progressive disease course, albeit still able to walk unaided for 10 meters at that moment. However, this change in inclusion criteria also resulted in the fact that patients with a less severe disease course were included in the SID-GBS trial and thereby lowering the percentage of patients with a poor prognosis. This resulted in a long recruitment period as it took longer to randomize the numbers of patients with poor prognosis needed in the trial according to the power calculations.

Unfortunately, and in our view surprisingly, we did not find any significant added positive effect of a second IVIg course in GBS patients with a poor prognosis. The primary endpoint, nor any of the secondary endpoints were significantly different between groups, nor in any of the pre-specified subgroups an effect of a second IVIg course was shown. However, we did find significantly more serious adverse events in the group treated with a second IVIg course. The results of the trial are discussed in **Chapter 3.3**. General conclusion is that a second IVIg course should not be given in GBS patients with a poor prognosis because of the lack of therapeutic effect and the added risk of thromboembolic complications.

It remains a matter of debate why a positive effect of a second IVIg course was not found in the SID-GBS trial. Either a positive effect does not exist, or a small effect was not detected in our study. Of course, the latter could have been the case. In the end, the sample size was relatively small (of the 327 included patients, 93 patients were randomized) which resulted in a broad confidence interval. But this was logistically the maximum sample size possible, considering the rarity of GBS and the fact that we selectively randomized patients with a poor prognosis only in the study conducted by the Dutch GBS Study Group. However, inclusion of more patients would probably not have changed the conclusions of the trial.

Considering that a positive effect of a second IVIg course was not found, we have to take a critical look at the initial arguments for launching the SID-GBS trial.

1. About 10% of the GBS patients have a "treatment-related fluctuation" that usually respond to a second course of IVIg.[46]

A treatment related fluctuation (TRF) has been defined as a secondary deterioration after initial improvement or stabilization in the first 8 weeks after IVIg treatment and is seen in 8-16% of GBS patients.[46] Following expert opinion, these patients require re-treatment with a second IVIg course, which seems often successful. This suggests that, at least in patients with a TRF, one course of IVIg is insufficient. In the SID-GBS trial, 3 (6%) patients in the second IVIg course group versus 5 (11%) patients in the single course group had a TRF, which was not significantly different. Also, 2 (4%) patients per treatment group turned out to have an acute onset chronic inflammatory demyelinating polyneuropathy (A-CIDP), which subsequently was treated with one or multiple IVIg courses. This percentage of 4% resembles the percentage of A-CIDP in treatment trials known from literature.[46] It is often suggested that GBS, GBS with TRF(s), A-CIDP and CIDP are part of a continuum of immune mediated polyradiculoneuropathies.[54] Therefor a parallel in treatment response may exist between CIDP and GBS. In CIDP 24% (retrospective study) to 46% (ICE trial) of the patients did not respond adequately to IVIg, 75% of the non-responders in the retrospective study improved after either plasma exchange, corticosteroids or both.[55,56] In part this may be related to the presence of paranodal antibodies.[57] It would be interesting to investigate if paranodal antibodies also play a role in the GBS patients who responded poorly to IVIg treatment in the SID-GBS trial. Unlike CIDP, GBS has a small window of opportunity to select the most adequate treatment and identification of IVIg non-responders is needed early in the disease course. A prediction model for IVIg response in GBS does not exist. In CIDP predictors for non-response to IVIg are pain and a difference between level of weakness in arms and legs.[56] Further research is needed to find early, clinical predictors for IVIg non-response in GBS, but also to find biomarkers related with IVIg non-response like paranodal antibodies (NF155, Caspr1, Contactin1). This may lead to further understanding of the pathogenesis of GBS, which may not be identical in every patient and the working mechanism of IVIg.

2. A second course of IVIg is suggested to be effective in two small uncontrolled series of severe unresponsive GBS patients.[47,48]

As both studies were uncontrolled, selection bias probably played an important role. Only patients with a remarkable effect after a second IVIg course will be selected for publication. This argument for performing the SID-GBS trial was considered the weakest among these three. However, the contrasting results of the case series and the RCT is underlining the importance of performing randomized blinded studies.

3. A smaller increase in serum IgG level after IVIg treatment is related with poor recovery after 6 months.[37]

Patients with a low delta IgG (two weeks after IVIg compared with baseline) more often have a poor prognosis compared to patients with a high delta IgG.[37] The differences in pharmacokinetics of IVIg may underlie the heterogeneous clinical response to therapy.[37] The results of this study were validated with the data of the SID-GBS trial; GBS patients with a poor prognosis and who were randomized to the placebo group had a lower delta IgG level after 2 weeks than patients with a good prognosis (unpublished data). However, the high serum IgG peak level at one week after baseline was not different between patients with a poor or good prognosis (Figure 2 A, B). Possibly, at one week after start of IVIg the serum IgG level is still high because the redistribution of plasma IgG to tissues is ongoing and only afterwards differences in plasma IgG level arise between patients with good and poor outcome. Unfortunately, serum samples two weeks after initiation of the second IVIg course (3 weeks after baseline) were not collected in the SID-GBS trial and it remains unclear if the patients treated with two IVIg courses really reached a higher delta IgG compared with patients who were treated with one single course. Reasons for the differences in delta IgG after IVIg treatment may be the following. First, patients with a poor outcome may have a more severe auto-immune response with an increased catabolism of IVIg, resulting in a lower serum IgG level at two weeks after IVIg treatment. Second, there may be more 'consumption' of IgG. For example, by leakage of IgG through a damaged blood-nerve barrier, or by a highly activated complement cascade consuming large amounts of neutralizing antibodies from IVIg. Third, it may be that the differences in delta IgG result also from another source than exogenous IgG (by giving IVIg). An increase of blood plasmablasts after high dose IVIg was observed in GBS, but also after IVIg treatment in patients with other indications for IVIg.[58] The increase in plasmablasts in GBS patients was transient, being the highest at 1 week after the start of IVIg treatment. Perhaps the endogenous produced IgG by IVIg-induced plasmablasts peaks at two weeks after IVIg and influences outcome more than the IgG derived from IVIg. A high number of plasmablasts after IVIg treatment was associated with an earlier start of recovery.[58]

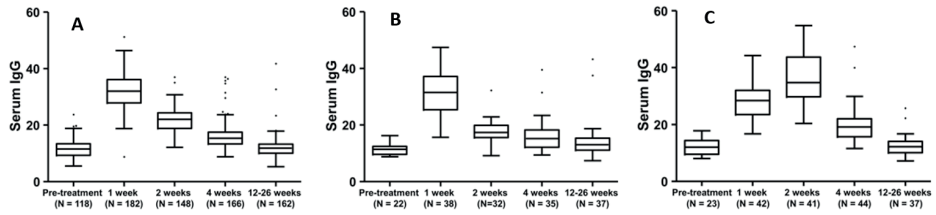

Figure 2 | Serum IgG at serial time points. Boxplots represent median serum IgG (line), with interquartile range (boxes) and range (whiskers) in (A) patients with good prognosis, (B) patients with poor prognosis treated with IVIg and placebo (5% albumin) and (C) patients with poor prognosis treated with two courses of IVIg (day 1-5 and day 7/8/9-11/12/13).

Probably, intertwined mechanisms play a role. This implies that in patients with poor predicted outcome, which is associated with low IgG levels, a second course of IVIg probably induces an increase in IgG level but apparently does not improve outcome. Probably other critical factors than IgG level limit the improvement in these patients.

We conducted a pre-specified subgroup analysis in patients with the 50% highest delta IgG at one week after the standard IVIg course compared with the 50% lowest delta IgG. This showed a trend towards a favorable effect of a second IVIg course in the lowest delta IgG group, and a trend towards a favorable effect of placebo in the subgroup of patients with the 50% highest delta IgG (data not published). This may suggest that there may be an optimal (and not the highest) delta IgG for a favorable outcome. However, in neither group a significant difference was found and the study wasn't powered to conduct these analyses properly.

Another reason why an effect could have been overlooked in the SID trial may have been the comparison with 4% albumin (placebo). Albumin was chosen because of similar fluid aspects, both solutions are slightly foaming liquids. In **Chapter 2.3** we describe a study in which we showed that a low serum albumin is a predictor for poor outcome. Albumin may have exerted its own positive effect in the 'placebo' group. Just like IgG, albumin uses the FcRn receptor to prevent degradation.[59] After IVIg treatment, serum IgG rises and serum albumin lowers.[36] One of the proposed working mechanisms of IVIg is that IgG from IVIg saturates the binding sites of FcRn, which then results in a more rapid degradation of pathogenic IgG. When exogenous albumin saturates the binding sites of FcRn, both the pathogenic IgG, as well as the IgG from IVIg cannot bind to FcRn, which may have positive and negative effects. It is however not sure if a direct competition between IgG and albumin for FcRn binding sites exists.[38] Hypoalbuminemia is an independent risk factor for poor outcome in acutely ill patients.[60] However, correction of hypoalbuminemia in critically ill patients of different cause did not led irrefutably to a better outcome.[60,61] To rule out a possible positive effect of albumin on outcome in the SID trial, a second control group can be created by selecting patients with propensity score matching from another prospective database who are treated with a standard course of IVIg alone.[62]

FUTURE PERSPECTIVES

Predicting outcome

Large prospective cohorts including the full spectrum of variants and severities of GBS will be needed to externally validate the reported prediction models (mEGOS and EGRIS). Currently the IGOS consortium has included the largest cohort of GBS patients worldwide and was designed specifically for prognostic modelling. This IGOS started in May 2012, and in March 2021 2000 patients were included. Patients are prospectively followed by members of the consortium

in 22 countries on 5 continents for at least 12 months, with an option to extend the follow-up with an additional 2 years. A validation of the EGRIS study in this cohort was described in **Chapter 2.2** (submitted). Also, the mEGOS was validated in this cohort and showed good performance, especially after recalibration for specific regions.[27] A limitation of the EGOS and mEGOS is that these models predict ambulation (GBS disability scale <3). Further research should focus on additional clinical outcome measures, for instance on predicting the disability of the arms and cranial nerves, and on patient reported outcome measures (PROMS). An example of a PROM is the I-RODS (Inflammatory Rasch-built Overall Disability Scale), which is a 24-item functional scale which assesses the ability of different components of everyday living like taking a shower, eating and sitting on the toilet. Prediction of long-term outcome is an important issue and frequently asked for in the outpatient clinic. A four week endpoint was used in the SID-GBS trial, a later endpoint may be even more relevant for the patient and may be used in new trials. Also interesting is longitudinal data analysis, in which a combined endpoint is used over multiple time points. Lastly, a model that predicts treatment response to IVIg can be very helpful to finally improve outcome in GBS. When an accurate prediction can be made if a patient will be a non-responder to IVIg in a very early stage, this patient may better be treated with plasma exchange or be a candidate for treatment trials with additional new treatments which are on the horizon.

Treatment for GBS

According to current trial evidence, GBS patients unable to walk unaided improve from treatment with IVIg or plasma exchange when treatment was started within the first two weeks from onset of weakness. It is possible that patients who are mildly affected (GBS disability score of 0-2) recover faster after two plasma exchanges compared to no exchanges.[63] It is not known if mildly affected patients benefit from IVIg also, however a recent observational study in this patient group showed no effect of IVIg.[64] It is not well known if mildly affected patients recover well with respect to neuropathic pain and fatigue. This leaves the opportunity to treat mildly affected patients with IVIg or plasma exchange, especially when within the first 2 weeks after onset of weakness, have severe arm dysfunction, cranial nerve involvement, still have progressive disease, or autonomic disturbances. This will be advised in the new European Academy of Neurology / Peripheral Nerve Society (EAN/PNS) guideline on GBS (personal communication).

A proportion of patients unable to walk unaided fully recover with IVIg. Especially for the remainder with a poor response to standard treatment with IVIg, new or more intensified treatment is needed. Treatments focusing on the active inflammation or complement activation in the early stage of disease, should start as soon as possible to prevent further axonal damage which then may still be reversible. To be able to select patients with a poor response to standard treatment for treatment trials we have developed prognostic models. As a first step towards personalized treatment of GBS we incorporated the mEGOS model in the design of

the SID-GBS trial. In this study we could confirm that the mEGOS model indeed was capable to accurately select patients with a poor outcome. Unfortunately the SID-GBS trial did not show improvement in outcome of these patients after a second IVIg course compared to a standard single course.[51,65] In future selective treatment trials, mEGOS (which can be used at hospital admission and 1 week after hospital admission) could be used to select the patient group which potentially will benefit the most of the treatment under investigation and avoid exposing patients with a good outcome to potential harms of the treatment. Also future treatment trials should use state of the art statistical approach to gain as much information as possible from the small sample sizes in this rare disease. Covariate adjustment and proportional odds analysis should preferentially be incorporated in trial design because these techniques make most efficiently use of trial data.[50]

Potentially relevant research is currently done to further elucidate the working mechanism of IVIg and the pathogenesis of GBS. This research is complicated by the fact that IVIg may have pleiotropic effects and that not all these effects may be equally relevant for all patients with GBS. IgG plays an important role both in the working mechanism of IVIg and the pathogenesis of GBS. It is complicating that we are currently unable to make a distinction in vivo between different types of IgG, namely: (1) pathogenic (endogenous) IgG directed against gangliosides and other glycolipids enriched in the peripheral nerve causing GBS, and (2) exogenous IgG infused as IVIg treatment. Promising now is an allotype ELISA, with which the proportion of infused IgG (from IVIg) can be determined. Because the blood donors population used to prepare IVIg do not display the same allotype as the individual patient with GBS (van Tilburg et al. manuscript in preparation). These studies may help to elucidate which of the multiple effects of IVIg exerts the most benefit in GBS. If known, it potentially may be possible to adapt the IVIg preparation in such a way to maximize de beneficial effects and minimize the detrimental effects (precision-based medicine).

Potential new treatments for GBS

Studies on the pathogenesis of GBS demonstrated that antibodies to gangliosides on peripheral nerves and local complement activation play a key role in the neural injury. Not surprisingly, there is now focus on the development of new treatments that focus on either inhibition of complement activation or deletion of pathogenic antibodies.[66]

The first complement inhibitor which was tested in a phase 2 trial in patients with severe GBS was eculizumab, a humanised monoclonal antibody against the complement protein C5. Patients were randomized to receive eculizumab or placebo in conjunction with IVIg. The first randomized clinical trial (ICA-GBS study) with eculizumab had difficulty recruiting patients and was prematurely stopped after 8 of the planned 30 randomizations because of a low inclusion rate and discontinuation of funding.[67] Conclusion from this study was that eculizumab

was well-tolerated and safe when administered in conjunction with IVIg.[67] In the second study (JET-GBS study) 34 patients were randomized. The primary outcome measure (the proportion of patients who reached functional grade 2 (able to walk 5 m independently in this study) or lower by week 4), did not reach the predefined response rate.[68] However, patients who received eculizumab did reach the ability to run (GBS disability score 1 or 0) earlier than the controls, but this was only a secondary endpoint and the clinical relevance seems debatable.[68] A phase 3, prospective, multicenter, double blind, randomized, placebo controlled study to evaluate the efficacy and safety of eculizumab in GBS patients will be started soon in Japan (NCT04752566).

Another promising complement inhibitor is a novel anti-C1q antibody (ANX005) that blocks initiation of the classical complement cascade. In two mouse models of GBS this treatment attenuated complement cascade activation and deposition, reduced immune cell recruitment and axonal injury, along with improvement in respiratory function.[66] A multicenter, phase 1b study to evaluate the safety, tolerability and drug-drug interactions of ANX005 in conjunction with IVIg is was recently conducted in GBS patients in Denmark and Bangladesh (ClinicalTrials.gov Identifier: NCT04035135). Preliminary results show that ANX005 in combination with IVIg was well tolerated and safe and C1q suppression was maintained within the 1-3 weeks targeted range of complement inhibition (personal communication).

The new treatments described above focus on inhibition of complement activation, other new treatments focus on pathogenic antibodies. For example, immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* (IdeS), which very rapidly cleaves IgG antibodies into F(ab')2 and Fc fragments, is secreted by *S. pyogenes*.[69] IdeS is an interesting candidate for a new treatment as it has been shown to block complement activation mediated by anti-ganglioside IgG antibodies *in vitro*.[70] IdeS potentially can be seen as a very rapid plasma exchange, as IdeS almost completely eliminates IgG (pathogenic and physiological) within about 2 hours. Afterwards IVIg should be given to replace physiological IgG and because this is a registered treatment for GBS. In 24 out of 25 kidney recipients IdeS reduced or eliminated donor-specific antibodies and permitted HLA-incompatible kidney transplantation.[71] A study with IdeS (Imlifidase) rapidly followed by IVIg is recently started in France and will also be conducted at Erasmus MC (ClinicalTrials.gov Identifier: NCT03943589).

Those new treatments likely will be extremely costly, although probably still cost-effective in a subgroup of patients when preventing long-term admission at ICU, medium care and rehabilitation units. In this situation it will become even more important to discriminate between patients that cost-effectively benefit from these treatments and those who are not. For this discrimination, prognostic models are likely very much helpfula. In developing countries IVIg and plasma exchange are for the most people too expensive, let alone the potential use of new biologicals. A phase two study was recently published with small volume plasma exchange

(SVPE). SVPE is blood cell sedimentation in a blood bag, followed by re-transfusion of the red blood cells and replacement of the supernatant plasma (with pathogenic IgG) by fresh frozen plasma. This treatment seems an affordable, safe and feasible alternative treatment to standard plasma exchange or IVIg for GBS in Bangladesh.[72] Further controlled studies of clinical efficacy are awaited.

FINAL REMARKS

GBS is a very heterogeneous , but often a severe condition that warrants optimal treatment for the whole spectrum of patients. The studies included in the thesis show that prognostication of various traits and outcomes for individual patients is possible in GBS, but should be further refined in the future. More knowledge about the clinical course and outcome of the disease now enables early intervention to improve the final outcome. A considerable proportion of GBS patients currently still has a poor outcome and unfortunately this outcome was not alleviated by a second IVIg course. In 2021 the first European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) GBS diagnostic and treatment guideline likely will be published and studies presented in this thesis will be incorporated in this guideline. Such a guideline likely will lead to more rapid and accurate diagnostics, and optimal use of current treatments. Fortunately, for the first time in decades both novel causative treatments and a relatively cheap treatment that potentially could be used in low-income countries are in sight. Very accurate prediction models, further understanding of the complex pathogenesis of GBS, and hopefully the promising results of novel potential treatments would ultimately lead to a better and more personalized treatment of patients with GBS.

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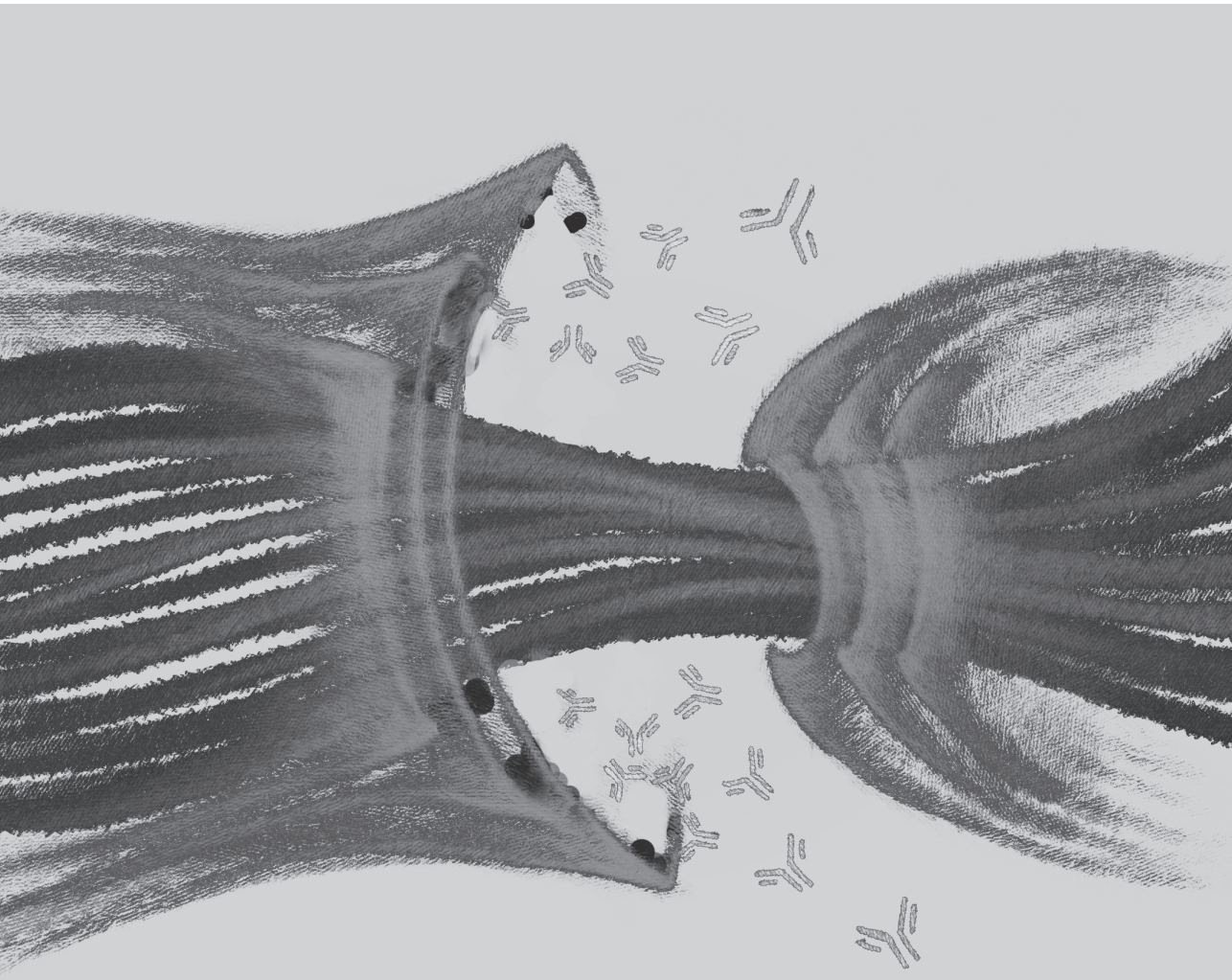


5

Summary / Samenvatting

SUMMARY

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy with a large variation in symptoms, severity of the disease and prognosis. In **Chapter 1**, the introduction, an overview is given of the pathogenesis, diagnosis, treatment en prognosis of the disease.

Because of the clinical diversity, it is important to make accurate prediction models. Those models can help to guide clinical decisions, to educate patients and their families and to design and interpret clinical trials. **Chapter 2** is focused on prediction of outcome in GBS. In **Chapter 2.1** we report an accurate prediction model (Erasmus Respiratory Insufficiency Score; EGRIS), which uses clinical predictors available at hospital admission to predict the probability of respiratory insufficiency within the first week after hospital admission. Points are allocated according to the following variables: the number of days between onset of weakness and hospital admission, the existence of facial or bulbar weakness and the MRC sum score (a score for the severity of weakness in arms and legs). The total score corresponds with a risk of respiratory insufficient (ranging between 2% and 89%). This model is currently incorporated in several national guidelines on GBS, will be incorporated in the new European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline on GBS and available as online tool to maximize user-friendliness (https://gbstools.erasmusmc.nl/prognosis-tool). This Dutch EGRIS model was validated in an international cohort of 1023 GBS patients from the International GBS Outcome Study (IGOS; included patients in 22 countries on 5 continents) in **Chapter 2.2**. This is important because substantial variability in the clinical presentation, disease course and outcome of GBS exists among patients from different regions worldwide. The study showed that the EGRIS model is valid for use in GBS patients from countries outside The Netherlands. The duration of mechanical ventilation ranges widely in GBS patients who needed mechanical ventilation. In **Chapter 2.3** we analysed the predictors of prolonged mechanical ventilation (>2 weeks). This is important for patient counselling and aids the decision to perform a tracheostomy or not. Ventilated GBS patients who are unable to lift the arms from the bed after one week of mechanical ventilation and patients who have axonal degeneration or unexcitable nerves at 1 week are at high risk of prolonged mechanical ventilation (resp. 87% and 90%), and tracheostomy should be considered in those patients.

In search for a biomarker with predictive abilities for long term outcome albumin was analysed in **Chapter 2.4**. Albumin is a relatively easily measurable biomarker. Serum albumin levels were measured before and after IVIg treatment and related to clinical outcome; muscle weakness, respiratory failure, and ability to walk. It turned out that patients with GBS may develop hypoalbuminemia after IVIg treatment and this is related to a more severe clinical course and a poor outcome. Even after correction for other known prognostic factors, hypoalbuminemia after IVIg was independently associated with poor outcome. Further studies are required to

confirm that serum albumin indeed can be used as a biomarker to monitor disease activity and treatment response to IVIg.

In **Chapter 2.5** a model that predicts the ability to walk at 4, 12, and 26 weeks after the beginning of the disease was described. This modified EGOS (mEGOS) model is a modification of the previous EGOS model which predict the ability to walk 6 months after the beginning of the disease. The EGOS model uses the following predictors for outcome; age, preceding diarrhea and GBS disability score at 2 weeks after hospital admission. Therefor this model cannot be used in the first two weeks of hospital admission. A model should be available as soon as possible for selection of patients for treatment trials. The mEGOS model is applicable at hospital admission and at one week after admission (after standard IVIg treatment) and uses the MRC sum score at admission or at one week after admission, age and preceding diarrhoea as predictors for functional outcome at 4, 12, and 26 weeks.

In **Chapter 3** the focus is on improving outcome for GBS patients. **Chapter 3.1** is a methodological study investigating the most efficient trial design. Randomized controlled trials pose specific challenges in GBS, as it is a rare and heterogeneous disease. Covariate adjustment and proportional odds analysis most efficiently use the available data and ensure balance between the treatment arms to obtain reliable and valid treatment effect estimates. Both techniques were used in the multicentre, randomized, double-blind, clinical trial which was initiated to study the additional value of a second IVIg course in GBS patients with a poor prognosis (SID-GBS trial). The protocol of the trial was published (**Chapter 3.2**). All newly diagnosed GBS patients (≥12 years of age) admitted to one of the in total 59 participating centres in the Netherlands could be included in the trial when there was an indication to start standard IVIg treatment (2 g/kg in 5 consecutive days) according to the treating neurologist. At one week after start of standard IVIg treatment, the prediction model described in **Chapter 2.4** was used to select GBS patients with a poor prognosis for randomization. Patients were randomized to receive a second IVIg course (2 g/kg in 5 consecutive days) or placebo (albumin 5% 8 ml/kg in 5 consecutive days). This trial medication was then started 7-9 days after start of the first standard IVIg course. The primary endpoint was improvement on the GBS disability score at 4 weeks after inclusion, secondary endpoints included MRC sum score, mechanical ventilation and adverse events at 4, 8, 12 and 26 weeks after inclusion. In **Chapter 3.3** the results of the trial were described. In total 339 patients were included, of those, 93 had a poor prognosis and were included in the analysis. No significant difference was found between the SID group and the placebo group for the primary endpoint; the adjusted common odds ratio for improvement on the GBS disability score at 4 weeks was 1.4 (95% confidence interval 0.6 to 3.3; p=0.4). All secondary outcomes were in the same direction as the primary outcome. However, the patients treated with SID had more serious adverse events, including thromboembolic events. We concluded that patients with a poor prognosis should not be treated with a second IVIg course.

GBS is a heterogeneous disease, this makes it important to construct accurate and user-friendly prediction models for various clinical outcomes. Prediction models are also important for the selection of patients for -and interpretation of clinical trials. Unfortunately a second IVIg course did not improve the outcome of GBS patients with a poor prognosis, but entails an increased risk of adverse events. Currently, one course of IVIg and precise supportive care is the mainstay treatment of all GBS patients. Ongoing and future treatment studies with biologicals against complement activation and IgG-degrading enzymes are urgently awaited.

SAMENVATTING

Guillain-Barré syndroom (GBS) is een immuun-gemedieerde polyradiculoneuropathie met een grote variatie in symptomen, ernst en prognose. In **hoofdstuk 1**, de introductie, wordt een overzicht gegeven van de pathogenese, diagnose, behandeling en prognose van de ziekte.

Omdat GBS een divers klinisch spectrum kent, is het belangrijk goede predictie modellen te maken. Deze modellen helpen om beslissingen over de behandeling te onderbouwen, om patiënten en hun familie voor te lichten en om de opzet en interpretatie van klinische trials te ondersteunen. **Hoofdstuk 2** focust op het voorspellen van uitkomst van GBS patiënten. In **hoofdstuk 2.1** wordt een accuraat predictie model (Erasmus GBS Respiratory Insufficiency Score; EGRIS) besproken, welke door gebruik te maken van eenvoudige klinische gegevens, direct op de eerste hulp, de kans op respiratoire insufficiëntie in de eerste week na ziekenhuis-opname kan voorspellen. Punten worden toegekend aan de volgende variabelen; aantal dagen krachtsverlies voor ziekenhuisopname, de aanwezigheid van bulbaire -of faciale parese en de MRC som score (een maat voor de ernst van spierzwakte van armen en benen). De totale score correspondeert met een bepaald risico op respiratoire insufficiëntie uitgedrukt in een percentage tussen de 2 en 89%. Dit model wordt inmiddels gebruikt in meerdere nationale richtlijnen over GBS, zal worden opgenomen in de nieuwe European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) richtlijn over GBS en is ook beschikbaar als gebruiksvriendelijke online tool (https://gbstools.erasmusmc.nl/prognosis-tool). Dit Nederlandse EGRIS model werd daarna gevalideerd in een internationaal cohort met 1023 GBS patiënten uit de International GBS Outcome Study (IGOS; patiënten werden geïncludeerd in 22 landen op 5 continenten) in **hoofdstuk 2.2**. Dit is belangrijk omdat er verschillen zijn wat betreft klinische presentatie, ziektebeloop en uitkomst tussen GBS patiënten uit verschillende regio's wereldwijd. Uit deze studie bleek dat het EGRIS model ook valide is voor gebruik bij GBS patiënten uit landen buiten Nederland. Bij GBS patiënten die moeten worden beademd, varieert de duur van de beademing sterk. In **hoofdstuk 2.3** worden de resultaten besproken van een studie naar voorspellers van lange beademingsduur (>2 weken). Dit is belangrijk voor de informatievoorziening van de patiënt en kan helpen in de beslissing al dan niet een tracheotomie te verrichten. Beademde GBS patiënten die de armen niet van het bed kunnen tillen na 1 week beademing en patiënten met een zenuwgeleidingsonderzoek met axonale degeneratie of waarbij in het geheel geen responsen opwekbaar zijn na 1 week hebben een hoog risico op langdurige beademing (respectievelijk 87% en 90%) en tracheotomie moet bij deze patiënten worden overwogen.

In de zoektocht naar een biomarker met sterke voorspellende waarde voor lange termijn uitkomst werd albumine onderzocht in **hoofdstuk 2.4**. Albumine is een relatief makkelijk en snel te bepalen biomarker. De concentratie van het albumine in het serum werd gemeten voor en na IVIg behandeling en dit werd gerelateerd aan de spierzwakte, het optreden van

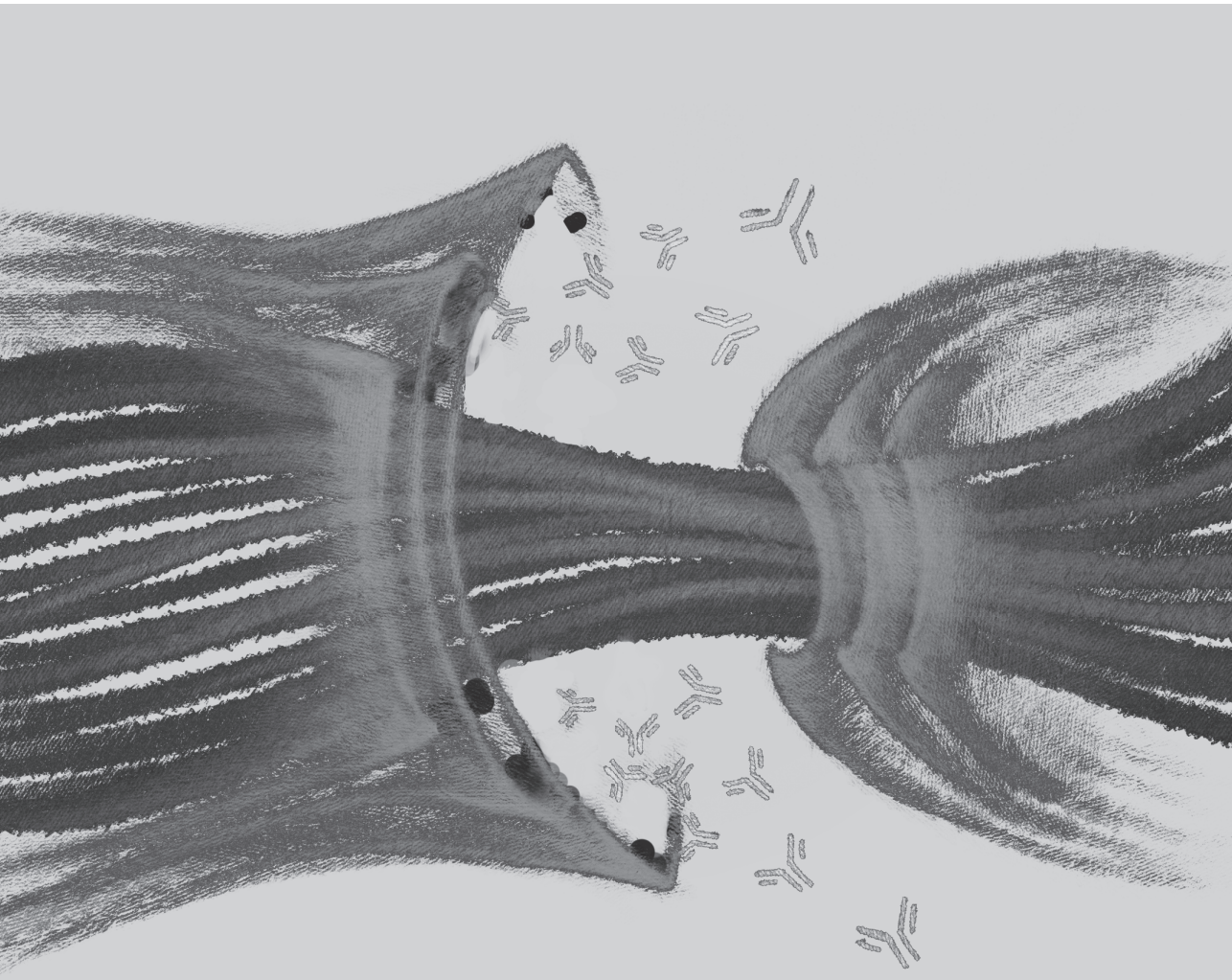
respiratoire insufficiëntie, en het vermogen zelfstandig te lopen. Het bleek dat er GBS patiënten waren die een hypoalbuminemie ontwikkelden na IVIg behandeling en dat deze groep patiënten een hoger risico had op een ernstiger ziektebeloop en een slechtere uitkomst. Dit effect bleef bestaan na correctie voor de andere bekende prognostische factoren. Aanvullende studies zijn nodig om onze resultaten te bevestigen en voordat albumine kan worden gebruikt als marker van ziekteactiviteit en het voorspellen van de uitkomst.

In **hoofdstuk 2.5** worden de resultaten besproken van een studie waarin een model werd ontwikkeld wat de kans op zelfstandig lopen voorspelt na 4, 12 en 26 weken na het begin van de ziekte. Het Erasmus GBS Outcome Score (mEGOS) model is een aanpassing op het eerdere EGOS model wat de mogelijkheid tot zelfstandig lopen voorspelt 6 maanden na begin van de ziekte. Het EGOS model gebruikt de volgende voorspellers: leeftijd, voorafgaande diarree en de GBS disability score twee weken na ziekenhuisopname. Om patiënten te selecteren voor trials met nieuwe behandeling moet een model vroeg in het ziektebeloop toepasbaar zijn. Het mEGOS model is toepasbaar bij ziekenhuisopname en 1 week na ziekenhuisopname en gebruikt leeftijd, voorafgaande diarree en MRC som score bij ziekenhuisopname of 1 week na opname als voorspellers voor de mogelijkheid tot zelfstandig lopen na 4, 12 en 26 weken na begin van de ziekte.

In **hoofdstuk 3** ligt de focus op het verbeteren van de uitkomst van GBS patiënten. **Hoofdstuk 3.1** is een methodologische studie gericht op efficiënt trial design. Het verrichten van gerandomiseerde studies bij GBS patiënten is een uitdaging, omdat het een zeldzame en heterogene ziekte betreft. Covariate adjustment en proportional odds analyse zorgen voor efficiënt gebruik van de beschikbare data en voor meer balans tussen de behandelarmen om op die manier een zo betrouwbaar en valide mogelijk trial resultaat te verkrijgen. Beide technieken werden gebruikt in de multicenter, gerandomiseerde, dubbelblinde, klinische trial die het effect van een tweede IVIg kuur bij GBS patiënten met een slechte prognose (SID-GBS) heeft onderzocht. Het protocol van de trial werd gepubliceerd (**hoofdstuk 3.2**). Alle nieuw gediagnosticeerde GBS patiënten (≥ 12 jaar) opgenomen in een van de in totaal 59 deelnemende ziekenhuizen in Nederland konden in de studie geïncludeerd worden wanneer er volgens de behandelend neuroloog een indicatie was voor standaard IVIg therapie (2 g/kg in 5 opeenvolgende dagen). Een week na het starten van de standaard IVIg kuur werd het predictiemodel (beschreven in **hoofdstuk 2.4**) gebruikt om patiënten met een slechte prognose te selecteren voor randomisatie. Patiënten werden gerandomiseerd voor een tweede IVIg kuur (2 g/kg verdeeld over 5 opeenvolgende dagen) of placebo (albumine 5% 8 ml/kg verdeeld over 5 opeenvolgende dagen). Deze trialmedicatie werd 7-9 dagen na het begin van de eerste standaard IVIg kuur gestart. De primaire eindmaat was verbetering op de GBS disability schaal 4 weken na start van de eerste standaard IVIg kuur, secundaire eindmaten waren onder andere MRC som score, beademing en adverse events 4, 8, 12 en 26 weken na inclusie. In **hoofdstuk 3.3** worden de resultaten van

de trial beschreven. In totaal werden er 339 patiënten geïncludeerd, 93 daarvan hadden een slechte prognose en werden geïncludeerd voor de uiteindelijke analyse. Er werd geen significant verschil gevonden tussen de SID groep en de placebo groep voor de primaire uitkomstmaat; de adjusted common odds ratio voor verbetering op de GBS disability schaal op 4 weken was 1.4 (95% betrouwbaarheidsinterval 0.6 tot 3.3; p=0.4). Geen van de secundaire uitkomstmaten was significant verschillend tussen beide trial armen. Echter, de patiënten die met SID behandeld zijn hadden vaker een ernstige bijwerking, inclusief trombo-embolische complicaties. Hieruit concluderen we dat GBS patiënten met een slechte prognose niet behandeld moeten worden met een tweede IVIg kuur.

GBS is een heterogeen verlopende ziekte, dit maakt het belangrijk om accurate en gebruiksvriendelijke predictiemodellen te ontwikkelen voor diverse klinische uitkomsten. Predictiemodellen zijn ook belangrijk voor de opzet en de interpretatie van de resultaten van klinische trials. Helaas heeft een tweede IVIg kuur de uitkomst van GBS patiënten met een slechte prognose niet verbeterd en geeft dit bovendien een verhoogd risico op complicaties. Momenteel is een standaard IVIg kuur en goede medische en verpleegkundige ondersteuning de behandeling voor alle GBS patiënten. De resultaten van nieuwe studies met biologicals die complement activatie remmen of IgG afbreken worden met spanning tegemoet gezien.



6

Appendices

DANKWOORD

En dan het dankwoord. Geen enkel onderdeel van mijn proefschrift heb ik zo lang voor me uitgeschoven als dit onderdeel. En dat wil wat zeggen…

Allereerst wil ik alle GBS patiënten bedanken die deelnamen aan onze SID-GBS studie. Op het moment dat zij met deze ernstige ziekte werden geconfronteerd, hebben zij besloten deel te nemen aan wetenschappelijk onderzoek. Dat is bewonderenswaardig en ik ben hen allen zeer erkentelijk voor hun deelname! Ook wil ik benadrukken dat de totstandkoming van dit proefschrift een enorme team effort is geweest van vele neurologen in Nederland die belangeloos GBS patiënten includeerden in onze studie. Ontzettend bedankt daarvoor.

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ABOUT THE AUTHOR

Christa Walgaard was born on November 2nd 1981 in Dirksland, the Netherlands. She studied medicine at the Erasmus Medical Centre in Rotterdam. During her study she was a board member of the Rotterdam Medical Student Association (MFVR) in 2002-2003. After obtaining her medical degree in 2007 she worked at the Department of Neurology at the Erasmus Medical Centre as a resident in neurology. Here, her interest in the Guillain-Barré syndrome started and resulted in PhD research under supervision of Prof. Dr. P.A. van Doorn and Prof. Dr. B.C. Jacobs which started in 2008. Between 2008 and 2021 she participated in the setup and completion of the nationwide, multicentre, randomized controlled trial which investigated the added effect of a second IVIg course in GBS patients with poor prognosis (SID-GBS trial). In 2010 she received the Neuromuscular year prize of the Dutch Prinses Beatrix Spierfonds for the best neuromuscular diseases related publication: "Prediction of Respiratory Insufficiency in Guillain-Barré Syndrome". In 2019 she won the international Prof. Richard A.C. Hughes prize for the best clinical trial abstract for the SID-GBS trial. In 2011 she started her neurology training at the Department of Neurology at the Erasmus Medical Centre (head: Prof. Dr. P.A.E. Sillevis Smitt). After completing her neurology training in 2019 she worked as a neurologist in the Maasstad hospital in Rotterdam and continued GBS research in the Erasmus Medical Centre for half a day per week until October 2021. From then on she works as a neurologist in the IJsselland Hospital in Capelle aan den IJssel. She lives with her partner Aart Geurtsen and their three children; Nora, Anouk and Cato, in Rotterdam.

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PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: C. Walgaard	PhD period: 2008 - 2021
Erasmus MC Department: Neurology	Promotor(s): Prof. P.A. van Doorn & Prof. B.C. Jacobs

1. PhD training

	Year	Workload (ECTS)
General courses		
- Principles of Research in Medicine and Epidemiology	2008	0.7
- Introduction to Data-analysis	2008	1.0
- Methods of clinical research	2008	1.0
- Clinical trials	2008	1.0
- Large scale multicenter studies	2008	1.0
- Pharmaco-epidemiology	2008	0.7
- BROK (Basic course Rules and Organization for Clinical researchers	2008	1.5
- Regression Analysis	2009	1.9
- Biomedical English Writing	2010	2.0
- Recertification BROK	2014 / 2019	
- Microsoft Access 2010: Basic	2018	0.3
- Microsoft Access 2010: Advanced	2018	0.4
Seminars and workshops		
- Department journal clubs and seminars	2008 - 2019	2.0
- Boerhaave neuromuscular course, Leiden/Amsterdam (10x)	2008 - 2021	5.0
Oral presentations (& conference attendance)		
- PNS/INC meeting Sydney	2010	0.9
- PNS/INC meeting Sitges	2017	1.2
- PNS Baltimore	2018	1.2
- PNS/INC meeting Genoa	2019	1.2
- European Academy of Neurology conference Oslo	2019	1.2
- Scientific Meeting NVN Garderen	2019	0.5
- PNS Virtual Event	2020	0.3
Poster presentations (& conference attendance)		
- PNS meeting Wurzburg (1 poster)	2009	1.2
- PNS meeting Potomac (3 posters)	2011	1.2
- PNS/INC meeting Rotterdam (2 posters)	2012	1.2
- Scientific Meeting NVN Garderen (1 poster)	2013	0.5
- INC meeting Dusseldorf (1 poster)	2014	1.2

- INC meeting Glasgow (1 poster)	2016	1.2
- PNS Virtually Anywhere	2021	0.3
(International) conferences		
- INC meeting Paris	2008	0.5

2. Teaching

	Year	**Workload (ECTS)**
Lecturing		
- Neuromuscular Study Group Utrecht (oral presentation)	2009	1.0
- Venticare Utrecht (oral presentation)	2010	1.0
- Muscle disease congress Veldhoven (oral presentation)	2010	1.0
- Muscle disease congress Veldhoven (poster presentation)	2012	0.5
- Muscle disease congress Veldhoven (poster presentation)	2018	0.5
- GBS-CIDP symposium Rotterdam (oral presentation)	2018	1.0
- Muscle disease congress Veldhoven (oral presentation)	2019	1.0
- Neuromuscular Study Group Utrecht (oral presentation)	2019	1.0
Continuous activities		
- Teaching nurses and medical students	2008 - 2021	0.5
- reviewing papers for international peer-reviewed journals	2013 - 2019	1.0
Other		
- Advising role CBO multidisciplinary guideline GBS	2011	0.5
Total		41.3