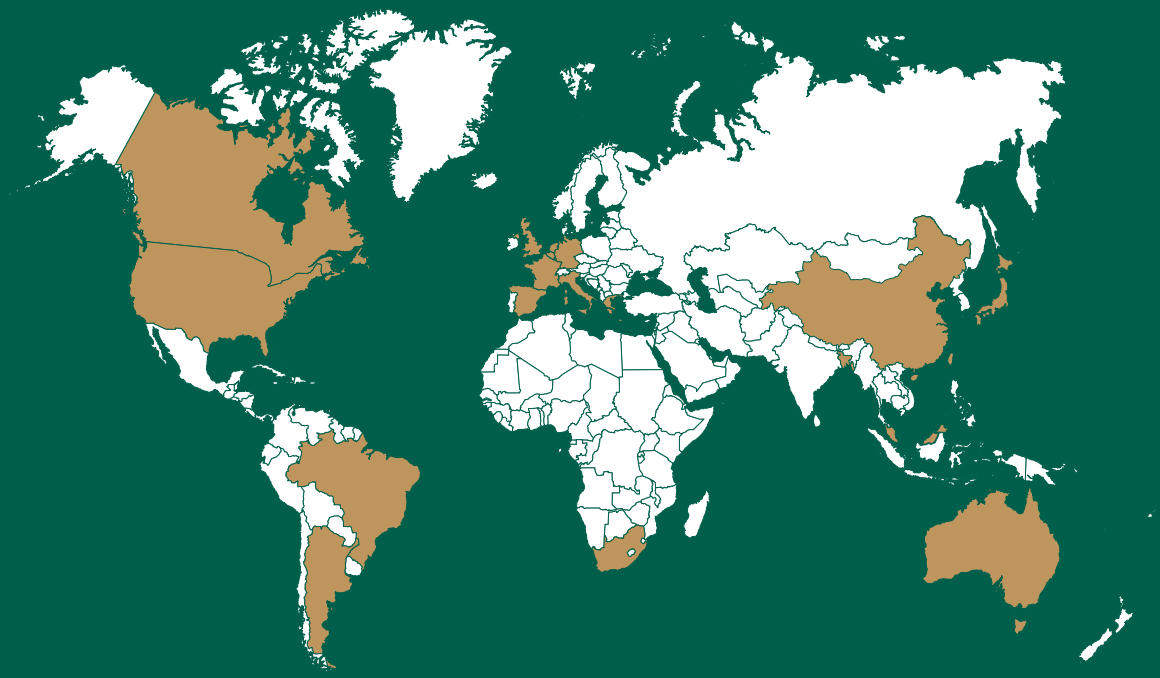
Regional variation in diagnosis, prognosis and treatment of Guillain-Barré syndrome



Alex Y. Doets

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Regional Variation in Diagnosis, Prognosis and Treatment of Guillain-Barré Syndrome

Regionale variatie van diagnose, prognose en behandeling van het Guillain-Barré syndroom

Thesis

to obtain the degree of Doctor from the
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Note: The research articles included in this thesis may have undergone some further (textual) editing during the publication process.

1

Background and Introduction

1.1

General introduction and scope of the thesis

In 1916, three neurologists – Georges Guillain, Jean Alexandre Barré and André Strohl – first reported on two soldiers who suffered from an acute flaccid paralysis, in whom the cerebrospinal fluid (CSF) showed an elevated protein level but a normal cell count[1]. Until that time, poliomyelitis was the most common cause of acute paralytic illness, which was characterized by an increased cell count in the CSF and poor recovery of muscle strength. In contrast, the two soldiers reported by Guillain, Barré and Strohl did show clinical recovery, and this distinct syndrome later came to be known as the Guillain-Barré syndrome (GBS)[1]. Further historical studies have taught us that the first cases of GBS were already described in 1859 by Landry. But this description lacked the characteristic features of the CSF and deep tendon reflexes, as these were not yet part of the routine neurological examination at that time[2]. Since the report of Guillain, Barré and Strohl, GBS has evolved into a recognized disorder of the peripheral nervous system with a highly diverse clinical presentation and disease course. Despite the existing treatments, morbidity and mortality remain substantial. To optimize disease management and improve outcome, accurate prediction of the clinical course in individual patients with GBS is required.

Guillain-Barré syndrome

Clinical presentation and diagnosis

The Guillain-Barré syndrome is an acute onset inflammatory disorder affecting the peripheral nervous system. Patients typically present with a rapidly progressive, symmetrical weakness and hypo- or areflexia of the limbs, often accompanied by sensory deficits and cranial nerve involvement[3, 4]. Up to 30% of GBS patients develop respiratory muscle weakness requiring admission to an intensive care unit (ICU). The autonomic nervous system is involved in about two-thirds of cases, resulting in a wide variety of symptoms, including bladder and bowel disturbances, blood pressure fluctuations and cardiac arrhythmias[4]. GBS is a rare disorder. The reported incidence ranges from 0.4 to 2.5 per 100.000 person-years, and varies considerably between countries. Although GBS can affect people from all age groups, the incidence rate increases with age, and males are more frequently affected than females[3, 5, 6]. Diagnosis is primarily based on the patient history and neurological examination, but can be supported by additional investigation of the CSF and peripheral nerve conduction. CSF examination is mainly performed to rule out other diagnoses, and typically shows an elevated protein level and a normal cell count, also referred to as 'albuminocytological dissociation'. Nerve conduction studies (NCS) can show features of demyelination, axonal damage or both. However, when performed early in the disease course, both CSF examination and NCS also may be normal[7-9]. GBS is often considered a disease spectrum in which various clinical variants and electrophysiological subtypes can be distinguished. Clinically, a distinction is made between sensorimotor GBS, pure motor GBS (without sensory in-

volvement), Miller Fisher syndrome (MFS), overlap syndromes and local variants such as the pharyngeal-cervical-brachial variant. The MFS is characterized by the clinical triad of ophthalmoplegia, ataxia and areflexia[8, 10]. In addition, different subtypes of GBS can be distinguished based on peripheral nerve pathology studies and NCS, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) [11-13].

Pathogenesis

The general consensus is that GBS is an immune-mediated disorder in which the immune system is activated by a preceding infection or other external stimulus. Symptoms of a preceding infection are reported by two-thirds of GBS patients, and mostly comprise upper respiratory and gastro-intestinal tract infections[4]. For some infectious agents, a temporal association with GBS has been established by case-control studies: *Campylobacter jejuni, Mycoplasma pneumoniae,* Epstein-Barr virus, cytomegalovirus, hepatitis E virus and Zika virus[14-16]. The role of vaccination and surgical procedures as potential triggers for GBS is more controversial[17-19]. The Covid-19 pandemic and the development of the Covid-vaccines have further promoted the debate on the potential role of vaccination in the pathogenesis of GBS. In post-vaccination GBS, clinical guidelines advise to weigh the benefits of vaccination with the potential risk of recurrent GBS, but a definitive association between vaccination and GBS has yet to be established[17]. Pathology studies in patients with GBS have shown infiltration of peripheral nerves and nerve roots by macrophages and lymphocytes. In addition, deposits of antibodies and activated complement factors on nerve myelin and axons have been demonstrated in GBS patients in relation to the presence of demyelination or axonal degeneration. In the serum of a subgroup of GBS patients, antibodies to various gangliosides (or ganglioside complexes) or other peripheral nerve glycolipids are found, some of which have been shown to induce complement-dependent peripheral nerve dysfunction in animal models[2, 13]. Most of these antibodies are likely induced during the preceding infectious illness as part of the immune defense mechanism, and disappear from the serum during follow-up and clinical recovery. Experimental studies have shown that in GBS patients with a preceding bacterial infection, the nerve dysfunction that is caused by these autoreactive antibodies is driven by a mechanism called “molecular mimicry”. This mechanism is defined by the resemblance between structures on the outer surface of bacteria and those on the peripheral nerve membranes[20-22].

Treatment

Standard treatment for GBS consists of either intravenous immunoglobulin (IVIg, 0.4 g/kg bodyweight daily, for 5 consecutive days) or plasma exchange (PE, 200-250 ml plasma/kg bodyweight in five sessions) in combination with supportive care[8, 23, 24]. Corti-

costeroids alone, either oral or intravenous, or in combination with IVIg, are not effective for GBS, and oral steroids might even delay recovery[25]. Respiratory insufficiency is a common complication of GBS that requires active monitoring to prevent delayed intubation. About 20-30% of GBS patients require mechanical ventilation at some point during the disease course, and in most cases ventilation is already initiated within the first week of hospital admission[4, 26]. Other symptoms and signs that require monitoring or treatment at a high care or intensive care facility include autonomic dysfunction, involving cardiac arrhythmia's and blood pressure disturbances, and bulbar involvement resulting in impaired swallowing or a decreased cough reflex[8]. Furthermore, immobilized GBS patients will require standard preventive measures to avoid complications such as pressure ulcers, nosocomial infections, deep vein thrombosis or contractures. In addition, special attention needs to be paid to pain, hallucinations and the psychological impact of the disease (e.g. anxiety and depression).

Clinical course and prognosis

The disease course in GBS is usually monophasic, with symptoms reaching maximum severity within 2 to 4 weeks. The clinical progressive phase is followed by a plateau phase – in which symptoms are stable – and a recovery phase. The duration of the plateau and recovery phase vary greatly between patients, ranging from days to weeks for the plateau phase, and weeks to years for the recovery phase[4]. This characteristic clinical course of GBS is explained by the immune-response directed against the peripheral nerves and nerve roots that (in most patients) is short-lasting (weeks) and results in Wallerian degeneration followed by a slow nerve recovery[13]. Five to 10% of GBS patients show a secondary deterioration after initial improvement or stabilization, also referred to as a 'treatment-related fluctuation (TRF)', and 2-5% have recurrent disease[27-31]. Some GBS patients may present with only mild weakness and sensory deficits, and show fast and complete recovery, while others may develop a tetraparalysis with respiratory and autonomic involvement, and have severe residual deficits or die because of complications. The clinical course and prognosis also differ between variants and subtypes of GBS. Patients with MFS usually have a favourable outcome, even without immunomodulatory treatment[32]. In contrast, patients with pure motor and axonal GBS (AMAN) – a variant that is associated with preceding diarrhea and a *C. jejuni* infection – often show more severe motor weakness and a worse outcome[33].

Variation of GBS and implications for disease management: knowledge gaps

Disease management in individual patients with GBS is highly complicated by the variability in clinical course and outcome. Previously, it has been suggested that part of this variability may be attributed to regional differences. Single country studies have shown differences in the distribution of GBS clinical variants and electrophysiological subtypes,

with sensorimotor and demyelinating GBS being more frequently reported in studies from Europe and North America, and higher prevalences of pure motor and axonal GBS in studies from Asian and South American countries[11, 34-40]. However, direct comparison between countries was limited as these studies often used different diagnostic criteria for GBS or focused on specific subgroups. Moreover, most previous studies had small sample sizes and used a retrospective study design, and the majority of prospective studies in GBS were based on trials with selective inclusion criteria. Gaining more insight into this regional variability could lead to a further understanding of the disease modifying factors, including the role of host and environmental factors. Moreover, a better understanding of factors defining disease diversity is required to develop a more "personalized" approach for the management of GBS (Fig 1).

Variation in CSF features: implications for diagnosis and prognosis

Although the CSF protein level and cell count are the only widely available diagnostic markers in GBS, their clinical usefulness has been debated. Previous studies have already shown that the CSF protein level varies with the time to lumbar puncture, and that some patients with GBS may have a normal protein level[41-43]. In addition, several studies have reported variations in the CSF protein level between different GBS clinical and electrophysiological subforms[43, 44]. While most GBS patients have a normal CSF cell count, reports have been published describing patients who present with the typical features of GBS but have an elevated cell count[41, 43, 45, 46]. Although in daily practice the CSF protein level is merely used to support the diagnosis of GBS, a high CSF protein has been related to more severe disease and a worse prognosis[47-49], which may be explained by more severe inflammation of the nerve roots, which are in close proximity to the CSF. However, most reports on CSF findings in GBS are based on retrospective studies in limited numbers of patients and whether the CSF protein level adds to existing clinical prediction models for GBS, is currently unknown.

Applicability of existing prediction models in an international setting

Many studies have been performed to identify clinical and electrophysiological features and biomarkers, that can be used to predict outcome in GBS early in the disease course. Some of these individual prognostic factors have been combined into clinical prediction models for GBS, including the modified Erasmus GBS Outcome Score (mEGOS) and the Erasmus GBS Respiratory Insufficiency Score (EGRIS)[26, 50]. With the mEGOS, clinicians can estimate the probability that an individual patient with GBS will not be able to walk independently at 4 weeks, 3 months and 6 months after disease onset. The mEGOS can be calculated at either hospital admission or day 7 after admission and is based on three clinical factors: age, the presence of diarrhoea before the onset of weakness, and the severity of limb weakness. The mEGOS total score ranges from 0 to 9 points at admis-

sion, and from 0 to 12 points at day 7, corresponding with a 6% to 95% risk of being unable to walk independently at 4 weeks, and 1% to 66% risk of being unable to walk independently at 6 months [50]. The EGRIS can be used to predict the risk of respiratory insufficiency within the first week of hospital admission, and is based on the number of days between onset of weakness and hospital admission, the presence of facial and/or bulbar weakness, and limb muscle strength at admission. The EGRIS score ranges from 0 to 7 points, and corresponds to a risk of respiratory insufficiency ranging from 1% to 90%[26]. Both the mEGOS and EGRIS have been developed with data from a Dutch GBS cohort, but are also used outside The Netherlands to predict outcome in GBS patients. It is currently unknown if the Western GBS phenotype is representative of GBS in Asian countries or South America, or if model performance may vary in these different regions.

Regional variation of treatment practice for GBS

Despite the efforts to improve treatment for GBS, standard therapy has remained unchanged for almost three decades. IVIg and PE are proven effective in severely affected GBS patients who have lost the ability to walk, but evidence for efficacy in specific subgroups of GBS patients, including mildly affected patients, MFS and GBS-TRF, is lacking. In addition, even with immunomodulatory treatment some patients still show disease progression, 20% is unable to walk independently after 6 months, and 3-10% die, emphasizing the need for more effective treatments [4]. Treatment guidelines for GBS are largely based on expert consensus, and currently there is no international treatment guideline, which may lead to extensive variability in treatment practice among countries. Describing the variability in treatment practice of GBS, and to identify factors that define this variability, may provide a basis for the development of new clinical trials and an international treatment guideline.

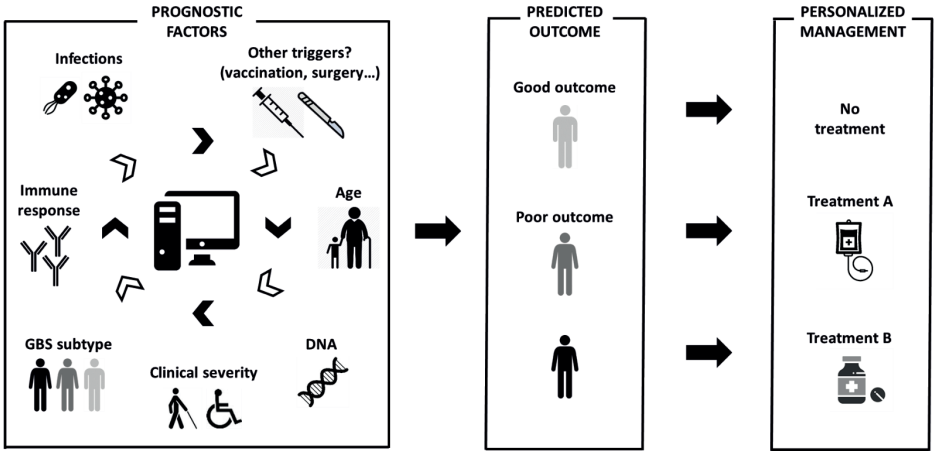


FIGURE 1.

International GBS Outcome Study (IGOS)

In 2012, the International GBS Outcome Study (IGOS) was initiated to define the diversity of GBS, and to identify clinical factors and biomarkers that can be used to predict the clinical course and outcome of GBS in an early phase of the disease. The IGOS aimed to include the full spectrum of patients diagnosed with GBS, independent of age, disease severity, clinical variant, subtype, treatment or outcome. The IGOS is a collaborative effort among clinicians and researchers from 21 countries and more than 160 hospitals around the world. The study uses a standardized protocol to prospectively collect clinical and electrophysiological data, and biomaterial (serum, CSF, DNA) during a follow up of minimum 1 year (Fig 2). Neurologists were free to conduct a diagnostic work-up and treat the patients in accordance with their local guidelines and personal preferences, and as such the IGOS can be classified as a study with 'real world data' representing current clinical practice. This study firstly allowed the comparison of GBS patients from different countries in a standardized manner. The IGOS aimed to include 2000 patients, a number that was reached in May 2021[51].

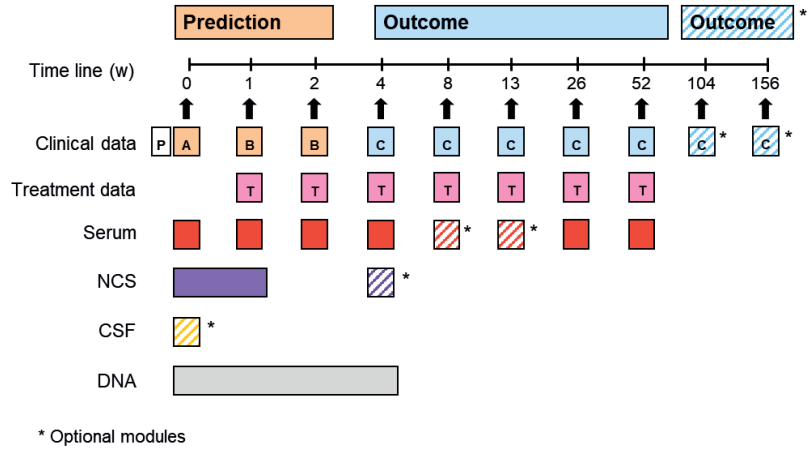
Thesis aim and objectives

The research described in this thesis focuses on the regional variation in clinical presentation, diagnosis, treatment and prognosis of GBS, and intends to validate the existing prediction models for GBS, and to develop new prognostic models to predict outcome in individual patients with GBS. More specifically, the objectives of the studies in this thesis are:

1. To define the variability in clinical presentation, diagnostic features, subtypes, and clinical outcome between GBS patients from various geographical regions.
2. To describe the variability in CSF protein level and cell count in relation to demography, disease severity, subtype and outcome of GBS.
3. To validate and improve current clinical prognostic models for GBS that predict the risk of respiratory insufficiency and the inability to walk independently.
4. To identify novel predictors for respiratory insufficiency in GBS.
5. To define the variation in the current treatment practice of GBS among countries.
6. To evaluate the efficacy of treatments other than IVIg, plasma exchange and corticosteroids for GBS

For the studies included under objectives 1 to 5 data were used from three separate IGOS cohorts: the IGOS-1000, the IGOS-1300 and the IGOS-1500 cohort. The study on the efficacy of other treatments for GBS was based on a review of the existing literature.

A. IGOS study protocol



B. IGOS participating countries

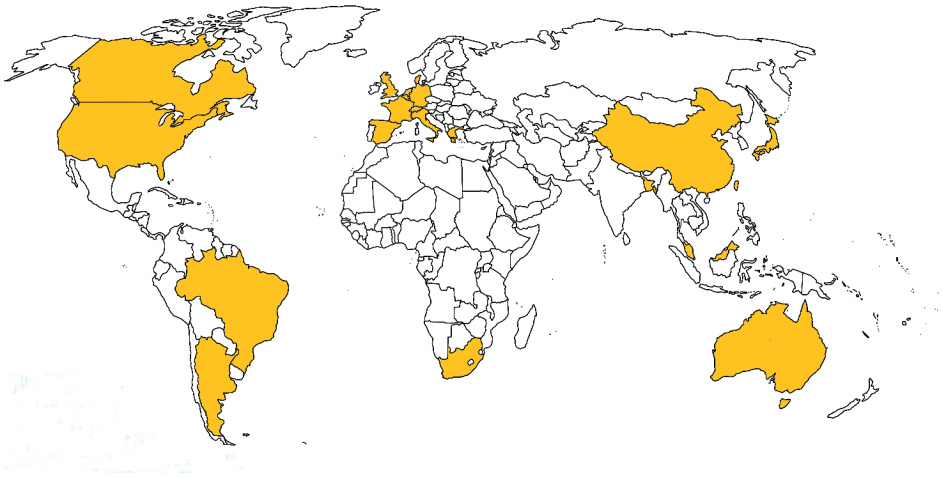


FIGURE 2.

Outline

Chapter 2 covers the clinical characteristics and diagnosis of GBS. In **Chapter 2.1** the clinical characteristics, disease course and outcome are compared among GBS patients from different geographical regions, who were included in the IGOS-1000 cohort. **Chapter 2.2** describes the variation in CSF protein level and cell count for the GBS patients included in the IGOS-1500 cohort, and evaluates these findings in light of the existing diagnostic criteria for GBS. In addition, the independent prognostic value of the CSF protein level is determined. **Chapter 3** elaborates on the prognosis and outcome of GBS. In **Chapter 3.1 and 3.2** the mEGOS - for the prediction of walking ability – and the EGRIS – for the prediction of respiratory insufficiency in GBS – are validated within

the IGOS-1500 cohort. Simple updating techniques are used to further improve model performance and to develop region-specific versions of the mEGOS and EGRIS models. In **Chapter 3.3** the predictive ability of the mEGOS model is evaluated in a patient cohort from Bangladesh, providing insight into mEGOS model performance in a low-income setting. In **Chapter 3.4** new predictors for respiratory insufficiency in GBS are identified by using the IGOS-1500 cohort, and a simplified multivariable model is developed. **Chapter 4** covers the treatment of GBS. In **Chapter 4.1** the current treatment practice of GBS is compared among the various countries participating in IGOS. **Chapter 4.2** contains a systematic review and meta-analysis on treatments other than IVIg, PE and corticosteroids for GBS. In **Chapter 5** the results of these studies are discussed in relation to the existing literature on GBS, and knowledge gaps and suggestions for future research are provided.

Chapter 6 provides a summary of the studies described in **Chapter 2-4**.

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1.2

Advances in management of Guillain-Barré syndrome

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Bart C. Jacobs
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Current Opinion in Neurology. 2018 Oct;31(5):541-550.

ABSTRACT

Purpose of review

The clinical presentation of Guillain-Barré syndrome (GBS) is highly variable, which can make the diagnosis challenging. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are the cornerstone of treatment since decades. But despite these treatments, 25% initially progress in muscle weakness, 25% require artificial ventilation, 20% is still not able to walk independently after 6 months, and 2-5% die, emphasizing the need for better treatment. We summarize new developments regarding the diagnosis, prognosis and management of GBS.

Recent findings

GBS is a clinical diagnosis that can be supported by cerebrospinal fluid examination and nerve conduction studies. Nerve ultrasound and MRI are potentially useful techniques to diagnose inflammatory neuropathies. Several novel infections have recently been associated to GBS. Evidence from experimental studies and recent phase 2 clinical trials suggests that complement inhibition combined with IVIg might improve outcome in GBS, but further studies are warranted. Prognostic models could guide the selection of patients with a relatively poor prognosis that might benefit most from additional IVIg or otherwise intensified treatment.

Summary

New diagnostic tools may help to have early and accurate diagnosis in difficult GBS cases. Increased knowledge on the pathophysiology of GBS forms the basis for development of new, targeted, and personalized treatments that hopefully improve outcome.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute onset immune-mediated polyradiculoneuropathy characterized by a rapidly progressive, bilateral weakness of the limbs and hypo- or areflexia. [1, 2] Weakness is often accompanied by sensory symptoms, and both cranial and autonomic nerve fibers can also be involved. [3] Pain may precede the onset of weakness. [3, 4] Several clinical variants can be distinguished, such as the Miller Fisher syndrome, the pharyngeal-cervical-brachial variant and paraparetic GBS. [3] Because the presentation is highly variable, the diagnosis can be challenging in clinical practice. The diagnosis can be supported by cerebrospinal fluid (CSF) examination and/or nerve conduction studies (NCS). Based on NCS, two main subtypes of GBS can be distinguished: acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) [3]. However, CSF and NCS findings are normal in a subset of patients, especially early in the course of disease, emphasizing the need for new diagnostic techniques. [5] Nerve ultrasound and MRI have been suggested as potentially useful diagnostic techniques for GBS. [6-9] Infections precede GBS in the majority of cases, but other events, such as vaccinations, have also been reported preceding GBS. [3, 10] Identifying the trigger for GBS is important to understand the underlying pathogenic mechanisms, but also to anticipate for a possible rise in incidence following an epidemic or pandemic, as was seen with the recent Zika virus (ZIKV) infection. [11, 12]

Current standard treatment for GBS is intravenous immunoglobulin (IVIg) or plasma exchange (PE), but despite these treatments morbidity and mortality is still substantial. [3] Previous experimental findings indicated an important role for antibody-mediated complement activation in the pathogenesis of GBS, providing a basis for therapeutic studies with complement inhibitors as the first "targeted therapy" for GBS. [13-16] Prognostic models are now available that can be helpful to select patients that may potentially benefit from new treatment modalities. [17-19]

In this review we will give an overview of the advances in the management of GBS. The main focus will be on new developments with respect to preceding infections, diagnostic techniques, treatment and prognosis. Results of recent phase 2 trials with the complement inhibitor eculizumab, and future perspectives regarding an intensified IVIg treatment schedule or other novel therapeutic agents will be discussed.

Preceding infections and pathophysiology

Extensive progress has been made in understanding how preceding infections result in peripheral nerve damage in GBS, especially in the AMAN subtype. Infections with *Campylobacter jejuni*, the predominant preceding infection of GBS, may result in the produc-

tion of cross-reactive antibodies that bind to human peripheral nerve gangliosides, a process that is referred to as "molecular mimicry". [3, 10] Binding of these antibodies to the peripheral nerves may result in activation of complement, and local deposition of membrane attack complexes and infiltration of macrophages, resulting in disruption of the axonal membrane. [3, 10] The underlying pathogenic mechanism for AIDP seems to be more complex, as in the majority of these patients no antibodies were found. In some patients with AIDP, antibodies were identified to individual gangliosides or ganglioside complexes, but their role in the pathogenesis in these cases is unknown. [3]

Various types of infections have previously been associated with GBS[3], but in about half of the cases a preceding infection remains elusive. Recently novel causative agents have been identified. Hepatitis E virus (HEV) infections were found in 5-11% of GBS cases, compared to less than 1% of controls. The definition of an acute HEV infection differed between studies, but was generally based on detecting viral genome or anti-HEV immunoglobulin M (IgM) antibodies in serum, sometimes supported by the presence of anti-HEV immunoglobulin G (IgG) antibodies. [20-24] In 75% of GBS patients with anti-HEV IgM seropositivity, liver enzymes were elevated, but this finding indicates that HEV-related GBS may also occur in absence of laboratory signs of hepatitis. [21-23] *Mycoplasma pneumoniae* has previously been associated to GBS, but only in a small subgroup (< 5%) of patients. [3, 25] Interestingly, a case-control study recently demonstrated IgM antibodies to *M.* pneumoniae in 21% of children with GBS, compared to 7% of pediatric controls. [26] Preceding *M. pneumoniae* infections were associated with antibodies to galactocerebroside (GalC), and cross-reaction of anti-GalC antibodies was seen with different strains of *M. pneumoniae,* including an isolate from a GBS patient. [26] In 2013, a Zika virus (ZIKV) outbreak in French Polynesia was followed by a 20-fold increase in GBS cases. A case-control study conducted during the outbreak period found neutralizing antibodies against ZIKV in 100% of GBS cases and 56% of controls. [11] Since then multiple studies have been performed on the association between ZIKV and GBS, but definitive causality has yet to be established. [12, 27]

At present, the identification of the type of preceding infection in GBS usually has no consequences for therapeutic management. However, some preceding infections are related to specific clinical variants or subtypes of GBS and may influence the prognosis. This could be important in future management of GBS, to predict the clinical course and develop a more individualized treatment approach. [3] In addition, knowing the trigger of GBS may be relevant to prevent cases of GBS in the future. [28] Most infections related to GBS are very common, indicating that host susceptibility factors probably play an additional role in the pathogenesis. For instance, patients with a *C. jejuni*-related GBS have an intrinsic higher dendritic cell response to *C. jejuni* lipo-oligosaccharides than

controls. [29] A recent cohort study investigated the role of a functional polymorphism of the neonatal Fc receptor in IVIg pharmacokinetics and disease course of GBS, but did not find any association. [30] More research is needed to gain better insight into the host-factors that are involved in GBS.

Diagnosis

Clinical criteria

The first diagnostic criteria for GBS date from 1978, and were revised in 1990 by Asbury and Cornblath. [1] In 2011, the Brighton Collaboration provided new case definitions for GBS and Miller Fisher syndrome (MFS) for vaccine safety monitoring. [2] For the Brighton classification, GBS diagnosis is subdivided into 4 levels of certainty (level 1: highest level of diagnostic certainty; level 4: lowest level of diagnostic certainty) based on clinical symptoms, CSF and NCS findings. Recently, the Brighton criteria were validated in three independent cohorts of patients with GBS. These studies showed that in patients with a complete dataset level 1 or 2 was reached in 94% of 335 Dutch adult patients, 99% of 220 adult patients from Bangladesh, and in 96% of 46 Dutch children. [5, 31, 32] The performance of the Brighton criteria is highly dependent on the completeness of data, and is possibly influenced by the timing of hospital admission. In previous validation studies it was not possible to determine the specificity of the Brighton criteria, because all included patients fulfilled the National Institute of Neurological Disorders and Stroke criteria for GBS and patients with alternative diagnosis were excluded. Owing to the incorporation of both CSF and NCS findings, the Brighton criteria are most likely less suitable for diagnosing GBS with a high level of certainty in the acute phase of disease, because these laboratory findings may then still be normal.

The presentation of GBS in children may differ from adults, and especially young children can be more difficult to examine, which may cause diagnostic delay. As pain is a frequent complaint in children with GBS, it should be taken into account for when considering the differential diagnosis. [32-34]

Cerebrospinal fluid (CSF)

A classical finding of CSF examination in GBS is the albuminocytological dissociation. A large cohort study showed that the CSF protein level is highly dependent on the timing of lumbar puncture. When lumbar puncture was performed within one day from onset of weakness, 49% of patients had an elevated protein level, which increased to 88% of patients after 2 weeks. [5] In the same study, only 64% of GBS patients showed the characteristic albuminocytological dissociation in CSF. [5] Recently, age-specific reference values for CSF protein level were defined for children. [35] In children younger than six

months of age, the additional value of CSF total protein determination was considered nihil, because of large physiological variation in protein levels. [35]

Nerve conduction studies (NCS)

Multiple electrophysiology criteria sets have been developed for GBS[36-38], however much debate is ongoing concerning the validity of these criteria, and on the optimal frequency of NCS for GBS subtype diagnosis. [39, 40] A recent cohort study compared subtype diagnosis based on different criteria sets, and found a higher proportion of axonal cases with more recent criteria, but similar anti-ganglioside antibody frequencies – which are considered the gold standard for subtype classification - among subtype classifications based on different criteria sets. [39] The main relevance of NCS for GBS in current clinical practice is to confirm the diagnosis, especially in atypical cases, such as paraparetic GBS, by finding either signs of demyelination or abnormalities in regions that are clinically not affected. Although nowadays classification into different subtypes has no direct therapeutic implications, this could potentially become more relevant in future management. In previous prognostic studies features of axonal degeneration were often associated with a poor prognosis, which could implicate that these patients might benefit from additional or more aggressive treatment. [3] Furthermore, the transient nature of the reversible conduction block, that has been deemed specific for AMAN[3, 41], could imply an underlying antibody-mediated mechanism, for which targeted therapies could potentially be developed.

Nerve ultrasound and MRI

Nerve ultrasound is already a commonly used diagnostic tool in mononeuropathies and traumatic neuropathies, and its use especially in the diagnosis of chronic immune-mediated polyneuropathies is increasing. [6] Nerve ultrasound could potentially provide a useful addition to or less-invasive alternative for some currently used diagnostic techniques in GBS, especially in children. Nerve enlargement in GBS is reported to be present 1-3 days following symptom onset, but is usually mild and segmentally distributed. [6, 7] Proximal nerve segments and spinal nerve roots seem to be most commonly involved, but the distribution of nerve enlargement may vary with subtype. [6, 7, 42] Cervical nerve root enlargement has been described in both demyelinating and axonal forms of GBS, and in MFS. [6, 7] Furthermore, several studies have been conducted on the diagnostic utility of contrast-enhanced spinal MRI in GBS. [7-9, 43] Enhancement and thickening of spinal nerve roots and cauda equina were both found in patients with typical, but also with paraparetic GBS (Figure 1). [7-9, 43] MRI therefore could be helpful not only to exclude differential diagnostic abnormalities, but also to indicate nerve (root) swellings that may add to the diagnosis of GBS. Additional studies in larger series of patients are however needed.

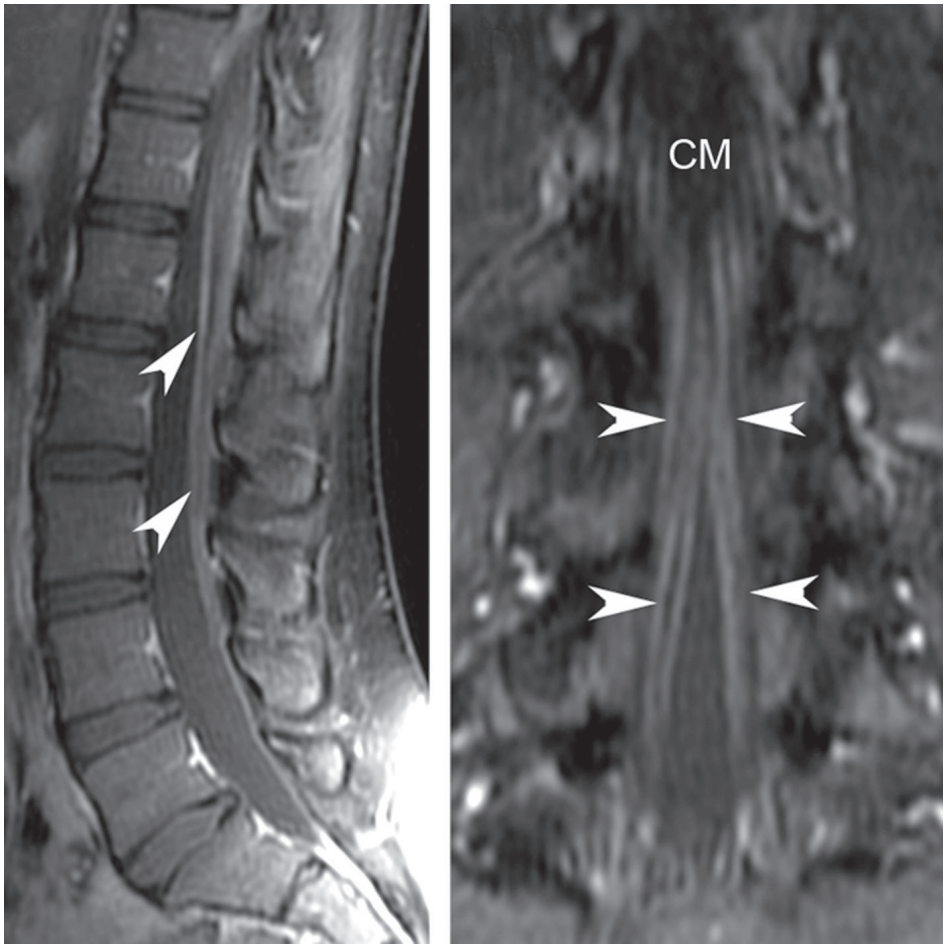

Figure 1. Enhancement and thickening of cauda equina nerve roots on contrast-enhanced MRI.[43]
Postcontrast sagittal (left) and coronal (right) T1-weighted, fat-saturation MRIs of the lower thoracic and lumbosacral spine, performed on day 4, showing diffusely thickened cauda equina (arrowheads). Adapted with permission.
[43] Berciano J, Gallardo E, Orizaola P, et al. Early axonal Guillain-Barre syndrome with normal peripheral conduction: imaging evidence for changes in proximal nerve segments. J Neurol Neurosurg Psychiatry. 2016;87(5):563-5.

Treatment

Plasma exchange started within 4 weeks, and IVIg initiated within 2 weeks from onset of weakness, are proven effective treatments for adult patients with severe GBS.[44, 45] However, GBS remains a life-threatening disorder with substantial morbidity and mortality, emphasizing the need for better treatment.

Trials that evaluated the effect of corticosteroids found no benefit compared to supportive care alone.[46] The combination of methylprednisolone with IVIg was not superior over IVIg alone, though post-hoc analysis indicated that the time to recovery seemed

somewhat shorter in the IVIg plus methylprednisolone group after correction for known prognostic factors.[46] No clear benefit was observed when plasma exchange was followed by IVIg, compared to plasma exchange or IVIg alone.[45] There have been other small randomized controlled trials (RCT) with various drugs that either showed no differences between the treatment arms or were impaired by small numbers of patients.[47]

In some patients, deterioration continues, even after standard treatment with plasma exchange or IVIg. These patients might potentially benefit from an additional course of treatment. There currently is a large RCT that investigates whether a second course of IVIg is of benefit when administered early in the course of disease in GBS patients with a poor prognosis. This second-dose IVIg study in GBS (SID-GBS trial) is conducted in the Netherlands, and the results are expected early 2019.[48]

Plasma exchange and IVIg are expensive treatments that most patients in low-income countries cannot afford. This explains in part why patients in, for instance, Bangladesh show a high morbidity and mortality rate. Currently, an open study is conducted investigating the safety and feasibility of small volume plasma exchange, a low-cost alternative for plasma exchange. Results of this pilot study are soon expected.[49]

Mild GBS

Most of the previously conducted RCTs are performed in adult GBS patients with severe disease. Whether patients with mild disease would benefit from treatment with IVIg or plasma exchange remains largely unknown, but some evidence suggests that the time to onset of motor recovery in mildly affected patients is reduced with two cycles of plasma exchange.[45] Treatment practice and effect of treatment in patients with mild GBS is currently being investigated in the International GBS Outcome Study (IGOS), a multicenter prospective cohort study on GBS.[50]

Children

Trials in children are sparse, but limited evidence suggests a benefit of IVIg in hastening recovery over supportive care alone.[44]

Pain

Pain is a frequently reported symptom, and occurs in the full spectrum of GBS, and at all stages of disease.[3,4]

In a subgroup of patients, pain precedes the onset of weakness, which may induce diagnostic delay, particularly in children.[3,4] Defining the appropriate management for pain in GBS is complicated, because of the varying types of pain and unknown underlying

pathogenic mechanisms.[3, 4] In the acute phase of GBS, significant reductions in pain scores and reduced analgesic consumption were reported for gabapentin and carbamazepine.[51] No effect on the frequency of reported pain or pain severity was observed for treatment with methylprednisolone.[51] Larger, high quality trials are needed to evaluate safety and efficacy of therapeutic interventions for pain in GBS, both in the acute and recovery phase of disease.

Novel therapies

Much effort has been made in the development of therapeutics that prevent the complement-dependent neuronal damage underlying GBS.[13, 14] Two randomized, double blind, placebo-controlled phase 2 trials have evaluated the safety and efficacy of eculizumab – a complement factor 5 inhibitor – in GBS (Figure 2). In the Inhibition of Complement Activation in GBS study, patients were randomized to receive IVIg with eculizumab or placebo. The small patient number precluded conclusions on efficacy, but eculizumab was deemed safe and well tolerated.[15] The Japanese Eculizumab Trial for GBS used the same study protocol, and randomized 23 patients to IVIg with eculizumab, and 12 patients to IVIg with placebo. The predefined response rate threshold for the eculizumab group was not reached, but a larger proportion of patients in the eculizumab group was able to run at 24 weeks (74%), than in the placebo group (18%). In most patients, eculizumab was well tolerated, although causality with two serious adverse events could not be excluded.[16] These studies implicate that eculizumab seems safe and well tolerated, and might potentially improve outcome in GBS as add-on treatment to IVIg, but larger trials are required. Another complement inhibitor that was shown effective in mouse models of AMAN and MFS is an anti-complement factor 1 (C1)q antibody (Figure 2).[13] Currently, a phase I clinical trial to assess safety and tolerability of anti-C1q antibody (ANX005) in healthy volunteers is being conducted.[52]

Another potentially promising therapeutic agent is the IgG-degrading enzyme that is secreted by *Streptococcus pyogenes* (IdeS). The enzyme cleaves IgG-molecules into the antigen-binding fragment - $F(ab')_2$ - and Fc-portion, and is therefore expected to be effective in GBS through the cleavage of pathogenic antibodies (Figure 2).[53] A phase 2 trial for IdeS is planned in Europe.[54] Furthermore, reports of *in vitro* and animal studies and case reports on the efficacy of biological drugs in GBS show promising results, but clinical trials are needed to extent these findings.[55]

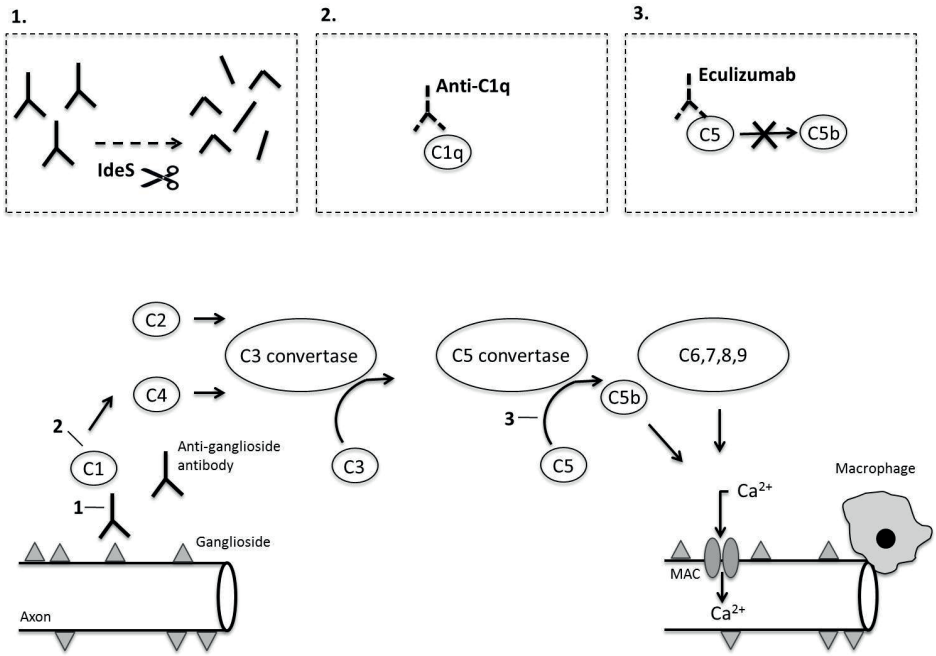

Figure 2. Novel potential therapies for Guillain-Barré syndrome.
IdeS cleaves IgG into the F(ab')$_2$ and Fc portion.
Anti-C1q inhibits complement factor C1q, thereby preventing downstream activation of the complement cascade. Eculizumab is a humanized monoclonal antibody that binds to complement factor 5, thereby preventing the conversion of C5 to C5b (and C5a), and the subsequent formation of MACs.
C1, complement factor 1; F(ab')$_2$, antigen-binding fragment; IdeS, IgG-degrading enzyme secreted by *Streptococcus pyogenes*; MAC, membrane attack complex; IgG, immunoglobulin G.

Prognosis and outcome

Relapses of GBS

GBS is usually a monophasic disease, but secondary deteriorations after initial stabilisation or improvement occur in 5-10% of treated GBS patients.[3,56] These "treatment-related fluctuation" (TRF) are thought to result from a transient treatment effect in patients with a prolonged disease activity. Some patients may have two or more deteriorations, and are eventually diagnosed with acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP), or have a recurrent episode of GBS. The differentiation between GBS-TRF, A-CIDP and recurrent GBS is important, especially because A-CIDP might require maintenance treatment or a switch from IVIg to corticosteroids. A-CIDP should specifically be considered in patients with three or more subsequent deteriorations, or when the first deterioration occurs more than eight weeks after the onset of weakness.[3,56] GBS recurrences are reported in 2-7% of GBS cases, and seem to occur more frequently in younger patients, patients with a mild disease course, and MFS.[57-59] Another study found more recurrences in patients with AIDP than in patients with axonal subtypes.[59]

MFS

Outcome in typical MFS is usually considered to be favorable, with high likelihood of complete recovery, even with a conservative approach. [60] However, a substantial proportion of patients with MFS develop additional limb weakness (± 25-40%), bulbar weakness (40%) or autonomic disturbances (10%) during the course of disease. [61-63] Early predictive factors for progression of MFS to MFS-GBS overlap syndromes have not yet been identified, but progression of MFS after 1 week from symptom onset is rare. [62, 63] Therefore, close monitoring of MFS patients for at least 1 week is advised. [60, 63]

Clinical predictors

Despite standard treatment, about 25% of patients with GBS require mechanical ventilation. [3] In a recent meta-analysis an increased risk of intubation was found in patients with a shorter duration from symptom onset to hospital admission, neck or bulbar weakness, and more severe muscle weakness at admission. [64] One study found an association between coexisting infectious illness at admission, specifically cytomegalovirus and herpes simplex virus infections, and the need for mechanical ventilation. [65] The Erasmus GBS Respiratory Insufficiency Score (EGRIS) is a prognostic model that predicts the probability of respiratory failure within the first week of admission in individual patients with GBS, based on the time from onset of weakness to hospital admission, presence of facial and/or bulbar weakness at admission, and the MRC sum score at admission (Figure 3). [18, 64] Mechanical ventilation appears to be a negative predictive factor for long-term outcome in GBS, and is often accompanied by both local and systemic complications. [19, 66] Several factors have been associated with prolonged mechanical ventilation, for example, the inability to lift the upper arms from the bed, axonal damage and unresponsive nerves on NCS. Presence of these features could guide the decision for early tracheostomy in individual patients, to prevent tracheal or vocal cord damage. [19] Poor outcome in GBS is often defined as the inability to walk unaided during follow up. The modified Erasmus GBS Outcome Score (mEGOS) is a clinical scoring system that predicts the probability of being unable to walk independently during the first six months follow up, based on age, preceding diarrhoea and MRC sum score (Figure 4). [17] Prognostic models can be applied in therapeutic trials to identify patients that might benefit from additional treatment, as has been done in the SID-GBS trial. The EGRIS and mEGOS were originally based on a cohort of Dutch GBS patients, and recently also showed good performance in a Japanese cohort. [67] Additional validation studies in other countries are required to assess the generalizability of these models.

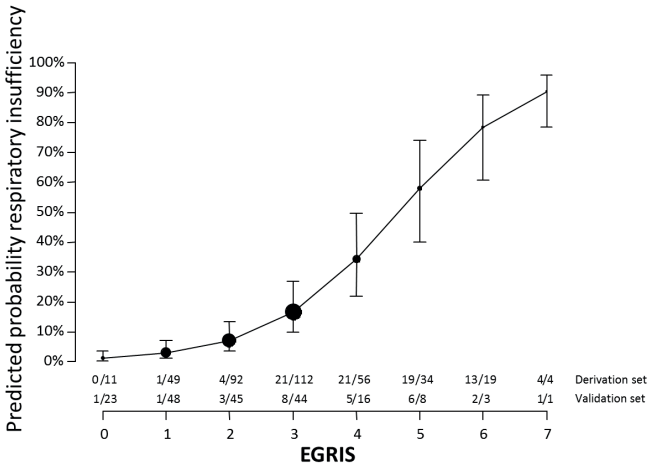

Figure 3. Erasmus GBS Respiratory Insufficiency Score (EGRIS).[18]
Erasmus GBS Respiratory Insufficiency Score (EGRIS). Prognostic variables and provided EGRIS scores: time from onset of weakness to hospital admission (days): >7 (score 0), 4–7 (score 1), ≤3 (score 2); facial and/or bulbar weakness: absent (score 0), present (score 1); MRC sum score at admission: 51–60 (score 0), 41–50 (score 1), 31–40 (score 2), 21–30 (score 3), ≤20 (score 4); the total score (0–7) is calculated by the sum of the subscores. GBS, Guillain–Barré syndrome; MRC, Medical Research Council. Adapted with permission.
[18] Walgaard C, Lingsma HF, Ruts L, et al. Prediction of respiratory insufficiency in Guillain-Barre syndrome. Ann Neurol. 2010;67(6):781-7.

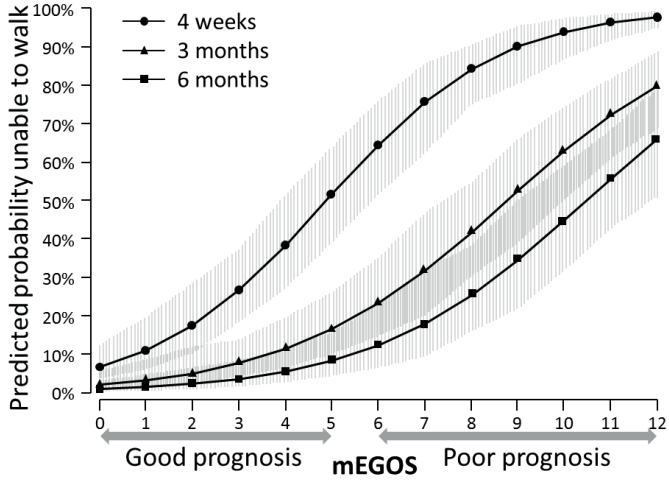

Figure 4. Modified Erasmus GBS Outcome Score (mEGOS) at day 7 of admission.[17]
Modified Erasmus GBS Outcome Score (mEGOS) at day 7 of admission. Prognostic variables and provided mEGOS scores: age: ≤40 (score 0), 41–60 (score 1), >60 (score 2); preceding diarrhea: absent (score 0), present (score 1); MRC sum score (day 7 of admission): 51–60 (score 0), 41–50 (score 3), 31–40 (score 6), 0–30 (score 9); the total score (0–12) is calculated by the sum of the subscores. GBS, Guillain-Barré syndrome; MRC, Medical Research Council. Adapted with permission.
[17] Walgaard C, Lingsma HF, Ruts L, et al. Early recognition of poor prognosis in Guillain-Barre syndrome. Neurology. 2011;76(11):968-75.

Biomarkers

Serum albumin was recently proposed as a new and easily accessible biomarker for GBS.[68] Low pre- and posttreatment serum albumin levels were associated with respiratory failure, and low posttreatment levels were associated with a more severe disease course and poorer outcome at 6 months. The addition of serum albumin to the EGRIS and mEGOS models resulted in a better predictive ability, indicating that biomarkers may improve the accuracy of existing clinical prediction models.[68, 69]

Conclusion and future perspectives

As GBS was first described over a century ago, knowledge on the pathophysiology and diversity of the clinical syndrome has greatly evolved, and treatment with IVIg or plasma exchange has been introduced.[10] The validity of existing electrophysiology criteria for GBS is under debate, and research is being performed on the diagnostic utility of nerve ultrasound and MRI in the diagnosis of GBS. A new international guideline for the management of GBS is currently being developed by the European Academy of Neurology and Peripheral Nerve Society. There is increasing evidence that complement activation plays a critical role in the pathophysiology of GBS. The first results of small trials with eculizumab are promising, but need to be confirmed in larger studies. Additional trials with other inhibitors of the complement cascade or with drugs that interfere with pathogenic or complement fixing antibodies are indicated. In the meantime, the results of the SID-GBS RCT, evaluating the effect of a second course of IVIg in GBS patients with a poor prognosis, are eagerly awaited. Current prognostic models for GBS are a required condition to personalize treatment. An opportunity to validate these models in an international population of patients and to discover new clinical and biological predictors of outcome will come from the International GBS Outcome Study, world's largest prospective study on GBS.[50]

Key points

- Identifying preceding infections and establishing causality with GBS increases knowledge on the epidemiology and pathophysiology of GBS, and additionally allows for anticipation to a rise in incidence of GBS following unusual epidemics.
- Nerve ultrasound is a potentially useful diagnostic tool for GBS in addition to NCS by detecting nerve enlargement in an early phase of disease.
- Contrast-enhanced MRI in GBS can show enhancement and thickening in the cauda equina and nerve roots, and could be helpful to diagnose GBS, especially in atypical cases.
- Complement inhibition constitutes the first potential "targeted therapy" for GBS, and might improve outcome as add-on treatment to IVIg.

- Prognostic models can help to identify patients with a poor outcome in an early stage of disease, which might provide a basis for a more personalized intensified or additional treatment.

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2

Clinical presentation and diagnosis of GBS

2.1

Regional variation of Guillain-Barré syndrome

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ABSTRACT

Guillain-Barré syndrome is a heterogeneous disorder regarding the clinical presentation, electrophysiological subtype and outcome. Previous single country reports indicate that Guillain-Barré syndrome may differ among regions, but no systematic comparative studies have been conducted. Comparative studies are required to identify factors determining disease susceptibility, variation and prognosis, and to improve diagnostic criteria. The International Guillain-Barré syndrome Outcome Study is a prospective, observational cohort study including all patients within the diagnostic spectrum, aiming to describe the heterogeneity of Guillain-Barré syndrome worldwide. The current study was based on the first 1000 inclusions with a follow up of at least 1 year and confirmed the variation in clinical presentation, course and outcome between patients. The full clinical spectrum of Guillain-Barré syndrome was observed in patients from all countries participating in the International Guillain-Barré syndrome Outcome Study, but the frequency of variants differed between regions. We compared three regions based on geography, income and previous reports of Guillain-Barré syndrome subtypes: 'Europe/Americas', 'Asia'(without Bangladesh), and 'Bangladesh'. We excluded 75 (8%) patients because of alternative diagnoses, protocol violations, or missing data. The predominant clinical variant was sensorimotor in Europe/Americas (*n* = 387/562, 69%) and Asia (*n* = 27/63, 43%), and pure motor in Bangladesh (*n* = 74/107, 69%). Miller Fisher syndrome and Miller Fisher-Guillain-Barré overlap syndrome were more common in Asia (*n* = 14/63, 22%) than in the other two regions (Europe/Americas: *n* = 64/562, 11%;Bangladesh: *n* = 1/107, 1%)($P < 0.001$). The predominant electrophysiological subtype was demyelinating in all regions (Europe/Americas: *n* = 312/573, 55%;Asia: *n* = 29/65, 45%;Bangladesh: *n* = 38/94, 40%). The axonal subtype occurred more often in Bangladesh (*n* = 34/94, 36%) than in Europe/Americas (*n* = 33/573, 6%) and other Asian countries (*n* = 4/65, 6%)($P < 0.001$). In all regions, patients with the axonal subtype were younger, had less sensory deficits, and showed a trend towards poorer recovery compared to patients with the demyelinating subtype. The proportion of patients able to walk unaided after 1 year varied between Asia (*n* = 31/34, 91%), Europe/Americas (*n* = 334/404, 83%) and Bangladesh (*n* = 67/97, 69%)($P = 0.003$). A similar variation was seen for mortality, being higher in Bangladesh (*n* = 19/114, 17%) than in Europe/Americas (*n* = 23/486, 5%) and Asia (*n* = 1/45, 2%)($P < 0.001$). This study showed that factors related to geography have a major influence on clinical phenotype, disease severity, electrophysiological subtype, and outcome of Guillain-Barré syndrome.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy that yearly affects approximately 100,000 people worldwide[1]. While GBS is an established clinical syndrome with defined diagnostic criteria[2, 3], patients differ considerably in clinical presentation, disease course, and outcome. Patients may have clinical variants of GBS, including Miller Fisher syndrome (MFS) and pure motor, paraparetic, or pharyngeal-cervical-brachial forms[4]. The electrophysiological characteristics of GBS are likewise heterogeneous and include two major subtypes with demyelinating or axonal features[4]. Some patients are mildly affected and recover spontaneously, but others develop tetraplegia and respiratory or autonomic failure requiring intensive care and remain severely disabled or die despite treatment[5]. The time to improvement is reduced with plasma exchange (PE) or intravenous immunoglobulin (IVIg) [6-8] but most patients in low-income countries receive supportive care only[9].

Comparison of previous studies conducted in single countries suggests that the variation of GBS may be influenced by factors related to the geographical origin of patients, such as endemic infections or unusual epidemics like the recent GBS peaks related to Zika virus[10, 11]. These studies illustrate a wide variability in prevalence of clinical variants and electrophysiological subtypes of GBS between regions, suggesting that sensorimotor and demyelinating GBS predominate in Europe and North-America, whereas pure motor and axonal GBS are more frequent in Asian and South-American countries[4, 12-20]. However, these single country studies had different study designs, inclusion criteria and definitions of GBS variants[15, 21]. Therefore, although valuable, these studies have intrinsic limitations and do not describe the full spectrum and geographical variation of GBS. Demonstrating the geographical variation is required to clarify the role of environmental and host factors in severity and subtypes of GBS, and point to the need for different diagnostic criteria and treatments in various parts of the world.

The International GBS Outcome Study (IGOS) is a multicentre, prospective, observational cohort study investigating factors that determine and predict the clinical course, subtype, and outcome of GBS [22]. The aim of the current study was to use the collected data from the first 1000 patient inclusions in IGOS with a follow-up of one year to describe the heterogeneity of GBS and to compare the clinical presentation, electrophysiological subtypes, disease course, and outcome between patients from different geographical regions.

MATERIALS AND METHODS

Study design

The IGOS study protocol has been described elsewhere[22]. The current study was based on the analysis of the first 1000 included patients. Patients fulfilled diagnostic criteria for GBS or its variants and were included within 2 weeks from onset[2, 3, 23]. Patients were enrolled between May 2012 and July 2015 from 135 active study sites in 18 countries across 5 continents. The study was approved by the review boards of Erasmus University Medical Centre, Rotterdam, The Netherlands, and the local institutional review boards of participating hospitals or universities. Written informed consent was obtained from all patients.

Data collection

Data were collected regarding demography, antecedent events, and neurological symptoms and signs of GBS at study entry and at 1, 2, 4, 8, 13, 26 and 52 weeks[22]. Muscle strength was recorded by the Medical Research Council (MRC) score[24] and disability by the GBS disability score[25]. Presence of autonomic dysfunction, defined as cardiac, blood pressure, gastro-enteric, bladder, pupil, or other (e.g. excessive perspiration) abnormalities, was left to the decision of the treating physician. Results of routine CSF examination and nerve conduction studies (NCS) were collected. We defined an elevated CSF protein level as > 0.45 g/l[22, 26]. A cytoalbuminological dissociation was defined as a CSF cell count < 50 cells/µl combined with a CSF protein level > 0.45 g/L. To determine the electrophysiological subtype, we used raw data of the first NCS, local reference values, and an algorithm to classify each NCS into demyelinating, axonal, inexcitable, equivocal, or normal subtype, according to criteria of Hadden and colleagues[15]. Patients with axonal and demyelinating neuropathy were compared for each region, in order to specify previously reported differences between these subtypes.

Disease nadir was defined by the lowest MRC sum score during the first 4 weeks from study entry. When two visits had equal lowest MRC sum scores, the first visit score was used. Patients who had reached nadir before study entry and patients lost to follow up in the first 4 weeks were excluded from the analysis of nadir. Asymmetrical weakness was defined as a difference in MRC sum scores of ≥ 5 points between the right- versus left-sided muscles[27].

Clinical variants were adopted from the reported variants at visit week 2, substantiated by recorded data, and were defined as: (1) sensorimotor, (2) pure motor, (3) MFS or MFS-GBS overlap syndrome, and (4) other, which included pure sensory, ataxic, and pharyngeal-cervical-brachial[4, 5, 23, 28].

Local treating physicians registered clinical fluctuations. We additionally checked the data for fluctuations defined as a deterioration in MRC sum score > 5 points and/or a deterioration on the GBS disability scale ≥ 1 point(s) during two consecutive visits, not caused by non-GBS related complications, within the first year of follow up. A deterioration on the GBS disability scale from 0 ('a healthy state') to 1 ('minor symptoms') was not considered a fluctuation. When MRC sum score, GBS disability score and information on clinical fluctuations were missing for two or more consecutive visits, the occurrence of a fluctuation was considered undeterminable. When patients received multiple immunomodulating treatments (i.e. combinations of IVIg and PE), we used the first administered therapy for the treatment analysis. The primary endpoints for clinical outcome were the ability to walk independently (GBS disability score ≤ 2) at six and twelve months. Patients who were lost to follow up at or after 26 and 52 weeks, or who had a missed visit and were able to walk independently at the previous visit, were considered to have reached this endpoint.

Geographical regions

To determine geographical influence on the variation of GBS, we subdivided patients into three different regions: 'Europe/Americas' (including Argentina, Belgium, Canada, Denmark, France, Germany, Greece, Italy, Spain, The Netherlands, United Kingdom, and United States), 'Asia' (including Japan, Malaysia, and Taiwan), and 'Bangladesh'. These regions were based on previously reported prevalences of clinical variants and electrophysiological subtypes of GBS, national income level[29], availability or affordability of specific immunotherapy with standard of supportive care, and geographical location of the participating countries. Europe and Americas were initially considered two separate regions based on their geographical location, but were later combined because of great similarity of the other determinative variables. The Asian group consisted only of high-income countries with good quality medical services and availability of treatment. For this study, we excluded patients from Africa (n = 11) and Australia (n = 4) from the geographical analysis because of small patient numbers.

Statistical analysis

We used SPSS Statistics 21.0 for data analysis. Continuous data are presented as medians with interquartile ranges (IQR) and dichotomised or categorical data as numbers and proportions. We used the Mann-Whitney U test and Kruskal-Wallis test to compare continuous data, and the χ^2-test or Fisher's exact test to compare proportions. Kaplan-Meier analysis was used to present the proportion of participants able to walk independently during follow up. A two-sided P-value < 0.05 was considered significant. P-values reflect comparisons of the three regions, unless stated otherwise.

Data Availability statement
Data collected in IGOS are not publically available.

RESULTS

We excluded 62 (6%) patients from analysis because of alternative diagnosis: acute onset chronic inflammatory demyelinating polyneuropathy (*n* = 37), other peripheral neuropathy (*n* = 8), central nervous system disorder (*n* = 12), functional disorder (*n* = 2), or disorder not specified (*n* = 3). We excluded five patients because of protocol violations, and eight patients because of insufficient data. The remaining cohort of 925 patients originated from Argentina (*n* = 43), Australia (*n* = 4), Bangladesh (*n* = 125), Belgium (*n* = 16), Canada (*n* = 25), Denmark (*n* = 76), France (*n* = 27), Germany (*n* = 45), Greece (*n* = 4), Italy (*n* = 82), Japan (*n* = 36), Malaysia (*n* = 28), The Netherlands (*n* = 67), South Africa (*n* = 11), Spain (*n* = 76), Taiwan (*n* = 5), United Kingdom (*n* = 129), and the United States (*n* = 126). At one year, 143 (16%) patients were lost to follow up.

Cohort description and heterogeneity of GBS

GBS occurred in all age categories with an overall median age of 51 years (IQR 33-64, range 6 months - 88 years) (Fig. 1). The number of patients increased with age and reached its peak at the age categories of 50-59 and 60-69 years. Males predominated in all age categories with an overall male to female ratio of 1.5.

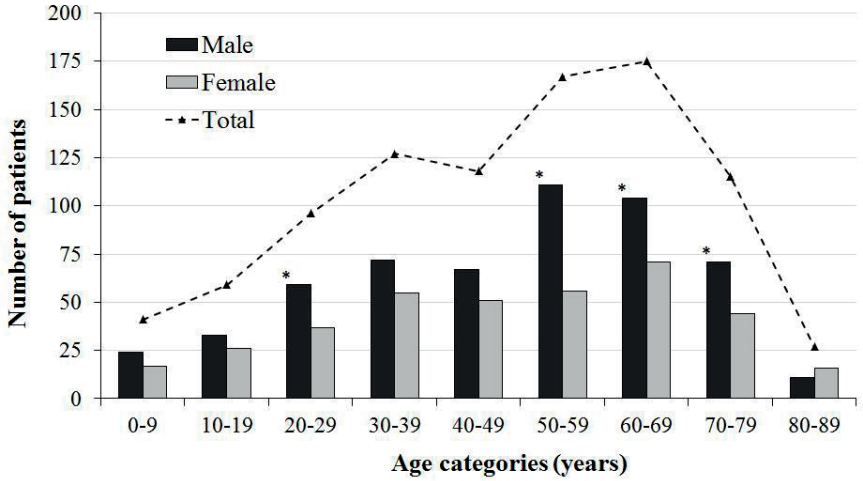


Figure 1 Age and gender distribution of IGOS cohort
* *P* < 0.05 for difference in number of males and females per age category. n = 919.

An antecedent event in the 4 weeks before neurological onset was reported in 649 (76%) patients, mainly upper respiratory tract infections (35%) and gastroenteritis (27%). At study entry, 677 (73%) patients had tetraparesis, 105 (11%) had paraparesis, and 19 (2%) had upper limb weakness only. During follow up, 22 (21%) patients who presented with paraparesis and 3 (16%) patients who presented with sole weakness of upper limbs also developed tetraparesis. Only five patients had asymmetrical limb weakness.

The median time from onset of symptoms to study entry was 6 days (IQR 3-9). Nadir was reached within 2 weeks in 824 (96%) patients, and within 4 weeks in 858 (99.8%) patients. One patient continued to deteriorate until week 8 and another until week 13. At nadir, the median MRC sum score was 44 (IQR 25-53), which was 2 points lower than at entry (46, IQR 33-54) (Wilcoxon signed ranks test $P < 0.001$).

The clinical course defined by the GBS disability score was highly variable (Fig. 2). For those unable to walk independently at nadir, 439 (77%) regained the ability to walk independently at six months, and 445 (81%) at twelve months. Overall, 19% required mechanical ventilation during the disease course. Seven percent died during follow-up, and the median time from onset of weakness to death was 33 days (IQR 16-88, range 6-280) (Table 1).

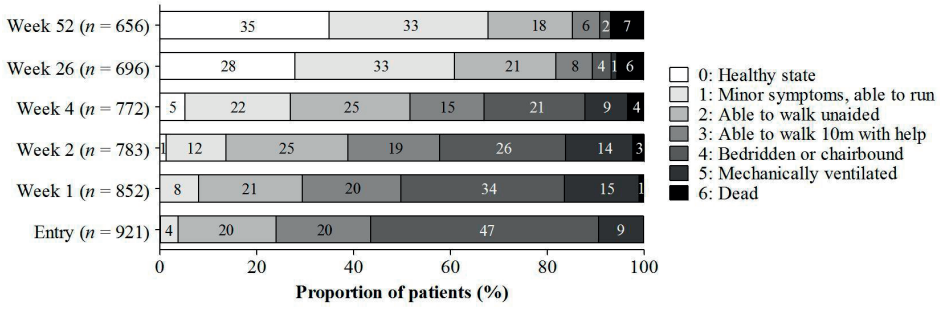


Figure 2 Clinical course during 1 year follow up

CSF was examined in 823 (89%) patients within a median time of 4 days (IQR 2-8) from onset of neurological symptoms. Elevated CSF protein level was detected in 561 (68%) of these patients. The CSF protein level was strongly influenced by the timing of the lumbar puncture: only 50% had an elevated CSF protein level when tested within 3 days from onset of neurological symptoms, compared to 84% when tested after 7 days. Median CSF protein level in the early group was 0.45 g/L (IQR 0.33-0.73), and in the late group 0.98 g/L (IQR 0.59-1.84) ($P < 0.001$). Most patients had a normal CSF leukocyte count (< 5 cells/µl**)** ($n = 641$, 80%). A mildly elevated cell count (5-50/µl**)** was found in 149 (19%) patients, but 14 (2%) patients had more than 50 leukocytes/µl (range 53 - 232). No alternative

diagnosis was found during follow up in these patients with CSF pleiocytosis (> 50µl) despite extensive diagnostic work-up. Six (43%) of these patients required mechanical ventilation, compared to 148 of 790 (19%) patients without pleiocytosis ($P = 0.035$), but the clinical course and outcome were similar between the two groups. Cytoalbuminological dissociation was present in 538 (67%) of patients.

Table 1. Demography and clinical features of IGOS cohort (*n* = 925)

Demographics	
Age (years)	51 (33-64)
Male:female ratio	552/373 (1.48)
Clinical features at entry	
Antecedent events	
URTI	303/857 (35%)
Gastroenteritis	229/857 (27%)
Other[a]	117/857 (14%)
None	208/857 (24%)
Severity and distribution of weakness	
MRC sum score (possible range 0-60)[b]	46 (32-54)
Tetraparesis	677/924 (73%)
Weakness lower limbs only	105/924 (11%)
Weakness upper limbs only	19/924 (2%)
Unilateral limb weakness	10/924 (1%)
Other[c]	15/924 (2%)
No limb weakness	98/924 (11%)
Sensory deficits	543/890 (59%)
Cranial nerve involvement	464/922 (50%)
Oculomotor weakness	139/922 (15%)
Facial weakness	286/922 (31%)
Bulbar weakness	234/922 (25%)
Reflexes upper limbs[d]	
Areflexia	541/920 (59%)
Hyporeflexia	259/920 (28%)
Normoreflexia	108/920 (12%)
Hyperreflexia	12/920 (1%)
Reflexes lower limbs[d]	
Areflexia	704/920 (77%)
Hyporeflexia	182/920 (20%)
Normoreflexia	18/920 (2%)
Hyperreflexia	16/920 (2%)
Autonomic dysfunction	228/924 (25%)

Table 1. Demography and clinical features of IGOS cohort (*n* = 925) (*continued*)

Pain	506/923 (55%)
Time from onset of weakness to admission (days)	3 (2-6)
Clinical features at nadir	
Severity and distribution of weakness	
MRC sum score (possible range 0-60)[b]	44 (25 – 53)
Tetraparesis	629/816 (77%)
Weakness lower limbs only	82/816 (10%)
Weakness upper limbs only	16/816 (2%)
Unilateral limb weakness	8/816 (1%)
Other[c]	11/816 (1%)
No limb weakness	70/816 (9%)
GBS disability score	
Healthy (0)	1/815 (0.1%)
Minor symptoms but able to run (1)	27/815 (3%)
Able to walk independently, unable to run (2)	144/815 (18%)
Not able to walk independently for at least 10 m (3)	159/815 (20%)
Bedridden or wheelchair bound (4)	359/815 (44%)
Mechanically ventilated for at least part of the day (5)	125/815 (15%)
Clinical course	
GBS variant after two weeks follow up	
Sensorimotor	453/744 (61%)
Pure motor	170/744 (23%)
MFS	40/744 (5%)
MFS-GBS overlap	39/744 (5%)
Other[e]	42/744 (6%)
Fluctuations in clinical course[f]	
Monophasic course	615/700 (88%)
Fluctuations during first 8 weeks	60/700 (9%)
Fluctuations after first 8 weeks	16/700 (2%)
Fluctuations during and after first 8 weeks	9/700 (1%)
Ventilator dependency	176/925 (19%)
Mortality	44/659 (7%)

Data are presented as *n* (%) or median (IQR). GBS = Guillain-Barré syndrome, IQR = interquartile range, MFS = Miller Fisher syndrome, MRC = Medical Research Council, URTI = upper respiratory tract infection.

[a] Other antecedent events: urinary tract infection, vaccination, surgery and other.

[b] Larger score indicates greater muscle strength.

[c] Other patterns of weakness (e.g. asymmetrical weakness).

[d] Reflexes in both paretic/paralytic and normal strength limbs.

[e] Other clinical variants: pharyngo-cervical-brachial, pure sensory, ataxic or other variant.

[f] Fluctuations defined as a decrease in the MRC sum score of > 5 points and/or an increase in the GBS disability score of ≥ 1 points, excluding fluctuations caused by complications not related to GBS (e.g. fractures, shin splint (medial tibial stress syndrome), pain, etc.). Changes in GBS disability score from 0 to 1 were not included.

A nerve conduction study was performed in 829/862 (96%) patients, median 7 days (IQR 4-11) from onset of weakness. In 84 (10%) of these patients, the NCS could not be evaluated due to missing raw data or missing local reference values. NCS of the remaining 745 patients were classified as demyelinating (*n* = 390, 52%), axonal (*n* = 71, 10%), inexcitable (*n* = 20, 3%), equivocal (*n* = 215, 29%), or normal (*n* = 49, 7%). Compared to the demyelinating group, patients with axonal GBS were younger (31 years, IQR 20-56 versus 54 years, IQR 36-67; *P* < 0.001) and more often reported preceding diarrhoea (24/71, 34% versus 85/390, 22%; *P* = 0.03). Furthermore, patients with axonal GBS had more severe limb weakness at both study entry (MRC sum score 33, IQR 14-44 versus 46, IQR 34-54; *P* < 0.001) and nadir (19, IQR 5-41 versus 42, IQR 24-51; *P* < 0.001). At six months, 31/50 (62%) patients with axonal neuropathy were able to walk independently, versus 216/262 (82%) in the demyelinating group (*P* = 0.001). At 12 months, 34/47 (72%) with axonal GBS and 220/252 (87%) with demyelinating GBS were able to walk independently (*P* = 0.01).

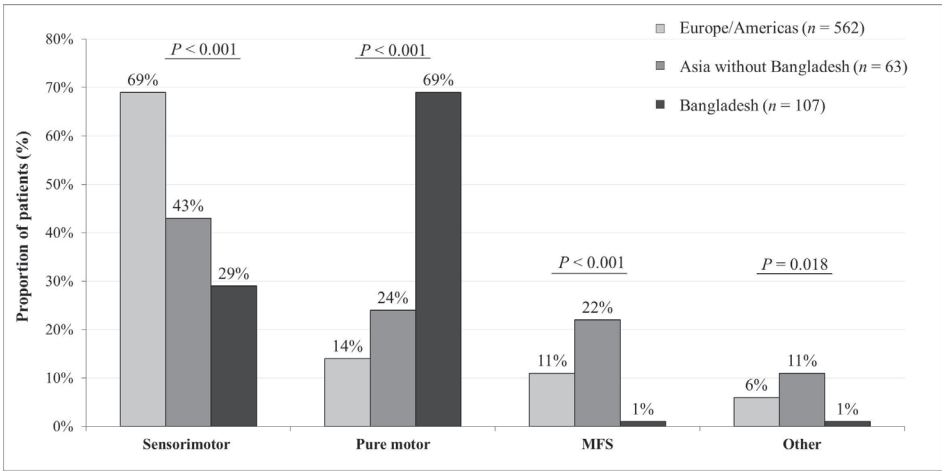
Geographical variation of GBS

The demography, antecedent events, clinical presentation, electrophysiological subtypes, diagnostic findings, treatment and outcome of GBS were compared between 'Europe/Americas' (*n* = 715), 'Asia'(*n* = 69), and 'Bangladesh' (*n* = 125) (Table 2, Fig. 3A and B, Fig. 4 and Supplementary Table 1).

Patients from Bangladesh were significantly younger (age 28 years, IQR 16-40) than patients from Europe/Americas (55 years, IQR 37-67, *P* < 0.001) and Asia (50 years, IQR 34-60, *P* < 0.001). An upper respiratory tract infection was the most common reported antecedent event in Europe/Americas (38%) and Asia (51%), whereas in Bangladesh, gastroenteritis was predominant (36%). Patients from Bangladesh had more severe muscle weakness than patients from the other two regions at study entry and nadir. Sensory deficits were more frequent in patients from Europe/Americas than in patients from the other two regions. Cranial nerve involvement was more frequent in patients from Asia and Bangladesh than in patients from Europe/Americas. In Asia, more patients had oculomotor weakness, whereas in Bangladesh the proportion of patients with bulbar weakness was significantly higher than in the other regions.

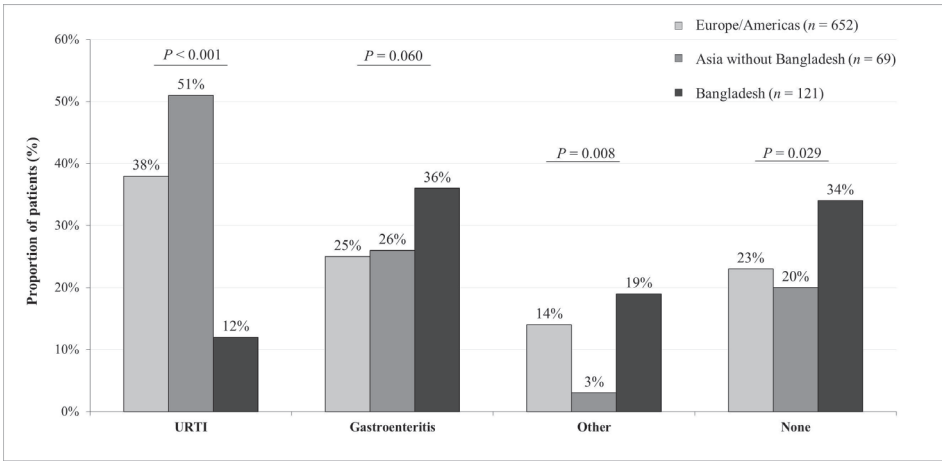
Patients from Asia reported pain less frequently than patients from Europe/Americas and Bangladesh. Seventy-seven (62%) of 125 patients from Bangladesh reported pain at study entry, of whom 73 (95%) patients had either muscle or joint pain, also including patients with a pure motor variant. Patients from Europe/Americas were less frequently ventilated (17%) than patients from Asia (25%, *P* = 0.13) and Bangladesh (29%, *P* = 0.003).

A



MFS: Miller Fisher and Miller Fisher GBS overlap syndromes.
Other: Pharyngeal-cervical-brachial, pure sensory, ataxic and other clinical variants.
GBS = Guillain-Barré syndrome, MFS = Miller Fisher syndrome.

B



Other: Urinary tract infection, vaccination, surgery and other antecedent events.
URTI = upper respiratory tract infection.

Figure 3 Clinical variants (Week 2) (A) and antecedent events (B) in different geographical areas

The predominant clinical pattern of GBS in Europe/Americas and Asia was sensorimotor (Europe/Americas: *n* = 387, 69%; Asia *n* = 27, 43%), whereas in Bangladesh most patients had pure motor GBS (*n* = 74, 69%). MFS or MFS-GBS overlap occurred more frequently in Asia (*n* = 14, 22%) than in Europe/Americas (*n* = 57, 11%) and Bangladesh (*n* = 1, 1%) (*P* < 0.001).

Table 2. Differences in GBS between geographical regions

	Regions			
	Europe/ Americas (*n* = 715)	**Asia (*n* = 69)**	**Bangladesh (*n* = 125)**	***P-value***
Demographics				
Age	55 (37-67)	50 (34-60)	28 (16-40)	**< 0.001**
Male:female ratio	418/297 (1.41%)	42/27 (1.56%)	84/41 (2.05%)	0.18
Clinical features at entry				
MRC sum score (possible range 0-60)[a]	48 (38-56)	49 (40-58)	22 (7-37)	**< 0.001**
Sensory deficits	463/686 (65%)	37/68 (54%)	35/120 (28%)	**< 0.001**
Cranial nerve involvement	330/712 (46%)	44/69 (64%)	84/125 (67%)	**< 0.001**
Oculomotor weakness	106/712 (15%)	26/69 (38%)	5/125 (4%)	**< 0.001**
Facial weakness	220/712 (31%)	28/69 (41%)	32/125 (26%)	0.10
Bulbar weakness	142/712 (20%)	23/69 (33%)	64/125 (51%)	**< 0.001**
Autonomic dysfunction	189/714 (27%)	7/69 (10%)	28/125 (22%)	**0.01**
Pain	415/713(58%)	8/69 (12%)	77/125 (62%)	**< 0.001**
Time from onset of weakness to admission (days)	3 (2-6)	4 (2-6)	4 (2-8)	**0.01**
Neurological symptoms at nadir				
MRC sum score (possible range 0-60)[a]	46 (30-54)	48 (34-58)	16 (3-32)	**< 0.001**
GBS disability score				
Unable to walk independently (> 2)	478/626 (76%)	50/66 (76%)	100/107 (93%)	**< 0.001**
Sensory deficits	408/588 (69%)	37/63 (59%)	29/100 (29%)	**< 0.001**
Cranial nerve involvement	304/620 (49%)	44/65 (68%)	73/107 (68%)	**< 0.001**
Oculomotor weakness	84/620 (14%)	25/65 (39%)	5/107 (5%)	**< 0.001**
Facial weakness	220/620 (36%)	31/65 (48%)	32/107 (30%)	0.06
Bulbar weakness	136/620 (22%)	24/65 (37%)	57/107 (53%)	**< 0.001**
Autonomic dysfunction	184/626 (29%)	11/66 (17%)	30/107 (28%)	0.09
Pain	354/625 (57%)	11/66 (17%)	67/107 (63%)	**< 0.001**
Ventilator dependency	121/715 (17%)	17/69 (25%)	36/125 (29%)	**0.004**
Electrophysiology classification				
Demyelinating	312/573 (55%)	29/65 (45%)	38/94 (40%)	**0.02**
Axonal	33/573 (6%)	4/65 (6%)	34/94 (36%)	**< 0.001**
Inexcitable	10/573 (2%)	1/65 (2%)	9/94 (10%)	**< 0.001**
Equivocal	182/573 (32%)	20/65 (31%)	12/94 (10%)	**0.001**
Normal	36/573 (6%)	11/65 (17%)	1/94 (1%)	**< 0.001**
Initial treatment				
None	54/715 (7%)	9/69 (13%)	108/125 (86%)	**< 0.001**
IVIg	612/715 (86%)	50/69 (73%)	7/125 (6%)	**< 0.001**
PE	43/715 (6%)	10/69 (15%)	9/125 (7%)	**0.03**

Table 2. Differences in GBS between geographical regions (*continued*)

	Regions			
	Europe/ Americas (*n* = 715)	**Asia (*n* = 69)**	**Bangladesh (*n* = 125)**	***P-value***
Other[b]	6/715 (1%)	0/69 (0%)	1/125 (1%)	0.75
Time from onset of weakness to treatment (days)	4 (2-7)	5 (3-7)	7 (5-12)	**0.003**
Outcome				
Median time to independent walking (days)	63 (28-186)	39 (17-94)	95 (36-190)	**0.002**
Able to walk independently at 6 months	331/418 (79%)	36/41 (88%)	60/97 (62%)	**< 0.001**
Able to walk independently at 12 months	334/404 (83%)	31/34 (91%)	67/97 (69%)	**0.003**
Mortality				
Patients deceased at 12 months	23/486 (5%)	1/45 (2%)	19/114 (17%)	**< 0.001**

Data are presented as *n* (%) or median (IQR). *P*-values represent a comparison between the three regions. P-values below 0.05 are highlighted in bold. GBS = Guillain-Barré syndrome, IQR = interquartile range, IVIg = intravenous immunoglobulin, MRC = medical research council, PE = plasma exchange.
[a] Larger score indicates greater muscle strength.
[b] Other treatment: steroids, immunoadsorption and trial medication.

Considerable variation was observed in treatment of GBS between regions. IVIg was the most common treatment for patients from Europe/Americas (*n* = 612, 86%) and Asia (*n* = 50, 73%), whereas in Bangladesh the majority of patients (*n* = 108, 86%) received no immunomodulating therapy.

The median time to regain the ability to walk independently was 63 days (IQR 28-186) in Europe/Americas, 39 days (IQR 17-94) in Asia, and 95 days (IQR 36-190) in Bangladesh (*P* = 0.002). The proportion of patients who regained the ability to walk independently after twelve months follow up was 69% in Bangladesh, 83% in Europe/Americas, and 91% in Asia (*P* = 0.003; Table 2 and Fig. 4). Mortality was significantly higher in Bangladesh (*n* = 19, 17%) than in Europe/Americas (*n* = 23, 5%, *P* < 0.001) and Asia (*n* = 1, 2%, *P* = 0.02).

The predominant electrophysiological subtype was demyelinating for all regions (Europe/Americas: *n* = 312, 55%; Asia: *n* = 29, 45%; Bangladesh: *n* = 38, 40%). The axonal subtype occurred more often in Bangladesh (*n* = 34, 36%). Clinical differences among electrophysiological subtypes were compared for each region (Supplementary Table 2). In all three regions, patients with the axonal subtype were younger than patients with the demyelinating subtype. Sensory deficits at entry and nadir were less frequent in patients with axonal neuropathy. There was a trend towards a lower MRC sum score at study entry and nadir (only significant for Europe/Americas), and poorer outcome at six and twelve months in the axonal groups compared to the demyelinating groups (Supplementary Table 2).

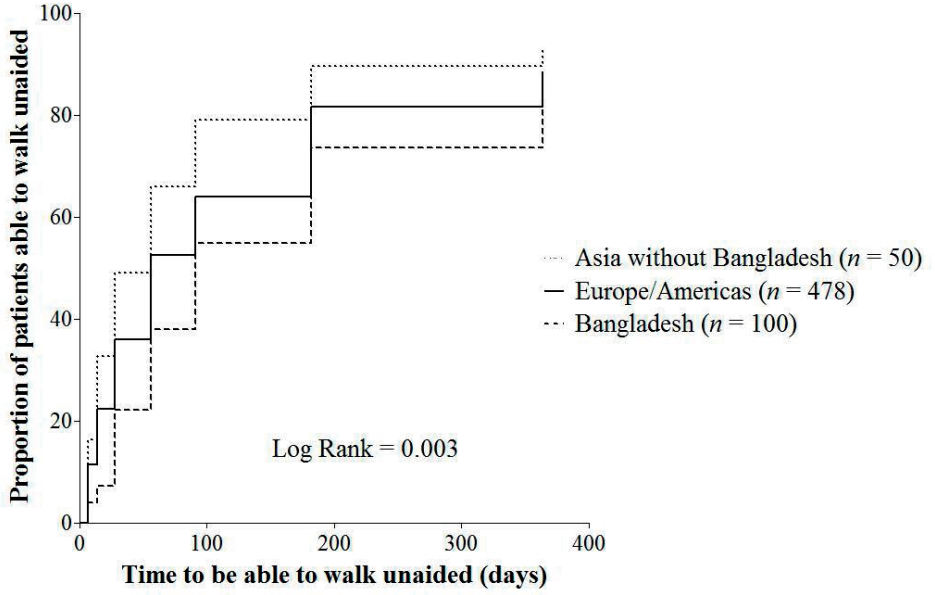


Figure 4 Kaplan-Meier analysis of time to walk unaided in different geographical areas
Kaplan-Meier analysis for patients that were unable to walk unaided (GBS disability score > 2) at disease nadir.

Table Kaplan-Meier analysis: numbers at risk

	Numbers at risk at different time points (days)					
	7	**14**	**28**	**56**	**91**	**182**
Europe/Americas	416	360	285	198	139	57
Asia	41	33	24	13	6	3
Bangladesh	92	81	64	51	34	19

DISCUSSION

Our study demonstrates the marked worldwide variation of GBS with respect to clinical variants, severity, electrophysiological subtypes, and outcome. This variation is influenced by regional differences in demography, preceding events, and treatment.

In all three regions, the frequency of GBS increased with age, for both males and females. Similar age distributions for GBS have been found previously[1, 30]. Patients from Bangladesh were younger than patients from the other two regions, which corresponds to results from a previous study in Bangladesh, where the median age was 21 years (range 2-65) [20]. The regional differences in age distribution may be explained by the variation in demography of the general populations and merely reflect the relative number of persons at risk in each age category per region[31]. Males were more frequently

affected than females in a ratio of 1.5:1, in all age categories and regions. Similar male to female ratios have been reported previously[5, 16]. Therefore, male gender and higher age are independent risk factors for developing GBS worldwide.

The full clinical spectrum of GBS was observed in patients from all countries participating in IGOS, but the frequency of variants differed considerably between regions. The predominant variant in Europe/Americas was sensorimotor, whereas in Bangladesh pure motor GBS predominated. The proportion of patients with MFS or MFS-GBS overlap syndrome was higher in Asia than in the other two regions. A similar distribution of clinical variants per region has been suggested in previous reports from single countries. In these studies, the frequency of pure motor GBS ranged from 10-18% in Europe[32] to as high as 92% in Bangladesh[20]. The frequency of MFS varied from 3% in Europe[33] to 34% in Eastern Asia[13, 34]. The clinical presentation of the patients in the IGOS cohort was similar to previous studies from single countries in Europe/Americas[27], Asia[35] and Bangladesh[9, 36]. Almost all patients reached nadir within 4 weeks after study entry (99.8%), and 96% of patients even within 2 weeks. In another study, 3% of the patients reached nadir between 4 and 6 weeks[27]. While a progressive phase of more than 4 weeks could be regarded as an exception, subacute inflammatory demyelinating polyradiculoneuropathy should be considered in these patients, a previously described intermediate form between GBS and chronic inflammatory demyelinating polyradiculoneuropathy[37]. At the other end of the GBS spectrum, patients reached clinical nadir within days. Some patients already had inexcitable nerves at first NCS. The mechanism of nerve inexcitability is unknown but may be mediated by early loss of axonal or myelin structural integrity or by functional block at the nodes of Ranvier or nerve terminals, caused by anti-nerve antibodies, ionic imbalance, or other inflammatory mediators.

Demyelinating and axonal subtypes of GBS were seen in all participating countries but the frequencies varied between regions. The demyelinating subtype was the predominant subtype in all regions. However, in Bangladesh a substantial proportion of patients had axonal neuropathy. These findings are in line with results from previous studies, where demyelinating GBS was found in 60-80% of North-American and European patients[5, 15]. Axonal GBS was reported in 3-17% in Europe[15, 17, 18], in 23-65% in Asia[13, 17], and up to 67% in Bangladesh[20]. Interestingly, in all three regions patients with axonal GBS were younger than patients with demyelinating GBS. The influence of electrophysiological subtype on prognosis is under debate, as recovery in axonal GBS can be slow and incomplete due to axonal degeneration, or faster due to resolving transient conduction blocks, and may depend upon the subtype criteria[5, 17]. The current study showed that the axonal subtype was significantly associated with poor recovery in the full cohort and a similar trend was observed in the subgroup analysis per region (Supplementary

Table 2). The association between axonal GBS and younger age may reduce the effect of axonal involvement on poor recovery. Further analysis of NCS and other prognostic factors is required to determine the association between GBS subtype and outcome.

The regional differences in frequencies of clinical and electrophysiological subforms of GBS may be explained in part by the variation in local exposure to infections. The frequency of patient-reported gastroenteritis in our cohort ranged from 25% in Europe/Americas to 36% in Bangladesh. Previous studies have shown an association between preceding gastroenteritis and pure motor and axonal GBS[17, 20]. *Campylobacter jejuni* is the predominant cause of gastroenteritis preceding GBS worldwide, but previous reports suggest that the frequency of this infection may differ substantially among regions. The association between preceding *C. jejuni* infection and axonal GBS is related to the induction of cross-reactive antibodies to gangliosides[4]. A recent retrospective study indicated a relatively high frequency of the demyelinating subtype (49%) and lower frequency of the axonal subtype (19%) in Southern China[19], while previous studies from Northern China from the 1990s reported the axonal subtype in 65% of GBS patients[21]. It is unknown whether this variation represents a regional difference within China or a change in GBS spectrum over time in parallel to changes in exposure to infections, especially with *C. jejuni*[19, 38]. Future serological studies will investigate the role of preceding infections, and immune responses to these infections, to explain the regional differences.

The clinical course and outcome varied substantially among the three regions. The best outcome was observed in Asia, in part related to the higher frequency of MFS in that region[13, 34]. The worst outcome was found in Bangladesh, despite the younger age of these patients. Several factors previously associated with poor prognosis were more frequent in Bangladesh, such as the frequency of preceding gastroenteritis, axonal subtype, and more severe disease in the acute stage. Most importantly, only 13% of the patients in Bangladesh received PE or IVIg and the facilities for supportive care were limited.

Although this study is the largest prospective study on GBS so far, there are several limitations. First, IGOS aimed to include the full spectrum of GBS, irrespective of age, disease severity, and treatment, but referral bias probably favoured inclusion of patients with more severe disease that required hospitalization and treatment. Participating centres were mostly tertiary care hospitals with specific neuromuscular expertise. It is unknown whether referral bias differed among countries and if this might have influenced the observed regional differences. Second, the number of inclusions varied per country and several areas, especially Asia, Africa, and Australia, were underrepresented. The centre in Dhaka, Bangladesh, in contrast, is the national and public tertiary care hospital for GBS, which explains the high number of inclusions and the high proportion of patients

receiving supportive care only[9, 20, 36]. Third, although IGOS included 1000 patients, the numbers in some subgroups were small and their analyses had limited power. Enrolment of patients in IGOS is continuing to overcome this problem. Lastly, patients were classified according to only one set of electrophysiological criteria using a single NCS, while the assigned GBS subtype depends on the criteria used and may change during follow-up. The electrophysiology of GBS and performance of different sets for classification will be evaluated in future dedicated studies.

The standardised collection of data in IGOS has enabled us to identify differences in the preceding factors, clinical presentation, neurophysiological classification and course of GBS between regions. In combination with the biosamples collected at the same time, this information will improve understanding of pathogenesis - involving identification of risk factors for GBS, including preceding infections of which some may be preventable - and allow better prognostic modelling, adapted to different parts of the world.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Comparison of characteristics of patients from various geographical regions.

	Regions		
	Europe/ Americas vs. Asia	Europe/ Americas vs. Bangladesh	Asia vs. Bangladesh
Demographics			
Age	**0.03**	**< 0.001**	**< 0.001**
Gender	0.80	0.08	0.43
Clinical features at entry			
MRC sum score	0.32	**< 0.001**	**< 0.001**
Sensory deficits	**0.03**	**< 0.001**	**0.001**
Cranial nerve involvement	**0.01**	**< 0.001**	0.64
Oculomotor weakness	**< 0.001**	**< 0.001**	**< 0.001**
Facial weakness	0.11	0.25	**0.04**
Bulbar weakness	**0.01**	**< 0.001**	**0.02**
Autonomic dysfunction	**0.002**	0.38	**0.05**
Pain	**< 0.001**	0.49	**< 0.001**
Time from onset of weakness to admission	0.59	**0.002**	0.10
Clinical features at nadir			
MRC sum score	0.30	**< 0.001**	**< 0.001**
GBS disability score > 2	1.000	**< 0.001**	**0.012**
Sensory deficits	0.09	**< 0.001**	**< 0.001**
Cranial nerve involvement	**0.01**	**< 0.001**	1.00
Oculomotor weakness	**< 0.001**	**0.01**	**< 0.001**
Facial weakness	0.06	0.27	**0.02**
Bulbar weakness	**0.01**	**< 0.001**	**0.04**
Autonomic dysfunction	**0.03**	0.82	0.10
Pain	**< 0.001**	0.29	**< 0.001**
Ventilator dependency during follow up	0.13	**0.003**	0.62
Electrophysiology classification			
Demyelinating	0.13	**0.01**	0.60
Axonal	0.78	**< 0.001**	**< 0.001**
Inexcitable	1.00	**< 0.001**	**0.049**
Equivocal	0.87	**< 0.001**	**0.01**
Normal	**0.01**	**0.04**	**< 0.001**
Initial treatment			
No treatment	0.11	**< 0.001**	**< 0.001**
IVIg	**0.01**	**< 0.001**	**< 0.001**
PE	**0.02**	0.55	0.13

Supplementary Table 1. Comparison of characteristics of patients from various geographical regions. (*continued*)

	Regions		
	Europe/ Americas vs. Asia	**Europe/ Americas vs. Bangladesh**	**Asia vs. Bangladesh**
Other	1.00	1.000	1.00
Time from onset of weakness to treatment	0.57	**0.001**	**0.003**
Prognosis			
Able to walk independently at 6 months follow up	0.224	**0.001**	**0.002**
Able to walk independently at 12 months follow up	0.240	**0.004**	**0.011**
Mortality			
Patients deceased at 12 months follow up	0.71	**< 0.001**	**0.02**

Data represent *P*-values for the comparison between individual regions.
MRC = medical research council, GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, PE = plasma exchange.

Supplementary Table 2. Clinical characteristics for each electrophysiological subtype per region.

	Regions					
	Europe/Americas		Asia		Bangladesh	
	Demyelinating (*n* = 312)	Axonal (*n* = 33)	Demyelinating (*n* = 29)	Axonal (*n* = 4)	Demyelinating (*n* = 38)	Axonal (*n* = 34)
Demographics						
Age (years)	**58 (41-69)**	**53 (30-60)†**	56 (48-66)	47 (30-64)	**35 (18-48)**	**22 (16-31)†**
Antecedent events						
URTI	116/312 (37%)	18/33 (55%)	14/29 (48%)	1/4 (25%)	5/38 (13%)	3/34 (9%)
Gastroenteritis	**66/312 (21%)**	**12/33 (36%)†**	7/29 (24%)	1/4 (25%)	9/38 (24%)	11/34 (32%)
Clinical features at entry						
MRC sum score (range 0-60)*	**48 (38-54)**	**42 (16-48)†**	44 (21-51)	41 (32-50)	23 (8-36)	26 (12-38)
Cranial nerve involvement	138/310 (45%)	16/33 (49%)	18/29 (62%)	2/4 (50%)	29/38 (76%)	20/34 (59%)
Sensory deficits	**225/299 (75%)**	**15/32 (47%)†**	**17/28 (61%)**	**0/4 (0%)†**	**17/35 (49%)**	**3/34 (9%)†**
Autonomic dysfunction	87/311 (28%)	13/33 (42%)	4/29 (14%)	0/4 (0%)	8/38 (21%)	8/34 (24%)
Pain	192/311 (62%)	19/33 (58%)	6/29 (21%)	0/4 (0%)	20/38 (53%)	25/34 (74%)
Clinical features at nadir						
MRC sum score (range 0-60)*	**42 (24-51)**	**19 (5-41)†**	36 (26-47)	30 (6-42)	22 (4-35)	16 (4-38)
Sensory deficits	**202/265 (76%)**	**11/26 (42%)†**	17/26 (65%)	1/3 (33%)	**15/31 (48%)**	**2/27 (7%)†**
Autonomic dysfunction	90/286 (32%)	11/29 (38%)	7/28 (25%)	0/4 (25%)	9/34 (27%)	9/28 (32%)
Ventilator dependency	61/312 (20%)	9/33 (27%)	12/29 (41%)	2/4 (50%)	11/38 (29%)	8/34 (24%)
Outcome						
Able to walk independently at 6 months	163/201 (81%)	15/23 (65%)	17/19 (90%)	1/3 (33%)	27/32 (84%)	15/24 (63%)
Able to walk independently at 12 months	168/195 (86%)	15/22 (68%)	13/14 (93%)	1/2 (50%)	29/33 (88%)	18/23 (78%)
Deceased at 12 months	10/232 (4%)	0/22 (0%)	0/15 (0%)	0/2 (0%)	3/36 (8%)	3/30 (10%)

Data are presented as *n* (%) or median (IQR). IQR = interquartile range, URTI = upper respiratory tract infection, MRC = medical research council. * Larger score indicates greater muscle strength. † $P < 0.05$ between demyelinating and axonal Guillain-Barré syndrome.

2.2

Cerebrospinal fluid findings in relation to clinical characteristics, subtype and disease course in patients with Guillain-Barré syndrome

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Submitted

3

Predicting outcome of GBS

3.1

Predicting outcome in Guillain-Barré syndrome: International validation of the modified Erasmus GBS Outcome Score

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ABSTRACT

Background and Objectives. The clinical course and outcome of the Guillain-Barré syndrome (GBS) are diverse and vary among regions. The modified Erasmus GBS Outcome Score (mEGOS) is a clinical model that predicts the risk of walking inability in GBS patients, and was developed with data from Dutch patients. The study objective was to validate the mEGOS in the International GBS Outcome Study (IGOS) cohort and to improve its performance and region-specificity.

Methods. We used prospective data from the first 1500 patients included in IGOS, aged ≥ 6 years and unable to walk independently. We evaluated if the mEGOS at entry and week 1 could predict the inability to walk unaided at 4 and 26 weeks in the full cohort and in regional subgroups, using two measures for model performance: (1) discrimination: area under the receiver operating characteristic curve (AUC), and (2) calibration: observed versus predicted probability of being unable to walk independently. To improve the model predictions we recalibrated the model containing the overall mEGOS score, without changing the individual predictive factors. Finally, we assessed the predictive ability of the individual factors.

Results. For validation of mEGOS at entry 809 patients were eligible (Europe/North America n=677, Asia n=76, other=56), and 671 for validation of mEGOS at week 1 (Europe/North America n=563, Asia n=65, other=43). AUC-values were >0.7 in all regional subgroups. In the Europe/North America subgroup observed outcomes were worse than predicted, while in Asia observed outcomes were better than predicted. Recalibration improved model accuracy and enabled the development of a region-specific version for Europe/North America (mEGOS-Eu/NA). Similar to the original mEGOS, severe limb weakness and higher age were the predominant predictors of poor outcome in the IGOS cohort.

Discussion. The mEGOS is a validated tool to predict the inability to walk unaided at 4 and 26 weeks in GBS patients, also in countries outside The Netherlands. We developed a region-specific version of mEGOS for patients from Europe/North America.

Classification of Evidence. This study provides Class II evidence that the mEGOS accurately predicts the inability to walk unaided at 4 and 26 weeks in GBS patients.

INTRODUCTION

The clinical course and outcome of Guillain-Barré syndrome (GBS) are highly variable, which complicates the management and evaluation of treatment effects in individual patients[1]. In the past, several prediction models based on sets of prognostic factors have been developed for GBS[2-4]. Such models could help to personalize disease management and conduct treatment studies in selected groups of patients. The modified Erasmus GBS Outcome Score (mEGOS) predicts the risk of being unable to walk independently within the first 6 months of disease based on age, muscle strength and preceding diarrhoea[4, 5]. With this model a patient >60 years with a severe tetraparesis and preceding diarrhoea will have the worst predicted outcome (Table 1). The mEGOS was developed with data from Dutch GBS patients, and until now has been validated in a Dutch cohort and two Asian cohorts[6, 7]. In our previous study, based on the first 1000 patients included in the International GBS Outcome Study (IGOS), we found marked regional differences in the clinical presentation, disease course, subtypes and outcome of GBS[8]. Western GBS patients most frequently showed the demyelinating subtype of GBS, with involvement of both sensory and motor nerves. In Asia the Miller Fisher syndrome (MFS) was more frequent, and the overall outcome was better[8]. Therefore, the first aim of our study was to validate the mEGOS in the IGOS cohort and to define its performance in various regions. The second aim was to determine if we could improve the mEGOS predictions by applying region-specific adjustments.

MATERIALS AND METHODS

Modified Erasmus GBS Outcome Score (mEGOS)

Details of the development of the mEGOS model have been published previously[4], see Table 1 for a summary. The model was developed using multivariable logistic regression analysis and was based on data from 394 severely affected GBS patients who were unable to walk independently and were enrolled in two randomised controlled trials (RCTs) and one pilot study[9-11]. Patients in the development cohort were mainly enrolled in Dutch centres, but some were enrolled in Belgian or German centres. The model was validated in an independent prospective cohort of 191 GBS patients who were enrolled in two Dutch studies, one open label pilot study and one observational study[12, 13]. The observational study also included GBS patients who were able to walk throughout the disease course, but these patients were excluded for validation [4]. Table 1 provides the scoring system for the mEGOS.

Table 1. mEGOS scoring system [4]

mEGOS at hospital admission			mEGOS at day 7 of admission		
Prognostic factors		**Score**	**Prognostic factors**		**Score**
Age at onset, y	≤40	0	Age at onset, y	≤40	0
	41-60	1		41-60	1
	>60	2		>60	2
Preceding	Absent	0	Preceding	Absent	0
diarrhoeaa	Present	1	diarrhoeaa	Present	1
MRC sum score at	51-60	0	MRC sum score at	51-60	0
hospital admission	41-50	2	day 7 of admission	41-50	3
	31-40	4		31-40	6
	0-30	6		0-30	9
mEGOS total score		**0-9**	**mEGOS total score**		**0-12**

mEGOS = modified Erasmus GBS Outcome Score; MRC = Medical Research Council. a Diarrhoea in the 4 weeks preceding onset of weakness.

The model can be used at hospital admission as a 9-point scale and at day 7 of admission as a 12-point-scale.

Dataset for external validation

For external validation of the mEGOS we used data from the first 1500 patients included in IGOS, an ongoing prospective multicentre cohort study on GBS in which all severities, variants and subtypes of GBS are represented[14]. 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.

Because we aimed to validate the mEGOS in an international GBS cohort that reflects the diversity as is seen in usual clinical practice, we included all patients with GBS who had lost the ability to walk (GBS disability score >2) at entry and at day 7 after study entry, including variants such as the Miller Fisher syndrome (MFS) and pure sensory GBS[15, 16]. We used the GBS clinical variants as classified by the treating physician at week 2, or if unavailable at week 1 or study entry. We excluded patients in whom the diagnosis was altered during the 1-3 years follow up (n=85, of whom 53 had CIDP). We also excluded children under six years, because the MRC scores cannot be assessed in young children, and patients from Bangladesh because the majority received no specific treatment and the facilities for supportive care and rehabilitation are limited in Bangladesh, which could influence the clinical course and outcome[8, 17]. Validation and recalibration of the mEGOS will be performed in Bangladesh separately.

STATISTICAL ANALYSIS

Predictive performance

For validation of the mEGOS we looked at outcome at 4 weeks and 6 months. We chose the 4-week time point because this time point is often used in RCT to assess treatment efficacy, and the 6-month time point because it reflects long-term outcome. We assessed model performance by determining the discrimination and calibration. Discrimination represents the ability of the model to distinguish between patients with a good and a poor outcome 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 with a good outcome and one with a poor outcome, the mEGOS is higher in the patient with the poor outcome. We also calculated the refitted AUC-value, which is obtained by refitting the model in the validation sample, and thus re-estimating the coefficients for age, diarrhoea and the MRC sum score. The refitted AUC-value provides the optimum for model discriminative ability in the validation sample for the model with these three clinical factors. Calibration defines the accuracy of model predictions by comparing predicted probabilities with observed frequencies of poor outcome. We compared mean predicted and observed probabilities, and also plotted calibration curves to graphically delineate the correspondence between the observed and predicted risks. In case of perfect calibration, observed frequencies of poor outcome are equal to predicted risks; i.e. in a group of patients who all have a predicted probability of 0.6 the event should occur in 60% of patients[18, 19].

We assessed model performance in the total group and in regional subgroups: Europe/North America (Eu/NA) (including the UK) and Asia. This subdivision was based on previously identified differences in clinical presentation, disease course and subtypes of GBS between different regions[8]. For external validation we used the original regression formulas with the mEGOS as a single predictor. We also assessed the predictive ability of the individual factors included in the mEGOS 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 mEGOS 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. This is done by applying correction factors to the original regression formula (intercept and coefficients), which is used to calculate the predicted probabilities. For recalibration of the mEGOS in this study, we corrected the regression formula that contained the mEGOS total score as single predictor. We did not separately correct the coefficients of the individual factors included in the mEGOS 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[18, 20]. We used bootstrapping to internally validate the recalibrated mEGOS model.

Missing values

We used multiple imputation (n=10) to impute missing values for the mEGOS predictors and the GBS disability scores at 4 weeks and 6 months (R function: *aregImpute*). In the imputation model we included demographic data (e.g. age, sex, region), data on preceding events, disease progression rate, involvement of cranial nerves, sensory deficits, pain, ataxia, autonomic dysfunction, treatment and supportive care, the clinical GBS variant and the nerve conduction study subtype, and longitudinal data (entry, week 1, 2, 4, 8, 13, 26 and 52) for the individual MRC scores and the GBS disability scores. We performed a separate analysis comparing cases with a complete dataset to those with imputed values. We used SPSS Statistics version 24 and R Studio version 3.6.1. for data analysis (*R packages: Hmisc, rms, devtools, CalibrationCurves*).

Standard protocol approvals, registrations, and patient consents

IGOS was approved by the review board of the Erasmus University Medical Centre, Rotterdam, The Netherlands, and the local institutional review boards of participating hospitals or universities. Written informed consent was obtained from all patients or their legal representatives.

Data availability

Data collected in IGOS will be used initially for planned research projects conducted by the IGOS Consortium. Data can be made available by the IGOS Steering Committee upon reasonable request for specific research projects. The data are not publicly available because they contain information that could compromise the privacy of the patients.

Classification of evidence

This study provides Class II evidence that the mEGOS accurately predicts the inability to walk unaided at 4 and 26 weeks in GBS patients.

RESULTS

From the IGOS-1500 cohort we excluded 85 patients (6%) because of an alternative diagnosis, 32 (2%) because of a protocol violation, and seven (0.5%) because of insufficient data. In addition, we excluded patients from Bangladesh (n=203), patients under 6 years or with missing age (n=38), patients who were still able to walk independently at study entry (n=315) or at 1 week after study entry (n=348), patients who had died within the first week after study entry (n=8), and those with missing values for the GBS disability score at entry (n=11) or week 1 (n=108). The remaining validation cohorts consisted of 809 GBS patients for the mEGOS at entry and 671 patients for the mEGOS at week 1 (Figure 1). For validation of the mEGOS at entry in the full IGOS cohort patients were included in the following countries: Argentina (n=25), Australia (n=6), Belgium (n=15), Canada (n=22), China (n=9), Denmark (n=83), France (n=25), Germany (n=36), Greece (n=9), Italy (n=75), Japan (n=40), Malaysia (n=25), The Netherlands (n=81), South Africa (n=25), Spain (n=70), Taiwan (n=2), United Kingdom (n=129) and United States of America (n=132). In total, 6% of the data points (2624/41280) were missing for the mEGOS predictors (age, preceding diarrhoea, MRC scores at entry and 1 week) and outcome variables (GBS disability scores at 4 weeks and 6 months), and were imputed using multiple imputation.

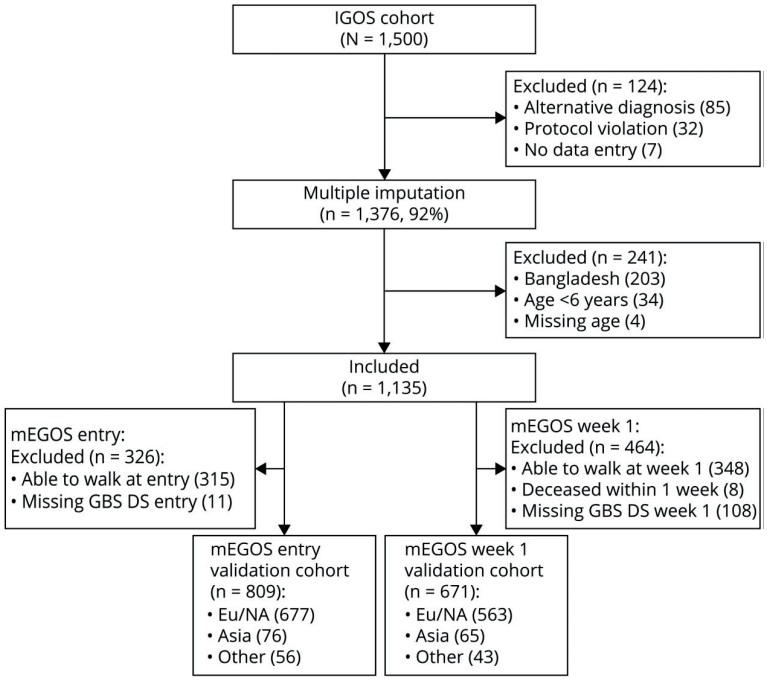

Figure 1. Study population

IGOS = International GBS Outcome Study; mEGOS = modified Erasmus GBS Outcome Score; GBS-DS = GBS disability score; Eu/NA = Europe/North America

Characteristics of the development and validation cohorts

Patients in the validation cohorts were slightly older and more often had mild muscle weakness (MRC sum score 51-60) than patients in the development cohort. Patients with the Miller Fisher syndrome (MFS) were excluded from the mEGOS development cohort, but were included in the IGOS validation cohorts (Table 2 and eTable 1).

Table 2. Clinical characteristics of mEGOS development and validation cohorts

Characteristics	Validation cohort		Development cohort[4] (n = 394)
	Patients unable to walk unaided at entry (n = 809)	Patients unable to walk unaided at week 1 (n = 671)	
Years	2012 - 2017	2012 - 2017	1985 - 2000
Data source	Cohort study	Cohort study	2 RCTs, 1 pilot study
Study country	Argentina, Australia, Belgium, Canada, China, Denmark, France, Germany, Greece, Italy, Japan, Malaysia, The Netherlands, South Africa, Spain, Taiwan, UK, USA	Argentina, Australia, Belgium, Canada, China, Denmark, France, Germany, Greece, Italy, Japan, Malaysia, The Netherlands, South Africa, Spain, Taiwan, UK, USA	The Netherlands, Belgium, Germany
Age	57 (43-69)	58 (45-69)	52 (33-66)
≤40	181 (22%)	132 (20%)	138 (35%)
41-60	276 (34%)	234 (35%)	114 (29%)
>60	352 (44%)	305 (46%)	142 (36%)
Range	7-90	7-90	5-89
Sex (male)	459 (57%)	388 (58%)	215 (55%)
Preceding diarrhoea[a]	194/797 (24%)	162/660 (25%)	89/392 (23%)
Time onset[b] to admission, days	2 (1-4)	2 (1-4)	*NA*
Time onset[b] to entry, days	5 (3-8)	5 (3-8)	5 (3-8)
MRC sum score at entry	45 (35-52)	44 (34-51)	43 (33-48)
51-60	228/803 (28%)	169/663 (26%)	47/393 (12%)
41-50	278/803 (35%)	239/663 (36%)	180/393 (46%)
31-40	138/803 (17%)	113/663 (17%)	82/393 (21%)
00-30	159/803 (20%)	142/663 (21%)	84/393 (21%)
Range	0-60	0-60	0-58
Sensory deficits at entry	536/782 (69%)	439/645 (68%)	255/388 (66%)
CNI at entry	399/806 (50%)	323/667 (48%)	152 (39%)
Autonomic dysfunction[c] at entry	229/808 (28%)	193/667 (29%)	*NA*
MRC sum score at week 1	46 (33-54)	45 (30-52)	43 (30-50)
51-60	275/730 (38%)	205/664 (31%)	95/385 (25%)
41-50	192/730 (26%)	188/664 (28%)	116/385 (30%)
31-40	95/730 (13%)	98/664 (15%)	75/385 (20%)

Table 2. Clinical characteristics of mEGOS development and validation cohorts (*continued*)

Characteristics		Validation cohort		Development cohort[4] (n = 394)
		Patients unable to walk unaided at entry (n = 809)	Patients unable to walk unaided at week 1 (n = 671)	
	00-30	168/730 (23%)	173/664 (26%)	99/385 (26%)
	Range	0-60	0-60	0-60
GBS variant[d]	Sensorimotor	519/765 (68%)	447/636 (70%)	*NA*
	Pure motor	117/765 (15%)	99/636 (16%)	*NA*
	MFS	45/765 (6%)	24/636 (4%)	*0 (0%)*
	MFS-GBS overlap	52/765 (7%)	39/636 (6%)	*NA*
	Other[d]	32/765 (4%)	27/636 (4%)	*NA*
Mechanical ventilation		170 (21%)	164 (24%)	118 (30%)
ICU admission		257 (32%)	241 (36%)	*NA*
IVIg/PE[e]		775 (96%)	658 (98%)	394 (100%)
Time onset[b] to start IVIg/PE, days		4 (2-7)	4 (2-6)	*NA*
GBS-DS >2 at week 4[f]		379/671 (57%)	373/579 (64%)	217/394 (55%)
GBS-DS >2 at 3 months[f]		182/595 (31%)	177/513 (35%)	111/389 (29%)
GBS-DS >2 at 6 months[f]		125/599 (21%)	118/512 (23%)	74/388 (19%)

This table provides an overview of the characteristics of the (non-imputed) development and validation cohorts. Numbers are provided as median (IQR) or n (%), unless stated otherwise. mEGOS = modified Erasmus GBS Outcome Score; CNI = cranial nerve involvement; GBS-DS = GBS disability score; NA = not available/applicable.

[a] Symptoms of a gastro-intestinal infection within the 4 weeks preceding onset of weakness

[b] Onset of weakness

[c] Autonomic dysfunction includes cardiac (arrhythmia, tachycardia, bradycardia), blood pressure (fluctuations, hypertension, hypotension), gastro-enteric, bladder, pupil dysfunction, excessive sweating and hyponatraemia etc.

[d] GBS variants represent the classification as reported by the local researchers at week 2 (and if missing at week 1 or study entry). Other variants include pharyngeal-cervical-brachial variant, pure sensory GBS, ataxic variant, Bickerstaff's brainstem encephalitis etc.

[e] Treated with IVIg and/or plasma exchange. This variable was based on the first two treatment episodes reported in the IGOS study.

f Proportion of patients unable to walk independently

Discriminative ability

For mEGOS at entry, AUC-values ranged from 0.74 to 0.79 for predicting outcome at 4 weeks and from 0.73 to 0.82 for predicting outcome at 6 months. For mEGOS at week 1, AUC-values ranged from 0.79 to 0.82 for outcome at 4 weeks, and from 0.74 to 0.89 for outcome at 6 months (Table 3). Compared to the AUC-values in the development cohort, AUC-values for the full cohort and Eu/NA subgroup were lower upon external validation (except for the week 4 AUC-values for the mEGOS at entry which were similar to the development AUCs). In Asia, all AUC-values were higher than the development AUCs (except for the week 4 AUC-value for the mEGOS at week 1), but 95% confidence intervals (CI) were wide. When we refitted the model in the validation cohorts, discriminative ability in the full IGOS cohort and Eu/NA subgroup was similar to the discriminative ability of

the externally validated original model for both the mEGOS at entry and week 1. In Asia, refitted AUC-values were higher than AUC-values derived upon external validation of the original model (Table 3).

Table 3. Discriminative ability

	mEGOS entry		mEGOS w1	
AUC-values	**Development [4]**		**Development [4]**	
4 weeks	0.73		0.87	
6 months	0.77		0.84	
AUC-values	**Ext. validation**	**Refitted**	**Ext. validation**	**Refitted**
4 weeks				
IGOS full	0.74 (0.71; 0.78)	0.75 (0.71; 0.78)	0.79 (0.75; 0.83)	0.80 (0.76; 0.83)
IGOS Eu/NA	0.74 (0.70; 0.78)	0.74 (0.71; 0.78)	0.79 (0.75; 0.83)	0.80 (0.76; 0.84)
IGOS Asia	0.79 (0.68; 0.89)	0.83 (0.73; 0.94)	0.82 (0.71; 0.93)	0.89 (0.79; 0.98)
6 months				
IGOS full	0.74 (0.69; 0.79)	0.74 (0.69; 0.79)	0.75 (0.70; 0.80)	0.76 (0.71; 0.81)
IGOS Eu/NA	0.73 (0.67; 0.78)	0.73 (0.68; 0.79)	0.74 (0.69; 0.80)	0.75 (0.70; 0.80)
IGOS Asia	0.82 (0.68; 0.96)	0.84 (0.71; 0.97)	0.89 (0.79; 0.99)	0.93 (0.84; 1.00)

Values between brackets represent 95% CIs.
mEGOS = modified Erasmus GBS Outcome Score; AUC = area under the receiver operating characteristic curve; Eu/NA = Europe/North America

When we compared the individual predictor effects for predicting outcome after 4 weeks between the development cohort and the full IGOS cohort and Eu/NA subgroup, we found similar effects for age and the MRC sum score, and a smaller, non-significant effect for diarrhoea upon external validation (diarrhoea OR (95% CI): mEGOS entry, full IGOS cohort 1.1 (0.8 – 1.6), Eu/NA 1.1 (0.7 – 1.6); mEGOS week 1, full IGOS cohort 1.0 (0.6 – 1.6), Eu/NA 1.0 (0.6 – 1.7)) [4]. For outcome after 6 months, diarrhoea was a significant predictor in both the full IGOS cohort and the Eu/NA subgroup (diarrhoea OR (95% CI): mEGOS entry, full IGOS cohort 1.9 (1.3 – 2.9), Eu/NA 1.7 (1.1 – 2.7); mEGOS week 1, full IGOS cohort 1.8 (1.2 – 2.9), Eu/NA 1.8 (1.1 – 2.9)), although its predictive effect was smaller than the predictive effects for age and the MRC sum score. The Asian sample was too small to estimate the individual predictor effects reliably.

Calibration

In the full cohort and Eu/NA subgroup the observed frequencies of poor outcome exceeded the predicted risks of poor outcome based on the mEGOS model (Figure 2). For example, in the full IGOS cohort 67% of the patients with an mEGOS entry score of 4 had a poor outcome after 4 weeks, while the predicted risk of poor outcome for patients with an mEGOS at entry of 4 was 54%. In contrast, in Asia the observed frequencies of poor

outcome were lower than the predicted risks (Figure 2). Differences between observed and predicted risks were more pronounced for outcome at 4 weeks than for outcome at 6 months (Figure 2). Calibration plots showed similar patterns of miscalibration, with underestimation of the risk of poor outcome in the full cohort and Eu/NA subgroup, and overestimation of the risk of poor outcome in the Asian subgroup (data not shown). Recalibration of the mEGOS model improved the accuracy of the model predictions for the full cohort and Eu/NA subgroup and enabled us to create a region-specific version (mEGOS-Eu/NA) (Figure 3). We also compared observed and (pre- and post-recalibration) predicted risks per score value of the mEGOS for the Eu/NA subgroup, which showed that for the majority of score values the predictions improved (i.e. predictions better corresponded to the observed outcomes) after recalibration (Figure 4). Due to the small sample sizes and wide 95% CIs around the calibration curves it was not possible to re-calibrate the model for the Asian cohort. Internal validation of the recalibrated mEGOS for European and North American patients (mEGOS-Eu/NA) by bootstrapping showed AUC-values similar to the AUC-values of the recalibrated mEGOS, indicating that the model was properly recalibrated and that there was no overfitting.

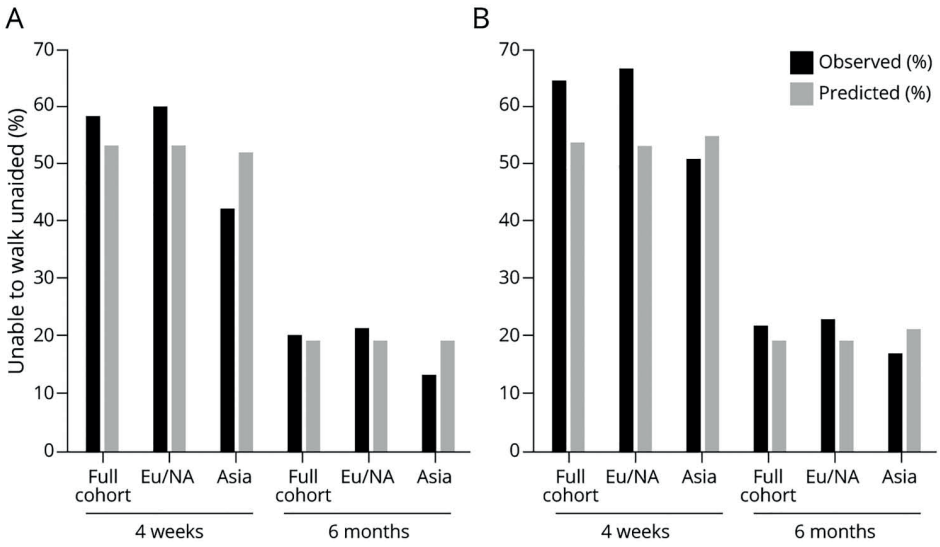

Figure 2. Mean observed probabilities of poor outcome versus mean predicted risks based on the original mEGOS model Panel A: mean observed and predicted risks based on the mEGOS at entry. Panel B: mean observed and predicted risks based on the mEGOS at 1 week. mEGOS = modified Erasmus GBS Outcome Score; Eu/NA = Europe/North America. mEGOS entry validation cohort: full IGOS cohort n=809, Europe/North America n=677, Asia n=76; mEGOS w1 validation cohort: full IGOS cohort n=671, Europe/North America n=563, Asia n=65.

Complete case analysis

External validation of mEGOS performed in a subgroup of patients with complete data showed similar results to the analysis that used the imputed dataset (data not shown).

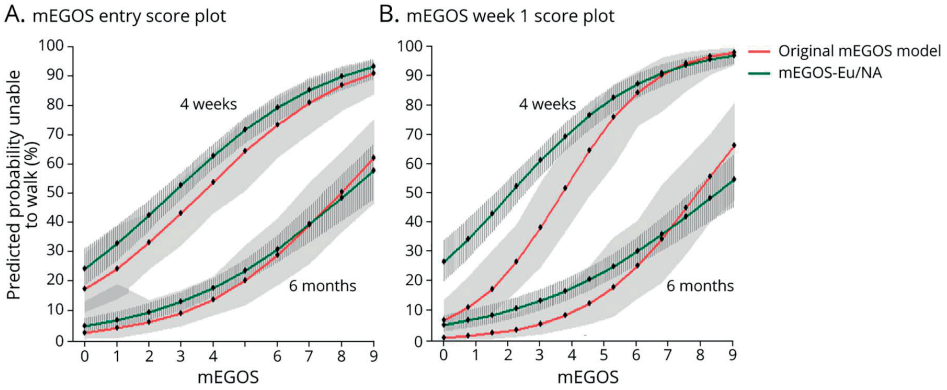

Figure 3. Predicted proportion of patients unable to walk independently based on original and recalibrated mEGOS
This figure provides the predicted probabilities of not being able to walk independently at 4 weeks and 6 months based on the mEGOS score at entry (panel A) and the mEGOS score at week 1 (panel B). Probability graphs are based on the original mEGOS model (red) and the recalibrated model for the Europe/North America subgroup (green). Dashed and grey areas around the curves represent the 95% CIs. The top (red and green) graphs provide the probabilities of not being able to walk independently at 4 weeks, and the bottom (red and green) graphs provide probabilities at 6 months. The mEGOS model can be used in all patients with GBS and variants of GBS who have lost the ability to walk. The mEGOS score can be calculated based on the scoring system provided in Table 1. Based on the mEGOS score and Figure 3, the probability of being unable to walk independently at 4 weeks or 6 months can be deduced for an individual patient. For predictions with the mEGOS in European and North American GBS patients the probability of poor outcome can be determined using the probability graphs based on the recalibrated model (green lines). For predictions in GBS patients from countries outside Europe and North America the probability graphs based on the original mEGOS model can be used (red lines). mEGOS = modified Erasmus GBS Outcome Score; 4w = 4 weeks; 6m = 6 months.

DISCUSSION

This study showed that the mEGOS is a useful tool to predict the inability to walk unaided in individual patients with GBS. In the IGOS-1500 cohort, the model was able to distinguish between patients with a good and a poor outcome, as defined by the inability to walk at 4 weeks or 6 months. In all validation subgroups the AUC-value was above 0.7. The accuracy of the model, as indicated by the comparison of the predicted and observed risks of poor outcome, varied between regions. In patients from Europe and North America the mEGOS underestimated the risk of poor outcome, while this risk was overestimated in patients from Asia. By recalibration of the original mEGOS model we were able to improve the accuracy of the predictions and to create a region-specific version of the model for patients from Europe and North America (mEGOS-Eu/NA). Recalibration of the model for patients from other regions was not possible, because of the smaller sample size.

The mEGOS also was recently validated in two studies conducted in Japan and Malaysia[6, 7]. Both studies showed a significant correlation between the mEGOS at hospital admission and at day 7 and the GBS disability score at 6 months (and also at 4 weeks

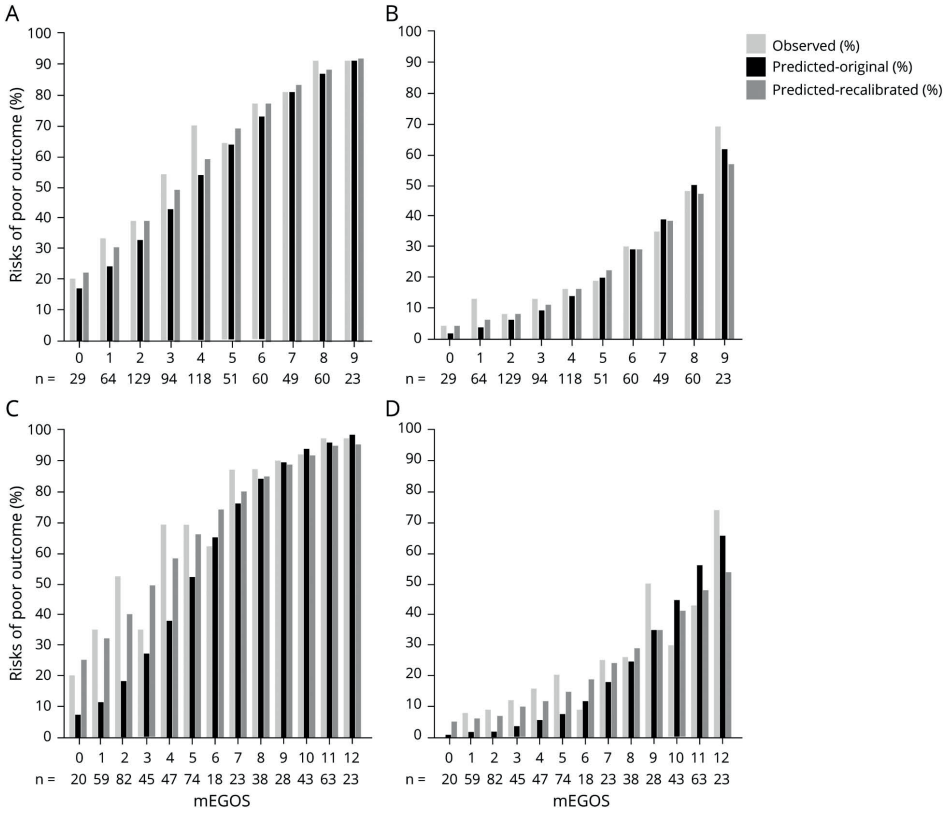

Figure 4. Observed versus predicted (pre- and post-recalibration) risks (%) of poor outcome per mEGOS score value for European and North American GBS patients

This figure compares the observed and predicted (pre- and post-recalibration) risks (%) of poor outcome per mEGOS score value for the Eu/NA subgroup. Panel A provides observed and predicted risks for the mEGOS at entry, predicting outcome at 4 weeks; panel B for the mEGOS at entry, predicting outcome at 6 months; panel C for the mEGOS at week 1, for predicting outcome at 4 weeks; and panel D for the mEGOS at week 1, predicting outcome at 6 months.

and 3 months for the Malaysian study). In patients with a poor outcome at 6 months, the mEGOS at admission and at day 7 were significantly higher than in patients with a good outcome[6,7]. In our IGOS validation study, AUC-values for the mEGOS at entry and 1 week in Asia ranged from 0.79 to 0.89. This indicates that in 79% to 89% of the random comparisons of one patient with a good outcome and one patient with a poor outcome, the mEGOS was higher in the patient with the poor outcome. These results do need to be interpreted with caution as confidence intervals for the AUC-values were relatively wide. The Malaysian study also provided AUC-values which ranged from 0.69 to 0.86 for the mEGOS at entry and from 0.78 to 0.92 for the mEGOS at day 7. These results show that the mEGOS can distinguish between GBS patients with a good and a poor outcome in Asia, and therefore support the use of the original, validated model in Asia. In external validation studies, discrepancies between observed and predicted risks

are usually explained by differences between the development and validation cohort, especially regarding factors that influence outcome but are not included in the prognostic model. The mEGOS was developed and validated in cohorts that largely contained patients with severe and typical forms of GBS from the Netherlands. In the IGOS-1500 cohort, there was a more diverse population of patients, especially with respect to the GBS variants, which could have influenced clinical recovery. For example, the IGOS-1500 cohort also included patients with the MFS, who usually have a more favourable outcome and may not require treatment. Furthermore, the mEGOS may perform differently in patients with the axonal subtype of GBS, as this subtype is commonly associated with a poor outcome, but may also show a rapid clinical recovery due to resolution of conduction blocks[21]. The differences between the observed and predicted risks, and also the differences in performance of the mEGOS between Europe/North America and Asia, may in part be explained by the regional variation in the prevalence of these clinical variants and subtypes. In this validation study we included patients with all variants of GBS considering that the distinction between typical and variant forms of GBS is complex and an inclusive model is most useful for clinical practice. Other factors that could have influenced the performance of the mEGOS are differences in treatment and health care facilities (including physiotherapy and rehabilitation) between hospitals and countries. Severity of limb weakness and age are the two predominant predictors of poor outcome in the mEGOS model, and constitute 8 out of 9 points for the score at entry and 11 out of 12 for the score at 1 week. Preceding diarrhoea has a relatively small prognostic effect and in the current study was not a significant predictor of poor outcome after 4 weeks in the full IGOS cohort and Eu/NA subgroup. This may be explained by the fact that preceding diarrhoea in GBS may have several causes. The strongest association with poor outcome is after an infection with *Campylobacter jejuni,* which is frequently followed by an axonal variant of GBS, with severe limb weakness and without sensory nerve involvement. Other causes of preceding diarrhea may have less impact on prognosis and their frequency may differ between countries.

Refitting of the mEGOS model in the full IGOS cohort and Eu/NA subgroup showed that re-estimation of the odds ratio's for age, preceding diarrhoea and the MRC sum score based on the IGOS data only resulted in minor improvement of the AUC-values. This finding indicates that additional prognostic factors are required to further improve the discriminative ability of the mEGOS. Potential prognostic (bio)markers are electrophysiological subtypes, preceding infections, anti-ganglioside antibodies, cerebrospinal fluid protein and serum ΔIgG levels and neurofilament light chain. Examples of previous studies reporting on serum biomarkers that could improve the mEGOS include a study from The Netherlands that found that low serum ΔIgG levels 2 weeks after standard IVIg treatment were independently associated with a worse outcome at 6 months. In this study,

the effect of serum ΔIgG on outcome was corrected for the age of the patient, preceding diarrhoea and the GBS disability score at study entry[22]. A recent retrospective study from Japan showed that patients with serum IgG anti-GD1a antiganglioside antibodies more often had a poor outcome at six months than patients without these antibodies, and that the addition of information about the presence of serum anti-GD1a IgG antibodies could improve the performance of the mEGOS[23]. Finally, a recent study from Spain showed that higher baseline serum levels of neurofilament light chain were associated with a worse clinical outcome, also when corrected for the individual factors included in the mEGOS[24].
How can the mEGOS model be used in clinical practice? The model can be applied to all patients diagnosed with GBS or a variant of GBS who are unable to walk independently in the acute stage of disease. The model can be used either at hospital admission or at day 7 of admission. To calculate the mEGOS score no other information is required than the MRC sum score, age of the patient and the presence of preceding diarrhea. Based on this information and the mEGOS scoring system (provided in Table 1[4]) one can calculate the mEGOS. The corresponding risk of being unable to walk independently at 4 weeks and 6 months can be deduced from the mEGOS and the probability graphs in Figure 3. For patients from Europe and North America we recommend using the recalibrated mEGOS-Eu/NA model. For patients from other geographical regions we recommend using the validated original mEGOS (Figure 3)[4]. The mEGOS can also be used via on online tool[25]. Currently, this tool provides the predicted probability of poor outcome based on the original mEGOS model, but this version will be updated to also incorporate the mEGOS-Eu/NA. The calculated risks for the inability to walk can be used to inform patients and their relatives about the expected clinical course and to plan further rehabilitation and care. Unfortunately, aside from the standard course of IVIg or plasma exchange, at present no additional treatment is available for patients with a poor expected outcome[26-29]. Several trials with new treatments for GBS are currently ongoing or planned, which may be reserved for patients with poor expected outcome, who may be identified in the earliest stage of the disease by the mEGOS(-Eu/NA). This clinical prognostic model can also be used in research to evaluate the independent contribution of other prognostic factors, including biomarkers, to select patients for treatment trials and to compare study cohorts by matching for the mEGOS. The stratification of patients by prognostic models provides a basis for the development of a more personalized treatment for GBS.
There are several limitations of this study. First, GBS disability scores were missing in about one-fifth of the patients, which were imputed using multiple imputation. To minimize the uncertainty induced by imputation, we imputed 10 times and took the average of the 10 imputed data sets. In addition, we used longitudinal data for the GBS disability score (and MRC scores) in our imputation model, i.e. in case the GBS disability score at week 4 was missing, scores at week 2 or 8 could be used to impute this value. Second, because the mEGOS focuses on walking ability, the model can only be applied

to severely affected patients who have lost the ability to walk. New prediction models are required that focus on different outcome measures and can be applied to the full GBS spectrum. Nevertheless, it will also remain important to use the GBS disability score as an outcome measure for comparison with previous studies. Finally, model validation is a continuous process. Given the varying patient populations and clinical settings to which the mEGOS will be applied, it will remain important to pay attention to differences in predicted and observed outcomes, especially in situations where clinical decision making is primarily driven by specific cut-off values for the predicted outcome. In conclusion, this study validated the mEGOS in an international GBS cohort and showed that the model, in its original form, can also be used in individual patients with GBS or its variants to predict the risk of poor outcome. A more accurate mEGOS-Eu/NA was developed for predicting poor outcome in patients from European countries and North America.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Clinical characteristics of mEGOS regional validation cohorts

		Patients unable to walk unaided at entry		Patients unable to walk unaided at week 1	
Region		Eu/NA (n = 677)	Asia (n = 76)	Eu/NA (n = 563)	Asia (n = 65)
Years		2012 - 2017	2012 - 2017	2012 - 2017	2012 - 2017
Study country		Belgium, Canada, Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, UK, USA	China, Japan, Malaysia, Taiwan	Belgium, Canada, Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, UK, USA	China, Japan, Malaysia, Taiwan
Age		59 (44-69)	52 (40-63)	59 (46-70)	52 (44-64)
	≤40	137 (20%)	19 (25%)	102 (18%)	11 (17%)
	41-60	227 (34%)	35 (46%)	188 (33%)	34 (52%)
	>60	313 (46%)	22 (29%)	273 (49%)	20 (31%)
	Range	7-90	19-83	7-90	19-83
Sex (male)		383 (57%)	45 (59%)	321 (57%)	40 (62%)
Preceding diarrhoeaa		159/665 (24%)	20 (26%)	135/552 (25%)	17 (26%)
Time onsetb to admission, days		2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)
Time onsetb to entry, days		5 (3-8)	4 (2-5)	5 (3-8)	3 (2-5)
MRC sum score at entry		46 (36-52)	44 (33-54)	45 (35-51)	42 (32-51)
	51-60	191/672 (28%)	25 (33%)	146/556 (26%)	18 (28%)
	41-50	246/672 (37%)	18 (24%)	208/556 (37%)	18 (28%)
	31-40	103/672 (15%)	18 (24%)	85/556 (15%)	15 (23%)
	00-30	132/672 (20%)	15 (20%)	117/556 (21%)	14 (22%)
	Range	0-60	0-60	0-60	0-60
Sensory deficits at entry		469/652 (72%)	39/74 (53%)	385/539 (71%)	29/63 (46%)
CNI at entry		327/674 (49%)	45/76 (59%)	267/559 (48%)	36/65 (55%)
Autonomic dysfunction at entryc		198/676 (29%)	15/76 (20%)	167/559 (30%)	12/65 (19%)
MRC sum score at week 1		47 (32-54)	47 (34-56)	45 (30-52)	44 (27-53)
	51-60	232/605 (38%)	28/72 (39%)	178/558 (32%)	19/64 (30%)
	41-50	157/605 (26%)	19/72 (26%)	160/558 (29%)	16/64 (25%)
	31-40	73/605 (12%)	9/72 (13%)	75/558 (13%)	10/64 (16%)
	00-30	143/605 (24%)	16/72 (22%)	145/558 (26%)	19/64 (30%)
	Range	0-60	0-60	0-60	0-60
GBS variantd	Sensorimotor	452/633 (71%)	33 (43%)	387/528 (73%)	31 (48%)
	Pure motor	85/633 (13%)	21 (28%)	70/528 (13%)	21 (32%)
	MFS	33/633 (5%)	8 (11%)	23/528 (4%)	1 (2%)

Supplementary Table 1. Clinical characteristics of mEGOS regional validation cohorts (*continued*)

	Patients unable to walk unaided at entry		Patients unable to walk unaided at week 1	
MFS-GBS overlap	40/633 (6%)	9 (12%)	28/528 (5%)	8 (12%)
Otherd	23/633 (4%)	5 (7%)	20/528 (4%)	4 (6%)
Mechanical ventilation	140 (21%)	19 (25%)	134 (24%)	20 (31%)
ICU admission	214 (32%)	17 (22%)	201 (36%)	17 (26%)
IVIg/PEe	652 (96%)	73 (96%)	552 (98%)	64 (99%)
Time onset to start IVIg/PE, days	4 (2-7)	5 (3-7)	4 (2-6)	4 (2-6)
GBS-DS >2 at week 4f	321/543 (60%)	31/74 (42%)	316/474 (68%)	32/63 (51%)
GBS-DS >2 at 3 monthsf	160/485 (33%)	12/67 (18%)	156/423 (37%)	13/57 (23%)
GBS-DS >2 at 6 monthsf	109/498 (22%)	7/55 (13%)	103/430 (24%)	8/48 (17%)

This table provides an overview of the characteristics of the (non-imputed) development and regional validation cohorts. Numbers are provided as median (IQR) or n (%), unless stated otherwise. mEGOS = modified Erasmus GBS Outcome Score; Eu/NA = Europe/North America; CNI = cranial nerve involvement; GBS = Guillain-Barré syndrome; GBS-DS = GBS disability score; NA = not available/applicable.

a Symptoms of a gastro-intestinal infection within the 4 weeks preceding onset of weakness

b Onset of weakness

c Autonomic dysfunction includes cardiac (arrhythmia, tachycardia, bradycardia), blood pressure (fluctuations, hypertension, hypotension), gastro-enteric, bladder and pupil dysfunction, excessive sweating and hyponatraemia etc.

d GBS variants represent the classification as reported by the local researchers at week 2 (and if missing at week 1 or study entry). Other variants include pharyngeal-cervical-brachial variant, pure sensory GBS, ataxic variant, Bickerstaff's brainstem encephalitis etc.

e Treated with IVIg and/or plasma exchange. This variable was based on the first two treatment episodes reported in the IGOS study.

f Proportion of patients unable to walk independently.

3.2

International validation of the Erasmus GBS Respiratory Insufficiency Score

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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.

Key words

Guillain-Barré syndrome, respiratory insufficiency/mechanical ventilation, prognostic modelling

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.

Table 1. 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.

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.

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: *aregImpute*). 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.

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).

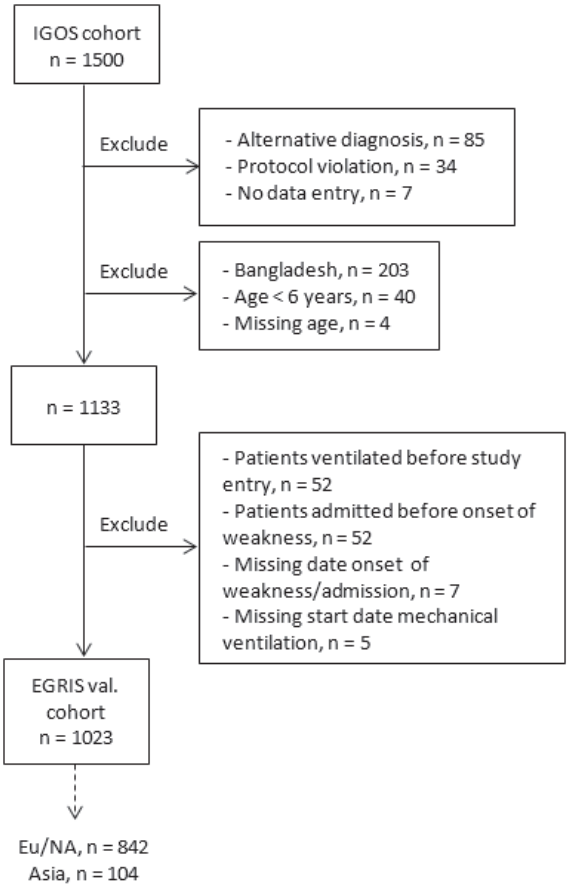

Figure 1. Study population
Eu/NA = Europe/North America;
The sum of the exclusions in the second and third box is higher than the total number of exclusions at the corresponding step because of overlap in patient characteristics, i.e. 6 patients with age <6 years were included in Bangladesh, 5 patients 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.

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). We also assessed the predictive ability of each of the individual factors included

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	> 7 days	107 (11%)	157 (28%)
to hospital admission	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) [28, 29, 31], (2) study 4: median age (95% CI) in years: 46 (23-76) [30], (3) study 5: median age (IQR) in years: 50 (35-63) [32].
[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.

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

		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)

* Values at study entry in the IGOS validation cohorts. Eu/NA = Europe/North America.

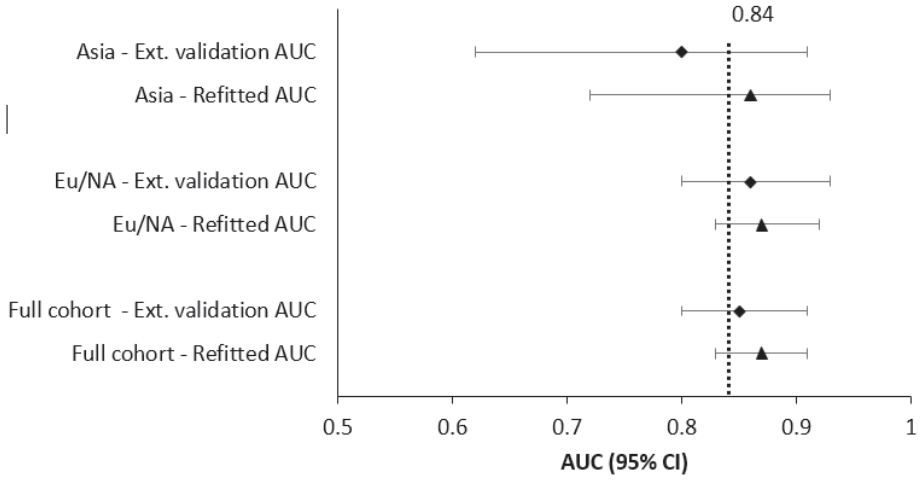

Figure 2. Discrimination upon external validation
The AUC value is a measure for the discriminative ability of a prediction model, ranging from 0.5 (flipping a coin) to 1.0 (perfect discrimination). For the EGRIS this represents the ability of the model to distinguish patients who need and do not need 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.

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.

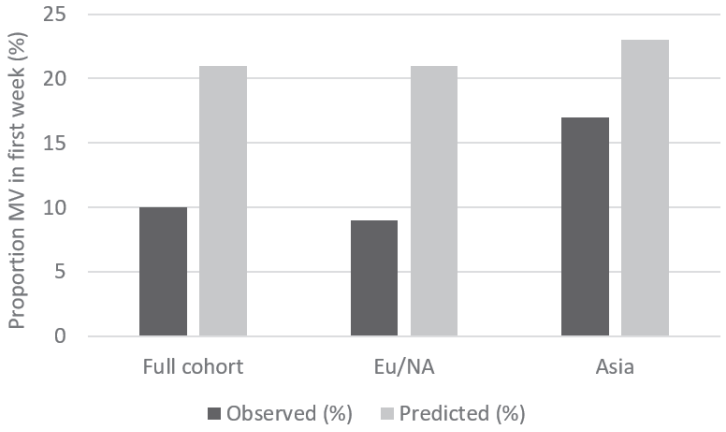

Figure 3. Observed probabilities versus predicted risks
Mean observed proportions of mechanical ventilation within 1 week in the IGOS validation cohorts versus predicted risks based on the EGRIS model.

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).

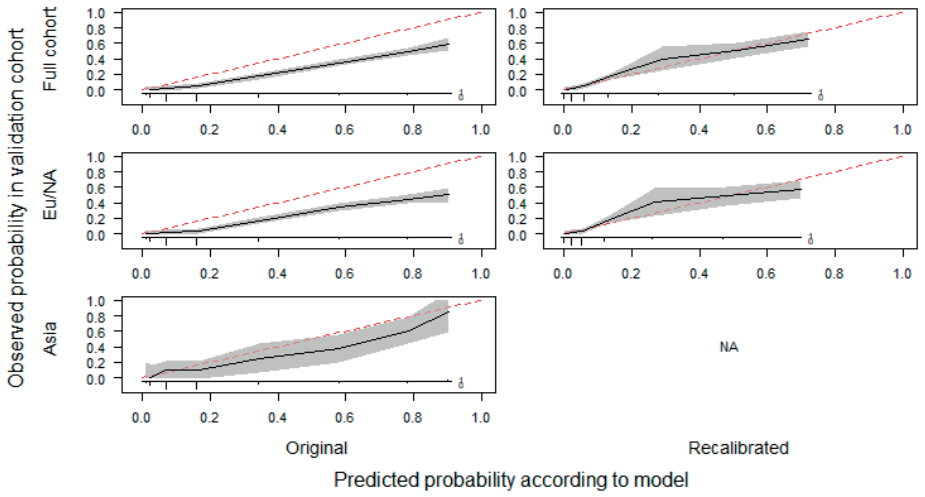

Figure 4. Calibration curves: original and after recalibration
This figure provides the calibration curves for the original (left) and recalibrated (right) EGRIS model, for the full IGOS cohort, Europe/North America and Asia. Observed probabilities of mechanical ventilation (y-axis) are plotted against 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.

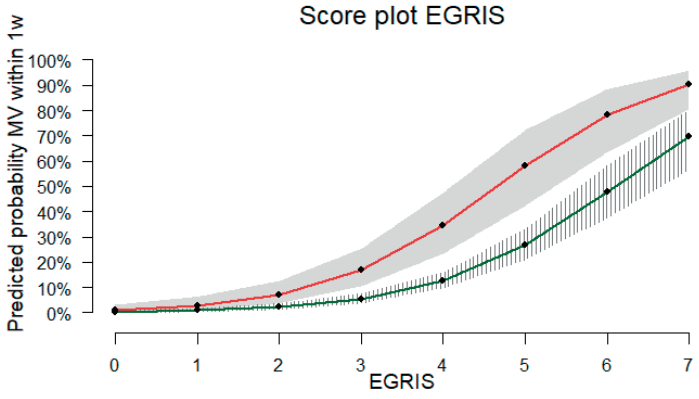

Figure 5. Predicted probabilities of mechanical ventilation within one week according to the recalibrated EGRIS-Eu/NA model
This figure provides the predicted probabilities of the need for mechanical ventilation within the first week from hospital admission based on the EGRIS (scores 0-7). Probability 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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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of the patients in the EGRIS development cohort and regional validation cohorts of IGOS

Predictors and outcome		IGOS validation cohort		EGRIS development cohort[5] (n = 565)
		Eu/NA (n = 842)	Asia (n = 104)	
Age, years		55 (40-67)	50 (36-62)	*NA*[a]
Time onset weakness	> 7 days	78 (9%)	11 (11%)	157 (28%)
to hospital admission	4-7 days	228 (27%)	31 (30%)	219 (39%)
	≤ 3 days	536 (64%)	62 (60%)	189 (34%)
MRC sum score at entry	51-60	380/836 (46%)	44 (42%)	127 (23%)
	41-50	279/836 (33%)	30 (29%)	250 (44%)
	31-40	93/836 (11%)	18 (17%)	106 (19%)
	21-30	44/836 (5%)	5 (5%)	53 (9%)
	≤ 20	40/836 (5%)	7 (7%)	29 (5%)
Facial and/or bulbar weakness at entry		309/841 (37%)	42 (40%)	170 (30%)
GBS disability score at entry	≤2	244/835 (29%)	32 (31%)	33 (6%)
	>2	591/835 (71%)	72 (69%)	532 (94%)
GBS variant	Sensorimotor	551/792 (70%)[c]	41 (39%)[b]	*NA*
	Pure motor	102/792 (13%)[c]	29 (28%)[b]	*NA*
	MFS	62/792 (8%)[c]	13 (13%)[b]	18 (3%)
	MFS-GBS overlap	40/792 (5%)[c]	13 (13%)[b]	*NA*
	Other	37/792 (5%)[c]	8 (8%)[b]	*NA*
MV during follow up		94 (11%)	18 (17%)	128 (23%)
MV within the first week of admission		77 (9%)	18 (17%)	110 (20%)
IVIg/PE		773 (92%)	93 (89%)	95%[c]

This table provides an overview of the characteristics of the patients in the EGRIS development cohort and the IGOS validation datasets from Europe/North America and Asia. Numbers are provided as median (IQR) or n (%), unless stated otherwise. Eu/NA = Europe/North America. 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) combined cohort of 3 studies, median age (IQR) in years: 52 (33-66)[27, 28, 30], (2) median age (95% CI) in years: 46 (23-76)[29], (3) 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 pharyngeal-cervical-brachial variant, pure sensory GBS, ataxic variant, Bickerstaff Brainstem encephalitis, etc.

[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.

Supplementary Table 2. Study design, in- and exclusion criteria of the studies included in the EGRIS development cohort and IGOS validation cohort

	IGOS validation cohort (n = 1023)	**EGRIS development cohort**[5], * **(n = 565)**	
Study design	Prospective, observational cohort study	**(1)** RCT (n=147): PE vs. IVIg **(2)** Pilot study (n=25): MP + IVIg vs. IVIg monotherapy **(3)** RCT (n=225): MP + IVIg vs. IVIg monotherapy **(4)** Pilot study: additional therapeutic effect mycophenolate mofetil with IVIg + MP (n=27)	**(5)** Prospective observational study on pain and autonomic dysfunction in GBS (n=164)
Years	2012 - 2017	**(1)** 1985 – 1991, **(2)** 1991-1994 **(3)** 1994 – 2000, **(4)** 2002 - 2005	2005-2008
Country	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)	The Netherlands (n=386), Belgium (n=16), Germany (n=22)	The Netherlands (n=168)
Inclusion criteria	- Fulfilment of the criteria for GBS or its variants [22, 23] - Inclusion within two weeks from the onset of weakness	- Fulfilment of the NINDS diagnostic criteria for GBS[22, 33] - Being unable to walk 10m unaided (GBS DS ≥3) - Onset of weakness within two weeks before randomization	- Fulfilment of the NINDS diagnostic criteria for GBS[22, 34]
Exclusion criteria	No exclusion criteria	- Age: **(1)** <4 y, **(2)** <16 y, **(3)**, <6 y, **(4)** <18 y - Previous GBS - Known severe allergic reaction to properly matched blood products - Pregnancy / breast feeding - Known selective IgA deficiency - Previous steroid therapy / immunosuppressive treatment - Severe concurrent (immune mediated) disease - Inability to attend follow-up - Contra-indications for corticosteroid treatment	- Age <12 y - Significant comorbidity with predicted survival <1 y - Patients with Bickerstaff encephalitis and A-CIDP

* The EGRIS development cohort included data from 5 studies. Four of these five studies had similar in- and exclusion criteria, and are therefore reported in one column. From studies (1), (2) and (3), 20 patients were excluded because they were ventilated prior to referral to one of the participating hospitals. From studies (4) and (5), 3 patients were excluded because ventilation was started before referral to a trial hospital. The full EGRIS development cohort included 565 patients.

3.3

Validation and adjustment of modified Erasmus GBS Outcome Score in Bangladesh

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ABSTRACT

Objective. We have assessed and improved the performance of the modified Erasmus GBS Outcome Score (mEGOS) among patients with Guillain-Barré syndrome (GBS) from Bangladesh.

Methods. Validation cohort consisted patients with GBS from two prospective cohort studies in Bangladesh. Poor outcome was defined as being unable to walk independently at week 4 and week 26. We excluded patients able to walk independently, patients who died within the first week, or with missing GBS disability scores. Performance of mEGOS at entry and week 1 was determined based on the discriminative ability (ability to differentiate between patients able and unable to walk independently; measured using area under receiver operating characteristic curves [AUC]) and calibration (observed probability versus predicted probability of poor outcome).

Results. A total of 506 patients aged ≥6-years-old were enrolled, with 471 and 366 patients included in mEGOS validation analysis at entry and week 1, respectively. The AUC values for predicting poor outcome (1) at week 4 were 0.69 (mEGOS entry) and 0.78 (mEGOS week 1) and (2) at week 26 were 0.67 (mEGOS entry) and 0.70 (mEGOS week 1). Mean predicted probabilities of poor outcome corresponded with observed outcomes except for the probability of poor outcome at week 4 which was overestimated by mEGOS week 1. This was resolved by updating the model intercept.

Interpretation. The mEGOS shows valid outcome predictions among patients with GBS from Bangladesh. The model can aid identification of patients at high risk of poor outcome and help to adequately allocate healthcare resources in low-resource settings.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute, immune-mediated peripheral neuropathy with a variable clinical presentation, disease course, and outcome[1-3]. The clinical spectrum of GBS ranges from mild distal limb weakness to complete paralysis, respiratory failure, and death[4]. Even after receiving standard therapy for GBS (intravenous immunoglobulin [IVIg] or plasma exchange [PE]), 20% of patients remain unable to walk unaided at 6 months after disease onset and 2–10% patients die during the disease course[1, 2, 5-7]. Compared to patients in high income countries, patients with GBS from Bangladesh are much younger, more often have the axonal variant of GBS, and present with more severe forms of the disease[3]. In addition, due to the low income per capita, the majority of patients in Bangladesh cannot afford treatment with IVIg or PE[8]. Facilities for supportive care such as ventilatory support are inadequate, and access to integrative rehabilitation services is limited[3, 4, 9-11]. Not surprisingly, the rates of poor outcome (30–40%) and mortality (14–17%) among patients with GBS are much higher in Bangladesh compared to patients in developed countries[3, 12]. Therefore, it is required to identify patients with GBS who have a high risk of poor outcome at the earliest stage of the disease. This will enable physicians in low-resource settings to take the necessary precautions and to personalize disease management.

To date, several prognostic models have been developed for GBS[13-15]. Among them, the modified Erasmus GBS Outcome Score (mEGOS) is one of the most commonly used models in clinical practice in high income countries. The mEGOS was originally developed in 2011[15] based on a set of three clinical predictors: age, Medical Research Council (MRC) sum score, and preceding diarrhea. The mEGOS can be used at hospital admission and on day 7 of hospital admission (Table 1). The model can predict the risk of being unable to walk independently at 4 weeks, 3 months, and 6 months after the onset of weakness. However, this model was derived from a distinct group of severely affected patients from a Dutch population participating in different GBS clinical trials, which may restrict the general applicability of the mEGOS. Until now, the mEGOS has only been validated in a Dutch cohort and two Asian cohorts (Japan and Malaysia, separately)[15-17]. In addition, the model was recently validated in a selected cohort of patients with GBS from high-income countries who were included in the International GBS Outcome Study (IGOS)[18]. However, the performance of the mEGOS among patients with GBS from low- and middle-income countries (LMIC) is currently unknown. Several factors could differentially influence the prognosis and outcome of patients with GBS in these countries compared to high-income countries, including the higher proportions of younger patients, axonal subtypes, and untreated patients. In the current study, we aimed to validate the mEGOS model using one of the largest prospective cohorts from Bangladesh. We also assessed if the performance of the mEGOS model could be improved specifically for patients with GBS from Bangladesh.

Table 1: Modified Erasmus GBS Outcome Score (mEGOS)

Prognostic factor	Score at hospital admission	Score at week 1
Age at onset (year)		
≤ 40	0	0
41-60	1	1
> 60	2	2
Preceding diarrhea		
Absent	0	0
Present	1	1
MRC sumscore		
51-60	0	0
41-50	2	3
31-40	4	6
00-30	6	9
mEGOS	**0-9**	**0-12**

The table presents the mEGOS scoring system, as originally developed in 2011 among Dutch patients with GBS[15]. The model is based on three clinical parameters and can be used at hospital admission (score ranging 0-9) and week 1 of hospital admission (score ranging 0-12) to predict the risk of being unable to walk independently at 4 weeks, 3 months, and 6 months after the onset of weakness.
MRC: Medical Research Council.

METHODS

Validation dataset from Bangladesh

The validation cohort consisted of prospective data collected for 506 patients with GBS aged ≥6 years who were recruited within 2 weeks of the onset of weakness and met the National Institute of Neurological Disorders and Stroke (NINDS) criteria for GBS[19]. All patients were derived from two GBS studies conducted by icddr,b, in Bangladesh[10, 20, 21] (Fig 1). The first study, a prospective observational cohort study, was conducted from February, 2010 to June, 2013 and included 313 patients with GBS[10]. The second study was the International GBS outcome study (IGOS), a prospective multicenter cohort study conducted in 21 countries worldwide[21]; 193 patients with GBS from Bangladesh were included in the IGOS between November, 2013 and December, 2016. The study protocols were reviewed and approved by the Ethical Committees at icddr,b. Written informed consent was obtained from all participants or their legal representatives. Baseline characteristics, including socio-demographic characteristics, history of preceding infection, and detailed clinical and neurological features (including GBS disability score and MRC sum score) were collected. After enrollment, patients underwent follow-up at standard time points (week 1, week 2, week 4, week 8, week 13, week 26, and week 52) according to predefined protocols. For the final analysis, we excluded patients who were able to walk independently (GBS disability score ≤ 2) at study entry or week 1; patients who died within the first week after study entry, and patients for whom data on GBS disability score was missing at entry or week 1.

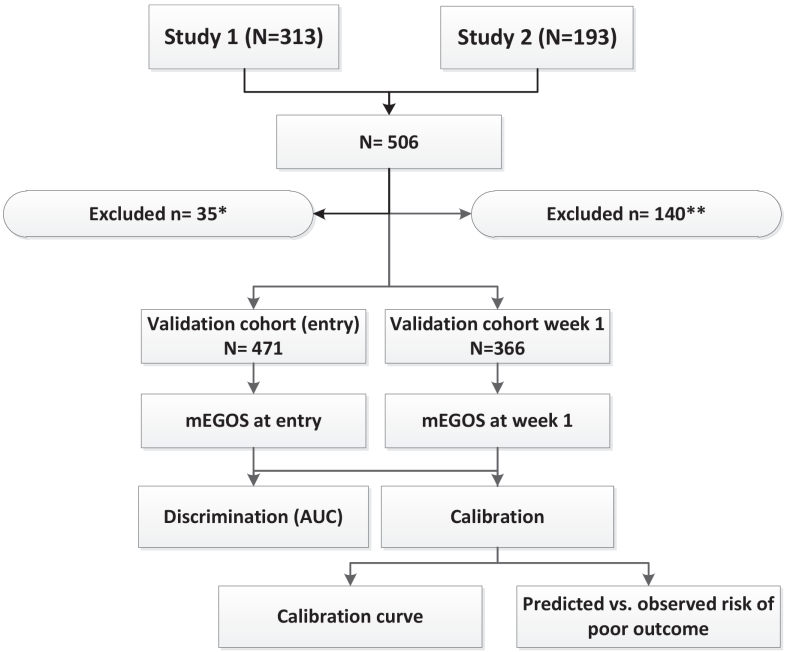

Figure 1. Study population of patients with GBS from Bangladesh used to validate the mEGOS model.
Study 1: Prospective observational cohort study, conducted between 2010 and 2013.[10]
Study 2: International GBS Outcome Study; a prospective multicenter cohort study conducted between 2013 and 2016.[20]
*Able to walk independently at study entry; *n* = 35.
**Able to walk independently at week 1, *n* = 40; died, *n* = 1, missing data for GBS-DS at week 1, *n* = 99.
AUC: area under the receiver operating characteristic curve; GBS-DS: GBS disability score; mEGOS: modified Erasmus GBS Outcome Score.

Statistical analysis

To validate mEGOS among patients with GBS from Bangladesh, we used the original regression formulas with mEGOS total score as a single predictor. Poor outcome was defined as being unable to walk independently (GBS disability score > 2)[19]. We evaluated the ability of mEGOS to predict a poor outcome in GBS at week 4, which is the most commonly used time point in treatment efficacy trials[22, 23], and at 6 months (week 26) to assess the ability of the model to predict long-term outcome[24].

Missing values for mEGOS predictors and GBS disability scores at week 4 and week 26 were imputed using a multiple imputation method with ten imputed datasets[25, 26]. We included information on age, sex, antecedent events, GBS variants, cranial nerve involvement, sensory deficits, pain, ataxia, autonomic dysfunction, treatment, and nerve conduction study findings in the imputation model. We also imputed the missing individual MRC scores and GBS disability scores using the available longitudinal data of the same variables at entry, week 1, week 2, week 4, week 8, week 13, week 26, and week 52.

Model performance was determined by discrimination (i.e., the ability of the model to differentiate between patients who are able and unable to walk independently) and calibration (i.e., the accuracy of the absolute risk estimates)[27, 28]. Discrimination was evaluated using the area under receiver operating characteristic curve (AUC), which ranges from 0.5 to 1.0. The AUC value indicates the probability that for any randomly selected pair of individuals, one with a good outcome and one with a poor outcome, mEGOS score will be higher for the patient with the poor outcome. A value of 1 indicates the model has perfect discriminative ability, while a value of 0.5 indicates that the model discriminates no better than chance. In addition, we refitted the model for the validation cohort, thereby re-estimating the values of the coefficients of individual predictors, to calculate the refitted AUC values. This allowed us to evaluate the highest possible discriminative ability of the model in the validation cohort.

Calibration was assessed by comparing the mean predicted and observed risks of a poor outcome in the validation cohort, and was graphically presented by plotting the observed versus predicted outcomes in a calibration plot. Calibration plots were based on data from the first imputation set. To select the appropriate method for updating the model, we used the closed testing procedure described by Vergouwe et al[29]. In the closed testing procedure, different updating methods, varying in extent (i.e., minimum: either keep the original model or systematically increase or decrease all predicted probabilities by the same number; maximum: full model revision with re-estimation of all coefficients) are compared to determine which updating method provides the most appropriate model for the validation sample. The closed testing procedure was performed using the first imputation set.

To assess the performance of mEGOS in different categories of patients, separate subgroup analyses were performed among patients who did not received any immunotherapy; younger patients (age ≤ 40 years), patients with pure motor variant of GBS, and patients with axonal subtype of GBS. The subgroup analyses were performed using the first imputation set and included discrimination (AUC) and calibration (predicted vs. observed proportion of poor outcome).

A separate analysis was performed with complete case data, and the results of this analysis were compared with the results from the main analysis using imputed data. We also assessed and compared the predictive ability of individual factors included in mEGOS between the development and validation cohorts. Data analysis was performed using SPSS Statistics version 20 and R Studio version 4.0.2 (R packages: Hmisc, rms, devtools, CalibrationCurves).

RESULTS

From a total of 506 patients with GBS from Bangladesh, we excluded the patients who were able to walk independently at study entry (*n* = 35) or week 1 (*n* = 40), patients who died within the first week (*n* = 1), and patients with missing data for GBS disability score at week 1 (*n* = 99). Thus, the cohorts from Bangladesh for validation of mEGOS at entry and week 1 contained 471 and 366 patients with GBS, respectively (Fig 1).

In total, 6% of the data points (224/4048) were imputed for the predictive factors of mEGOS (age, antecedent diarrhea, and MRC sum score at entry and week 1) and the outcome variables (GBS disability score at week 4 and week 26).

Characteristics of the development and validation cohorts

Compared to the original Dutch mEGOS development cohort[15], the patients with GBS in the current validation cohort from Bangladesh were younger (median age 28 years vs. 52 years), had a higher frequency of preceding diarrhea (51% vs. 23%), had more severe muscle weakness at study entry and week 1 based on MRC sum score, more frequently had cranial nerve involvement (62% vs. 39%), and less frequently had sensory deficits (19% vs. 66%; Table 2). The median duration from onset of weakness to study entry was longer in the validation cohort (8 days) than the development cohort (5 days). Most patients (86%) in the validation cohort did not receive any immunotherapy for GBS, whereas all patients in the development cohort received either IVIg or PE. The proportion of patients with a poor outcome was higher in the validation cohort than the development cohort at all follow-up time points.

Table 2. Characteristics of the patients in the validation cohorts and development cohort

	Validation cohort from Bangladesh			Development cohort[15]
	Total cohort (*N*=506)	**Patients unable to walk at study entry[a] (*n*=471)**	**Patients unable to walk at week1[b] (*n*=366)**	**Total cohort (*n*=394)**
Age (years)	28 (18-42)[c]	28 (18-42)[c]	28 (17-43)[c]	52 (33-66)
≤ 40	373 (74%)	347 (74%)	264 (72%)	138 (35%)
41-60	120 (24%)	111 (24%)	94 (26%)	114 (29%)
> 60	13 (2%)	13 (2%)	8 (2%)	142 (36%)
Sex (male)	337 (67%)	308 (65%)	232 (63%)	215 (55%)
Preceding diarrhoea	250/493 (51%)	234/459 (51%)	182/358 (51%)	89/392 (23%)
Weakness to admission (days)	(N=193) 4 (2-7)[c]	(N=177) 4 (2-7)[c]	(N=163) 4 (2-7)[c]	NA
Weakness to study entry (days)	8 (5-11)[c]	8 (5-11)[c]	8 (5-11)[c]	5 (3-8)

Table 2. Characteristics of the patients in the validation cohorts and development cohort (*continued*)

	Validation cohort from Bangladesh			Development cohort[15]
	Total cohort (*N*=506)	**Patients unable to walk at study entry[a] (*n*=471)**	**Patients unable to walk at week1[b] (*n*=366)**	**Total cohort (*n*=394)**
Total MRC sum score at study entry	22 (4-36)[c]	20 (4-32)[c]	18 (4-30)[c]	43 (33-48)
51-60	19 (4%)	7 (1%)	6 (1%)	47/393 (12%)
41-50	55 (11%)	37 (8%)	22 (6%)	180 (46%)
31-40	88 (17%)	83 (18%)	54 (15%)	82/393 (21%)
00-30	344 (68%)	344 (73%)	284 (78%)	84/393 (21%)
Cranial nerve involvement at study entry	311 (62%)	294 (62%)	227 (62%)	152 (39%)
Autonomic dysfunction at study entry	89/497 (18%)	88/462 (19%)	61/360 (17%)	NA
Total MRC sum score at week 1	(N= 430) 28 (8-40)[c]	(N=405) 26 (8-38)[c]	(N=348) 23 (6-36)[c]	(N=385) 43 (30-50)
51-60	18 (4%)	9 (2%)	5 (1%)	95 (25%)
41-50	78 (18%)	66 (17%)	45 (13%)	116 (30%)
31-40	86 (20%)	82(20%)	59 (17%)	75 (20%)
00-30	248 (58%)	248 (61%)	239 (69%)	99 (26%)
GBS clinical variant	(N=493)	(N=457)	(N=358)	
Sensorimotor	80 (16%)	80 (18%)	64 (18%)	NA
Pure motor	406 (82%)	375 (82%)	292 (82%)	NA
Miller Fisher syndrome/ataxic form	5 (2%)	2 (0%)	2 (0%)	0 (0%)
Mechanical ventilation	108 (21%)	108 (23%)	85 (23%)	118 (30%)
Treatment				
Intravenous immunoglobulin	39 (8%)	39 (8%)	32 (9%)	IVIg/PE
Plasma exchange	21 (4%)	21 (5%)	19 (5%)	394 (100%)
Small volume plasma exchange	10 (2%)	10 (2%)	10 (3%)	0
Supportive care only	436 (86%)	401 (85%)	305 (83%)	0
Disease onset to start treatment (days)	(N=63) 6 (4-9)[c]	(N=63) 6 (4-9)[c]	(N=57) 6 (4-9)[c]	NA
GBS disability score >2[d] at week 4	321/489 (66%)	320/457 (70%)	277/359 (77%)	217/394 (55%)
GBS disability score >2[d] at 3 months	211/484 (44%)	211/452 (47%)	177/351 (50%)	111/389 (29%)
GBS disability score >2[d] at 6 months	141/480 (29%)	141/448 (32%)	109/346 (32%)	74/388 (19%)
Nerve conduction study	(N=364)	(N=337)	(N=271)	NA
Axonal	178 (49%)	162 (48%)	129 (48%)	
AIDP	117 (32%)	111 (33%)	89 (33%)	
Inexcitable	14 (4%)	14 (4%)	14 (5%)	
Equivocal	49 (14%)	44 (13%)	35 (13%)	
Normal	6 (1%)	6 (2%)	4 (2%)	

The characteristics of the development cohort have been published previously[15], and are shown for comparison purposes only. [a]Included in mEGOS entry analysis; [b]Included in mEGOS week 1 analysis; [c] Median with interquartile range (IQR); [d]Proportion of patients unable to walk independently.MRC: Medical Research Council sum score; AIDP: Acute Inflammatory Demyelinating Polyradiculopathy.

Discrimination

The discriminative ability of mEGOS among the patients with GBS from Bangladesh is described in Table 3. For mEGOS at entry, the AUC values were 0.69 (95% CI: 0.63-0.74) and 0.67 (95% CI: 0.62-0.72) for predicting a poor outcome at week 4 and week 26, respectively. Thus, in 100 random pairwise comparisons of one patient with a good outcome and one patient with a poor outcome, the model gave a higher mEGOS score for the patient with poor outcome in 69% of cases at week 4 and 67% of cases at week 26. For mEGOS at week 1, the AUC values for predicting a poor outcome were 0.78 (95% CI: 0.71-0.85) at week 4 and 0.70 (95% CI: 0.64-0.75) at week 26. The AUC values of mEGOS were lower at all time points in the validation cohort from Bangladesh than in the development cohort.

Table 3. Discriminative ability of the mEGOS in the validation and development cohorts

		mEGOS entry	mEGOS week 1
Validation cohort			
Week 4	AUC	0.69 (CI: 0.63-0.74)	0.78 (CI: 0.71-0.85)
	AUC (refitted)	0.69 (CI: 0.63-0.74)	0.79 (CI: 0.71-0.86)
Week 26	AUC	0.67 (CI: 0.62-0.72)	0.70 (CI: 0.64-0.75)
	AUC (refitted)	0.68 (CI: 0.62-0.72)	0.70 (CI: 0.64-0.76)
Development cohort			
Week 4	AUC	0.73	0.87
Week 26	AUC	0.77	0.84

The table presents the discriminative ability of mEGOS in the validation cohort and compares the findings with the previously published development cohort (for comparison only)[15]. AUC is a measure of the discriminative ability of the model, and ranges from 0.5 (no better than chance) to 1.0 (perfect discrimination). The refitted AUC is calculated by re-estimating the values of the coefficients of the predictors that indicate the highest discriminative ability of the model.
AUC: area under the receiver operating characteristic curve; mEGOS: modified Erasmus GBS Outcome Score; CI: 95% confidence interval.

We refitted the model including the individual predictors (age, preceding diarrhea, and MRC sum score at entry or week 1) in the validation cohort. The refitted AUC values for mEGOS entry and mEGOS week 1 were almost similar to the AUC values obtained during validation of the model using mEGOS total score as a single predictor (Table 3). This indicates that the discriminative ability of the model for GBS population in Bangladesh cannot be further improved using the existing sets of predictor variables. We compared the predictive ability of the individual predictors included in the model in the development and validation cohorts to predict a poor outcome at week 4. All predictors from the original model had lower effects (measured by odds ratio [OR]) in the validation cohort compared to the development cohort; this was most prominent for the MRC sum score where considerable differences of OR between development and validation cohort were observed (Table 4). Surprisingly, some categories of predictors showed an opposite association with a poor outcome in the validation cohort compared to the development

cohort. This means that in these categories, the predictors were associated with an increased risk of a poor outcome (OR >1) in the development cohort, but a lower risk of a poor outcome (OR < 1) in the validation cohort. For example, in mEGOS entry cohort, patients with more severe muscle weakness (MRC sum scores of 41-50 and 31-40) had a lower risk of a poor outcome than the patients with less severe muscle weakness (MRC sum score of 51-60). Similarly, for mEGOS week 1 cohort, patients aged 41-60 years and patients with MRC sum scores of 41-50 had lower risks of a poor outcome compared to the patients aged ≤ 40 years and patients with MRC sum scores of 51-60, respectively. Compared to the overall cohort from Bangladesh, these groups of patients who had a lower OR than the reference categories less frequently required mechanical ventilation and had higher proportions of sensorimotor involvement and the AIDP variant of GBS—except for the subgroup of patients with MRC sum scores of 31-40, who more frequently had the axonal variant (Table 5).

Table 4. Effects of the individual predictors of the original mEGOS model for prediction of outcome at week 4 in the development and validation cohorts

Predictors	mEGOS at entry vs. outcome at week 4		mEGOS at week 1 vs. outcome at week 4	
	Validation cohort	Development cohort	Validation cohort	Development cohort
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, years				
≤ 40	1	1	1	1
41–60	1.11 (0.67-1.86)	1.9 (1.1–3.3)	0.81 (0.43-1.52)*	2.1 (1.0–4.2)
> 60	3.0 (0.52-17.35)	2.3 (1.3–3.8)	1.60 (0.19.08)	2.8 (1.4–5.4)
MRC ss				
60–51	1	1	1	1
50–41	0.19 (0.04-1.06)*	2.8 (1.3–6.2)	0.59 (0.08-4.06)*	3.8 (1.7–8.4)
40–31	0.88 (0.18-4.22)*	6.1 (2.5–14)	2.23 (0.34-14.63)	10 (4.2–26)
≤30	2.77 (0.6-12.72)	9.6 (3.8–24)	12.73 (1.95-83.16)	58 (18–188)
Diarrhea	1.12 (0.72-1.73)	1.7 (1.0–2.9)	1.14 (0.61-2.13)	2.1 (1.0–4.4)

The table presents the results for the previously published development cohort for comparison purposes only[15].
*Predictor showing an opposite association in the validation cohort as compared to the development cohort (OR < 1 in the validation cohort, versus OR > 1 in the development cohort). The characteristics of these subgroups are described in Table 5.
mEGOS: modified Erasmus GBS Outcome Score; MRC ss: Medical Research Council sum score; OR: odds ratio, 95% CI: 95% confidence interval.

Calibration

In the validation cohort, the mean predicted probabilities of a poor outcome at week 4 and week 26 based on the original mEGOS model at entry and week 1 corresponded to the observed outcomes (Fig 2). However, slight overestimation of a poor outcome at week 4 based on the original mEGOS model at week 1 was observed (81% predicted probability vs. 77% observed probability).

Table 5: Subgroup analysis of patients with MRC scores of 41-50 and 31-40 in the validation cohort

	Validation cohort (Entry)			Validation cohort (Week 1)		
	Patients with MRC ss 41-50 (*n*=37)	**Patients with MRC ss 31-40 (*n*=83)**	**mEGOS entry cohort (*n*=471)**	**Patients with MRC ss 41-50 (*n*=45)**	**Patients aged 41-60 (*n*=94)**	**mEGOS week 1 cohort (*n*=366)**
Age years						
Median with IQR	30 (21-50)	29 (19- 40)	28 (18-42)	34 (18- 50)	50 (45- 55)	28 (17- 43)
Age range	9-65	7-60	6-75	7-65	41-60	6-75
Sex (male)	23 (62%)	60 (72%)	308 (65%)	32 (71%)	56 (60%)	232 (63%)
Preceding diarrhea	18 (49%)	37 (45%)	234 (51%)	22 (49%)	48 (51%)	182/358 (51%)
Patients with MV at entry	2 (5%)	3 (4%)	86 (18%)	3 (7%)	13 (14%)	67 (18%)
Patients with MV at week 1	1 (4%)	3 (5%)	79 (21%)	3 (7%)	17 (18%)	80 (23%)
GBS clinical variant						
Sensorimotor	9 (24%)	16 (19%)	80 (18%)	11 (24%)	33 (36%)	64/358 (18%)
Pure motor	28 (76%)	66 (80%)	375 (82%)	34 (76%)	57 (63%)	292/358 (82%)
Nerve conduction study	N=30	N=61	N=337	N=39	N=71	
Axonal	12 (40%)	34 (56%)	162/337 (48%)	16 (41%)	23 (32%)	129/271 (48%)
AIDP	12 (40%)	19 (31%)	111/337 (33%)	14 (36%)	38 (54%)	89/271 (33%)
Treatment						
Supportive only	33 (89%)	76 (91%)	401 (85%)	36 (80%)	77 (82%)	305/366 (83%)
IVIg/PE	4 (11%)	6 (8%)	60 (13%)	6 (13%)	13 (13%)	51/366 (14%)

MRC ss: Medical Research Council sum score; MV: mechanical ventilation; IQR: interquartile range; AIDP: acute inflammatory demyelinating polyradiculopathy; IVIg: intravenous immunoglobulin; PE: plasma exchange.

The calibration plots showed more prominent discrepancies between the predicted and observed risks for the subgroup of patients with a low predicted probability (< 0.3) of a poor outcome at week 4 (Fig 3). The observed outcomes for this subgroup of patients were worse than predicted; in other words, mEGOS model underestimated the risk of a poor outcome for this subgroup. We performed sub-group analysis to describe the characteristics of patients with a low predicted probability of a poor outcome (< 0.3) at week 4 based on mEGOS at entry (*n* = 5; mEGOS entry score ranging from 0-1) and mEGOS week 1 (*n* = 18; mEGOS week 1 score ranging from 0-3). In this subgroup, the mean predicted probabilities (± SD) of a poor outcome at week 4 based on mEGOS at entry and week 1 were 20% ± 4% (vs. observed probability of 40%) and 23% ± 8% (vs. observed probability of 39%), respectively. The majority of these patients were ≤ 40-years-old, had a preceding upper respiratory tract infection, and the AIDP variant of GBS. Compared to the overall cohort, the patients with a low predicted probability of a poor outcome less frequently had cranial nerve involvement and a higher proportion were untreated compared to the overall validation cohort (data not shown).

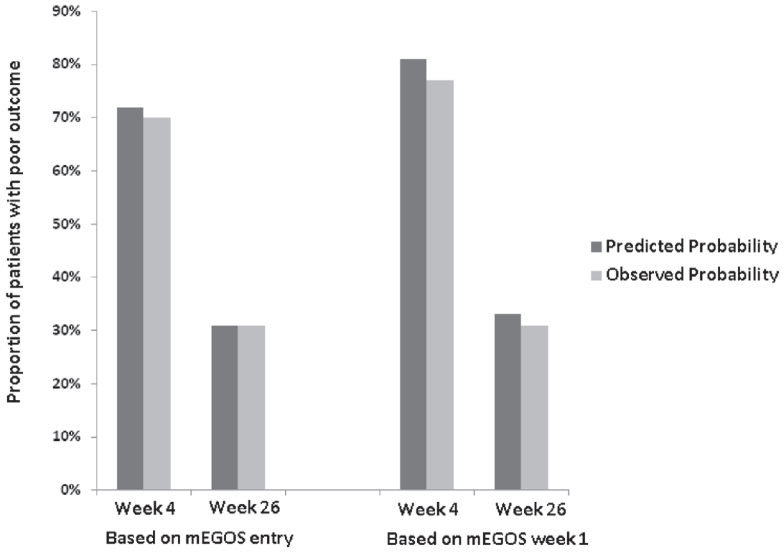

Figure 2. Mean observed vs. predicted risks of a poor outcome as per the original mEGOS model in the validation cohort. This figure represents the predicted probability of a poor outcome (GBS disability score >2) based on the original mEGOS at entry and week 1, which corresponded well with the observed frequency of a poor outcome in the validation cohort of patients from Bangladesh.
* For mEGOS at week 1, the model overestimated the probability of a poor outcome at week 4; after updating the model intercept, the predicted probability and observed frequency of a poor outcome became equal (77% vs. 77%).
mEGOS: modified Erasmus GBS Outcome Score.

Application of the closed testing procedure showed that the most appropriate model for Bangladesh GBS population was the "Original Model" at all time points, except for predicting week 4 outcome based on mEGOS at week 1 (the time point at which the original model overestimated a poor outcome). To predict the outcome at week 4 based on mEGOS at week 1, the model was further improved by systematically decreasing the predicted probabilities (updating the model intercept), which subsequently improved the performance of the model.

Subgroup analysis

Compared to the overall Bangladesh cohort, the AUC values (discrimination) for all time points were found almost similar in different subgroups e.g. patients who did not received immunotherapy, patients aged ≤40 years, patients with the pure motor variant and axonal subtype of GBS (supplementary table 1).

Regarding calibration, the differences between predicted probability and observed probability were minor for all subgroups of patients and were almost similar to the overall cohort.

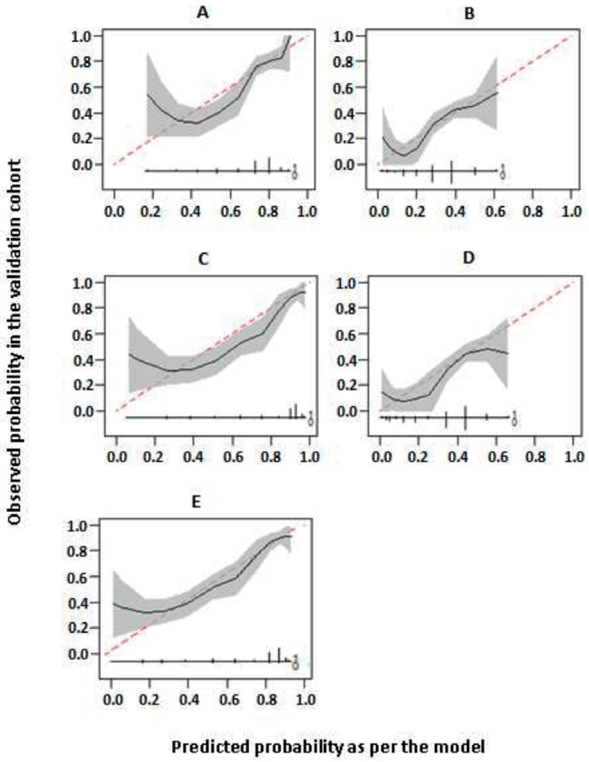

Figure 3. Calibration curves for the validation cohort as per the original and recalibrated models.
The calibration curves were generated by plotting the observed probability (*y*-axis) versus the predicted outcome (*x*-axis) for (A) mEGOS (original) at entry and outcome at week 4; (B) mEGOS (original) at entry and outcome at week 26; (C) mEGOS (original) at week 1 and outcome at week 4; (D) mEGOS (original) at week 1 and outcome at week 26, and (E) mEGOS (recalibrated) at week 1 and outcome at week 4.
The red dotted lines represent perfect calibration, when the predicted risk is equal to the observed frequencies; the grey-shaded areas around the calibration curves are 95% confidence intervals. Miscalibration is mostly observed (calibration plot away from the perfect calibration line) among the patients with a predicted probability of a poor outcome < 0.3 at week 4 for both mEGOS entry and week 1. Model recalibration was only performed for predicting a poor outcome at week 4 based on mEGOS week 1 (E). No recalibration was performed for other time points, as the "Closed test procedure" recommended keeping the original model for these time points.

Complete case analysis

External validation of mEGOS was performed among the subgroup of patients in the validation cohort with complete data (n = 430 for entry and n = 319 for week 1), and showed similar results to the analysis based on the imputed dataset (data not shown).

DISCUSSION

This study validated the ability of mEGOS model to predict the short- and long-term outcomes of patients with GBS from Bangladesh, and then improved the performance of mEGOS for local use through recalibration. We showed that, at entry, mEGOS can correctly differentiate between patients with good versus poor outcomes (discrimination) at week 4 in 69% of cases and at week 26 in 67% of cases. Similarly, when the model was used at week 1, the discriminative ability of the model for predicting a poor outcome was 78% and 70% at week 4 and week 26, respectively. In terms of calibration, the predicted probabilities for a poor outcome corresponded with the observed probabilities, except for an overestimation of the risk of a poor outcome at week 4 based on mEGOS at week 1. We adjusted the model for this time point by systematically decreasing the predicted probabilities by updating the model intercept, which substantially improved the model accuracy.

Till date, mEGOS has been validated in GBS population from Netherlands, Japan and Malaysia[15-17]. The model has been recently validated in patients participating in the IGOS where 809 patients were included in the analysis mostly from Europe/North America (n = 677)[18]. Patients from Bangladesh were excluded from the analysis of IGOS cohort because majority of patients in Bangladesh received no immunotherapy, which could influence the clinical course and outcome. The discriminative ability (AUC) of mEGOS entry and week 1 to predict outcome at week 4 and week 26 have been found better in the IGOS cohort as compared to Bangladesh cohort.

In general, an AUC value between 0.5 – 0.7 is considered sub-optimal performance; 0.70 – 0.80 as good performance, and > 0.8 indicates excellent performance[30]. Validation of the model to predict a poor outcome at week 4 and week 26 among Bangladeshi cohort revealed that mEGOS at entry had sub-optimal performance, whereas the model showed good performance when used at week 1. The discriminative ability of mEGOS (AUC) was lower at all time points in Bangladesh cohort than in the development cohort from the Netherlands[15]. This can be partially explained by the higher homogeneity of the Bangladeshi cohort compared to the Dutch cohort. More than two-thirds of the patients in the Bangladeshi cohort were males aged ≤ 40-years-old who presented with severe muscle weakness (as measured by the MRC sum score), a pure motor variant of GBS, and did not receive any immunotherapy. Due to the homogenous presentation of patients with GBS in Bangladesh, it is expected that the predicted risk of a poor outcome will be more or less similar for the majority of patients; therefore, it is more difficult for the model to discriminate between patients with a good and a poor outcome[27]. The homogeneity of the Bangladeshi cohort may have also influenced the predictive ability (OR)

of individual predictors in the model; the OR of individual predictors were lower in the validation cohort than the development cohort[27]. In Bangladesh, the higher proportion of pure motor and axonal neuropathy, lack of immunotherapy, and limited access to rehabilitation programs may have adversely affected the clinical outcomes of the validation cohort. In the current study, 70% and 32% of patients with GBS from Bangladesh had a poor outcome at week 4 and week 26, respectively; the rates of poor outcome were much lower in the development cohort (55% and 19%, respectively). Previous studies also reported higher proportions of patients from Bangladesh had poor outcomes[8,10,11].

Surprisingly, some categories of predictors showed an opposite association with poor outcome in the validation cohort compared to the development cohort. For example, for mEGOS entry and week1, categories of patients with more severe muscle weakness showed a lower risk of a poor outcome than the patients with less severe muscle weakness (MRC sum score of 51-60). In contrast, MRC sum score <40 were reported as an important predictor of poor outcome of GBS in the original model and also in previous studies including the international validation study of mEGOS in IGOS[7,18]. The contradictory findings in the current study might be due to the low sample size in the reference category (patients with MRC sum score of 60–51). For instance, in Bangladesh cohort, only 4% of the patients (n=19) had an MRC sum score of 60-51 which might be too low for the comparison.

Refitting of the model with the existing sets of predictors did not improve the discriminative ability of mEGOS among the validation cohort. This indicates that novel predictive factors not included in the original model need to be added, such as biomarkers, in order to further improve the performance of mEGOS, especially its discriminative ability, for patients with GBS from Bangladesh. Examples of biomarkers that have been associated with poor outcomes in GBS are serum anti-ganglioside antibodies, e.g. antibodies against the gangliosides GM1 and GD1a, albumin and IgG, neurofilament light chain, glial fibrillary protein, and cerebrospinal fluid proteins[7, 16, 31]. In addition, electrophysiological findings, including the degree of conduction block, inexcitable nerves, and low distal compound muscle action potential (CMAP) have also been associated with a poor prognosis in GBS[7]. All of these factors could potentially be used to further update and improve the performance of the model in specific regions.

In situations where the discriminatory power of a prediction model may be affected by the population distribution, as observed for the homogeneity of the current study population, model calibration becomes a more important measure of performance than discrimination[28]. As per the original mEGOS, the overall mean predicted risks of a poor outcome in the Bangladeshi GBS cohort corresponded with the observed frequencies.

However, based on mEGOS at week 1, the predicted risk of poor outcome at week 4 was 81%, which was a slight overestimation compared to the observed probability of 77%. This difference was resolved after recalibration of the model, as the predicted probabilities and observed probabilities were equal after recalibration (77%). As the difference in the predicted probabilities between the original and recalibrated model is very narrow (4%), we recommend the original mEGOS model should be used at both time points (mEGOS entry and week 1) to predict the outcomes at week 4 and week 26 for patients with GBS from Bangladesh.

Based on the calibration plot, the model underestimated the risk of a poor outcome at week 4 for the patients with mEGOS entry scores of 0-1 and/or mEGOS week 1 scores ranging from 0 to 3 (predicted probability < 0.3 as per the model). This discrepancy can be partially explained by the low sample size of this subgroup (n = 5 and n = 18 for mEGOS entry and week 1, respectively). In addition, a higher proportion of patients in this subgroup were untreated compared to the overall Bangladesh cohort (100% and 92% for mEGOS entry and week 1, respectively, vs. 85% for the overall validation cohort).

There are several limitations to this study. Firstly, around 6% of the data points for predictive factors and outcome variables were missing; these data were imputed using a multiple imputation method. We generated ten imputation sets to minimize the uncertainty induced by imputation, and took the average values for interpretation. We also used longitudinal data for imputation of missing GBS disability scores and MRC sum scores. Secondly, we excluded patients <6-years-old; therefore, the applicability of the model among younger pediatric patients could not be confirmed. But, it is worth mentioning that the current study validated and performed region-specific adjustment of mEGOS to predict the outcome at an early stage of the disease for patients with GBS from Bangladesh. The clinical management of GBS and health infrastructure of Bangladesh is representative of most other low- and middle-income countries around the world; therefore, this study also indicates the applicability of mEGOS in other resource-poor settings. In addition, this study also showed that mEGOS is applicable in different subgroups of GBS patients e.g. among the patients who do not receive any immunotherapy, patients age ≤ 40 years, patients with pure motor variant and axonal subtype of GBS.

In conclusion, we recommend the mEGOS can be used as an easy-to-administer and useful tool to predict both the short-term and long-term outcomes of patients with GBS from Bangladesh. The greatest advantage of this model is that it requires easily accessible clinical parameters in the acute phase of the disease, without the need for data from serological or other investigations. In addition, mEGOS model may be of special importance in low- and middle-income countries, where the majority of patients cannot

afford standard treatment for GBS and ICU facilities and rehabilitation services are very limited[4]. The mEGOS model can identify patients who are at risk of being unable to walk within the first six months after disease onset, and therefore may enable physicians to take the necessary measures to ensure this group of patients receives standard immunotherapy and other supportive cares. Unfortunately, there is no low-cost treatment for GBS at present, other than IVIg or PE. Thus, mEGOS model may be useful in the future for conditional clinical trials and stratification of patients who are at risk of a poor outcome for development of new, low-cost effective treatment interventions. Currently, a number of efficacy trials at different phases for new investigational products are ongoing in patients with GBS in Bangladesh, [32] and mEGOS or similar models could also be used to assess the treatment efficacy in these trials. Future studies need to be conducted to evaluate the ability of other clinical, electrophysiological, and biological factors to further improve the model predictions. Moreover, new predictive models need to be developed for other outcome measures, such as activity limitations and quality of life, to enable integrated management of GBS.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Discrimination and calibration of the model in different subgroups of GBS patients from Bangladesh

Time points of outcome		mEGOS entry	mEGOS week 1
Overall Validation cohort		(n=471)	(n=366)
Week 4	AUC (95% CI)	0.69 (0.63-0.74)	0.78 (CI: 0.71-0.85)
	Predicted probabilty	72%	81%
	Observed probability	70%	77%
Week 26	AUC (CI)	0.67 (0.62-0.72)	0.70 (CI: 0.64-0.75)
	Predicted probabilty	31%	33%
	Observed probability	31%	31%
Non treated patients		(n=401)	(n=305)
Week 4	AUC (CI)	0.69 (0.63-0.75)	0.77 (0.69-0.84)
	Predicted probabilty	71%	81%
	Observed probability	71%	77%
Week 26	AUC (CI)	0.68 (0.62-0.73)	0.70 (0.63-0.76)
	Predicted probabilty	31%	33%
	Observed probability	32%	31%
Patients with age <40 years		(n=347)	(n=264)
Week 4	AUC (CI)	0.69 (0.62-0.75)	0.77 (0.67-0.85)
	Predicted probabilty	70%	81%
	Observed probability	70%	78%
Week 26	AUC (CI)	0.66 (0.60-0.73)	0.68 (0.61-0.74)
	Predicted probabilty	29%	32%
	Observed probability	31%	32%
Pure motor variant		(n=385)	(n=297)
Week 4	AUC (CI)	0.68 (0.61-0.74)	0.76 (0.67-0.84)
	Predicted probabilty	73%	82%
	Observed probability	70%	78%
Week 26	AUC (CI)	0.67 (0.61-0.72)	0.68 (0.62-0.74)
	Predicted probabilty	32%	34%
	Observed probability	32%	33%
Axonal Subtype		(n=161)	(n=128)
Week 4	AUC (CI)	0.74 (0.63-0.82)	0.75 (0.57-0.87)
	Predicted probabilty	72%	83%
	Observed probability	73%	83%
Week 26	AUC (CI)	0.66 (0.57-0.75)	0.65 (0.55-0.75)
	Predicted probabilty	31%	34%
	Observed probability	31%	32%

The table presents the discrimination (measured by AUC) and calibration (Predicted probability vs. observe probability) of mEGOS in the different sub groups of patients from Bangladesh and compares the findings with the overall validation cohort from Bangladesh. The data was based on first imputed data set.
AUC: area under the receiver operating characteristic curve; mEGOS: modified Erasmus GBS Outcome Score; CI: 95% confidence interval.

3.4

The modified Erasmus GBS Respiratory Insufficiency Score: a simplified clinical tool to predict the risk of mechanical ventilation in Guillain-Barré Syndrome

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ABSTRACT

Background

This study aimed to determine the clinical and diagnostic factors associated with mechanical ventilation (MV) in Guillain-Barré syndrome (GBS) and to simplify the existing Erasmus GBS Respiratory Insufficiency Score (EGRIS) for predicting the risk of MV.

Methods

Data from the first 1500 patients included in the prospective International GBS Outcome Study were used. Patients were included across five continents. Patients <6 years and patients from Bangladesh were excluded. Univariable logistic and multivariable Cox regression were used to determine which pre-specified clinical and diagnostic characteristics were associated with MV and to predict the risk of MV at multiple time-points during disease course.

Results

1133 (76%) patients met the study criteria. Independent predictors of MV were a shorter time from onset of weakness until admission, the presence of bulbar palsy and weakness of neck flexion and hip flexion. The modified EGRIS (mEGRIS) was based on these factors and accurately predicts the risk of MV with an area under the curve (AUC) of 0.84 (0.80-0.88). We internally validated the model within the full IGOS cohort and within separate regional subgroups, which showed AUC-values of 0.83 (0.81-0.88) and 0.85 (0.72-0.98) respectively.

Conclusions

The mEGRIS is a simple and accurate tool for predicting the risk of MV in GBS. Compared to the original model, the mEGRIS requires less information for predictions with equal accuracy, can be used to predict MV at multiple time points and is also applicable in less severely affected patients and GBS variants. Model performance was consistent across different regions.

Key messages

What is already known on this topic

The Erasmus GBS Respiratory Insufficiency Score (EGRIS) predicts the risk of respiratory failure in the first week of hospital admission in patients with Guillain-Barré syndrome (GBS). A recent validation study within the International GBS Outcome Study (IGOS) showed that the EGRIS can be applied to the full spectrum of GBS, including mild cases and variants, and to patients from different regions. The original model however requires testing of 12 separate muscle groups and only includes clinical factors, while

several studies have shown that nerve conduction study parameters and biomarkers may add to the prediction of respiratory failure in GBS.

What this study adds

This study provides an overview of the clinical and diagnostic factors associated with mechanical ventilation in GBS based on data collected in the IGOS-1500 cohort. Based on this analysis we developed a simplified version of the EGRIS (mEGRIS), that can be used to predict the risk of respiratory failure in both the first week and other time-points during follow-up with equal accuracy.

How this study might affect research, practice or policy

The mEGRIS broadens the clinical applicability of the model in daily practice, as it only requires testing of three instead of 12 bilateral muscle groups without losing accuracy; can predict the risk of respiratory failure at any given time point during the first two months from disease onset; and also can be applied to GBS variants, mild forms and patients from different regions.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a rapidly progressive, immune-mediated polyradiculoneuropathy.[1] During the acute phase of the disease 10-30% of patients develop respiratory insufficiency requiring mechanical ventilation (MV).[2] Early recognition of patients at high risk of respiratory failure in GBS is crucial for triaging patients who need to be transferred to wards with stricter monitoring and for preventing pulmonary complications. In previous studies several features have been reported as predictors for the risk of MV,[2, 3] including facial and bulbar palsy,[4-6] autonomic dysfunction,[4] severe muscle weakness at admission,[4-7] rapid disease progression,[5, 7] respiratory parameters (e.g. vital capacity)[6, 8] and the presence of a conduction block in the distal peroneal nerve.[8]

The Erasmus GBS Respiratory Insufficiency Score (EGRIS) has been developed to predict the need for MV in the first week of admission based on the presence of facial/bulbar weakness, time from onset of weakness until admission, and the Medical Research Council (MRC) sum score at admission.[5] This model was recently validated in the International GBS Outcome Study (IGOS),[9] an ongoing prospective, observational, multicenter cohort study on the disease course and outcome of GBS, which showed that the EGRIS can be used in the full spectrum of GBS.[10] Although the EGRIS can be applied early in the disease course, it requires testing of strength in 12 separate limb muscle groups. A simplified version of the EGRIS that only includes selected muscle groups from the MRC sum score, with equal accuracy, would broaden the clinical applicability. Furthermore, neck flexion strength is currently not included in the EGRIS, but may provide additional prognostic information as a recent study from the USA showed that severe weakness of neck flexors at time of admission was associated with a poor respiratory status.[11] In addition, the EGRIS only includes clinical factors, while certain electrophysiological characteristics and biomarkers also have been associated with MV in GBS,[8, 12] and may further improve the model in specific clinical settings.

IGOS collects detailed and standardized clinical and diagnostic data from a large cohort of GBS patients, providing the opportunity to search for novel predictors of MV. Our study aimed to: (I) provide an overview of the clinical and diagnostic determinants associated with MV in GBS, and (II) develop a simplified version of the EGRIS for predicting the risk of MV at different time points (e.g.< 1 day, <3 days and <1 week from admission) during the disease course in order to facilitate its use in daily practice.

METHODS

Study design

Data were used from the first 1500 patients with GBS who were prospectively enrolled in IGOS. Patients fulfilled the National Institute of Neurological Disorders and Stroke diagnostic criteria for GBS (or its clinical variants), and were included between May 2012 and May 2017, <2 weeks from the onset of weakness, regardless of the disease severity or treatment. [13, 14] Patients with alternative diagnoses, protocol violations or insufficient data were excluded. In addition, we excluded patients <6 years, because they have a different disease course than adults and therefore may have other risk factors for MV, and because some neurological tests (e.g. the MRC scores) are challenging in preschool children. [15] Patients from Bangladesh were also excluded, because of the limited resources to provide MV and treatment, which could underestimate the effect of the studied predictors. [16]

In the first part of the study, we identified factors associated with MV. In the second part, to develop a simplified score to predict the risk of MV at different time-points, we excluded patients in whom MV was started prior to study entry and patients who developed weakness after admission as 'time between onset weakness and admission', a predictor in current models, could not be determined in these patients. Patients in whom MV was started >2 months after the onset of GBS were not included in the primary outcome, because respiratory insufficiency in these patients is more likely to be caused by (pulmonary) complications rather than respiratory weakness caused by GBS.

The IGOS study was approved by the review boards of the Erasmus MC University Medical Center (MEC-2011-477) and the participating local site institutes. Written informed consent was obtained from each patient or their legal representative.

Data collection

Clinical data and biomaterials were prospectively collected at standard time points according to the original IGOS study protocol, which is elaborately described in previous publications. [9, 17]. In study part I, we assessed several characteristics, including demographics, antecedent events, comorbidities, clinical features and severity of GBS at study entry, cerebrospinal fluid (CSF) parameters, forced vital capacity (FVC), electrophysiological subtype, positive serology for recent preceding infections and treatment with intravenous immunoglobulins (IVIg) or plasma exchange. Muscle strength was expressed using MRC scores. [18] Both individual muscle MRCs and combined scores were assessed, including the MRC sum score (sum of MRCs of bilateral shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors and foot extensors) as well as

separate sum scores of proximal arm and leg, distal arm and leg, only arm and only leg muscles. Bulbar weakness was assessed clinically and defined as problems with speech or swallowing caused by lower cranial nerve involvement. Disease severity was indicated by the GBS disability scale (GBS-DS). [19] The presence of autonomic dysfunction was determined by the local clinician and defined as disturbances in cardiac, gastro-enteric, bladder, pupillary and sudomotor functions. For patients whose nerve conduction study (NCS) data were available, the Hadden criteria were used to determine the electrophysiological subtype. [20] In addition, we investigated the presence of a conduction block of the peroneal nerve between the fibular head and ankle. We used two separate definitions for a conduction block: (I) a ≥30%[21] and (II) ≥50%[8] decrease (proximal vs distal) in the compound muscle action potential amplitude in early NCS, performed in the first week after onset of weakness. For 635 patients, blood samples were available and tested for preceding infections with *Campylobacter jejuni, Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus and hepatitis E virus, and interpreted as positive or negative for a recent infection. A detailed description of the test methods and interpretation is described in a previous publication. [22]

In study part II, we only considered variables that were previously reported in literature as independent predictors of MV in GBS, [2-8] and for which data were available in the IGOS database. In addition, the variables had to be suitable for the early prediction of MV.

Statistical analysis

Numeric variables were described as median (interquartile range, IQR) and categorical variables as count (percentage). Comparative statistics were performed using a Mann-Whitney U test for numerical and a chi-square test or Fisher-Exact test for categorical variables.

In study part I, univariable logistic regression was performed to calculate odds ratios (OR) and corresponding 95% confidence intervals (CI) for the association between the specified characteristics and MV. For the prediction of MV in study part II we used multivariable Cox regression, which also takes into account the time to start of MV. Patients not requiring MV were censored at the time-point of 2 months or, if they were lost-to-follow-up or deceased before reaching the 2 month-time-point, at the assessment date of the last visit before they were lost or at the date of death, respectively. For each predictor the proportional hazard and linearity assumptions were graphically inspected and no major violations were found. Variables were only included as predictor if <15% of values were missing.

In the final model we included all predictors with a p-value <0.15. Using this higher p-value avoids overfitting of the model to the IGOS dataset, and provides a model that is more generalizable. [23] The effect of the predictors was expressed using a hazard ratio (HR). Based on the coefficients of the model, a scoring system was developed, in which each coefficient was multiplied by a factor five to obtain rounded numbers that maintained the balance between the coefficients. The score plot shows the predicted probabilities of MV, which we provided for MV within 1 day, 3 days and 1 week from admission, and is based on the point estimates of the score and CIs of the coefficients.

Because the variables FVC and early conduction block of the peroneal nerve had too many missing values, these could not be included in our prediction model. Instead, we conducted an association analysis by using multivariable logistic regression, with adjustment for our newly developed prediction score to assess their (independent) relation with MV.

Model performance was assessed by the area under the receiver operating characteristic curve (AUC), which indicates the ability of the model to correctly distinguish a patient who required MV and who did not, where an AUC of 0.5 equals flipping a coin and a value of 1 indicates perfect discriminative ability. An AUC between 0.5–0.7 is usually considered as suboptimal, 0.7–0.8 as good, and >0.8 as excellent. [24] Bootstrapping was used to internally validate the model, and a geographic four-folded cross-validation was used for internal-external validation. [25, 26] Hereto, the dataset was divided into 4 different regions: Asia, Europe, North America and other (Argentina, Australia, Africa). Then, the model was trained on a subset that consisted of 3 regions and validated in the region left out. This procedure was repeated 4 times, so that each region was used for both training and validation. For each region a separate AUC-value and calibration curve is provided in which the observed probabilities of MV within one week were compared to the predicted probabilities based on the model.

Statistical analyses were performed with R studio (version 4.0.2). Two-sided P-values <0.05 were considered statistical significant. Variables with <15% missing values were imputed using multiple imputation.

RESULTS

Study population

From the IGOS-1500 cohort, patients with alternative diagnoses (n=85), protocol violations (n=34), insufficient data (n=11), included in Bangladesh (n=203) and age <6 years (n=34) were excluded (Figure 1). In the remaining cohort (n=1133), the median age was 54 years (IQR 39-66, range 6-91), and 671 (59%) patients were male. Patients were enrolled within a median of 1 day (IQR 0-4, range -2-13) from hospital admission. In 185/1133 (16%) patients MV was needed, and 149/182 (82%) patients required MV <1 week from admission. The median time from onset of weakness until start of MV was 4 days (IQR 3-8, range 0-44, n=178). Median total duration of MV (including 11 patients with a 2nd and two with a 3rd MV episode) was 20 days (IQR 10-54, range 1-525, n=170).

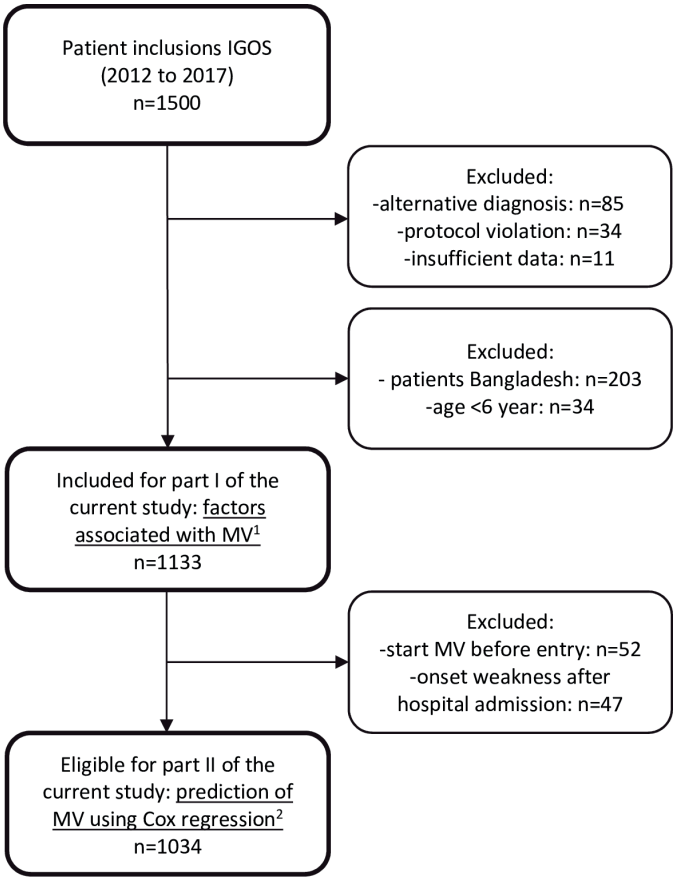

Figure 1 Study population

[1] Part I consisted of univariable logistic regression analysis of clinical and diagnostic factors in association with MV.
[2] In part II a prediction model was developed for the risk of MV using multivariable Cox regression analysis.
Abbreviations: IGOS = International GBS Outcome Study; MV = mechanical ventilation; OR = odds ratio.

Clinical and diagnostic factors associated with MV

In univariable analysis, factors strongly associated with MV were older age, a shorter time from onset of weakness until admission, facial- and bulbar palsy, more severe neck flexor weakness, both a lower MRC sum score as well as lower individual muscle MRC scores, areflexia, autonomic dysfunction, a lower forced vital capacity, a higher GBS-DS and treatment (Table 1).

MRC sum scores of both bilateral proximal muscles (shoulder abduction and hip flexion) and distal muscles (wrist extension and ankle dorsiflexion) were associated with MV (OR 0.77, 95% CI 0.74-0.80 vs. OR 0.81, 95% CI 0.79-0.84). Also sum scores of bilateral muscle groups in the arms (shoulder abduction, elbow flexion and wrist extension) and legs (hip flexion, knee extension and ankle dorsiflexion) were associated with MV (OR 0.84, 95% CI 0.83-0.87 vs. OR 0.87, 95% CI 0.85-0.88). Subcategories of autonomic dysfunction that were associated with MV included cardiac, bladder and pupillary dysfunction, whereas gastro-intestinal dysfunction and sudomotor changes were not. Forced vital capacity (n= 414) was significantly lower in patients with facial or bulbar weakness compared to those with normal facial and bulbar function: 2.4 L (IQR 1.7-3.2) and 3 L (IQR 2.2-3.7), respectively. After adjusting for facial/bulbar weakness using multivariable logistic regression, a lower FVC was still associated with MV (adjusted OR 0.46, 95% CI 0.33-0.63, p=0.008). Patients who required MV were significantly more often treated with either IVIg or plasma exchange and had a shorter time from onset weakness until start of treatment (Table 1).

Table 1 Clinical features in association with mechanical ventilation

	MV (n=185)	No MV (n=948)	OR (95% CI)	P-value
Demographics				
Age (years)	59 (44-70)*	53 (38-65)	1.02 (1.01-1.03)	<0.001*
Male sex	101 (55%)	570 (60%)	0.80 (0.58-1.10)	0.16
Region				
Asia	21 (11%)	88 (9%)	1.25 (0.74-2.04)	0.38
Europe/North-America	153 (83%)	789 (83%)	0.96 (0.64-1.48)	0.86
Other[1]	11 (6%)	71 (7%)	0.78 (0.38-1.44)	0.46
Disease onset in summer[2]	40/184 (22%)	199/943 (21%)	1.04 (0.70-1.51)	0.85
Antecedent event				
Respiratory tract symptoms	73 (39%)	437/944 (46%)	0.76 (0.55-1.04)	0.09
Gastro-intestinal symptoms	47 (25%)	246/944 (26%)	0.97 (0.67-1.38)	0.85
Neurological features at study entry				
Cranial nerve involvement				
Oculomotor	41/182 (23%)*	152/943 (16%)	1.51 (1.02-2.22)	0.037*
Facial	101/182 (55%)*	253/943 (27%)	3.40 (2.46-4.72)	<0.001*
Bulbar	96/182 (53%)*	144/943 (15%)	6.19 (4.41-8.73)	<0.001*

Table 1 Clinical features in association with mechanical ventilation (*continued*)

	MV (n=185)	No MV (n=948)	OR (95% CI)	P-value
Weakness (MRC score)				
Sum score (0-60)[3]	30 (16-44)* n=183	50 (44-56) n=938	0.92 (0.90-0.93)	<0.001*
Neck flexion (0-5)	3 (2-4)* n=176	5 (4-5) n=924	0.33 (0.28-0.39)	<0.001*
Shoulder abduction (0-10)	4 (2-8)* n=184	8 (8-10) n=940	0.64 (0.60-0.68)	<0.001*
Elbow flexion (0-10)	6 (4-8)*	9 (8-10) n=944	0.64 (0.59-0.68)	<0.001*
Wrist extension (0-10)	6 (3-8)*	8 (8-10) n=941	0.69 (0.64-0.73)	<0.001*
Hip flexion (0-10)	4 (1-6)* n=184	8 (6-10) n=944	0.64 (0.60-0.68)	<0.001*
Knee extension (0-10)	5 (2-8)* n=184	9 (8-10) n=943	0.70 (0.66-0.74)	<0.001*
Foot extension (0-10)	4 (2-8)* n=184	8 (6-10) n=944	0.74 (0.71-0.78)	<0.001*
Days from onset weakness – admission	1 (0-2)* n=184	3 (1-5) n=942	0.91 (0.87-0.94)	<0.001*
Sensory deficits	111/163 (68%)	615/938 (66%)	1.12 (0.79-1.61)	0.53
Pain	82/183 (45%)	496/941 (53%)	0.73 (0.53-1.00)	0.05
Areflexia	137/181 (76%)*	439/942 (47%)	3.57 (2.50-5.18)	<0.001*
Ataxia	22/40 (55%)	315/672 (47%)	1.39 (0.73-2.66)	0.32
Autonomic dysfunction[4]	84/184 (46%)	195/941 (21%)	3.21 (2.31-4.47)	<0.001*
GBS disability score[5]				
1	0/183 (0%)	48/939 (5%)	-	-
2	8/183 (4%)	258/939 (28%)	0.12 (0.05-0.23)	<0.001*
3	6/183 (3%)	234/939 (25%)	0.10 (0.04-0.21)	<0.001*
4	95/183 (52%)	398/939 (42%)	1.47 (1.07-2.02)	0.018*
Clinical GBS variant				
Sensorimotor	134/176 (76%)*	581/898 (65%)	1.74 (1.21-2.55)	0.004*
Pure motor	20/176 (11%)	137/898 (15%)	0.71 (0.42-1.15)	0.18
Miller Fisher syndrome	1/176 (0.6%)*	82/898 (9%)	0.07 (0.01-0.26)	0.004*
Miller Fisher overlap syndrome	13/176 (7%)	54/898 (6%)	1.25 (0.64-2.27)	0.49
Other[6]	8/176 (5%)	44/898 (5%)	0.92 (0.40-1.90)	0.84
Respiratory features at study entry				
Respiratory comorbidity	19/183 (10%)	84/943 (9%)	1.18 (0.68-1.96)	0.53
Forced vital capacity at entry (liter)	2.0 (1.2-2.8)* n=55	2.8 (2.1-3.5) n=359	0.42 (0.30-0.58)	<0.001*
Treatment				
IVIg or plasma exchange	183 (99%)	848 (89%)	10.79 (3.38-65.81)	<0.001*
Days from onset weakness – treatment	3 (2-5) n=182	5 (3-7) n=852	0.83 (0.78-0.88)	<0.001*

*Significant values P < 0.05.

This table provides an overview of the unadjusted odds ratio's for the association of clinical factors with mechanical ventilation. Numerical variables are expressed as median (interquartile range) and categorical variables as number (percentage). Comparative statistics are performed between the MV and no MV group.

[1] Including South-Africa, Argentina and Australia.

[2] Defined as the meteorological summer of 1th June – 31th August for the Northern Hemisphere and 1th December – 28 February for the Southern Hemisphere.

[3] Sum of the MRC scores of bilateral shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot extension.

[4] Disturbances in cardiac, gastro-enteric, bladder, sudomotor and pupillary functions.

[5] GBS disability score per category vs. the other categories combined.

[6] Including pharyngeal-cervical-brachial weakness, pure sensory and ataxic.

Abbreviations: CI = confidence interval; MRC = medical research council; MV = mechanical ventilation; OR = odds ratio.

Diagnostic investigations including CSF, NCS and preceding infections in relation to MV are shown in Table 2.

Apart from a slightly elevated cell count in CSF, which was associated with a lower frequency of MV, there was no association between MV and CSF parameters, nor between MV and positive serology for recent preceding infections. NCS data were available for 796/1133 (70%) patients, of whom 358 patients underwent an early NCS (<1 week of onset weakness). A demyelinating subtype according to the Hadden criteria and a conduction block in the distal peroneal nerve were both associated with a higher risk of MV (Table 2).

Table 2 Diagnostic features in association with mechanical ventilation

	MV (n=185)	No MV (n=948)	OR (95% CI)	P-value
Cerebrospinal fluid examination				
Leukocytes count (cells/μL)				
<5	135/162 (83%)	670/857 (78%)	1.40 (0.91-2.21)	0.14
5-10	9/162 (6%)*	115/857 (13%)	0.40 (0.18-0.72)	0.007*
11-50	14/162 (9%)	63/857 (7%)	1.19 (0.63-2.12)	0.57
>50	4/162 (2%)	9/857 (1%)	2.39 (0.64-7.42)	0.15
Protein level (g/L)	0.6 (0.4-1.1) n=167	0.6 (0.4-1.1) n=863	1.02 (0.86-1.17)	0.73
Nerve conduction study (NCS)				
Electrophysiological subtype				
Demyelinating	85/131 (65%)*	363/665 (55%)	1.54 (1.05-2.28)	0.031*
Axonal	11/131 (8%)	39/665 (6%)	1.47 (0.70-2.86)	0.28
Normal	0/131 (0%)*	49/665 (7%)	-	-
Equivocal / Inexcitable	35/131 (26%)	214/665 (32%)	0.77 (0.50-1.16)	0.22
Early NCS parameters (<1 week)[1]				
Conduction block peroneal nerve ≥50%	26/64 (41%)	53/294 (18%)	3.11 (1.73-5.55)	<0.001*
Conduction block peroneal nerve ≥30%	37/64 (58%)	104/294 (35%)	2.50 (1.45-4.38)	0.001*
Positive infection serology[2]				
Campylobacter jejuni	24/117 (21%)	150/518 (29%)	0.63 (0.35-1.02)	0.07
Mycoplasma pneumonia	11/117 (9%)	50/518 (10%)	0.97 (0.47-1.86)	0.93
Epstein-Barr virus	1/117 (1%)	5/518 (1%)	0.88 (0.05-5.55)	0.91
Cytomegalovirus	8/117 (7%)	22/518 (4%)	1.65 (0.68-3.68)	0.24
Hepatitis E virus	3/117 (3%)	12/518 (2%)	1.11 (0.24-3.56)	0.87

*Significant values P < 0.05.

This table provides an overview of the unadjusted odds ratio's for the association of diagnostic factors with mechanical ventilation. Numerical variables are expressed as median (interquartile range) and categorical variables as number (percentage). Comparative statistics are performed between the MV and no MV group.

[1] For patients whose raw NCS data were available and underwent NCS <1 week from onset of weakness. Both a decrease of ≥50% and ≥30% in compound muscle action potential amplitude between the fibular head and ankle of the distal peroneal nerve were assessed.

[2] Infection serology was only tested for the first 1000 patients included in IGOS.

Abbreviations: CI = confidence interval; MV = mechanical ventilation; NCS = nerve conduction study; OR = odds ratio.

Prediction of MV

After excluding patients in whom MV was started prior to study entry (n=52) and who developed muscle weakness after admission (n=47), 1034 patients were eligible for multivariable prediction analysis (Figure 1). From these patients, 126 (12%) needed MV, within a time range of 0 to 33 days from hospital admission (Figure 2). The majority of patients required MV within the first week (98/126, 78%). The following predictors were assessed in multivariable analysis: age, facial- and bulbar palsy, time from onset weakness until admission, autonomic dysfunction and MRC scores of neck flexion, bilateral hip flexion and bilateral elbow flexion. In Supplementary Table 1 a more detailed overview of the selection procedure is provided. The included predictors in the final and simplified model are indicated in Table 3.

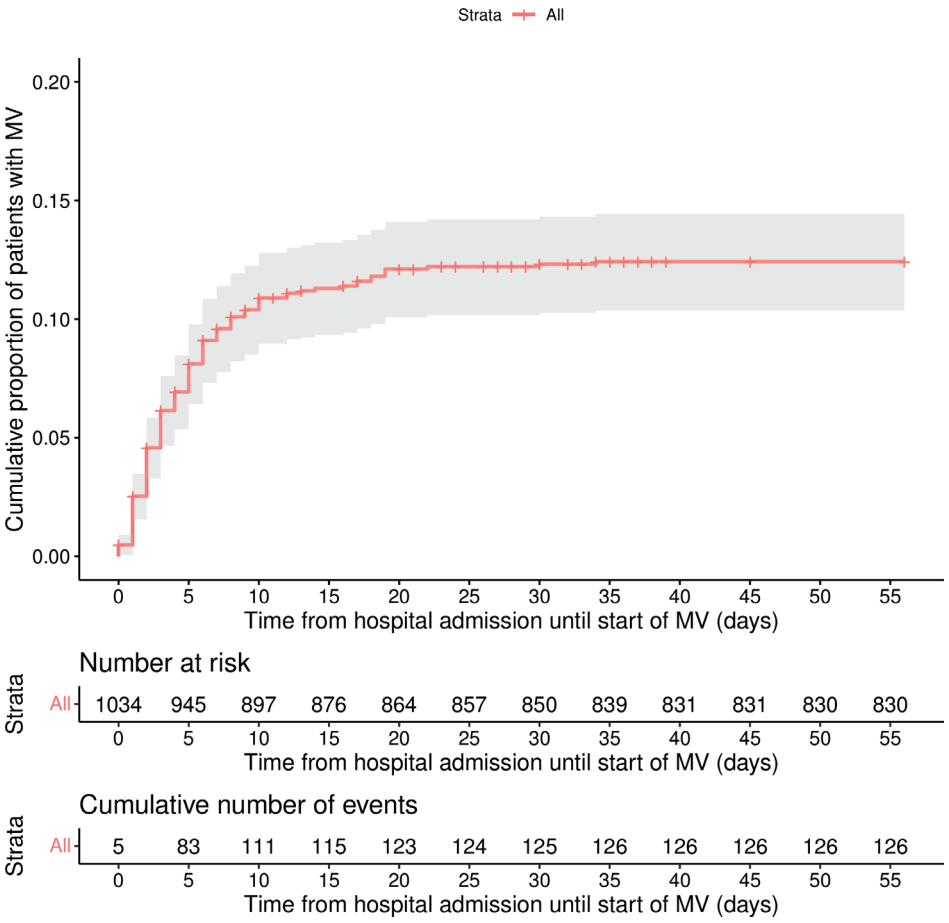

Figure 2 Cumulative incidence function for the time to start of mechanical ventilation
Abbreviations: MV = mechanical ventilation

Table 3 Multivariable Cox regression for prediction of the risk of MV

Predictor	Coefficient (SE)	HR (95% CI)	P-value
Bulbar weakness	1.07 (0.18)	2.92 (2.04-4.19)	<0.001*
Time from weakness -admission (per day)	-0.19 (0.05)	0.83 (0.76-0.91)	<0.001*
Neck flexion strength (per MRC score)	-0.43 (0.09)	0.65 (0.56-0.78)	<0.001*
Bilateral hip flexion strength (per MRC score)	-0.20 (0.04)	0.82 (0.76-0.88)	<0.001*

*Significant values P < 0.05.
The coefficients of the final model were corrected for overfitting by multiplying with a heuristic shrinkage factor (a penalty for the complexity of the model) calculated with the formula: s = (modelχ^2-degrees of freedom)/ modelχ^2.
Reference: Steyerberg EW. Clinical Prediction Models - A practical approach to development, validation, and updating: Springer 2009.
Abbreviations: CI = confidence interval; HR = hazard ratio; MRC = Medical Research Council; MV = mechanical ventilation, SE = standard error.

Bulbar palsy, a shorter time from onset of weakness to admission, and lower MRC scores of neck flexion and bilateral hip flexion significantly increased the hazard of MV. This model showed excellent discriminative ability (AUC 0.84, 95% CI 0.80-0.88). Internal validation by bootstrapping showed an AUC of 0.83 (95% CI 0.81 - 0.88). Geographic 4-folded cross validation showed a mean AUC of 0.85 (95% CI 0.72-0.98) with no significant miscalibration and no extreme variability across settings (Supplementary Figure 1).

The modified EGRIS (mEGRIS) ranges from 0 to 32 (Table 4). The predicted probabilities for a patient to be mechanically ventilated within 1 day (yellow), 3 days (blue) and 1 week (light blue) from admission for each score are indicated in Figure 3. For example, a patient with bulbar weakness (5 points), admitted to the hospital one day after onset weakness (6 points), with neck flexion weakness MRC 4 (2 points) and bilateral symmetrical hip flexion weakness MRC 3/5 (4 points), has a total score of 17, corresponding to a predicted risk of 17% to be mechanically ventilated <1 day, 26% <3 days and 35% <1 week.

Additional analysis

In multivariable logistic regression analysis with correction for the mEGRIS, a lower FVC was no longer associated to MV (adjusted OR 1.37, 95% CI 0.76-2.49, p=0.30). A ≥50% conduction block of the peroneal nerve remained significantly associated (adjusted OR 3.67, 95% CI 1.66-8.21, p=0.001) with MV, whereas a ≥30% conduction block was not (adjusted OR 1.96, 95% CI 0.95-4.11, p=0.07).

Table 4 The modified EGRIS score

Predictor	Category	Score
Bulbar weakness	Yes	5
	No	0
Time from weakness – admission (days)	0	7
	1	6
	2	5
	3	4
	4	3
	5	2
	6	1
	≥ 7	0
Neck flexion MRC score (0-5)	0	10
	1	8
	2	6
	3	4
	4	2
	5	0
Bilateral hip flexion MRC score (0-10)	0	10
	1	9
	2	8
	3	7
	4	6
	5	5
	6	4
	7	3
	8	2
	9	1
	10	0
Total		0-32

DISCUSSION

In this study, we developed a simplified and broadly applicable model for predicting the risk of MV in GBS based on a large dataset from the IGOS study, including all clinical variants and patients from various regions. The mEGRIS is based on four clinical features available at admission: time from weakness onset until admission, bulbar palsy, neck flexion weakness and bilateral hip flexion weakness. Advantages compared to the original model are that the mEGRIS: (I) requires testing of only three muscle groups, while model accuracy is similar,[5] (II) accurately predicts the risk of MV at multiple time points (e.g. <1 day, <3 days, <1 week), and (III) is also applicable in GBS variants and mildly

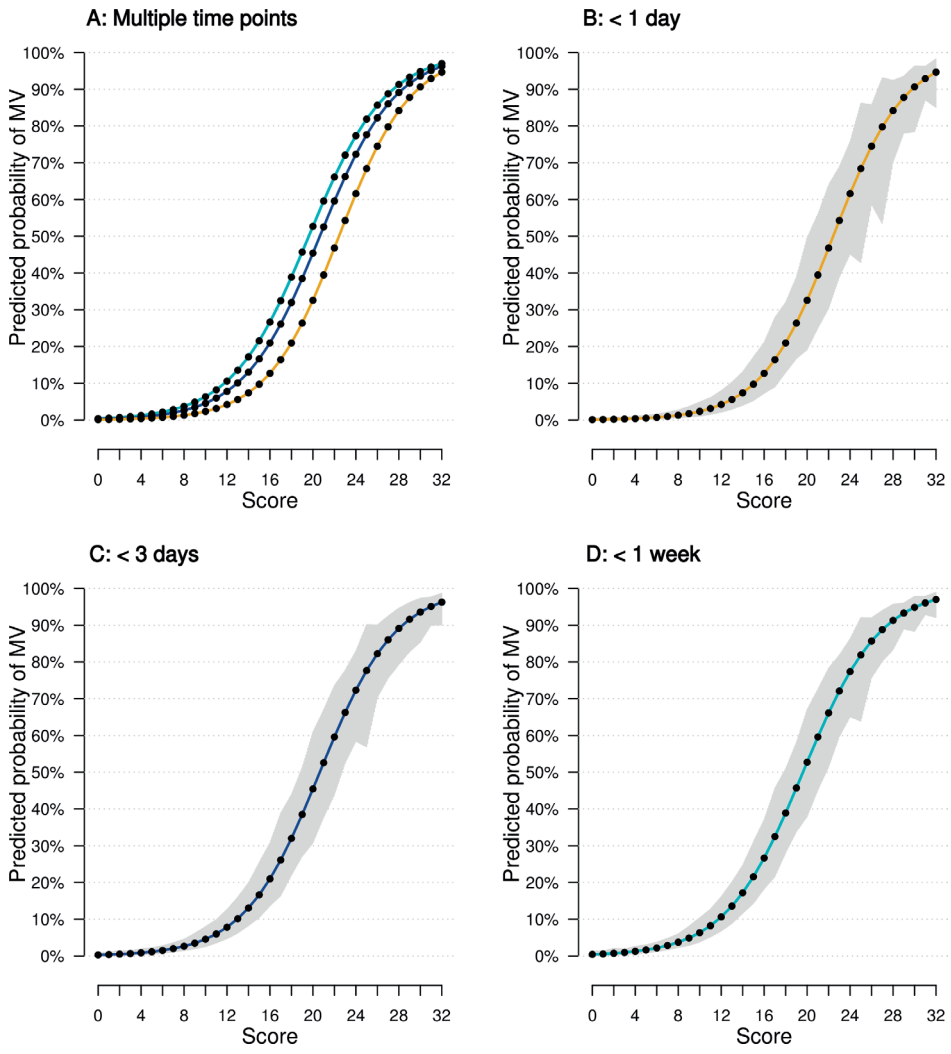

Figure 3 Predicted probabilities for MV within 1 day, 3 days and 1 week per mEGRIS score

Figure A shows the predicted probabilities of MV within 1 day (yellow), 3 days (blue) and 1 week (light blue) from hospital admission for each mEGRIS score. The mEGRIS score can be calculated based on the scoring system (Table 4). The corresponding 95% confidence intervals for each time-point are shown in figure B (<1 day), C (< 3 days) and D (<1 week). For example, a patient with an mEGRIS score of 17 has a predicted probability to be mechanically ventilated of 17% (20%-28%) within one day, 26% (17%-29%) within 3 days and 32% (22%-45%) within one week.

affected patients. Adding more clinical predictors, previously identified in the literature as risk factors for respiratory failure, did not improve the predictive ability of the model.

We found a strong independent association of MV with bulbar weakness, rapid disease progression and severe limb muscle weakness at admission, consistent with previous publications.[2, 4-7] In addition, our study demonstrated that weakness of individual limb

muscle groups was strongly associated as well, especially weakness of neck flexion. A previous case series describing ultrasonographic changes in GBS, showed more profound involvement of cervical spinal roots compared to peripheral nerves in patients requiring MV. [27] This may suggest that GBS patients with involvement of the cervical spinal roots are more prone to develop respiratory failure.

In line with prior studies, [6, 8] we found an association between a lower FVC at admission and MV, which persisted after adjusting for facial/bulbar weakness. However, FVC is less attractive to use as a predictor because it is not always available in clinic and may not be accurate in patients with facial/bulbar weakness. After adjusting for the mEGRIS, a lower FVC was no longer significant, which means that FVC is less contributory than other clinical variables for the prediction of MV.

NCS is often used to support the clinical diagnosis of GBS. Although early NCS is not routinely performed, this may have prognostic value, as our study indicated a strong association of MV with an early ≥50% conduction block of the distal peroneal nerve, even after correcting for the mEGRIS. The prognostic value of this variable also has been previously demonstrated by Durand et. al. [8] They proposed a model based on conduction block of the distal peroneal motor nerve and FVC. [8] Although the predictive value of this model is good (AUC 0.79), [8] it is less applicable in settings where no NCS is available.

A previous study reported a high rate of respiratory insufficiency in CMV-related GBS. [28] Our study did not find an association between positive infection serology for *Campylobacter jejuni, Mycoplasma pneumoniae,* Epstein Barr virus, cytomegalovirus or hepatitis E virus and MV. Since only a small subgroup of patients tested positive for these recent preceding infections, we suppose that the added value of this predictor for clinical practice is small.

The proportion of patients requiring MV (16%) was lower compared to prior studies, which were mainly based on trial cohorts (patients with GBS-DS >2 only), while IGOS also included patients with mild forms of GBS and GBS variants. Since the mEGRIS was developed based on this more representative cohort, it has a broader applicability and can also be used in mildly affected patients and GBS variants. Although, the need for MV in MFS patients is exceptional, it is not fully ruled out when these patients develop severe bulbar palsy or transit to MFS-GBS overlap (limb weakness), [29] which are both represented in the mEGRIS.

The mEGRIS is based on only four clinical characteristics available at admission, and is easily applicable in daily practice, especially in the emergency setting or in hospitals

without specialized neurological care. No additional diagnostic tests are necessary. The score ranges from 0 to 32 and corresponds with a predicted risk of respiratory failure between 0 and 100%. The model is able to accurately predict the risk of MV in individual GBS patients and provides consistent predictions across different settings as is shown by the internally-externally 4-fold cross-validation procedure. However we cannot draw conclusions regarding model performance in some specific regions (Australia, South-Africa and South-America) as patients numbers were small.[26] Model predictions remained good in subgroups enrolled in IGOS ≤1 day and >1 day after hospital admission. In daily practice, the mEGRIS can be used as a simple bedside tool that assists in triaging patients who need to be transferred to wards with stricter monitoring. The score can be calculated via the scoring system in Table 4 and corresponding probability plots provided in Figure 3, and in future also via de QxMD app or online (https://gbstools.erasmusmc.nl). The mEGRIS and the recalibrated version of the original EGRIS for Europe and North-America have equal performance and are both recommended, but for practical purposes we prefer the use of the mEGRIS.

Our study has several limitations. First, our model was not externally validated. However, recent literature showed that internal-external validation by geographic cross-validation can be alternatively used and has the advantage of validating the model across different settings.[25,26] Second, we were unable to include NCS and biological factors in our model, because in only a limited number of patients an early NCS was conducted (consistent with clinical practice), and assessment of novel biological factors in IGOS patients is still ongoing. Future research is needed to establish the potential predictive value of these determinants in addition to clinical predictors, although such models might be less applicable in settings where no NCS or biological testing is available. Furthermore, it would be interesting to define cut-offs for mEGRIS that could enhance the clinical impact and guide the decision to admit a patient to a hospital ward, monitored telemetry bed or intensive care unit, based upon the calculated risk for MV. This can be assessed by decision curve analysis, which will define the net benefit of the model while incorporating factors specific to the hospital and the country, such as resource availability and cost-effectiveness issues. Lastly, separate models need to be developed for children <6 years and patients from Bangladesh.

In conclusion, the mEGRIS is a simple and broadly applicable clinical score that can predict the risk of MV for individual GBS patients at different time points during disease course. Future studies are needed to establish the net benefit of this score in clinical practice and whether early NCS and biological factors can further improve the model predictions.

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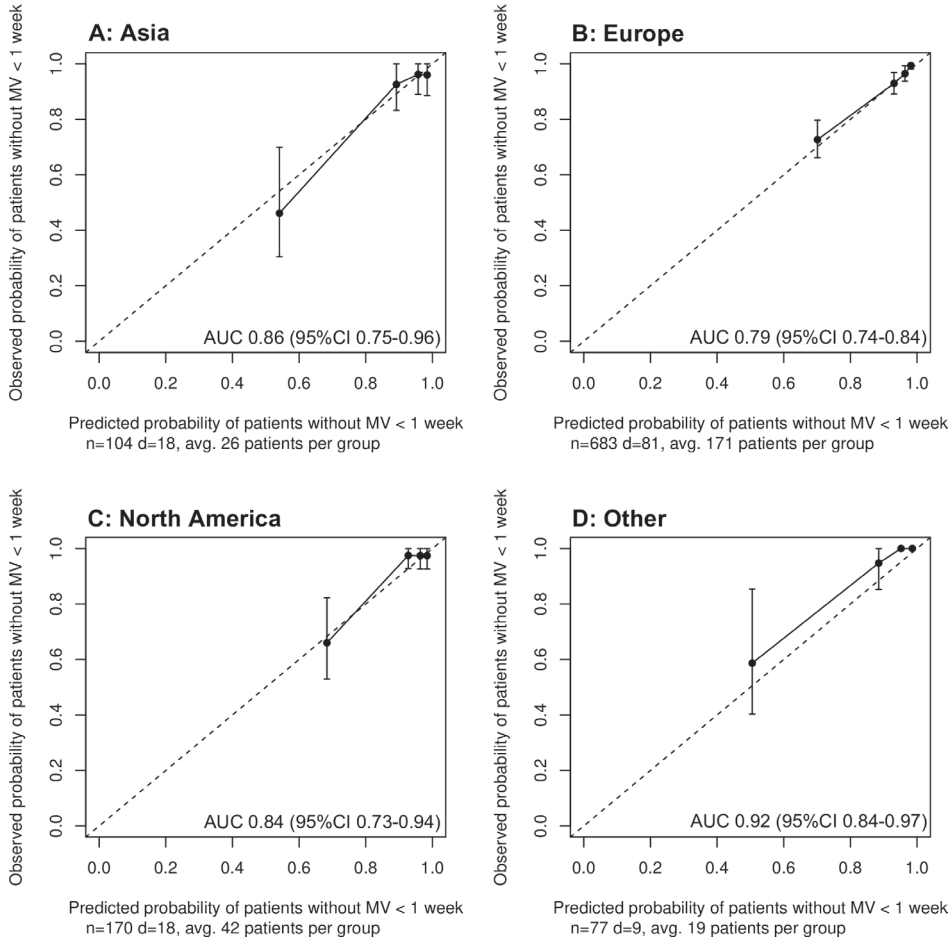
SUPPLEMENTARY MATERIAL

Supplementary Table 1 Selection of predictors for the prediction of MV

Independent predictors of MV in literature	Collected IGOS	Eligible for early prediction	Missing values <15%[1]	Included in Cox model
Demographics:				
Age	X	X	X	X
Neurological features at study entry:				
Facial weakness	X	X	X	X
Bulbar weakness	X	X	X	X
Autonomic dysfunction	X	X	X	X
Limb muscle weakness[2]	X	X	X	X
Neck flexion weakness	X	X	X	X
Time to reach nadir	X			
Time from onset weakness - admission	X	X	X	X
GBS disability score	X			
Respiratory features:				
Vital capacity	X	X		
Single breath count				
Ineffective cough				
Laboratory features:				
Albumin				
Increased liver enzymes				
Electrophysiological features:				
Conduction block distal peroneal nerve	X	X[3]		
Phrenic nerve latency				
Axonal or inexcitable subtype	X	X[3]		

[1] Variables with <15% missing values were imputed using multiple imputation.
[2] Both MRC sum score as proximal weakness (inability to lift elbows above bed, and inability to stand) are previously reported as independent predictors of MV. Because our aim was to develop a simplified and clinical applicable model, we tried different combinations of individual muscle scores in our model. For our final model , which is presented, we started with the input variables bilateral hip flexion and bilateral elbow flexion.
[3] Only eligible when NCS performed early in disease course (before the start of MV).



Supplementary Figure 1 Calibration plots based on 4-folded geographic cross-validation

This figure shows the calibration curves (predicted vs. observed probability for a patient to be not mechanically ventilated within week 1) for four different subsets using four-folded cross-validation: A Asia, B Europe, C North America, D Other (Argentina, Australia and Africa). The model was trained on a trainings subset – 1 region and validated in the region left out. This procedure was repeated 4 times. The overall (mean) cross-validated AUC was 0.85 (95%CI 0.72-0.98).

4

Treatment

4.1

Current treatment practice of Guillain-Barré syndrome

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Neurology. 2019 Jul 2;93(1):e59-e76.

ABSTRACT

Objective

To define the current treatment practice of Guillain-Barré syndrome (GBS).

Methods

The study was based on prospective observational data from the first 1300 patients included in the International GBS Outcome Study. We described the treatment practice of GBS in general, and for (1) severe forms (unable to walk independently), (2) no recovery after initial treatment, (3) treatment-related fluctuations, (4) mild forms (able to walk independently), and (5) variants forms including Miller Fisher syndrome, taking patient characteristics and hospital type into account.

Results

We excluded 88 (7%) patients because of missing data, protocol violation or alternative diagnosis. Patients from Bangladesh (n=189, 15%) were described separately because 83% were not treated. Intravenous immunoglobulin (IVIg), plasma exchange (PE) or other immunotherapy was provided in 941 (92%) of the remaining 1023 patients, including patients with severe GBS (724/743, 97%), mild GBS (126/168, 75%), Miller Fisher syndrome (53/70, 76%) and other variants (33/40, 83%). Of 235 (32%) patients who did not improve after their initial treatment, 82 (35%) received a second immune modulatory treatment. A treatment-related fluctuation was observed in 53 (5%) of 1023 patients, of whom 36 (68%) were re-treated with IVIg or PE.

Conclusions

In current practice, patients with mild and variant forms of GBS, or with treatment-related fluctuations and treatment failures are frequently treated, even in absence of trial data to support this choice. The variability in treatment practice can be explained in part by the lack of evidence and guidelines for effective treatment in these situations.

INTRODUCTION

Plasma exchange (PE) and intravenous immunoglobulin (IVIg) are the only proven effective treatments for Guillain-Barré syndrome (GBS), although there has been little formal exploration of optimal dosage and treatment duration for either.[1,2] The implementation of these treatments in clinical practice is complicated by the variability in disease presentation and severity. Most therapeutic trials with PE or IVIg focused on adult patients who were unable to walk independently.[1-3] At present it is unclear whether these treatments are also effective in children, patients with mild GBS, or clinical variants including Miller Fisher syndrome (MFS).[4,5] It is also unknown if treatment is still effective when administered at a later stage of the disease. Furthermore, it is not uncommon that patients continue to deteriorate or demonstrate poor recovery after initial treatment.[6] In some patients, there can be subsequent deterioration after initial stabilization or recovery, a phenomenon referred to as treatment-related fluctuation (TRF).[6] To date, there has been a paucity of studies describing the effects of treatment in these clinical scenarios. In the absence of adequate evidence and consensus on treatment guidelines, dilemmas continue to exist in the treatment of GBS.[7] Such dilemmas may result in substantial variation in the current treatment of GBS. The aim of this study was to define the variation in current treatment practice of GBS and to identify factors that may contribute to this variation. This in turn will allow us to identify areas of variation, develop new clinical trials to address these, and initiate the development of treatment guidelines.

METHODS

Study design

Data were collected from the International GBS Outcome Study (IGOS), an ongoing, prospective, observational cohort study.[8] Patients were included from 154 hospitals (106 (69%) university hospitals, including university affiliated teaching hospitals, and 48 (31%) non-university hospitals) in 19 countries. All patients were included within 2 weeks from onset, independent of age, disease severity, GBS variant or treatment.

Standard Protocol Approvals, Registrations, and Patient Consents

IGOS received approval from the Institutional Review Boards from individual participating centers and written informed consent was obtained from all patients.

Patient groups

The study was based on the first 1300 inclusions in IGOS (May 2012 - January 2017). We described the type, regimen, and timing of immunotherapy. The treatment practice

was related to the country of residence, clinical variant (sensorimotor, pure motor, MFS, and other variants), disease severity, and electrophysiological subtype (demyelinating versus axonal GBS). We also compared the treatment practice in children (younger than 18 years at diagnosis) to that in adults. Patients from Bangladesh, who rarely received immunotherapy for GBS, were excluded from further analyses. [9, 10, 11] In addition, we described treatment practice in the following specific clinical scenarios: (1) severe GBS, (2) severe GBS with no clinical recovery after initial treatment, (3) GBS with TRF, (4) mild GBS, and (5) GBS variants including MFS. Severe GBS was defined as being unable to walk independently at nadir (GBS disability score ≥ 3) and mild GBS as being able to walk independently at nadir (GBS disability score < 3). [12] Initial failure of clinical recovery was defined as worsening or failure to improve by at least one grade on the GBS disability scale from nadir to week 4 (or not improving from the first to the second week in case of a missed visit at week 4). The presence of a TRF was determined by the treating physician. Electrophysiological subtypes were defined by the first nerve conduction study (NCS) based on local reference values and the Hadden and colleagues criteria. [13]

Data collection

We collected data on demography (age, sex, country of residence), clinical characteristics including disease severity (GBS disability score, limb weakness, sensory deficits, facial, bulbar and oculomotor weakness, pain and autonomic dysfunction) at entry, one, two and four weeks follow-up. Documentation of the presence of autonomic dysfunction was left to the discretion of the treating physician and was defined as cardiac, blood pressure, gastro-enteric, bladder, pupil, or other autonomic dysfunction. Limb muscle strength was recorded by the Medical Research Council (MRC) sum score, ranging from 60 (full muscle strength) to 0 (total paralysis). [14] The disability caused by GBS was defined by the highest GBS disability score in the first four weeks after study entry (nadir), ranging from 0 (healthy) to 6 (dead). [15] When assessing treatment practice in patients without clinical recovery or with GBS-TRF, second line treatment that was provided as part of a clinical trial (e.g. 'Second Immunoglobulin Dose in GBS' (SID GBS) trial[16] and 'Inhibition of Complement Activation in GBS' (ICA-GBS) trial [17]) was not taken into account. Disease severity during a TRF was defined by the GBS disability score and MRC sum score. When a TRF occurred between two consecutive study visits, the data recorded at the first visit after the TRF were used to determine severity of symptoms.

Statistical analysis

We analyzed the data using SPSS Statistics version 24. Continuous data were presented as medians with interquartile ranges (IQR) and were compared with Mann-Whitney U test. Categorical data were presented as proportions with percentages and were com-

pared with Chi-square or Fisher's exact tests. A two-sided p-value <0.05 was considered significant.

Data availability statement

Data collected in IGOS will be used initially for planned research projects conducted by the IGOS Consortium. Some data will be made available from the corresponding author, upon reasonable request. The data are not publicly available because they contain information that could compromise the privacy of our patients.

RESULTS

Study cohort

From the IGOS 1300 cohort, we excluded 71 (5%) patients who had an alternative diagnosis, 6 (0.5%) due to protocol violation and 11 (0.8%) due to insufficient data (Figure 1). The remaining 1212 (93%) patients originated from the following continents: Europe n=664 (55%), Asia n=277 (23%), North- and South-America n=238 (20%), Africa n=25 (2%), and Australia n=8 (1%). Most of these patients were included by university hospitals (n=978, 81%). In the Asian group, 189 patients were from Bangladesh. The majority of Bangladeshi patients were not able to walk independently at nadir (n=174, 92%), but 144 (83%) of these severely affected patients did not receive immunotherapy. Of the remaining 30 patients who did receive immunotherapy, 16 (9%) received PE, 12 (7%) IVIg, 1 (1%) small volume plasma exchange (SVPE) and 1 (1%) dexamethasone monotherapy. Since the treatment practice in the Bangladesh cohort deviated strongly from that of other countries, these patients were excluded from further analyses, leaving the Asian group with 88 patients.

Initial treatment

Of the remaining study cohort of 1023 patients, 941 (92%) received immunomodulatory treatment. Most patients were initially treated with IVIg (n=862, 84%), which was started within a median of 4 days after the onset of symptoms (IQR 2-7). IVIg was initiated after two weeks in 18 (2%) patients, and after 4 weeks in five (1%) patients. A total IVIg dosage of 2 g/kg bodyweight was given in 5 days in 754 (87%) patients, in 2 days in 61 (7%) patients, in 3-4 days in 36 (4%) patients, and in 6-7 days in 8 (1%) patients. Two patients received 2.5 g/kg in 5 days. In 36 (4%) of the 1001 administered IVIg courses methylprednisolone (MP) was used as add-on treatment. Sixty-seven patients (7%) were initially treated with PE within a median of 6 days (IQR 3-9) after onset of symptoms. Most patients underwent 5 PE sessions (n=47, 70%). Others received 2 sessions (n=2, 3%), 3 sessions (n=2, 3%), 4 sessions (n=9, 13%), 6 sessions (n=6, 9%), or 7 sessions (n=1, 1%).

The PE sessions were performed during a median of 8 days (IQR 6-9, range 2-16). Eight (1%) patients were initially treated with other treatments, such as monotherapy with corticosteroids (n=5) or immunoadsorption (n=3). Of the five patients initially treated with corticosteroids only, one received an additional course of IVIg, and one received two additional courses of IVIg with MP add-on. The remaining 86 (8%) patients in the study cohort received no immunotherapy. Fifty-seven (66%) of these patients had mild GBS, and 22 (26%) had Miller Fisher syndrome or another local variant (sensory ataxic GBS, n=6; pharyngeal-cervical-brachial variant, n=1).

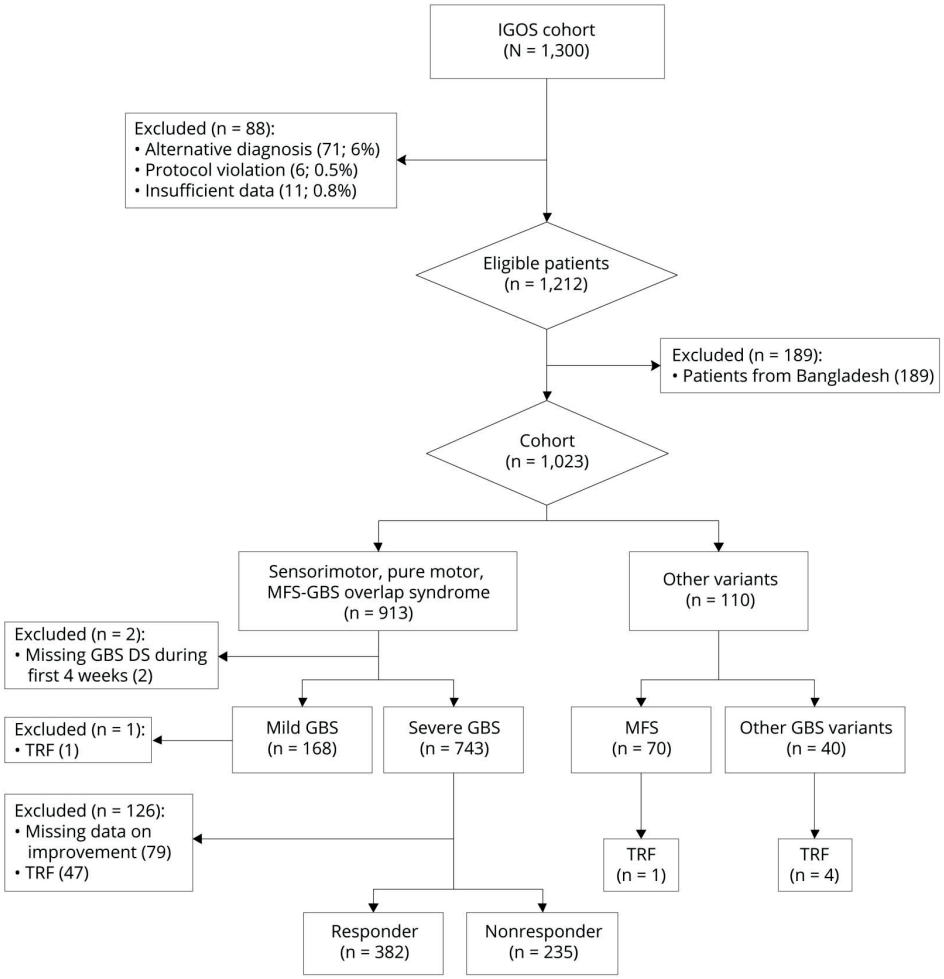

Figure 1. Patient and study cohort

Abbreviations: GBS = Guillain-Barré syndrome, GBS DS = GBS disability score, MFS = Miller Fisher syndrome, TRF = treatment related fluctuation.

Non-responder was defined as: Worsening or failure to improve by at least one grade on the GBS disability scale from nadir to week 4 (or not improving from the first to the second week in case of a missed visit at week 4).[27]

Other GBS variants = Pharyngeal-cervical-brachial, sensory ataxic, Bickerstaff brainstem encephalitis and bilateral facial weakness.

Treatment of severe GBS

There were 743 (81%) patients with severe GBS who were unable to walk independently at nadir (Figure 1). In the majority of countries, these patients were treated with IVIg (57-100%) (Figure 2). PE was seldom administered (about 4%) except in Malaysia (33%), Italy (30%) and USA (15%). Immunoadsorption was applied only in Germany, where it was administered in 3 (8%) of the 36 severely affected patients. There were no differences in the type of initial treatment (IVIg, PE or other) in severely affected patients with sensorimotor GBS versus the pure motor variant, or between demyelinating and axonal subtypes of GBS. However, patients with the axonal subtype (n=16/42, 38%) were more often treated with multiple courses than patients with the demyelinating subtype (n=49/296, 17%; p=0.001). Axonal GBS was associated with more severe limb weakness (indicated by lower MRC sum score) during the first four weeks as compared to demyelinating GBS.

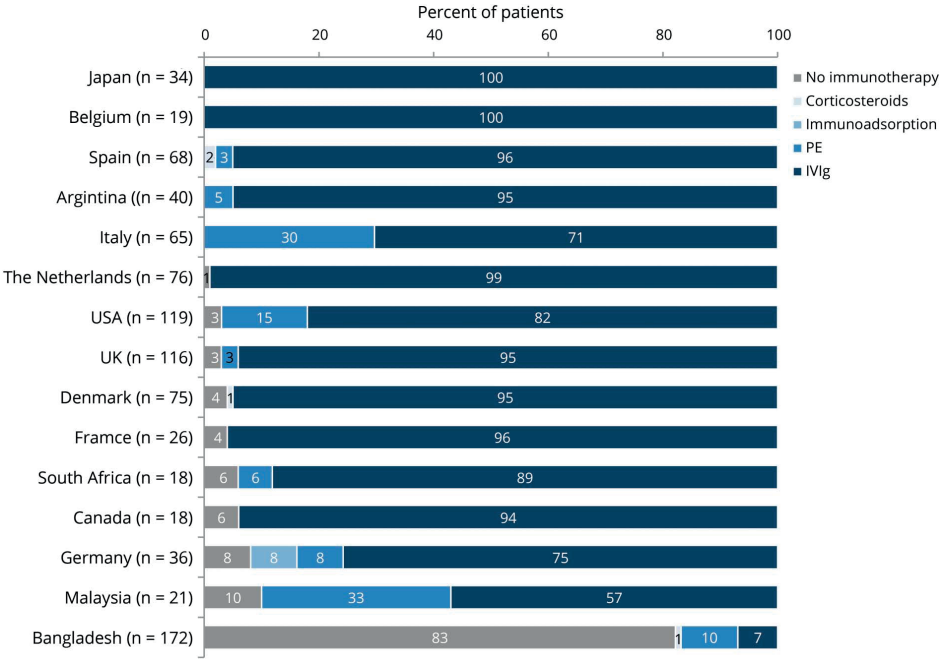

Figure 2. Country-specific initial treatment of severely affected GBS patients
This figure contains data from countries that have included at least 10 patients in IGOS. Abbreviations: GBS = Guillain-Barré syndrome, IGOS: International GBS Outcome Study, IVIg = intravenous immunoglobulin, PE = plasma exchange, UK = United Kingdom, USA = United States of America

Treatment of patients not improving after initial treatment

In 235 (32%) of the 743 severely affected patients, we observed no initial clinical improvement on the GBS disability scale from nadir to 4 weeks (excluding patients with a TRF). A second immunotherapy was instituted in 82 (35%) of these patients, most often in the Americas (n=26/55, 47%), compared to Europe (n=50/159, 31%, p=0.04) and Asia (n=6/15, 40%, p=0.77) (Table 1). The proportion of patients that received a second immunotherapy did not differ between university (n=59/179, 33%) and non-university hospitals (n=23/56, 41%, p=0.27). Of the 211 IVIg-treated patients without initial clinical improvement, 73 (35%) received additional immunotherapy. Most patients received a second course of IVIg (n=48, 66%), which was started at median 12 days (IQR 8-17) after completing the first IVIg course. In other IVIg-treated patients the treating physician switched to PE (n=22, 30%), which was started within 2 weeks after completing IVIg in 17 (77%) of the 22 patients (median 6 days, IQR 3-13). Three other IVIg-treated patients received other forms of immunotherapy. Twenty-three (11%) of 211 IVIg-treated patients received a third, fourth or even fifth immunotherapy (Figure 3). Of the 17 PE-treated patients not showing clinical recovery in the first 4 weeks, 8 (47%) received additional immunotherapy. In seven (41%) of these, the treating physician switched to IVIg after a median time of 2 days (IQR 1-4) after completing PE. One (6%) patient was re-treated with a second round of PE sessions. Three (18%) of 17 PE-treated patients received a third immunotherapy (Figure 3).

Treatment of treatment-related fluctuations (TRFs)

A TRF occurred in 53 (5%) of 1023 patients included in this study (Figure 1). TRFs occurred at a median of 23 days (IQR 16-31) after the start of initial treatment. Of the 50 patients initially treated with IVIg, 31 (62%) were re-treated with IVIg for their TRF. In four (8%) other patients, the physician switched treatment from IVIg to PE. Of the three patients initially treated with PE, one was retreated with IVIg. The remaining 17 (32%) patients received no treatment for their TRF. In patients that were re-treated for their TRF, the TRF occurred at an earlier time point than in untreated patients (median time to TRF after start of initial treatment (IQR): treated 21 days (14-27), untreated 32 days (25-54), p=0.008). In addition, a higher proportion of treated patients was unable to walk independently around the time of the TRF (treated n=33/36 (92%), untreated n=10/17 (59%); p=0.008), and the MRC sum score was lower (median MRC sum score (IQR): treated 41 (18-51), untreated 49 (43-60); p=0.019). Lastly, patients admitted to a university hospital were more often re-treated for their TRF (n=30/38, 79%) than those admitted to a non-university hospital (n=5/14, 36%, p=0.01).

Table 1. Regional differences in treatment of subgroups of patients with GBS.

Clinical situation and treatment		Full cohort (n=1023)	Europe (n=664)	America (n=238)	Asia[a] (n=88)
Severe GBS		**n=743**	**n=485**	**n=177**	**n=57**
	IVIg	662 (89)	442 (91)	152 (86)	46 (81)
	PE	56 (8)	27 (6)	20 (11)	9 (16)
	Other	6 (1)	5 (1)	0 (0)	0 (0)
	None	19 (3)	11 (2)	5 (3)	2 (4)
Non-improving		**n=235**	**n=159**	**n=55**	**n=15**
	Second immunotherapy[b]	82 (35)	50 (31)	26 (47)	6 (40)
TRF		**n=53**	**n=45**	**n=7**	**n=0**
	Second immunotherapy[b]	36 (68)	31 (69)	5 (71)	na
Mild GBS		**n=168**	**n=112**	**n=39**	**n=12**
	IVIg	121 (72)	80 (71)	31 (79)	8 (67)
	PE	5 (3)	3 (3)	1 (3)	1 (8)
	None	42 (25)	29 (26)	7 (18)	3 (25)
MFS		**n=70**	**n=38**	**n=18**	**n=11**
	IVIg	49 (70)	30 (79)	12 (67)	6 (55)
	PE	2 (3)	1 (3)	1 (6)	0 (0)
	Other	2 (3)	2 (5)	0 (0)	0 (0)
	None	17 (24)	5 (13)	5 (28)	5 (46)

Values are n (%).
[a] Asia not including Bangladesh
[b] Consisting of IVIg, PE, or corticosteroids alone
Abbreviations: GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, MFS = Miller Fisher syndrome, PE = plasma exchange, TRF = treatment related fluctuation

Treatment of mild GBS

Of the cohort of 913 patients with limb weakness, 168 (18%) had a mild form of GBS and were still able to walk independently at nadir. In this group of patients, 126 (75%) were treated with immunotherapy, being either IVIg in 121 (72%) or PE in 5 (3%) patients. The remaining 42 (25%) received no immunotherapy. The proportion of mildly affected patients receiving immunotherapy varied among countries, and was highest in the Americas (82%), followed by Asia (75%) and Europe (74%, Table 1) (Americas versus Europe p=0.32, Americas versus Asia p=0.68). The subgroup of patients with mild GBS receiving immunotherapy more often had autonomic dysfunction in the first four weeks from study entry (n=29/126, 23%) compared to those with mild GBS not receiving immunotherapy (n=2/42, 5%, p=0.01). The most frequently reported autonomic symptoms were blood pressure fluctuations (n=14/126, 11%), gastro-enteric dysfunction (n=10/126, 8%), bladder dysfunction (n=9/126, 7%), and cardiac dysfunction (n=8/126, 6%). The treated versus the untreated patients with mild GBS did not differ with respect to age, sex, MRC

sum score, GBS disability score, cranial nerve dysfunction, sensory deficits, ataxia or pain during the first four weeks after study entry. There was no difference in treatment provided by university (n=97/132, 74%) versus non-university hospitals (n=29/36, 81%, p=0.39).

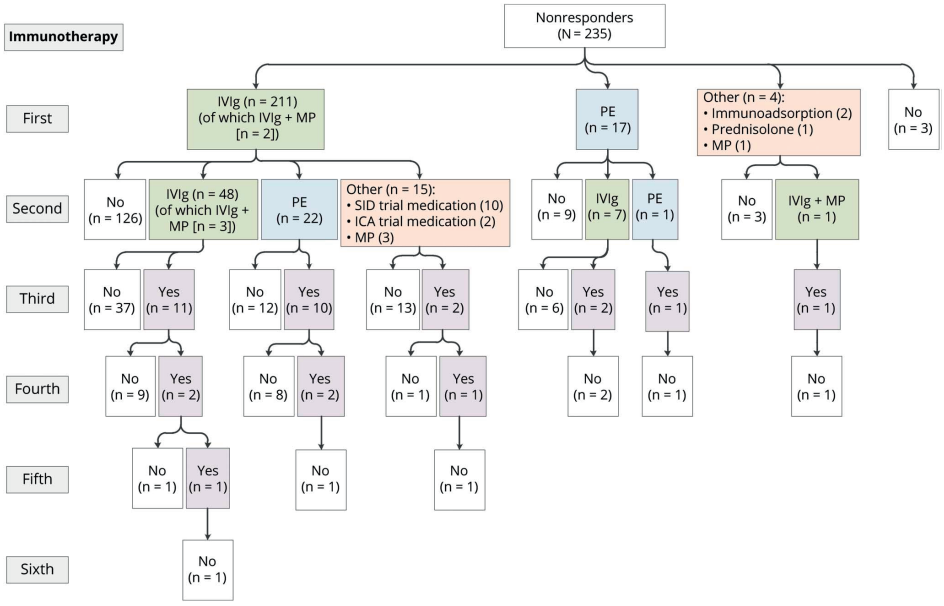

Figure 3. Treatment of patients with a severe form of GBS not responding to initial treatment.
Treatment of 235 patients with a severe form of GBS who showed no improvement after initial treatment. Abbreviations: IVIg = intravenous immunoglobulins; PE = plasma exchange; SID-GBS trial = Second Immunoglobulin Dose in GBS trial; ICA-GBS trial = Inhibition of Complement Activation in GBS trial.

Treatment of MFS and other variants

In the study cohort, 70 (7%) patients had MFS, and 40 (4%) patients had another distinct variant of GBS. The patients with MFS were treated with IVIg (n=49, 70%), PE (n=2, 3%), or other immunotherapy (n=2, 3%), and 17 (24%) received no treatment. In Europe (n=33/38, 87%) and America (n=13/18, 72%) more patients with MFS received immunotherapy than in Asia, where 6 out of 11 (55%) of the MFS patients were treated (Europe versus Asia p=0.03, America versus Asia p=0.43). The subgroup of treated MFS patients slightly more often reported pain during the first 4 weeks (n=26/53, 49%) than the untreated patients (n=4/17, 24%, p=0.064). The decision to treat a patient with MFS was not associated with the clinical phenotype or type of hospital. The rare variants of GBS included sensory ataxic GBS (n=24), pharyngeal cervical brachial variant (n=13), Bickerstaff brainstem encephalitis (n=2) and bilateral facial weakness (n=1). Thirty patients (75%; 15 sensory ataxic, 12 PCB, 2 BBE and 1 bilateral

facial weakness) were treated with IVIg, 3 (8%; all sensory ataxic) with PE, and 7 (18%; 6 sensory ataxic, 1 PCB) received no therapy.

Treatment of children

There were 60 (6%) children aged below 18 years (median 4 years, IQR 2-12), of whom 53 (90%) were unable to walk independently at nadir. Five (8%) were not treated with immunotherapy; they all had mild GBS. All others received IVIg. Children were similarly treated in university and non-university hospitals. Compared to adults, children were more often treated with a 2-day IVIg regimen (children n=30/54, 56% versus adults n=31/775, 4%) than a 5-day regimen (children n=24/54, 44% versus adults n=744/775, 96%, p<0.001). A considerable subgroup of children (n=23) came from Argentina, who were all treated with IVIg 2 g/kg in 2 days.

DISCUSSION

This study demonstrates a considerable variation in the current treatment practice of patients with GBS. Our study showed that in high-income countries, nearly all patients with severe GBS received initial treatment with IVIg or PE. In patients without clinical improvement, about one-third received a second treatment. Patients developing a secondary deterioration after initial stabilization or improvement (treatment-related fluctuation, TRF) were retreated in only two-thirds of cases. Patients with a milder form of GBS who were still able to walk independently were treated with IVIg or PE in 75% of cases. A similar proportion of patients with MFS or other (local) variants received this immunotherapy. The observed variation in treatment of GBS is in part explained by the lack of therapeutic trials that have investigated treatment efficacy in these specific clinical situations.

IVIg was the first choice of treatment in 92% of treated GBS patients. Most patients received the recommended dosage of 2g/kg bodyweight in 5 days, but some received a 2-day regimen. Children were more frequently treated with the latter scheme, presumably because this is better tolerated in young children. The optimal regimen of IVIg for GBS is currently undefined, but a randomized controlled trial (RCT) comparing a 5-day and 2-day regimen in children indicated that a 2-day regimen is equally effective, but is more frequently followed by a TRF. [18] Methylprednisolone was provided as add-on treatment in only 4% of the total number of administered IVIg courses. A single RCT indicated a short-term effect of MP as add-on to IVIg after correction for known prognostic factors, but showed no difference in improvement on the GBS disability scale. [7, 19] PE was provided as initial treatment in 7% of treated patients, and the proportion of PE treated

patients depended on the country of origin. PE is considered equally effective to IVIg for GBS, and the local preference may depend upon presence of contra-indications to IVIg, the availability of resources, health care insurances or protocols. [1-3, 20, 21] The number of sessions and duration of treatment with PE varied between patients. One trial investigated the optimal number of PE sessions and found that four sessions were better than two, but equally effective to six sessions in relation to time to walk with aid and time on a ventilator. [12] Immunoadsorption was instituted only in Germany, where two immunoadsorption trials were conducted. This may explain why the use was limited to German centers, in addition to reimbursement differences and costs. [22, 23] Some patients were treated with corticosteroids only, even though this treatment is considered ineffective for GBS. [24] The treatment practice in high-income countries is in marked contrast with the situation in Bangladesh, where only 15% of patients with severe GBS received immunotherapy. Most inhabitants of Bangladesh cannot afford treatment with either IVIg or PE. [9, 10] Low-cost alternative treatments for GBS are required and small volume plasma exchange is currently under investigation. [25]

Multiple treatment courses were administered in patients without improvement after initial treatment. In severely affected patients who did not improve after a first treatment with IVIg or PE, 35% received a second treatment, 11% even a third treatment, and some even a fourth and a fifth treatment. Patients who received multiple courses of treatment more often had axonal GBS, which in the IGOS cohort is associated with more severe limb weakness, and could have influenced the decision to repeat treatment. [11] The efficacy of a second course of IVIg is yet unknown, but is currently investigated in the SID-GBS trial. [16] In some of these patients initially treated with IVIg, the treating physician switched to PE, which was often started within two weeks of completion of IVIg. While the efficacy of this treatment practice is unproven, one may argue that IVIg and PE have different therapeutic targets and that if one treatment fails, the other might still be effective. A consequence however of this early secondary treatment with PE is that IVIg is washed out and cannot further contribute to the recovery. [7] Other patients were treated with PE followed by IVIg. Previously, a RCT comparing PE or IVIg alone to PE followed by IVIg showed no difference in outcome. [20] This trial was however not designed to address IVIg treatment efficacy in patients not responding to PE.

Another group of patients receiving secondary treatments were those with a TRF. Previous studies have shown that TRFs may occur in up to 12% of GBS patients[11]. In the current study, TRFs were reported in 53 (5%) patients of whom 68% were re-treated with IVIg or PE. A higher proportion of re-treated TRF patients was unable to walk independently and the treated group had more severe limb weakness around the time of the TRF, which indicates that the decision to start treatment in case of a TRF may depend on

the severity of symptoms. In addition, re-treatment for a TRF was more often provided in university versus non-university hospitals. No trials have investigated the efficacy of treatment of a TRF in patients with GBS. The rationale for re-treatment of TRFs is that these likely result from a transient effect of the first treatment in a patient with ongoing disease activity. [3, 7] Yet, 32% of patients with a TRF in the study cohort received no additional treatment.

Although the treatment efficacy of IVIg and PE was largely demonstrated in GBS patients unable to walk, our study showed that in current clinical practice 75% of patients with mild disability were also treated. One RCT demonstrated that in patients with mild GBS, 2 sessions of PE shortened the time to onset of motor recovery and hospital discharge compared to supportive care only. [12] Moreover, more than three-quarter of patients with MFS and other variants of GBS were treated with IVIg or PE, despite the fact that treatment efficacy has not been demonstrated for these subgroups and the prognosis of MFS in general is considered to be good independent of treatment. [26] In our study cohort, patients with MFS had a higher chance of receiving immunotherapy in Europe and America compared to Asia. The decision to start treatment may have been prompted by the higher frequency of autonomic dysfunction in patients with mild GBS, and pain in patients with MFS. No other differences were found between the treated and untreated patients with mild GBS and MFS.

The decision to treat may have been influenced by the expertise of the treating clinician and the policy in the local hospitals. University hospitals were overrepresented in the IGOS Consortium, although the treatment practice did not differ from non-university hospitals except in the situation of a TRF. In addition, clinicians with a special interest in GBS are likely overrepresented. This may have resulted in an underestimation of the variation in treatment practice because of their expertise, or in an overestimation because of the access to multiple treatment options in tertiary reference centers. We were not able to assess the effect of expertise and years of clinical experience on treatment practice, because this information was not collected in IGOS. Another limitation of the study was that while the IGOS aims to include the full spectrum of GBS and variants, the included patient population may be biased, especially towards more severe cases. In addition, data were collected in IGOS at standard time points, and changes between visits – that may have prompted the decision to start treatment – are possibly unobserved. This limitation could also have influenced the number of TRFs which is relatively low compared to other studies. Furthermore, data on the GBS treatment practice in regions and countries not represented in IGOS are lacking.

The treatment practice currently provided for GBS varies between patients, especially with respect to initial treatment of mild and variant forms, and retreatment of TRF and non-responding patients. Such treatment could be beneficial in terms of clinical outcome and cost-effectiveness, but selective treatment trials are lacking and complicated because of the rarity and diversity of GBS. Whether such evidence can be generated by comparative treatment studies based on observational data needs to be determined. Further studies are required to develop evidence-based guidelines on the treatment of GBS.

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4.2

Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

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Cochrane Database of Systematic Reviews 2020, Issue 1.

ABSTRACT

Background

Plasma exchange and intravenous immunoglobulin, but not corticosteroids, are beneficial in Guillain-Barré syndrome (GBS). The efficacy of other pharmacological agents is unknown. This review was first published in 2011 and previously updated in 2013, and 2016.

Objectives

To assess the eLects of pharmacological agents other than plasma exchange, intravenous immunoglobulin and corticosteroids for GBS.

Search methods

On 28 October 2019, we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, and Embase for treatments forGBS. We also searched clinical trials registries.

Selection criteria

We included all randomised controlled trials (RCTs) or quasi-RCTs of acute GBS (within four weeks from onset) of all types and degrees of severity, and in individuals of all ages. We discarded trials that investigated only corticosteroids, intravenous immunoglobulin or plasma exchange. We included other pharmacological treatments or combinations of treatments compared with no treatment, placebo or another treatment.

Data collection and analysis

We followed standard Cochrane methodology.

Main results

We found six trials of five different interventions eligible for inclusion in this review. The trials were conducted in hospitals in Canada, China, Germany, Japan and the UK, and included 151 participants in total. All trials randomised participants aged 16 years and older (mean or median age in the trials ranged from 36 to 57 years in the intervention groups and 34 to 60 years in the control groups) with severe GBS, defined by the inability to walk unaided. One trial also randomised patients with mild GBS who were still able to walk unaided. We identified two new trials at this update.The primary outcome measure for this review was improvement in disability grade four weeks after randomisation. Four of six trials had a high risk of bias in at least one respect.

We assessed all evidence for the outcome mean improvement in disability grade as very low certainty, which means that we were unable to draw any conclusions from the data. One RCT with 19 participants compared interferon beta-1a (IFNb-1a) and placebo. It is uncertain whether IFNb-1a improves disability after four weeks (mean difference (MD) -0.1; 95% CI −1.58 to 1.38; very low-certainty evidence). A trial with 10 participants compared brain-derived neurotrophic factor (BNDF) and placebo. It is uncertain whether BDNF improves disability after four weeks (MD 0.75; 95% CI −1.14 to 2.64; very low-certainty evidence). A trial with 37 participants compared cerebrospinal fluid (CSF) filtration and plasma exchange. It is uncertain whether CSF filtration improves disability after four weeks (MD 0.02; 95% CI −0.62 to 0.66; very low-certainty evidence). One trial that compared the Chinese herbal medicine tripterygium polyglycoside with corticosteroids with 43 participants did not report the risk ratio (RR) for an improvement by one or more disability grade after four weeks, but did report improvement after eight weeks. It is uncertain whether tripterygium polyglycoside improves disability after eight weeks (RR 1.47; 95%CI 1.02 to 2.11; very low-certainty evidence). We performed a meta-analysis of two trials comparing eculizumab and placebo with 41 participants. It is uncertain whether eculizumab improves disability after four weeks (MD -0.23; 95% CI −1.79 to 1.34; very low-certainty evidence). Serious adverse events were uncommon in each of the trials and evidence was graded as either low or very low. It is uncertain whether serious adverse events were more common with IFNb-1a versus placebo (RR 0.92, 95% CI 0.23 to 3.72; 19 participants), BNDF versus placebo (RR 1.00, 95% CI 0.28 to 3.54; 10 participants) or CSF filtration versus plasma exchange (RR 0.13, 95% CI 0.01 to 2.25; 37 participants). The trial of tripterygium polyglycoside did not report serious adverse events. There may be no clear difference in the number of serious adverse events after eculizumab compared to placebo (RR 1.90, 0.34 to 10.50; 41 participants). We found no clinically important differences in any of the outcome measures selected for this review in any of the six trials. However, sample sizes were small and therefore clinically important benefit or harm cannot be excluded.

Authors' conclusions

All six RCTs were too small to exclude clinically important benefit or harm from the assessed interventions. The certainty of the evidence was low or very low for all interventions and outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Interferon beta-1a versus placebo for Guillain-Barré syndrome

Interferon beta-1a versus placebo for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome
Settings: 4 UK hospitals
Intervention: interferon beta-1a (IFNb-1a)
Comparison: placebo

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (95% CI)	Certainty of the evidence (GRADE)	Comments
		Assumed risk Placebo	Corresponding risk IFNb-1a				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean improvement in disability grade after 4 weeks in the control group was **1.3 grades**[a]	The mean improvement in disability grade after 4 weeks in the intervention group was **0.1 grades lower** (1.58 lower to 1.38 higher)		19 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c]	It is uncertain whether IFNb-1a improves disability (defined by mean disability grade) after 4 weeks.
Improvement in disability grade Defined as achievement of a specified degree of improvement	**Improvement by 1 or more disability grade after 4 weeks** Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	**500 per 1000**	**540 per 1000** (210 to 1000)	**RR 1.08** (0.42 to 2.77)	19 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c]	It is uncertain whether IFNb-1a improves disability (by ≥ 1 disability grade) after 4 weeks.
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Not measured					

Time from randomisation until recovery of unaided walking (median, days (95% CI))	**18** (11 to 70)	**59** (16 to infinity)	-	19 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,d]	It is uncertain whether IFNb-1a has an effect on the time from randomisation until recovery of unaided walking.
Time from randomisation until discontinuation of ventilation (for those ventilated)	Not measured					
Death	0 of 6 participants died in the control group	1 of 13 died in the IFNb-1a group	**RR 1.50** (0.07 to 32.29)	19 (1 RCT)	⊕⊕⊖⊖ **Low**[c]	There may be no difference in the number of deaths after IFNb-1a compared to placebo.
Death or disability after 12 months	Not measured					
Participants with 1 or more serious adverse events	**333 per 1000**	**306 per 1000** (77 to 1000)	**RR 0.92** (0.23 to 3.72)	19 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,d]	It is uncertain whether IFNb-1a has an effect on the number of serious adverse events compared to placebo.

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IFNb-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Since there is only one trial, we took the assumed risk to be that of the control group.
[b]Downgraded once for trial limitations, as there was the potential for unblinding.
[c]Downgraded twice for very serious imprecision. The confidence interval encompass potential benefit and potential harm.
[d]Downgraded twice for very serious imprecision. The trial included only 19 participants, and confidence interval encompass a broad range of values.

Summary of findings 2. Brain-derived neurotrophic factor versus placebo for Guillain-Barré syndrome

Brain-derived neurotrophic factor versus placebo for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome
Settings: 1 Canadian and 2 UK hospitals
Intervention: brain-derived neurotrophic factor (BDNF)
Comparison: placebo

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (95% CI)	Certainty of the evidence (GRADE)	Comments
		Assumed risk Placebo	Corresponding risk BDNF				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean improvement in disability grade after 4 weeks in the control group was **0.25**[a]	The mean improvement in disability grade after 4 weeks in the intervention group was **0.75 higher** (1.14 lower to 2.64 higher)		10 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c]	It is uncertain whether BDNF improves the disability grade after 4 weeks.
Improvement in disability grade Defined as achievement of a specified degree of improvement	**Improvement by 1 or more disability grade after 4 weeks** Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	**500 per 1000**	**500 per 1000** (140 to 1000)	**RR 1.00** (0.28 to 3.54)	10 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c]	It is uncertain whether BDNF has an effect on improvement in disability (of ≥ 1 disability grades) after 4 weeks.
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Not measured					
Time from randomisation until recovery of unaided walking (median, days (95% CI))		**84** (2 to infinity)	**84** (4 to infinity)	-	10 (1 RCT)	⊕⊖⊖⊖ **Very low**[c,d]	It is uncertain whether BDNF has an effect on the time from randomisation until recovery of unaided walking.

Time from randomisation until discontinuation of ventilation (for those ventilated) (median, weeks (range))	1 participant in the placebo group required mechanical ven-tilation, initiated during follow-up as a probable re-sult of neurologi-cal deterioration. Ventilation was discontinued 4 weeks from ran-domisation	4 of 6 participants in the BNDF group were ventilated; median time to dis-continuation was 12 weeks (12 weeks to infinity)		5 (1 RCT)	⨁⊖⊖⊖ **Very low**[c,e]	It is uncertain whether BDNF has an ef-fect on the time from randomisation until discontinuation of ventilation, for those ventilated
Death	**250 per 1000**	**168 per 1000** (15 to 1000)	**RR 0.67** (0.06 to 7.85)	10 (1 RCT)	⨁⊖⊖⊖ **Very low**[b,c]	It is uncertain whether BDNF has an effect on the number of deaths com-pared to placebo.
Death or disability after 12 months	**250 per 1000**	**332 per 1000** (43 to 1000)	**RR 1.33** (0.17 to 10.25)	10 (1 RCT)	⨁⊖⊖⊖ **Very low**[b,c]	It is uncertain whether BDNF has an effect on death or disability after 12 months compared to placebo.
Participants with 1 or more serious adverse events	**500 per 1000**	**500 per 1000** (140 to 1000)	**RR 1.00** (0.28 to 3.54)	10 (1 RCT)	⨁⊖⊖⊖ **Very low**[b,c]	It is uncertain whether BDNF has an ef-fect on the number of serious adverse events compared to placebo.

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IFNb-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]We used the control group to provide the assumed risk.
[b]Downgraded twice for very serious imprecision. The trial included only 10 participants. Confidence interval encompass potential benefit and potential harm from brain-derived neurotrophic factor.
[c]Downgraded once for risk of bias. Participants with brain-derived neurotrophic factor had more severe disease at randomisation and were randomised later.
[d]Downgraded twice for very serious imprecision. The trial included only 10 participants, and confidence intervals encompass a broad range of values.
[e]Downgraded twice for very serious imprecision. Only five participants were included in this analysis, and the range (weeks) is broad.

Summary of findings 3. Cerebrospinal fluid filtration versus plasma exchange for Guillain-Barré syndrome

Cerebrospinal fluid filtration versus plasma exchange for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome
Settings: 1 German hospital
Intervention: cerebrospinal fluid (CSF) filtration
Comparison: plasma exchange

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (95% CI)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Plasma exchange	CSF filtration				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean improvement in disability grade after 4 weeks in the control group was **0.8**[a]	The mean improvement in disability grade after 4 weeks in the intervention group was **0.02 higher** (0.62 lower to 0.66 higher)		37 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c]	It is uncertain whether CSF filtration improves disability more than plasma exchange (defined by mean disability grade) after 4 weeks.
Improvement in disability grade Defined as achievement of a specified degree of improvement	**Improvement by 1 or more disability grade after 4 weeks** Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	**500 per 100**	**470 per 1000** (240 to 920)	**RR 0.94** (0.48 to 1.84)	37 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,c]	It is uncertain whether CSF filtration improves disability more than plasma exchange (by ≥ 1 disability grade) after 4 weeks.
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Not measured					
Time from randomisation until recovery of unaided walking (median, days (95% CI))		**90** (6 to 420)	**42** (13 to 433)		37 (1 RCT)	⊕⊖⊖⊖ **Very low**[b,d]	It is uncertain whether CSF filtration has an effect on the time from randomisation until recovery of unaided walking.

Time from randomisation until discontinuation of ventilation (for those ventilated) (median, weeks (range))	Not measured					
Death	**50 per 1000**	**59 per 1000** (4 to 871)	**RR 1.18** (0.08 to 17.42)	37 (1 RCT)	⨁⨁⊖⊖ **Low**[c]	There may be no difference in the number of deaths after CSF filtration compared to plasma exchange.
Death or disability after 12 months	Not measured					
Participants with 1 or more serious adverse events	**200 per 1000**	**26 per 1000** (2 to 450)	**RR 0.13** (0.01 to 2.25)	37 (1 RCT)	⨁⊖⊖⊖ **Very low**[b,c]	It is uncertain whether CSF filtration has an effect on the number of serious adverse events compared to plasma exchange.

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IFNb-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]We took the assumed risk to be the risk in the plasma exchange group.
[b]Downgraded once for trial limitations, as participants were not blinded.
[c]Downgraded twice for very serious imprecision. Confidence interval encompassed the possibility of effects favouring cerebrospinal fluid filtration or plasma exchange. [d]Downgraded twice for very serious imprecision. The trial included only 37 participants, and confidence intervals encompass a broad range of values.

Summary of findings 4. Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome

Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome
Settings: China
Intervention: tripterygium polyglycoside
Comparison: corticosteroids

Outcomes		Illustrative comparative risks* (95% CI) Corresponding risk		Relative effect (95% CI)	No. of participants (95% CI)	Certainty of the evidence (GRADE)	Comments
		Assumed risk Corticosteroids	Tripterygium polyglycoside				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		Not measured					
Improvement in disability grade Defined as achievement of a specified degree of improvement	**Improvement by 1 or more disability grade after 4 weeks** Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead In absence of data at 4 weeks, we report the outcome at 8 weeks	**619 per 1000**[a]	**910 per 1000** (631 to 1000)	**RR 1.47** (1.02 to 2.11)	43 (1 RCT)	⨁⊖⊖⊖ **Very low**[b,c,d]	It is uncertain whether Tripterygium polyglycoside has an effect on improvement in disability compared with corticosteroids (of ≥ 1 disability grades) after 8 weeks.
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Not measured					
Time from randomisation until recovery of unaided walking (median, days (95% CI))		Not measured					

Time from randomisation until discontinuation of ventilation (for those ventilated) (median, weeks (range))	Not measured				
Death	No deaths reported in this trial in either the tripterygium or corticosteroid groups	Not estimable	43 (1 RCT)	-	-
Death or disability after 12 months	Not measured				
Participants with 1 or more serious adverse events	Not reported	Not estimable	43 (1 RCT)		0 of 21 participants treated with corticosteroids experienced adverse events and 1 of 22 participants treated with tripterygium polyglycoside (gastrointestinal toxicity, of unclear severity)

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IFNb-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Assumed risk has been taken as that of the corticosteroid group.
[b]Primary outcome for this review was to be measured at 4 weeks but the only available data comes from 8 weeks (downgraded once for indirectness).
[c]Downgraded once for trial limitations. The translator of the Chinese text classified the risk of bias as unclear. The trial compared oral tripterygium versus intravenous corticosteroids and was unblinded.
[d]Downgraded once for serious imprecision. CI encompass the possibility of little or no effect from tripterygium polyglycoside and substantial benefit.
[e]Downgraded twice for very serious imprecision. CI encompass the possibility of large differences between the treatment groups in either direction.

Summary of findings 5. Eculizumab versus placebo for Guillain-Barré syndrome

Eculizumab versus placebo for Guillain-Barré syndrome

Patient or population: adults with severe Guillain-Barré syndrome (GBS disability score > 2), within 2 weeks form onset
Setting: specialist hospitals
Intervention: eculizumab
Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (95% CI)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with eculizumab				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean improvement in disability grade after 4 weeks was **1.08**[a]	MD **0.23 lower** (1.79 lower to 1.34 higher)	-	40 (2 RCTs)	⨁⊖⊖⊖ **Very low**[b,c]	It is uncertain whether eculizumab improves disability grade after 4 weeks
Improvement in disability grade Defined as achievement of a specified degree of improvement	**Improvement by 1 or more disability grade after 4 weeks** Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	Trial population[d] **692 per 1000**	**588 per 1000** (298 to 1000)	**RR 0.85** (0.43 to 1.69)	40 (2 RCTs)	⨁⨁⊖⊖ **Low**[c]	Eculizumab may have no clear effect on improvement in disability (of ≥ 1 disability grades) after 4 weeks
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Trial population[d] **769 per 1000**	**700 per 1000** (292 to 1000)	**RR 0.91** (0.38 to 2.16)	40 (2 RCTs)	⨁⊖⊖⊖ **Very low**[c,e]	It is uncertain whether eculizumab affects the proportion of people with an improvement in disability (of ≥ 6 points in I-RODS score) after 4 weeks.

Time from randomisation until recovery of unaided walking (median, days (95% CI))	**7.5** (SD 7.8)	**8.5** (SD 6.4)	-	7 (1 RCT)	⊕⊕⊖⊖ **Low**[f]	There may be no clear difference in the time from randomisation until recovery of unaided walking after eculizumab compared to placebo.
Time from randomisation until discontinuation of ventilation (for those ventilated) (median, weeks (range))	In one trial, the median time from randomisation until discontinuation of ventilation was shorter in the eculizumab-treated group (18 days, 95% CI 11.0 to 31.0) than in the placebo group (34 days, 95%CI 27.0 to 41.0; P = 0.198). In this trial 4 participants in the eculizumab group required ventilation, and 2 in the placebo group. In a second trial (N = 7), median time to discontinuation of ventilation in those venti-lated (2 participants, both in the eculizumab group) was 102 days (range 20 days to 182 days).		-	8 (2 RCTs)	⊕⊖⊖⊖ **Very low**[g,h]	It is uncertain whether eculizumab affects the time from randomisation until discontinuation of ventilation (for those ventilated), compared to placebo.
Death	Trial population[d] **0 deaths** in the con trol group (11 participants	**1 death** in the eculizumab group (27 participants)	**RR 1.50** (0.08 to 26.86)	38 (2 RCTs)	⊕⊕⊖⊖ **Low**[c]	There may be no clear difference in the number of deaths after eculizumab compared to placebo. The absence of any deaths in the control group prevented calculation of the absolute effect.

Death or disability after 12 months **91 per 1000**	Trial population[d] **110 per 1000** (14 to 919)	**RR 1.21** (0.15 to 10.11)	38 (2 RCTs)	⊕⊖⊖⊖ **Very low**[c,i]	It is uncertain whether eculizumab has an effect on death or disability after 6 months compared to placebo. This 6-month outcome was not one selected for this review - our protocol specified 12 months.
Participants with 1 or more serious adverse events **77 per 1000**	Trial population[d] **146 per 1000** (26 to 808)	**RR 1.90** (0.34 to 10.50)	41 (2 RCTs)	⊕⊕⊖⊖ **Low**[c]	6 of 28 eculizumab participants had serious adverse events, of which 3 had a possible causal relationship to the trial drug. 1 of 13 control participants had a serious adverse event. There may be no clear difference in serious adverse events after eculizumab compared to placebo.

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IFNb-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Based on mean scores of control groups.
[b]Downgraded once for inconsistency. I^2 statistic was 71%, which indicates substantial heterogeneity.

[c]Downgraded twice for very serious imprecision. Confidence interval encompass important potential benefit and harm.
[d]Based on overall event rate across control participants in both trials.
[e]Downgraded once for inconsistency. I^2 statistic was 61%, which indicates substantial heterogeneity.
[f]Downgraded twice for very serious imprecision. The trial included only seven participants, and the standard deviations are large.
[g]Downgraded twice for very serious imprecision. Data were provided by eight ventilated participants in two trials.
[h]Downgraded once for inconsistency as median times to discontinuation of ventilation diLered substantially between the two trials.
[i]Downgraded once for serious indirectness, as outcome at six months was provided instead of outcome at 12 months.

BACKGROUND

Description of the condition

Guillain-Barré syndrome (GBS) is an acute paralysing disease that causes the rapid development of weakness of the limbs and often the facial, swallowing and breathing muscles. Tingling and numbness usually occur in the limbs at the same time. The disease is usually due to multifocal inflammation of the spinal roots and peripheral nerves, especially their myelin sheaths. The axons are often damaged as a secondary consequence of the inflammatory response. In some cases the axons are the primary focus of the attack. The weakness can reach its nadir within a few days or within four weeks. In 25% of people with GBS the disease is sufficiently severe to require the use of artificial ventilation (Van den Berg 2014; Willison 2016). Between 3% and 17% die during the first year after onset (Van den Berg 2013; Doets 2018). Recovery takes several weeks or months and is often incomplete.

The cause of GBS is still under investigation. The favoured hypothesis is that it is due to an autoimmune response directed against antigens in the peripheral nerves that is triggered by a preceding bacterial or viral infection. The triggering mechanism is incompletely understood but may be the consequence of molecular mimicry whereby antibodies or T cells stimulated by antigenic epitopes on the infecting microbe cross-react with neural epitopes. In the most common form of GBS in Europe and North America, the underlying pathological process is acute inflammatory demyelinating polyradiculoneuropathy. The responsible antigen is likely to be in the Schwann cell membrane or the myelin sheath. Axonal forms of the disease are uncommon in Europe and North America but more common in Asia and Central America. In axonal varieties, the axon membrane is probably the target of the immune response (Yuki 2012). Distinguishing the different forms of the disease during life is difficult but has been attempted through neurophysiological studies (Hadden 1998).

Description of the intervention

Evidence from randomised controlled trials (RCTs) summarised in Cochrane Reviews has shown that plasma exchange and intravenous immunoglobulin (IVIg), but not corticosteroids, have a beneficial effect in GBS by hastening recovery (Hughes 2007; Hughes 2014; Hughes 2016; Chevret 2017). Plasma exchange and IVIg have reduced but not prevented prolonged stays in intensive care unit and hospital and long-term disability (Hughes 2014; Chevret 2017). Many people with GBS have persistent fatigue (Merkies 2016); 9% to 31% of people still require aid to walk one year after the onset of GBS (Rees 1998; Doets 2018), and 62% still notice its effect on their own or their carers' lives three to six years later (Bernsen 1999). Exercise and rehabilitation programmes are used and

evidence for their benefit is being sought (Simatos 2016), but it is likely that the need for improved pharmacological treatments will persist.

Guillain-Barré syndrome is thought to be caused by an aberrant immune response directed against the peripheral nerves resulting in damage to the myelin sheath or axonal membrane. Trials investigating the efficacy of pharmacological treatments other than corticosteroids, IVIg or plasma exchange have focused on inhibiting or modulating the immune response (interferon beta-1a (IFNb-1a), tripterygium polyglycoside and eculizumab), neuroprotection and stimulation of axonal regeneration (brain-derived neurotrophic factor), or novel techniques to remove pathogenic factors from the circulation (cerebrospinal fluid filtration; Bensa 2000; Zhang 2000; Wollinsky 2001; Pritchard 2003; ICA-GBS 2017; JET-GBS 2018).

How the intervention might work

Each intervention in this review had a different rationale. IFNb-1a had been shown to have multiple beneficial effects and had been licensed for treatment in multiple sclerosis, an inflammatory disease of the central nervous system (Rice 2001). It reduced the severity of experimental autoimmune neuritis in an animal model of GBS (Zou 1999). Pritchard 2003 tested its efficacy in a pilot study in GBS.

Brain-derived neurotrophic factor (BNDF) is a trophic factor known to be important in the development of motor neurons, in people with GBS. Bensa 2000 tested it for GBS in a pilot study. Subsequently, experimental evidence emerged for a neuroprotective role of BDNF in mouse experimental allergic encephalomyelitis (Linker 2010).

Wollinsky 2001 developed a technique for removing, filtering and re-infusing the cerebrospinal fluid (CSF) with the aim of removing cells, bacteria, endotoxins, immunoglobulins, and inflammatory mediators that might be harmful. The theoretical basis was that inflammation of the spinal roots is important in the pathogenesis of GBS and that CSF filtration would remove 'blocking factors' that block nerve conduction (Brinkmeier 1992). However, the inflammation in GBS also affects the trunks and terminal portions of nerves (Feasby 2001), and the existence of 'blocking factors' has been questioned (Cummins 2003; Otto 2005).

Zhang 2000 undertook a RCT of tripterygium polyglycoside, an extract of the herb Tripterygium wilfordii (Thunder God Vine). It has been used as an anti-inflammatory agent in traditional Chinese medicine for many years. There are reports of it benefiting prevention of renal allograft rejection and treatment of Crohn's disease and rheumatoid arthritis (Goldbach-Mansky 2009). Tripterygium polyglycoside extracts contain 380 metabolites.

The most active ingredients are terpenoids, some of which inhibit key pathways in T cell activation and cyclo-oxygenase and nitric oxide production (Goldbach-Mansky 2009).

Evidence from clinicopathological and animal model studies has indicated a role for the complement cascade as a terminal effector in the induction of nerve damage in GBS, which has increased the interest in complement factor inhibitors as potential therapeutic agents for GBS (Goodfellow 2016). Eculizumab, a humanised anti- C5 antibody, has already been shown to be effective in animal models for Miller Fisher syndrome in vivo and in vitro, and safe and effective in several other complement-mediated human diseases (Hillmen 2004; Halstead 2005; Halstead 2008; Fitzpatrick 2011; Legendre 2013). The safety and efficacy of eculizumab in people with GBS have now been assessed in two small RCTs that compared IVIg with eculizumab to IVIg and placebo, which have been included in this review (ICA-GBS 2017; JET-GBS 2018).

Why it is important to do this review

The treating doctor has a responsibility to know about the evidence for all treatments that have been used for the condition under consideration, in this case GBS. It is also an ethical requirement to undertake a systematic review before embarking on trials of other agents to make sure that they have not already been tested. Such a review should help to identify appropriate agents, outcomes and trial designs. We therefore undertook this systematic review of RCTs of pharmacological treatments other than corticosteroids, IVIg and plasma exchange for GBS. This is a further update of a review first published in 2011, and previously updated in 2013 and 2016.

OBJECTIVES

To assess the effects of pharmacological agents other than plasma exchange, intravenous immunoglobulin and corticosteroids for GBS.

METHODS

Criteria for considering studies for this review

Types of studies

We included all eligible RCTs or quasi-RCTs (using alternate or other systematic allocation) identified by the searches. The rationale to include quasi-randomised trials was based on the rarity of GBS and the knowledge that few RCTs had been performed. In fact

we discovered no quasi-randomised trials. As anticipated, during the search for RCTs we also identified trials of pharmacological treatments that had not been subjected to randomised trials, including cohort studies, case reports and case series, which we addressed in the Agreements and disagreements with other studies or reviews section of the Discussion. We did not include nonrandomised studies in the Results and only noted them if the diagnosis, treatment and results were sufficiently described to enable us to be confident of the diagnosis, and to deduce the pretreatment and outcome disability grade. We might have missed (and therefore have not included) some non-randomised studies because there is no method for searching systematically that would have identified all such studies. Although not planned in the protocol, we also searched our personal databases for nonrandomised trials.

Types of participants

We included children and adults with GBS of all degrees of severity. GBS was defined according to internationally accepted diagnostic criteria (those of Asbury 1990), as acute polyradiculoneuropathy causing progressive weakness of two or more limbs, having an onset phase of not more than four weeks and reduced or absent tendon reflexes, and lacking alternative causes. We included acute inflammatory demyelinating polyradiculoneuropathy and axonal forms of the disease, although in practice the published reports of the included treatment trials never distinguished between the two forms. We included trials that did not conform exactly to these criteria provided that the trial authors regarded GBS or one of its synonyms, such as acute idiopathic neuropathy or acute inflammatory demyelinating polyradiculoneuropathy, as the preferred diagnosis. We noted any departure from the internationally accepted diagnostic criteria.

Types of interventions

We included all pharmacological treatments or combinations of treatments for acute GBS other than corticosteroids, IVIg and plasma exchange, compared with placebo, no treatment or another treatment. We confined our attention to treatments delivered in the acute stage to modify the duration and severity of clinical disease as defined by the outcome measures below. We defined acute as within the first four weeks after the onset of symptoms of weakness. We did not include treatments for symptoms of GBS unrelated to weakness or disability (for example, treatments for neuropathic pain or fatigue).

Types of outcome measures

Primary outcomes

We assessed the outcomes selected for previous Cochrane Reviews of treatments for GBS.

The primary outcome was improvement in disability grade (Hughes 1978), four weeks after randomisation.

We accepted the disability scale used by the authors of each trial provided that it was closely similar to that selected for this review (Hughes 1978), or could be adapted to correspond to that scale, now called the GBS disability scale:

1. healthy;
2. minor symptoms or signs of neuropathy but capable of manual work;
3. able to walk without support of a stick but incapable of manual work;
4. able to walk with a stick, appliance or support;
5. confined to bed or chair;
6. requiring assisted ventilation;
7. dead.

The minimum clinically important difference of change in average GBS disability grade has never been calculated but a half grade has been arbitrarily defined as the amount that would be clinically important (Plasma 1997).

Secondary outcomes

- Improvement by one or more GBS disability grades after four weeks
- Improvement by six or more centile points in the Inflammatory Rasch-built Overall Disability Scale (I-RODS; Draak 2014) after four weeks
- Time from randomisation until recovery of unaided walking
- Time from randomisation until discontinuation of ventilation (for those ventilated)
- Death
- Death or disability (inability to walk without aid) after 12 months
- Serious adverse events (that is adverse events that are life-threatening or fatal, or require or prolong hospital stay).

Search methods for identification of studies

Electronic searches

On 28 October 2019, we searched the following databases:

- Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web; Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 10) via the Cochrane Register of Studies (CRS-Web; Appendix 2);
- MEDLINE (1946 to 25 October 2019; Appendix 3);
- Embase (1974 to 25 October 2019; Appendix 4).

We also searched the following trials registries:.

- www.clinicaltrials.gov (Appendix 5) on 17 October 2019;
- WHO trials registry (ICTRP; apps.who.int/trialsearch/) on 4 November 2019.

Searching other resources

We contacted trial authors and other experts in the field to identify additional published or unpublished data. We did not use a treatment term but discarded trials that investigated only corticosteroids, IVIg or plasma exchange during the selection process. We searched the references retrieved by the above process and our personal databases for non-randomised cohort studies, case series and case reports in which the diagnosis, treatment and results were sufficiently described to deduce the pretreatment and outcome disability grade. We applied no language limitations. We contacted 13 trial authors or disease experts for information about other trials, including unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (RACH and RDMH or JP or AD) checked titles and abstracts identified by the search and decided independently which should be studied further. We obtained the full text of all trials selected as being potentially relevant. Two review authors (RACH and RDMH or JP or AD) studied the full texts with the aid of a specially designed form and decided independently which fitted the inclusion criteria. We resolved disagreements about inclusion by discussion, if necessary with the help of the third review author. We have reported all the RCTs identified in the Results section. We have reported relevant non-randomised trials in the Discussion.

Data extraction and management

Two review authors (RACH, and RDMH or JP or AD) independently extracted data on characteristics of included trials and trials outcomes and entered this information into specially designed forms. The review authors compared the forms and resolved disagreements by reference to the original reports. We attempted to obtain missing data from the trial authors. Additionally, for two trials that involved two review authors as trial authors, two other review authors (RB and AD), who had not been involved in the trials, independently extracted data using data extraction forms. For trials requiring translation, the translator extracted data into a data extraction form.

Assessment of risk of bias in included studies

Two review authors (RACH, and RDMH or JP or AD) independently assessed the risk of bias in each identified RCT using specially designed forms, using the methods described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Hig-

gins 2011a). A third review author (RB) independently assessed risk of bias and data extraction for Bensa 2000 and Pritchard 2003 as these trials involved two review authors as trial authors. We considered the following attributes: sequence generation, allocation concealment, blinding of participants and medical personnel, blinding of outcome assessment, completeness of follow-up, freedom from selective reporting and other sources of bias. We graded these items as at low, high or unclear risk of bias and described the evidence on which we based our conclusions in a 'Risk of bias' table. If the assessments differed, we obtained agreement by consensus, if necessary in consultation with a third review author.

Measures of treatment effect

For dichotomous outcomes, such as 'improvement by one or more GBS disability grade after four weeks', we used Review Manager 5 (Review Manager 2014), to calculate a risk ratio (RR). For continuous outcomes we tested the significance of the difference between each pharmacological treatment and placebo, no treatment or other treatments by calculating the mean difference (MD). This method of calculating the outcome is a more sensitive measure than change in proportions of participants improved. We expressed uncertainty with 95% confidence intervals (CIs). For time-to-event measures we used the median (95% CI), median (range) or mean (standard deviation (SD)), depending on how the data were presented in the trials.

Unit of analysis issues

If in future we identify trials where multiple trial arms are reported in a single trial, we will include only the treatment arms relevant to the review topic. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will follow guidance in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting (Higgins 2011b). Our preferred approach will be to halve the control group.

Dealing with missing data

We sought missing data from the trial authors and reported its absence when not available.

Assessment of heterogeneity

Where there were multiple trials of one intervention and evidence of significant heterogeneity between trials had been detected using the I^2 statistic (Higgins 2003), we sought explanations for the heterogeneity.

We planned to used the rough guide to interpretation as outlined in Chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2011), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We avoided the use of absolute cut-off values, but interpreted the I^2 statistic in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for I^2 statistic; Deeks 2011).

Assessment of reporting biases

If there had been sufficient trials of one intervention we would have constructed funnel plots and inspected them for evidence of publication bias.

Data synthesis

We conducted a meta-analysis using the data from the two eculizumab trials, where we calculated a pooled treatment effect across trials using Review Manager 2014.

We used a random-effects model in Review Manager 2014, as this is usually a more conservative approach and carried out a sensitivity analysis using a fixed-effect model.

Summary of findings and assessment of the certainty of the evidence

We provided a 'Summary of findings' table for each comparison and reported in them the primary and secondary outcomes for this review. We used the five GRADE considerations (trial limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence (trials that contribute data for the prespecified outcomes), according to methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We based decisions on downgrading for imprecision due to small trial size on the 95% CIs, which is considered a reasonable approach in rare diseases. We would have resolved disagreements by discussion or by involving another review author. We considered RCTs as high-certainty evidence if the five factors above were not present to any serious degree, but downgraded the certainty to moderate, low or very low if any of them were present. We downgraded the certainty of the evidence once if a GRADE consideration was serious and twice if very serious. We used GRADEpro GDT software to prepare the tables (GRADEpro GDT). Using our assessments we drew conclusions about the certainty of the evidence within the text of the review.

Subgroup analysis and investigation of heterogeneity

We would have liked to examine the effect of treatments in the following subgroups, chosen because of their prognostic importance in previous prospective trials.

- Younger and older participants (children aged less than 18 years; adults from 18 to 49 years of age; adults aged 50 years or more).
- Participants more severely or less severely aLected (able to walk (GBS disability grades 1 to 3), unable to walk (grade 4), or requiring ventilation (grade 5) at randomisation).
- Participants having or not having a documented relevant sensory deficit on routine neurological examination at randomisation (symptoms alone would have been ignored).
- Participants having or not having a history of diarrhoea (gastroenteritis) within the six weeks before the onset of neuropathic symptoms.
- Time from onset of symptoms of neuropathy to start of treatment (seven days or less after onset, more than seven and up to 14 days after onset, and more than 14 days after onset).
- Axonal versus demyelinating forms of GBS, defined by neurophysiological criteria (Hadden 1998).

No information was available for any of these subgroups.

Sensitivity analysis

If there had been more than one trial of one intervention we would have performed sensitivity analyses in which trials that had a high risk of bias were omitted from the meta-analysis. We compared random-effects and fixed-effect analyses.

RESULTS

Description of studies

Results of the search

The previous versions of this review included four completed RCTs. Our new database search for this update yielded 467 records and we found an additional record in the WHO International Clinical Trials Registry Platform. After deduplication, we screened 368 references. Thirty-six were already listed in the review; we therefore screened 332 records and excluded 319, which were not relevant or not RCTs. We assessed 13 full-text articles for eligibility. We included two new RCTs (previously identified as ongoing), each of eculizumab in severe GBS (ICA-GBS 2017; JET-GBS 2018). These accounted for 12 references. We excluded a third trial, of hyperbaric oxygen and acupuncture in children

because of lack of clear evidence of randomisation (Ding 2015). Figure 1 illustrates the trial selection process.

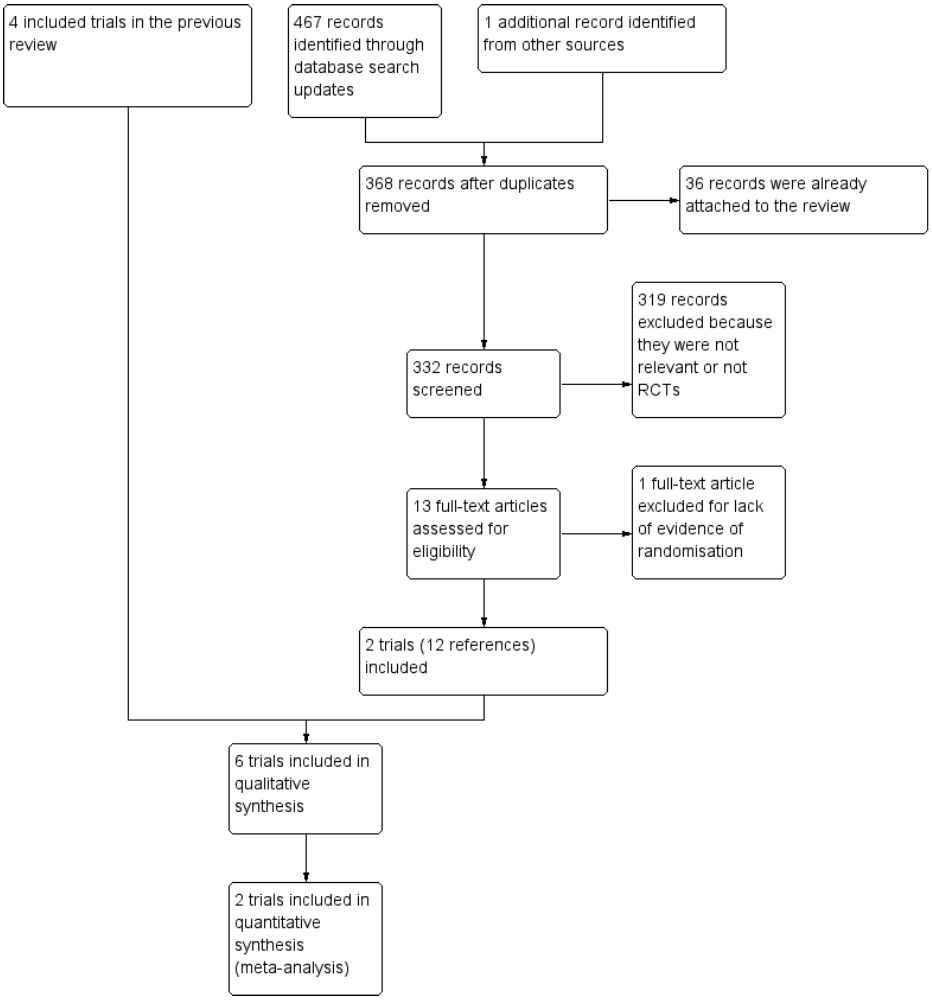

Figure 1. Study flow diagram

ClinicalTrials.gov included an open, non-randomised, phase I trial of cord blood regulatory T cells that has not yet been started (NCT03773328), an open-label, single-arm, phase I trial of a C1q inhibitor that has started recruitment (NCT04035135), and an open-label, single-arm, multicenter, phase II trial of imlifidase, an immunoglobulin G (IgG)-degrading enzyme, that has also started recruitment (NCT03943589). We did not identify any ongoing RCTs or quasi-randomised trials during our searches.

Included studies

We included four small, randomised, placebo-controlled, double-blind trials, one of IFNb-1a (Pritchard 2003), one of brain-derived neurotrophic factor (BDNF) (Bensa 2000), and two phase II clinical trials of the complement inhibitor eculizumab (ICA-GBS 2017; JETGBS 2018). We also included two trials that were not double-blind: one small, randomised, open, controlled trial comparing CSF filtration with plasma exchange (Wollinsky 2001), and another comparing the Chinese herbal medicine tripterygium polyglycoside with intravenous corticosteroids (Zhang 2000). The trials included a total of 151 participants with acute GBS aged 16 years or more. Disease severity at randomisation was severe, defined as the inability to walk unaided, in all the trials, except that Zhang 2000 also included participants who were still able to walk unaided. Included participants came from hospitals in the UK, Canada, China, Germany and Japan. The funding source of Zhang 2000 is not known. The other trials were all investigator-led but either the trial was funded by a drug company (Bensa 2000; ICA-GBS 2017; Pritchard 2003), or the intervention was paid for by a pharmaceutical company (JET-GBS 2018; Wollinsky 2001).

Excluded studies

We excluded 32 studies. The most common reasons for exclusion were that the diagnosis was not clear or was not GBS, or that the intervention was not a pharmacological treatment. We reported non-randomised trials of pharmacological treatments for GBS with sufficient description of the diagnosis, treatment, and pretreatment and outcome disability grade in both the Characteristics of excluded studies and the Discussion. These included one historically-controlled trial of mycophenolate mofetil (Garssen 2007), and other non-randomised case series or case reports of other agents (Bos Eyssen 2011; Hammond 1993). We reported other excluded studies only in Characteristics of excluded studies.

Studies awaiting assessment

There are no trials to report that are awaiting assessment.

Risk of bias in included studies

We have summarised the risk of bias for the included trials in Figure 2 and Characteristics of included studies.

The very small trials of IFNb-1a (Pritchard 2003) and BDNF (Bensa 2000) had a high risk of bias for blinding of outcome assessment and baseline imbalance, respectively but were otherwise at low risk of bias.

The trial of CSF filtration had a high risk of bias for allocation concealment, blinding of outcome assessment and other bias (from individual analysis issues), an unclear risk of bias for blinding of participants and medical personnel, and a low risk of bias for random sequence generation and selective outcome reporting (Wollinsky 2001).

The trial of tripterygium polyglycoside had a high risk of bias for blinding of medical personnel, participants and outcome assessors and an unclear risk of bias in other domains (Zhang 2000).

Both eculizumab trials were at low risk of bias in all respects (ICA-GBS 2017; JET-GBS 2018).

Effects of interventions

See: **Summary of findings for the main comparison** Interferon beta-1a versus placebo for Guillain-Barré syndrome; **Summary of findings 2** Brain-derived neurotrophic factor versus placebo for Guillain-Barré syndrome; **Summary of findings 3** Cerebrospinal fluid filtration versus plasma exchange for Guillain-Barré syndrome; **Summary of findings 4** Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome; **Summary of findings 5** Eculizumab versus placebo for Guillain-Barré syndrome

Interferon beta-1a versus placebo

One small RCT (Pritchard 2003), with a low risk of bias other than that for blinding (see Figure 2; Characteristics of included studies; Summary of findings for the main comparison), randomised 13 participants with severe early GBS (unable to walk without aid and within two weeks from the onset of symptoms, mean disability grade 4.1) to IFNb-1a (Rebif) and six to placebo (mean disability grade 4.0). The drug or placebo was given by subcutaneous injection three times a week starting with 22 µg per injection for the first week and continuing with 44 µg for the subsequent 23 weeks. Participants stopped treatment if they became able to walk without aid (grade 2). The trial stopped after 24 weeks.

Primary outcome: improvement in disability grade four weeks after randomisation

The mean improvement in disability grade (Hughes 1978), after four weeks was 1.2 grades (SD 1.6) in the IFNb-1a group and 1.3 grades (SD 1.5) in the placebo group. Thus, the difference in mean change in disability grade after four weeks was 0.10 of a grade less improvement in the IFNb-1a group (MD −0.10, 95% CI −1.58 to 1.38; 1 RCT, 19 participants; very low-certainty evidence; Analysis 1.1).

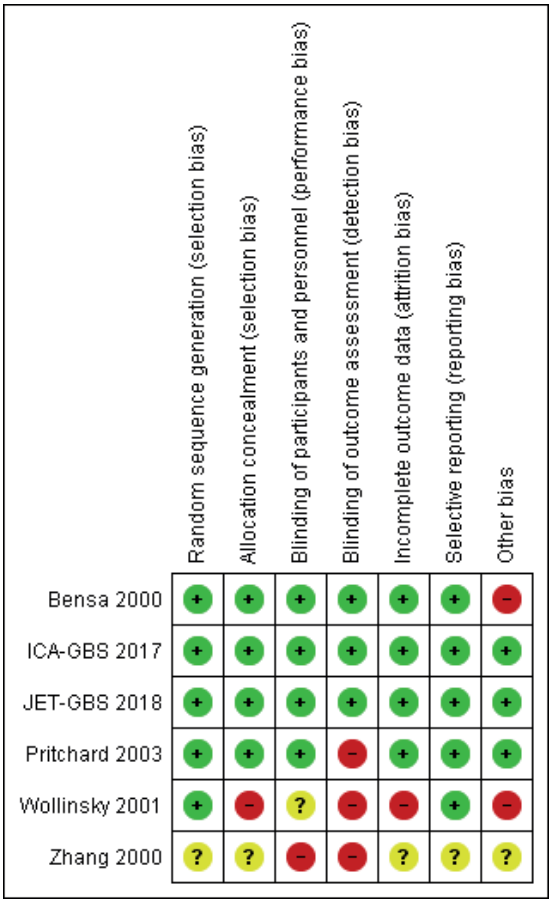

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial.

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

Correspondingly, the RR of improvement by one or more GBS disability grades after four weeks was 1.08 in favour of IFNb-1a (95% CI 0.42 to 2.77; 1 RCT, 19 participants; very low-certainty evidence; Analysis 1.2).

Improvement by six or more centile points in the Inflammatory Raschbuilt Overall Disability Scale (I-RODS) after four weeks

Pritchard 2003 predated I-RODS (Draak 2014).

Time from randomisation until recovery of unaided walking
The median time (95% CI) to unaided walking was 59 (16 to infinity) days in the IFNb-1a group and 18 (11 to 70) days in the placebo group (1 RCT, 19 participants; very low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)
Pritchard 2003 did not measure this outcome.

Death
The RR for death was 1.50 greater in the IFNb-1a group (95% CI 0.07 to 32.29; 1 RCT; 19 participants; low-certainty evidence; Analysis 1.3).

Death or disability (inability to walk without aid) after 12 months
Pritchard 2003 did not measure this outcome.

Serious adverse events
The RR for having one or more serious adverse events was 0.92 (95% CI 0.23 to 3.72; 1 RCT, 19 participants; very low-certainty evidence), and thus was slightly lower in the IFNb-1a group (Analysis 1.4).

Other outcome measures
None of the other differences in selected outcome measures reported by the trial authors, listed in the Included studies, was significantly diLerent.

Pritchard 2003 was much too small to exclude clinically important benefit or harm from IFNb-1a.

Brain-derived neurotrophic factor versus placebo
One very small RCT (Bensa 2000), with a low risk of bias in all domains except for other bias (see Figure 2; Characteristics of included studies; Summary of findings 2), randomised six participants with severe early GBS to BDNF (four disability grade 5 and two grade 4) and four to placebo (all grade 4). The trial was terminated early because the manufacturer withdrew the drug after it was found to be ineffective in a trial for motor neuron disease. The drug, r-metHuBDNF 25 µg/kg, or placebo was given by daily subcutaneous injection for 24 weeks. Participants stopped treatment upon reaching GBS disability grade 2. None of the outcomes reported was significantly different between the groups.

Primary outcome: improvement in disability grade four weeks after randomisation
The mean improvement in disability grade (Hughes 1978) after four weeks was 1.0 grade (SD 1.1) in the BDNF group and 0.25 grade (SD 1.71) in the placebo group, thus resulting in 0.75 of a grade more improvement in the BDNF group than in the placebo group (95% CI −1.14 to 2.64; 1 RCT, 10 participants; very low-certainty evidence; Analysis 2.1).

Secondary outcomes
Improvement by one or more GBS disability grade after four weeks

The RR for improvement by one or more GBS disability grade after four weeks was the same in both groups (RR 1.00, 95% CI 0.28 to 3.54; 1 RCT, 10 participants; very low-certainty evidence; Analysis 2.2).

Improvement by six or more centile points in the Inflammatory Raschbuilt Overall Disability Scale (I-RODS) after four weeks
Bensa 2000 predated I-RODS (Draak 2014).

Time from randomisation until recovery of unaided walking
The time to unaided walking had a median (95% CI) value of 84 (4 to infinity) days in the BDNF group and 84 (2 to infinity) in the placebo group (10 participants; very low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)
Four of six (67%) participants in the BDNF group and one of four (25%) participants in the placebo group required mechanical ventilation during follow-up. Median times (range) from randomisation until discontinuation of ventilation were estimated from Figure 1 in the paper. Median time to discontinuation of ventilation for the participants in the BDNF the placebo group required mechanical ventilation during follow-up as a probable result of neurological deterioration, and this was discontinued after four weeks from randomisation (N = 5; very low-certainty evidence).

Death
The RR for death was lower in the BDNF group (RR 0.67, 95% CI 0.06 to 7.85; 1 RCT, 10 participants; very low-certainty evidence; Analysis 2.3).

Death or disability (inability to walk without aid) after 12 months
The RR for death or disability after 12 months was greater with BDNF than with placebo (RR 1.33, 95% CI 0.17 to 10.25; 1 RCT; 10 participants; very low-certainty evidence; Analysis 2.4).

Serious adverse events

In the BNDF group, three of six participants experienced serious adverse events, in comparison to two of four participants in the placebo group (RR 1.00, 95% CI 0.28 to 3.54; 1 RCT, 10 participants; very low-certainty evidence; Analysis 2.5).

Other outcome measures reported

Bensa 2000 did not report any significant differences for the disability grade and arm grade at any of the follow-up assessments. Other prespecified outcome measures included the Medical Research Council (MRC) sum score, time taken to walk 10 m, grip strength, vital capacity and haematology, clinical chemistry and urine analysis, but Bensa 2000 did not provide results for these measures (Included studies).

Bensa 2000 was much too small to exclude clinically important benefit or harm from BDNF.

Cerebrospinal fluid filtration versus plasma exchange

One RCT (Wollinsky 2001), with a high risk of bias (see Figure 2; Characteristics of included studies; Summary of findings 3), compared 17 participants treated with CSF filtration with 20 who received a conventional course of five plasma exchanges, removing a total of 200 mL/kg to 250 mL/kg of plasma altogether. CSF filtration consisted of removing, filtering and re-infusing 30 mL to 50 mL CSF five to six times a day for between 5 and 15 consecutive days. Of the 17 participants treated with CSF filtration, four had disability grade 5 and 13 disability grade 4 at randomisation. Of the 20 who received plasma exchanges, two had disability grade 5 and 18 had disability grade 4 at randomisation. The outcomes selected for this review showed no significant differences between the groups.

Primary outcome: improvement in disability grade four weeks after randomisation

The mean improvement in disability grade (Hughes 1978) after four weeks was almost equal in the CSF filtration and the plasma exchange groups (MD 0.02, 95% CI −0.62 to 0.66; 1 RCT, 37 participants; very low-certainty evidence; Analysis 3.1).

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

Similarly, the number of participants with one or more grade of improvement after four weeks was almost equal in both groups (RR 0.94; 95% CI 0.48 to 1.84; 1 RCT, 37 participants; very low-certainty evidence; Analysis 3.2). These CIs were consistent with either a halving or almost doubling of the number.

Improvement by six or more centile points in the Inflammatory Raschbuilt Overall Disability Scale (I-RODS) after four weeks
Wollinsky 2001 predated I-RODS (Draak 2014).

Time from randomisation until recovery of unaided walking
The time until recovery of unaided walking in the surviving participants was shown by the authors in a Kaplan-Meier figure of an analysis from which nine participants were censored at different times. From this published figure, we estimated the median (range) time until recovery of unaided walking as 42 (13 to 433) days in the CSF filtration group and 90 (6 to 420) days in the plasma exchange group. The trial authors commented that the times were similar in both groups (37 participants; very low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)
Wollinsky 2001 did not measure this outcome.

Death
There was one death in each group resulting in a RR of 1.18 in favour of the plasma exchange group (95% CI 0.08 to 17.42; 1 RCT, 37 participants; low-certainty evidence; Analysis 3.3).

Death or disability (inability to walk without aid) after 12 months
Wollinsky 2001 did not measure this outcome.

Serious adverse events
Four participants in the plasma exchange group had serious adverse events compared with none in the CSF filtration group (RR 0.13, 95% CI 0.01 to 2.25; 1 RCT; 37 participants; very low-certainty evidence; Analysis 3.4). One participant in each group had side eLects leading to cessation of treatment (RR 1.18, 95% CI 0.08 to 17.42; 1 RCT, 37 participants; very low-certainty evidence; Analysis 3.5).

Other outcome measures reported
We found no important diLerences in the other outcomes measured by the trial authors and listed in the Included studies.

The small sample sizes in Wollinsky 2001 prevent us from drawing conclusions about the relative eLicacy of CSF filtration and plasma exchange.

As explained in the Discussion, this treatment is no longer being used because of the danger of producing an inflammatory reaction in the CSF.

Tripterygium polyglycoside versus intravenous high-dose corticosteroids

One RCT (Zhang 2000), with an unclear risk of bias except for blinding, which was at high risk (see Figure 2; Characteristics of included studies; Summary of findings 4), compared 22 participants treated with the Chinese herbal medicine tripterygium polyglycoside (randomisation disability grade 2 in six participants, grade 3 in 12 participants and grade 4 in four participants) with 21 participants treated with high-dose corticosteroids (randomisation disability grade 2 in seven participants, grade 3 in 11 participants and grade 4 in three participants).

Primary outcome: improvement in disability grade four weeks after randomisation

Zhang 2000 did not report improvement in disability grade (Hughes 1978) four weeks after randomisation, but after eight weeks 20 of 22 participants treated with tripterygium polyglycoside had improved by one or more GBS disability grade compared with 13 of 21 treated with high-dose corticosteroids: RR 1.47 (95% CI 1.02 to 2.11; 1 RCT, 43 participants; very low-certainty evidence; Analysis 4.1).

Secondary outcomes

Adverse events

Zhang 2000 reported only one adverse event: gastrointestinal toxicity in one person treated with tripterygium polyglycoside (RR 2.87, 95% CI 0.12 to 66.75; 1 RCT, 43 participants; very low-certainty evidence; Analysis 4.2).

Zhang 2000 did not measure other clinical outcomes nor the outcomes for this review.

Eculizumab versus placebo

Two trials investigated eculizumab in comparison to placebo (ICAGBS 2017; JET-GBS 2018).

ICA-GBS 2017 had a low risk of bias (Figure 2; Characteristics of included studies; Summary of findings 5). The trial was funded by the company that produced the drug. It randomised eight participants with acute GBS and who were unable to walk independently to eculizumab (five participants, mean disability grade 4) or placebo (three participants, mean disability grade 4). Eculizumab or placebo was provided intravenously once weekly for the first four weeks. Additionally, all participants were treated with a standard course of IVIg (0.4 g/kg/day for five days) and ciprofloxacin either 400 mg oral or 500 mg intravenously once weekly for the first 10 weeks. The trial had a 26-week follow-up period. JET-GBS 2018 had similar inclusion and exclusion criteria and trial protocol to ICA-GBS 2017 (Characteristics of included studies). Eculizumab or placebo was provided intravenously once weekly for the first four weeks, with standard IVIg treatment and

antibiotic prophylaxis. Antibiotic prophylaxis was continued until eight weeks after the last trial drug administration. Twenty-three participants were randomised to receive eculizumab (mean disability grade at baseline 3.9), and 11 to receive placebo (mean disability grade 4.0). The trial had a 24-week follow-up period.

Primary outcome: improvement in disability grade four weeks after randomisation

After four weeks, the mean difference in disability grade (Hughes 1978) was −0.23 (95% CI −1.79 to 1.34; I^2 = 71%; 2 RCTs, 40 participants; very low-certainty evidence) in favour of the placebo group (Analysis 5.1; Figure 3).

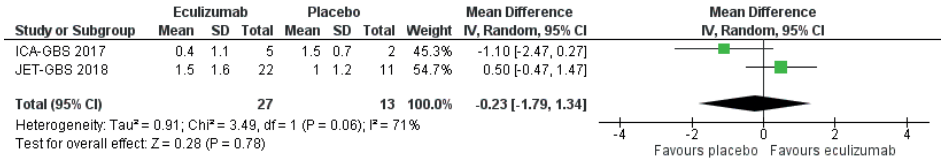

Figure 3. Forest plot of comparison: 5 Eculizumab versus placebo, outcome: 5.1 Improvement in disability grade after 4 weeks.

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

Seventeen of 27 participants in the eculizumab group and nine of 13 participants in the placebo group had improved by at least one disability grade after four weeks (RR 0.85, 95% CI 0.43 to 1.69; I^2 = 36%; 2 RCTs, 40 participants; low-certainty evidence; Analysis 5.2).

Improvement by six or more centile points in the Inflammatory Raschbuilt Overall Disability Scale (I-RODS) after four weeks

Both trials also recorded the Inflammatory Rasch-built Overall Disability Scale (I-RODS) scores for all participants (Draak 2014). Both defined a clinically relevant improvement as an improvement of 6 or more points on the centile metric scale (Van Nes 2011). After four weeks, the RR of a clinically relevant improvement on the I-RODS was 0.91 (95% CI 0.38 to 2.16; I^2 = 61%; 2 RCTs, 40 participants; very low-certainty evidence) in favour of the placebo group (Analysis 5.3).

Time from randomisation until recovery of unaided walking

Only ICA-GBS 2017 provided mean time from randomisation until recovery of unaided walking and was 8.5 (SD 6.4) weeks in the eculizumab group and 7.5 (SD 7.8) weeks in the placebo group (7 participants; low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)
In ICA-GBS 2017, two of five participants in the eculizumab group needed mechanical ventilation, while neither of the participants in the placebo group were mechanically ventilated. The median time from randomisation until discontinuation of ventilation was 102 days (range 20 days to 182 days). In JET-GBS 2018, four of 23 participants in the eculizumab group and two of 11 participants in the placebo group needed mechanical ventilation. The median time from randomisation until discontinuation of ventilation was shorter in the group treated with eculizumab (18 days, 95% CI 11.0 to 31.0) than in the group treated with placebo (34 days, 95% CI 27.0 to 41.0). The P value was 0.198 (8 participants; very low-certainty evidence).

Death
Only one participant died. This participant had been treated with eculizumab: the death occurred from sepsis at week 21 and was not deemed due to the trial drug (ICA-GBS 2017). The RR of death was 1.50 (higher with eculizumab than placebo) but with very wide CI (95% CI 0.08 to 26.86, 2 RCTs, 38 participants; low-certainty evidence; Analysis 5.4).

Death or disability (inability to walk without aid) after 12 months
In absence of data for follow-up after one year, we have reported outcomes after six months. At that time, the difference in mean change in disability grade was 0.75 of a grade less improvement in the eculizumab group (95% CI −3.88 to 2.37; I^2 = 87%; 2 RCTs, 38 participants; Analysis 5.5). Correspondingly, 24 of 27 participants in the eculizumab group had improved by at least one disability grade compared with 10 of 11 in the placebo group, RR 1.03 (95% CI 0.78 to 1.36; I^2 = 6%; 2 RCTs, 38 participants; Analysis 5.6).

Both trials also reported the I-RODS scores after six months, which showed an improvement of at least 6 centile points on the I-RODS for all participants (11 of 11) in the placebo group and for 25 of 26 participants in the eculizumab group (RR 0.99, 95% CI 0.83 to 1.17; I^2 = 0%; 2 RCTs, 37 participants; Analysis 5.7).

Four of 27 participants in the eculizumab group and one of 11 participants in the placebo group were either not able to walk independently or were dead after six months (RR 1.21, 95% CI 0.15 to 10.11; I^2 = 23%; 2 RCTs, 38 participants; very low-certainty evidence; Analysis 5.8).

Serious adverse events
All the participants in both the eculizumab and the placebo groups had adverse events (RR 1.00, 95% CI 0.88 to 1.14; I^2 = 0%; Analysis 5.9). Participants on eculizumab were

possibly more likely to have serious adverse events than those on placebo: RR 1.90, 95% CI 0.34 to 10.50; I^2 = 0%; 2 RCTs, 41 participants; low-certainty evidence; Analysis 5.10). Participants with serious adverse events with a possible causal relationship to the trial drug were one with a lower respiratory tract infection that prevented trial drug administration in ICA-GBS 2017, and one with anaphylaxis and another with an intracranial abscess following a haemorrhage in JET-GBS 2018.

Heterogeneity

We found a high level of heterogeneity for Analysis 5.1, Analysis 5.3, and Analysis 5.5. Both trials used the same trial protocol and intervention, but we identified some differences in participant characteristics between the two trial populations that might have contributed to this heterogeneity, including the geographic location, antecedent illness, electrophysiological subtypes and presence of anti-ganglioside antibodies. We did not perform a subgroup analysis because of the small numbers that would have been included in each of the subgroups.

Sensitivity analyses

Table 1 shows a sensitivity analysis comparing random-effects and fixed-effect models. For most analyses, we found similar results with both approaches. However, for improvement on the I-RODS after four weeks and for mean improvement in disability grade after six months we found a reverse effect when we compared the fixed-effect to the random-effects approach. After four weeks, the RR of improvement by 6 or more centile points on the I-RODS was 1.07 (95% CI 0.75 to 1.54) with a fixed-effect model, and 0.91 (95% CI 0.38 to 2.16) with a random-effects model. After six months, the mean improvement in disability grade with a fixed-effect approach was 0.24 grade (95% CI −0.55 to 1.03) more in the eculizumab group than in the placebo group, while this was 0.75 grade (95% CI −3.88 to 2,37) less with a random-effects approach (Table 1). However, differences between the treatment groups were still not significant and the CIs encompass the possibility of clinically important differences in either direction. Furthermore, the level of heterogeneity was the same with either approach.

Other outcome measures

No clinically meaningful differences were reported in the other outcomes listed in the Included studies, except for the proportion of participants that were able to run at week 24 in JET-GBS 2018. Seventeen of 23 participants in the eculizumab group were able to run after 24 weeks compared to two of 11 in the placebo group (P = 0.004; JET-GBS 2018).

Due to the small sample sizes results were very imprecise. Therefore, a clinically important benefit or harm from eculizumab cannot be excluded.

Table 1. Sensitivity analysis eculizumab versus placebo: random-effects versus fixed-effect analysis

Analysis	Outcome	Random-effects	Random-effects heterogeneity	Fixed-effect	Fixed-effect heterogeneity
Analysis 5.1	Improvement in disability grade af-ter 4 weeks	MD −0.23 (95% CI −1.79 to 1.34)	71%	MD −0.04 (95% −0.83 to 0.75)	71%
Analysis 5.2	Improvement by 1 or more disability grades after 4 weeks	RR 0.85 (95% CI 0.43 to 1.69)	36%	RR 0.92 (95% 0.58 to 1.47)	36%
Analysis 5.3	Improvement by 6 or more points on the I-RODS score after 4 weeks	RR 0.91 (95% CI 0.38 to 2.16)	61%	RR 1.07 (95% 0.75 to 1.54)	61%
Analysis 5.4	Death	RR 1.50 (95% CI 0.08 to 26.86)	Not applicable	RR 1.50 (95% 0.08 to 26.86)	Not applicable
Analysis 5.5	Improvement in disability grade after 6 months	MD −0.75 (95% CI −3.88 to 2.37)	87%	MD 0.24 (95% −0.55 to 1.03)	87%
Analysis 5.6	Improvement by 1 or more grades after 6 months	RR 1.03 (95% CI 0.78 to 1.36)	6%	RR 0.99 (95% 0.76 to 1.28)	6%
Analysis 5.7	Improvement by 6 or more points on the I-RODS score after 6 months	RR 0.99 (95% CI 0.83 to 1.17)	0%	RR 0.99 (95% 0.82 to 1.19)	0%
Analysis 5.8	Death or disability after 6 months	RR 1.21 (95% CI 0.15 to 10.11)	23%	RR 1.40 (95% 0.27 to 7.26)	23%
Analysis 5.9	Participants with adverse events	RR 1.00 (95% CI 0.88 to 1.14)	0%	RR 1.00 (95% 0.86 to 1.16)	0%
Analysis 5.10	Participants with serious adverse events	RR 1.90 (95% CI 0.34 to 10.5)	0%	RR 2.13 (95% 0.43 to 10.61)	0%

CI: confidence interval; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RR:** risk ratio

DISCUSSION

Summary of main results

This review identified and analysed six small RCTs investigating five different interventions in a total of 151 participants: each provided only very low- or low-certainty evidence. In a trial with 19 participants comparing IFNb-1a with placebo there was no clinically meaningful difference in improvement in disability grade after four weeks (Pritchard 2003). In a trial with 10 participants comparing BDNF with placebo, on average there was more improvement in disability grade after four weeks with BDNF, but the results were also consistent with much more or much less improvement (Bensa 2000). In a trial with 37 participants, there was no clinically meaningful difference between plasma exchange and CSF filtration in improvement in disability grade after four weeks

(Wollinsky 2001). In a trial comparing the Chinese herbal medicine tripterygium polyglycoside with high-dose corticosteroids, the primary outcome for this review was not available but those receiving tripterygium polyglycoside possibly had more improvement in disability grade after eight weeks (Zhang 2000). The finding, if real, could have been due to a beneficial effect of tripterygium polyglycoside or a deleterious effect of corticosteroids. A Cochrane Review assessing the efficacy of corticosteroids for the treatment of people with GBS concluded that corticosteroids given alone do not have a significant beneficial or harmful effect, so a possible beneficial effect of tripterygium polyglycoside was more likely (Hughes 2016). In two trials with altogether initially 42 participants comparing eculizumab with placebo, there was no clinically meaningful difference in improvement in disability grade after four weeks (ICA-GBS 2017; JET-GBS 2018). Furthermore, we did not find clinically important differences in any of the secondary outcome measures selected for this review in any of the six trials. However, sample sizes were small and therefore clinically important benefit or harm cannot be excluded.

Overall completeness and applicability of evidence

The evidence from published RCTs is likely to be complete because we have made use of Cochrane methods to search the literature. The evidence from the case studies and series described below cannot be complete since there is no known search strategy that will detect all published non-randomised trials.

Certainty of the evidence

We graded the certainty of the evidence from the RCTs as either low or very low due to:

- the very small number of participants randomised in all trials resulting in either serious or very serious imprecision;
- trial limitations including risk of bias due to the potential for unblinding (Pritchard 2003), an unblinded trial design (Wollinsky 2001; Zhang 2000), or baseline imbalances in disease severity (Bensa 2000); and
  - inconsistency across trials resulting in substantial heterogeneity (ICA-GBS 2017; JET-GBS 2018).

Need for more trials

The long duration of illness, severe persistent disability and continued mortality from GBS emphasise the need for better treatments. Existing treatments with IVIg and plasma exchange are partially effective (Willison 2016). Where these are available, it is unethical to compare new treatments against placebo. The evidence in this systematic review is of such low certainty that it does not establish whether any of the treatments reviewed are beneficial or harmful. This emphasises the dearth of evidence on treatments other than IVIg, plasma exchange and corticosteroids for GBS, but also provides a basis on

which future trials of these regimens could be launched. One major ongoing interest is in pursuing trials of complement inhibitors such as eculizumab because of strong experimental evidence of complement-fixing antibodies to gangliosides in the acute motor axonal neuropathy form of GBS (Willison 2016). An open trial of a C1q inhibitor that will be administered in conjunction with standard IVIg treatment is in progress (NCT04035135). But other approaches besides complement inhibition are also being considered. A multi-centre, open trial of imlifidase, an enzyme that rapidly breaks down IgG, is in progress. The trial plans to recruit up to 30 participants with severe acute GBS and treat them with imlifidase on day 1 and standard IVIg on days 3 to 7. Disease course and outcome will subsequently be compared with matched controls from the International GBS Outcome Study (IGOS; NCT03943589; Jacobs 2017). Furthermore, an open, dose-ranging trial to assess safety and applicability of cord-blood-derived T-regulatory cell product is also being planned (NCT03773328).

Need for better outcome measures

Future trials will need to use the standard GBS disability grade scale to facilitate comparison with previous trials. At the last update of this review we stipulated that we would incorporate the new I-RODS scale in this update (Draak 2014), and we have included it as a secondary outcome. We also recommended the use of minimum clinically important differences (MCIDs) in the selected outcome measures (Merkies 2010). Although almost all the RCTs of GBS that have been conducted used the GBS disability scale, its MCID has never been calculated. One trial that compared plasma exchange with IVIg used less than half a grade difference as the arbitrary definition of equivalence (Plasma 1997). The MCID in IRODS has been developed but not validated. We therefore accepted the arbitrary threshold of 6 points on the centile conversion of IRODS used by the authors of ICA-GBS 2017 and JET-GBS 2018 in our calculations for this review. This decision will need revision in future versions of this review if ongoing work to define the MCIDs of I-RODS prefers a different calculation for this outcome. With more experience, a MCID in I-RODS may become preferred as the primary outcome for this and other reviews of GBS treatments, but a decision about such a change must await the next update.

Potential biases in the review process

This review might be biased by the fact that one of the review authors, RACH, co-authored two of the six included RCTs with two other review authors; one with JP and one with RDMH. We took steps to address this: two review authors who were independent of these trials also extracted and checked data, and independently assessed risk of bias. Two of the review authors (RACH, RDMH) have received funding from companies that manufacture medications that are used or might be used for treating GBS (see Declarations of

interest). RB is Managing Editor of Cochrane Neuromuscular. The editorial process of the review update from peer review to publication was conducted independently.

Not all prespecified outcomes selected for this review were provided by the included trials. Zhang 2000 only reported disability at eight weeks, and neither eculizumab trial reported death or disability at 12 months (ICA-GBS 2017; JET-GBS 2018). In the absence of data at these prespecified time points, we decided to report data at the nearest available time points. All six RCTs were too small to detect rare serious adverse events.

Agreements and disagreements with other studies or reviews

Observational studies of included interventions

There are no observational studies of IFNb-1a in GBS apart from two single case reports of improvement following its use combined with other treatments (Créange 1998; Schaller 2001): such improvement could merely reflect the natural history of the disease. The evidence in this review is insufficient to either support or discourage further investigation of IFNb-1a for GBS.

There are no other case reports or series investigating the use of BDNF in GBS. The use of neurotrophic factors to protect nerves from axonal degeneration and to encourage regeneration remains a possible strategy. Pursuit of this line of research would require investigation of the optimal combination, route and dose of trophic factors.

Before the trial of CSF filtration was performed, a series of 24 people with acute GBS had received this treatment: their median time to improve one GBS disability grade was 19 days and their median time to walk unaided was 42 days (Wollinsky 1995). Insufficient information was published for us to judge the clinical significance of these findings and, in the absence of contemporary controls, we are not able to draw conclusions from this series. There have been no subsequent published case reports or series of the use of CSF filtration in GBS. Although there were no serious adverse events in the Wollinsky 2001 trial, CSF lymphocytic pleocytosis was noted in all 14 people in whom this was assessed. There is a theoretical risk that CSF filtration may cause meningitis. Meningitis was observed in one participant in the trial but was attributed to an earlier lumbar puncture. However, granulocytic reactions have been observed in up to 20% of people with GBS treated with CSF filtration and the procedure has been discontinued in the department responsible for this trial (Ludolph 2010 [pers comm]). The treatment is not known to have been pursued since then and concern about causing meningitis discourages further pursuit of this treatment.

There are no other reports of the use of tripterygium polyglycoside in GBS, and its active ingredients and mechanisms of action are unknown. In the Zhang 2000 trial, tripterygium polyglycoside lowered the inflammatory cytokine interleukin-6 concentration in the serum more than corticosteroids. If it were desired to pursue this treatment it would be necessary to identify the active ingredient or ingredients in the herbal extract.

There is a single report of recovery following the use of eculizumab in a child with GBS, although the diagnostic criteria were not specified (Ram 2014). There have not been any other trials, case series or reports of the use of complement inhibitors in GBS. Because of strong experimental evidence that complement fixing antibodies are important in some types of GBS, there is continued interest in pursuing their use in treatment (Goodfellow 2016).

Treatments tested in other studies

Table 2 summarises these studies.

Mycophenolate mofetil

Mycophenolate mofetil has been licensed since 1996 for use "in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in participants receiving allogeneic renal, cardiac or hepatic transplants" (Roche). It is often used in autoimmune diseases but the evidence for its efficacy is limited (Sanders 2008; Burns 2015; Doukaki 2015; Tunnicliffe 2018).

Mycophenolate mofetil has been investigated in one nonrandomised (therefore having a high risk of bias), historically-controlled clinical trial in GBS, which compared 26 participants treated with oral mycophenolate mofetil 1000 mg a day for six weeks with 112 participants who had been treated without the drug in a previous RCT run by the same investigators in the same centres (Van Koningsveld 2004; Garssen 2007). The participants treated with mycophenolate mofetil and the historical controls were simultaneously also treated with IVIg 0.4 g/kg/day and intravenous methylprednisolone 500 mg/day for five consecutive days. There were no meaningful differences between the groups for any of the outcomes measured. The mean change in disability grade was not given. The RR of improving one disability grade after four weeks was 0.91 (95% CI 0.65 to 1.26) less in the mycophenolate mofetil group than in the controls but included the possibility of a better or worse outcome in the mycophenolate mofetil group. There were no meaningful differences in other outcomes measured, which included the ability to walk independently after eight weeks, time to improve one disability grade, need for artificial ventilation, MRC sum score, sensory impairment and death. There are no other case reports or series on the use of mycophenolate mofetil in GBS. Since the dose used

Table 2. Other treatments studied in case reports, case series or other non-randomised study designs

Reference	Regimen	Number treated	Results
Acupuncture and hyperbaric oxygen			
Ding 2015	Quote: "54 cases of GBS admitted to this hospital from March 2009 to October 2013 are selected. They are divided in those ac-cording to their treatment. Both groups received standard medical care, including treatment of infections, clearance of airway, maintenance of respirato-ry function, infusion of gamma globulin, corticosteroids, and B vitamins. The treated group had in addition hyperbaric oxygen and acupuncture."	27 children in each group	At the end of treatment participants were classified as "Cured (resolution of respiratory and global paralysis, no other symptom, normal 4-limb power) Good response (sig-nificant improvement of respiratory and global paralysis, 4-limb power raised by 2 grades [not defined] without being normal). Some response (fundamental improvement of respiratory and global paralysis, 4-limb power raised by 1 grade without being normal) No response (no improvement of respiratory and global paralysis, 4-limb power not elevated)." 26 out of 27 in treated group were cured or had a good response compared with 20 out of 27 in the comparison group.
Azathioprine			
Yuill 1970	125 mg/day	1	By 4 weeks: 1 improved By end of follow-up:1 had mild residual deficit Adverse events: none reported
Cyclophosphamide			
Ahuja 1980	100 mg/day route not stated	4	4 improved by 4 weeks 1 stopped because of diarrhoea
Rosen 1976	40 mg/kg IV total over 3-4 days	12 (3 other cases had CIDP)	By 4 weeks:10 improved and 1 died By end of follow-up:3 died, 6 improved and 3 were not followed Adverse events (of all 15 cases including CIDP): 2 had pneumonia, 1 haematuria and 11 alopecia
Mycophenolate mofetil			
Garssen 2007	Oral mycophenolate mofetil 1000 mg a day for 6 weeks All participants and historical controls were treated with IVIg 0.4 g/kg/day and IV methylpred-nisolone 500 mg/day for 5 consecutive days	26 (126 'historical controls')	The mean change in disability grade was not given. The RR of improving 1 disability grade after 4 weeks was 0.91 (95% CI 0.65 to 1.26) less in the mycophenolate mofetil group than in the controls There were no meaningful differences in other outcomes measured (the ability to walk independently after 8 weeks, time to improve 1 disability grade, need for artificial ventilation, MRC sum score, sensory impairment and death)
Murine monoclonal antibody muromonab-CD3 against CD3 antigen on T cells			
Feasby 1991	5 mg muromonab-CD3 IV for 10 days (1 stopped treatment after 3 days because EBV infection diagnosed)	3	1 worse, 1 same and 1 improved by 4 weeks 1 developed aseptic meningitis

Table 2. Other treatments studied in case reports, case series or other non-randomised study designs (*continued*)

Reference	Regimen	Number treated	Results
Selective gut decontamination (SDD)			
Bos Eyssen 2011	Selective decontamination of the digestive tract	54	Retrospective comparison with 70 not treated with selective decontamination of the gut. "The median duration of mechanical ventilation without SDD was 42 days (interquartile range, IQR 25-77 days) versus 29 days with SDD (IQR 17-45 days)." There was no difference in neurological recovery after 6 months from first symptoms. Ventilator-associated pneumonia occurred in 12% (95% CI 2% to 22%) in the treated cohort and in 47% (95% CI 35% to 59%) in the non-treated cohort

CI: confidence interval; **CIDP:** chronic inflammatory demyelinating polyradiculoneuropathy; **EBV infection:** Epstein Barr infection; **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **MRC:** Medical Research Council; **RR:** risk ratio

in the GBS trial was only 1000 mg daily, half the dose usually recommended in other autoimmune conditions, a higher dose should be considered if it were decided to pursue this drug for GBS.

Selective digestive tract decontamination

Selective digestive tract decontamination (SDD) has been tested in a retrospective trial of 124 mechanically ventilated people with GBS comparing people in centres in which SDD was standard treatment with those in other centres where it was not (Bos Eyssen 2011; Table 2). The results suggested that SDD reduced the time on the ventilator, probably by preventing pneumonia. It did not affect neurological recovery after six months. Because of the lack of randomisation and the possibility of unrecognised confounding factors, this result requires confirmation. However, this treatment has been extensively tested in 36 trials involving 6914 people admitted to intensive care units. The participants had a wide variety of conditions and were not necessarily on artificial ventilation. According to the relevant Cochrane Review (D'Amico 2009), a combination of topical and systemic antibiotics significantly reduced respiratory tract infections and mortality whilst topical antibiotics alone significantly reduced respiratory tract infections but not mortality. Our search, conducted for this review on GBS, identified one trial of SDD which included 15 participants with GBS out of its whole sample of 40 participants with various neurological diseases (Hammond 1993). This trial on its own did not show significant reductions in the incidence of infections, the duration of intensive care unit or hospital stay, or mortality. The detailed results of this trial are given in the Characteristics of excluded studies. Separate results for the participants with GBS are not available.

Other treatments studied in case reports and case series

Only three other treatments, azathioprine, cyclophosphamide and the anti-T-cell antibody muromonab-CD3 (OKT3), have been reported in observational studies fulfilling the criteria for inclusion in this Discussion (Table 2). Yuill 1970 reported the use of azathioprine in one person with severe GBS who was left with only mild deficit after five months. Cyclophosphamide was used in two small series of people with GBS. Ahuja 1980 treated four people with severe GBS with 100 mg cyclophosphamide daily (route not stated) starting between 3 and 28 days after onset. All improved and there were no serious adverse events, but one person had to stop treatment because of diarrhoea. Rosen 1976 reported a series of 15 people with GBS treated with cyclophosphamide 40 mg/kg intravenously, 12 of whom had severe GBS. Ten of the 12 improved by four weeks. Three eventually died. Reversible alopecia was common. The muromonab-CD3 monoclonal antibody against T cells was used in three people with severe GBS (Feasby 1991) but the results were not encouraging (Table 2). None of these studies was large enough to confirm or refute clinically significant benefit or harm of any of these interventions. Although the criteria for the diagnosis were not reported in a form that we could verify, we have also included in Table 2 a series of 27 children treated with hyperbaric oxygen and acupuncture for 10 days and compared with 27 children not so treated (Ding 2015). The trial authors concluded that recovery was faster and more complete in the treated children than the comparison group: in the absence of randomisation in the trial authors' description of treatment allocation it would be unsafe to draw conclusions about the efficacy of these combined treatments.

An extensive electronic search in 2016 did not reveal any other trials than those included in this review (Motamed-Gorji 2017). We know of no other systematic reviews of pharmacological treatments other than corticosteroids, IVIg or plasma exchange for GBS.

AUTHORS' CONCLUSIONS

Implications for practice

The certainty of the evidence from randomised controlled trials (RCTs) was low or very low. Five trials of pharmacological agents other than intravenous immunoglobulin, plasma exchange or corticosteroids did not show a clinically important effect in people with Guillain-Barré syndrome (GBS), one testing interferon beta-1a against placebo, one brain-derived neurotrophic factor against placebo, one cerebrospinal fluid filtration against plasma exchange, and two testing eculizumab against placebo. None were large enough to show or refute clinically important benefit or harm. A sixth trial suggested that the Chinese herbal medicine tripterygium polyglycoside might be superior to cor-

ticosteroids in hastening recovery but this requires confirmation. There have been very few observational studies and no randomised trials of other agents.

Implications for research

Since currently used immunotherapy does not prevent prolonged illness and leaves many people with GBS with clinically important residual disability, there is a need to discover and test new treatments. In addition, further work is needed to identify the best disability outcome measure in GBS and define its minimum clinically important change.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bensa 2000		
Methods		Double-blind, parallel-group, RCT
Participants		10 participants aged 18-75 years with GBS fulfilling Asbury 1990 criteria within 14 days from the onset of symptoms and having Hughes 1978 disability grade > 3
Interventions		Daily SC injections of r-metHuBDNF 25 µg/kg (n = 6) or placebo (n = 4) (vehicle for active treatment, i.e. 150 mM sodium chloride with 0.004% polysorbate 20 buffered to pH 7 with 10 mM sodium phosphate) in vials identical in appearance for 24 weeks or until unaided walking achieved, if earlier
Outcomes		Primary: to investigate safety and tolerability of r-metHuBDNF Secondary: to conduct a pilot investigation of the effects of treatment on overall disability after 24 and 48 weeks Assessments were performed on the day of randomisation, and after 2, 4, 8, 12, 24 and 48 weeks, and included performing/determining: general medical examination disability grade arm grade MRC sum score time taken to walk 10 m grip strength vital capacity haematology, clinical chemistry and urine analysis
Funding source		Amgen funded the trial and provided the drug and placebo
Declarations of interest		Not given in the paper but the trial authors had no relationship with Amgen other than funding of the trial.
Notes		Investigators intended to randomise 14 participants to r-metHuBDNF and 7 to placebo but the trial was curtailed prematurely because the manufacturer removed the drug from the market after negative re-sults in a trial of its use in motor neuron disease Dates: not given Location: UK and Canada
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was performed from a computer-generated table of ran-dom numbers known only to the trial statistician and hospital pharmacy.

Treatment

Allocation concealment (selection bias)	Low risk	Quote: "The pharmacist dispensed the coded medication that consisted of r-metHuBDNF 25 µg/kg or placebo in vials identical in appearance. Only the trial statistician and the pharmaceutical company knew the identity of the con-tents" Quote: "The patients were randomised by opening an opaque sealed envelope that contained the code number of treatment to be received."
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Quote: "The pharmacist dispensed the coded medication that consisted of r-metHuBDNF 25 µg/kg or placebo in vials identical in appearance. Only the tri-al statistician and the pharmaceutical company knew the identity of the contents"
Blinding of outcome as-sessment (detection bias) All outcomes	Low risk	Quote: "The pharmacist dispensed the coded medication that consisted of r-metHuBDNF 25 µg/kg or placebo in vials identical in appearance. Only the trial statistician and the pharmaceutical company knew the identity of the contents"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants and outcomes are reported. 2 participants died: 1 in the BDNF group 34 weeks after randomisation and 1 in the placebo group before week 2 of the trial
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	BDNF participants had more severe disease and were randomised later.

ICA-GBS 2017	
Methods	Parallel-group, single-centre (in 4 local hospitals), RCT with 2:1 active:placebo allocation
Participants	8 participants with GBS fulfilling the Asbury 1990 diagnostic criteria and having a GBS disability score of at least 3 and within 2 weeks from onset of symptoms Inclusion criteria Written informed consent, or witnessed verbal informed consent Male or female ≥ 18 years of age Participants diagnosed with GBS according to NINDS diagnostic criteria Onset of weakness due to GBS within 2 weeks of enrolment Participants who are being considered for or already on IVIg treatment Unable to walk 10 m independently (grade ≥ 3 on GBS disability scale) 1st dose of eculizumab must be started within 2 weeks from onset of weakness and any time during the IVIg treatment period. Exclusion criteria Pregnant, lactating women or participants who wish to become pregnant during the trial period and for 5 months following treatment completion Participants who are being considered for or already on plasma exchange Clear clinical evidence of a polyneuropathy caused by, e.g. diabetes mellitus (except mild sensory), alcoholism, severe vitamin deficiency, and porphyria Immunosuppressive treatment during the last month. Severe concurrent disease, inability to comply with trial-related procedures or appointments during 6 months Any condition that in the opinion of the investigator could increase the participant's risk by taking part in the trial or confound the outcome of the trial Enrolment in another controlled trial of an investigational medical product 6 months prior to consent Contraindications to the administration of eculizumab: unresolved N. meningitidis infection or history of meningococcal infection unsuitable for antibiotic prophylaxis, known hypersensitivity to eculizumab, murine proteins or any of the excipients known or suspected hereditary complement deficiencies. women of child-bearing potential who are unwilling to use effective contraception during the eculizumab treatment period and for a minimum of 5 months thereafter.
Interventions	Eculizumab 900 mg IV weekly for 4 weeks (4 doses) or placebo identical in appearance and consistency in identical packaging. All participants received IVIg 0.4 g/kg for 5 days and ciprofloxacin 400 mg oral or 500 mg IV for 10 weeks.

Outcomes		Primary safety outcome: Incidence of adverse events and serious adverse events during the treatment period. Primary efficacy outcome: Improvement by one or more grades in the GBS disability score at 4 weeks. Secondary outcomes: Ability to walk unaided (GBS disability score ≤2) at 8 weeks Time taken to improve in one grade on the GBS disability score Time taken to walk independently Difference in GBS disability score at maximum disability compared with 6 months Percentage of participants with a clinically relevant improvement in I-RODS score defined as an in-crease from baseline in I-RODS score by at least 6 points on the centile metric score at 4 weeks and 6 months Percentage of participants with a clinically relevant improvement in ONLS defined as a decrease from baseline in ONLS score by at least one point at 4 weeks and 6 months Requirement for ventilatory support (GBS disability score =5) Duration of ventilatory support Recurrence of relapse Death within first 6 months Baseline defined as week 0, or day 1 prior to drug administration.
Funding source		The trial was investigator-led, funded by Alexion Pharmaceuticals, New Haven, CT, USA and co-spon-sored by University of Glasgow and NHS Greater Glasgow
Declarations of interest		The senior trial author has undertaken experimental work demonstrating the efficacy of eculizumab in an animal model of one form of GBS
Notes		The trial authors provided additional information to that in the paper Location: UK
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation and concealed allocation were performed by comput-er and an interactive web response system." Quote: "Based on baseline characteristics (mean values for Eculizumab and placebo groups) participants seem to be equally distributed across groups."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation and concealed allocation were performed by comput-er and an interactive web response system." Manuscript page 5, Study design
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Quote: "ICA-GBS was designed as a phase 2, single centre 2 : 1 randomised, **double-blind,** placebo-controlled trial" Manuscript page 5, Study design Quote: "The placebo was an exact match in compound to Eculizumab, with-out the active ingredient. It was identical in appearance and consistency to eculizumab, and came in identical packaging." Contact with 1st trial author

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The placebo was an exact match in compound to eculizumab, with-out the active ingredient. It was identical in appearance and consistency to eculizumab, and came in identical packaging."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All predefined outcomes except for 'recurrence of relapse' and 'duration of ventilation' were described in the manuscript text, and further illustrated in the tables and figures. The missing outcomes were provided by the 1st author.
Selective reporting (reporting bias)	Low risk	All predefined outcomes except for 'recurrence of relapse' and 'duration of ventilation' were described in the manuscript text, and further illustrated in the tables and figures. The missing outcomes were provided by the 1st author.
Other bias	Low risk	The trial was funded by the manufacturer of eculizumab but we did not deem this to increase the risk of bias in the absence of any other risk factors

JET-GBS 2018	
Methods	Double-blind, parallel group, placebo-controlled, multicentre (13 hospitals in Japan), phase 2 RCT with 2:1 eculizumab to placebo ratio
Participants	34 participants with acute GBS (within 2 weeks from onset of weakness), aged ≥ 18 years, fulfilling the Asbury 1990 diagnostic criteria, and having a GBS disability score of 3 (when also progressively deterio-rating), 4 or 5 Inclusion criteria People ≥ 18 years of age at the time of informed consent People with onset of weakness due to GBS < 2 weeks before the time of consent People unable to walk unaided for ≥ 5 meters (progressively deteriorating FG3 or FG 4-5) People who are undergoing or are deemed eligible for and will start IVIg treatment (generally 400 mg/kg for 5 days) People with GBS who can start their 1st dose of eculizumab within 2 weeks from onset of weakness and before the end of the IVIg treatment period Women of child bearing potential with a negative result in their pregnancy test. All participants must be able to practice an effective, reliable, medically approved method of contraception during the IP administration period and up to 5 months after IP administration is ended. People who can be hospitalised during the IP administration period. People who have signed the informed consent form Exclusion criteria: People who are being considered for or already on plasmapheresis Pregnant or lactating women People showing clear clinical evidence of peripheral polyneuropathy other than GBS, e.g. diabetic (except for mild sensory disturbance) or severe vitamin B1 deficiency related (except for mild sensory disturbance) People who have received immunosuppressive treatment (e.g. azathioprine, cyclosporine, tacrolimus, or > 20 mg prednisolone daily) during the 4 weeks prior to providing consent People who are known to have severe concurrent disease (such as malignancy with uncontrolled pri-mary tumours or metastatic lesions, severe cardiovascular disease, COPD, or TB People who are who are unable to comply with trial procedures and the treatment regimen People who have received rituximab within 24 weeks prior to providing consent providing consent 7 People with unresolved Neisseria meningitidis infection or a history of meningococcal infection People with active infectious diseases determined by the investigator or subinvestigator to be clini-cally severe, and are not being appropriately treated with antibiotics People who cannot be treated with antibiotic prophylaxis due to allergies People who are allergic to eculizumab People who are known to have or suspected of having hereditary complement deficiencies People who have been administered another investigational product within 12 weeks prior to provid-ing consent or are currently participating in another trial People with any condition that, in the opinion of the investigator or subinvestigator, could increase the person's risk by participating in trial or could confound the outcome by participating in trial or could confound the outcome of the trial People with a history of eculizumab treatment for GBS
Interventions	Weekly IV administration of eculizumab 900 mg (n = 23) or placebo (n = 11), for the 1st 4 weeks

Outcomes		Primary efficacy outcome: proportion of people who reached GBS disability grade 2 (able to walk 5 m unaided) or lower by week 4. Primary safety outcome: incidence and severity of adverse events during the trial Secondary outcomes: proportion of people improving by ≥ 1 disability grade from baseline at each visit proportion of people with disability ≤ grade 2 at each visit time to improvement by at least 1 disability grade proportion of people with disability grade 1 (able to run) or 0 (healthy) at week 24 changes from peak disability grade and disability grade at each visit up to 24 weeks proportion of people with a clinically relevant improvement in I-RODS score (≥ 6 centile points in-crease) and the ONLS score (≥ 1 point decrease) at each visit proportion of people requiring ventilator support and its duration incidence of relapse overall survival changes in grip strength (using the Smedley-spring type hand dynamometer) manual muscle testing score (sum of scores from 13 muscles, total score 65) median and ulnar nerve conduction trial parameters vital capacity at each visit from baseline proportion of IVIg re-administration Exploratory outcomes: antiganglioside IgG antibodies (GM1, GD1a, GalNAc-GD1a, GQ1b, and GM1/GD1a, GM1/GalNAc-GD1a, GM1/GQ1b, and GD1a/GQ1b) eculizumab serum concentrations serum haemolytic activity
Funding source		The trial was funded by the Ministry of Health, Labor and Welfare research grants and the Japan Agency for Medical Research and Development. Alexion Pharmaceuticals provided eculizumab and placebo free of charge.
Declarations of interest		Alexion Pharmaceuticals funded the trial drug and one of the trial authors reported personal fees (outside the submitted work) from Alexion Pharmaceuticals.
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done centrally by an independent company (AD-JUST, Sapporo, Japan) through a computer-generated process and web re-sponse system with dynamic allocation and minimisation for functional grade (3 vs. 4 or 5) and age (<60 years vs. ≥60 years)".

Allocation concealment (selection bias)	Low risk	Quote: "The study drugs were assigned and labelled with random numbers ac-cording to the randomisation table created by ADJUST personnel who were not involved in the conduct or analysis of the trial. Patients, investigators, and study staff were not able to access the randomisation table and were masked to treatment group assignment".
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Quote: "Patients, investigators, and study staff were not able to access the randomisation table and were masked to treatment group assignment. The ADJUST personnel verified that placebo and eculizumab were indistinguishable in external appearance".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, investigators, and study staff were not able to access the randomisation table and were masked to treatment group assignment. The ADJUST personnel verified that placebo and eculizumab were indistin-guishable in external appearance".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were incomplete for 1 participant in the eculizumab group and 3 participants in the placebo group. Quote: "One patient in placebo group did not receive study drug, because of neurological improvement before administration. One participant in the eculizumab group withdrew consent and discontinued during treatment. Two participants in the placebo group dropped out in the post-treatment period: one with neurological deterioration, and one with depression resulting from severe disability."
Selective reporting (reporting bias)	Low risk	Most outcomes were reported in full. A few prespecified outcomes were not re-ported in either the main text or supplementary material, including change in I-RODS score from baseline: week 1, 2, 3; change in nerve conduction measures from baseline: week 1, 2, 3, 8, 12, 16; change in vital capacity from baseline: week 1, 2, 3, 8, 12, 16. We did not consider that these omissions biased the reporting of the trial since reporting was otherwise exhaustive.
Other bias	Low risk	Alexion provided the trial drug but not other support and we did not consider this a source of bias

Pritchard 2003		
Methods		Double-blind, randomised, parallel-group trial with 2:1 IFNb-1a to placebo ratio
Participants		19 people with GBS fulfilling Asbury 1990 criteria within 14 days from the onset of symptoms and having Hughes 1978 disability grade > 2
Interventions		IFNb-1a (Rebif) by SC injection 3 times a week starting with 22 µg per injection for the 1st week and continuing with 44 µg for subsequent weeks until a total of 24 weeks (n = 13) or placebo (n = 6). Participants stopped treatment upon reaching grade 2
Outcomes		Primary aim: to assess the safety and tolerability of IFNb in GBS Serious adverse events (defined as "fatal, life threatening, requiring or prolonging hospitalization, severely or permanently disabling, a new malignancy, or a known or suspected overdose") Secondary aim: to conduct pilot investigations of the effect of IFNb on overall disability in GBS. Outcome measures: improvement in disability grade 4 weeks after randomisation improvement by 1 or more disability grade 4 weeks after randomisation improvement in disability grade 24 weeks after randomisation improvement by 1 or more disability grade 24 weeks after randomisation time from randomisation to recovery of unaided walking increase in MRC sum score at week 4 and 24 increase in grip strength at week 4 and 24
Funding source		Serono International provided financial support and supplied the drug and placebo
Declarations of interest		The trial authors declared receipt of honoraria or travel grants and departmental research grants from Serono International
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Each centre was given trial drug in a computer-generated (information from the authors) random sequence by the trial statistician balanced to achieve a 2:1 ratio of IFNb-1a to placebo
Allocation concealment (selection bias)	Low risk	Each centre was given trial drug in random sequence balanced to achieve a 2:1 ratio of IFNb-1a to placebo and concealed until all outcome measures, including attribution of causality of adverse events, had been collected
Blinding of participants and personnel (perfor-mance bias) All outcomes	Low risk	Participants and personnel were unaware whether the participants received IFNb-1a or placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt was made to mask skin lesions from assessors

Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant died in the IFNb-1a group before week 8 after randomisation. Complete case analysis reported
Selective reporting (reporting bias)	Low risk	Complete case analysis of all outcomes reported
Other bias	Low risk	None detected

Wollinsky 2001		
Methods		Parallel-group, open, randomised trial
Participants		37 people with GBS fulfilling standard Asbury criteria, unable to walk 5 m unaided, < 30 days from onset, age > 15 years
Interventions		CSF filtration 30-50 mL removed, filtered and re-infused usually 5-6 times daily for 5-15 consecutive days (n = 17) versus plasma exchange total 200-250 mL/kg in 5 or 6 treatments daily or on alternate days for 7-14 days (n = 20)
Outcomes		Improvement in GBS disability grade after 28 days Improvement by 1 GBS disability grade after 28 days Improvement in GBS disability grade after 56 days Reaching grade 2 by 56 days Reaching grade 2 by 6 months (having reached grade 2) Relapse Side effects
Funding source		Pall Medical (Dreieich, Germany) supplied filters and bidirectional pumps, and trial authors acknowledged financial support from L and B Brandt
Declarations of interest		Not stated
Notes		Location: Germany (2 hospitals)
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "by means of Documenta Geigy table"
Allocation concealment (selection bias)	High risk	Quote: "Blocks of two. Investigators aware of block size"
Blinding of participants and personnel (perfor-mance bias) All outcomes	Unclear risk	The nature of the interventions means that blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk of bias for all outcomes except death. No mention of blinding assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	The scores of 2 participants, 1 from each group, who died were carried forward (for calculation of the primary and secondary outcome variables) with the last score before death and the actual score was not given
Selective reporting (reporting bias)	Low risk	Complete case analysis of all outcomes reported
Other bias	High risk	2 participants who underwent plasma exchange had transverse myelitis and were retained in the analysis without presentation of the results without them 1 participant in each group was crossed over: it was not possible to place a spinal catheter in the CSF filtration participant. The plasma exchange partici-pant went into hypovolaemic shock during the first plasma exchange. In both cases the last value under the initial treatment was carried forward for calculation of the primary outcome variable but the actual value was not given. For the calculation of secondary outcome variables these participants were entered as missing values.

Zhang 2000		
Methods		Parallel-group RCT
Participants		43 people with GBS diagnosed according to Asbury 1990 criteria
Interventions		Oral tripterygium polyglycoside (a Chinese herbal medicine) 60-80 mg daily for 4 weeks and then 30-45 mg daily for 4 further weeks (n = 22), versus IV dexamethasone 15-20 mg daily for 15 days, then 5-10 mg daily for 7 days, then oral prednisone 30-60 mg daily decreased by 5-10 mg daily every 2 weeks (n = 21)
Outcomes		Number improved at 8 weeks, adverse events and serum interleukin-6 concentrations
Funding source		Unknown
Declarations of interest		Information not given in the translation
Notes		English abstract available. Data extracted from full text by translator Location: China
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Divided into two groups on layer randomize principle" but method not described according to the translator
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (perfor-mance bias) All outcomes	High risk	Oral tripterygium polyglycoside compared with IV corticosteroids - no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators likely to have been aware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

BDNF: brain-derived neurotrophic factor; **CSF:** cerebrospinal fluid; **GBS:** Guillain-Barré syndrome; **IFNb-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **metHuBDNF:** recombinant methionyl human brain-derived neurotrophic factor; **MRC:** Medical Research Council; **NHS:** National Health Service; **NINDS:** National Institute of Neurological Disorders and Stroke; **ONLS:** Overall Neuropathy Limitations Scale; **RCT:** randomised controlled trial; **SC:** subcutaneous

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahuja 1980	Observational study of cyclophosphamide
Bos Eyssen 2011	This was a retrospective study of 54 mechanically ventilated people with GBS treated with selective decontamination of the digestive tract compared with 70 from other centres treated without. Non-randomised retrospective comparison. The method of selective decontamination of the digestive tract was not described
Colin-Jones 1965	Not in GBS. 1 person with CIDP treated with 6-mercaptopurine
Créange 1998	Not a RCT. Single case report of improvement following IFNb-1a. See text and Table 2
De Grandis 1995	Only 8 of 426 participants had GBS and their results were not described separately
Ding 2015	Not a RCT. Although the abstract states that the trial was randomised, the main text does not describe randomisation. "54 cases of GBS admitted to this hospital from March 2009 to October 2013 are selected. They are divided in those according to their treatment. Both groups received standard medical care, including treatment of infections, clearance of airway, maintenance of respiratory function, infusion of gamma globulin, corticosteroids, and B vitamins. The treated group had in addition hyperbaric oxygen and acupuncture." There were 27 in each group.
Feasby 1991	Not a RCT. 3 cases treated with muromonab-CD3. See text and Table 2
Francesconi 1972	No GBS cases included
Gamstorp 1996	Not in GBS. Single case of CIDP treated with 6-mercaptopurine
Garssen 2007	Non-randomised trial of mycophenolate mofetil. See Summary of main results
Gorbunov 1995	RCT of pulsed versus continuous short-wave diathermy versus no treatment: not a pharmacological treatment
Hammond 1993	Only 15 participants had GBS and their results were not separately available in this double-blind, placebo-controlled trial of IV cefotaxime with amphotericin B, polymyxin E, and tobramycin applied to the oropharynx and enterally. There were altogether 40 participants with neurological diseases requiring intensive care. "There was no reduction in the incidence of infections (11 in the active group vs 10 in placebo), and duration of ICU stay (30.1 +/- 22.5 vs 20.6 +/- 17.7 days) and hospital stay (49.3 +/- 31.9 vs 40 +/- 33.4 days) were unaffected as was the mortality (15 percent vs 15 per-cent)"
Hilz 1992	Not a RCT but a single case of a method for treating pressure sores
Huang L 1998	UV irradiation. It is debatable whether this is a pharmacological treatment but in any case we could not include it because there was no description of randomisation or of time from onset when the UV irradiation was applied
Huang X 1998	Time when treatment given not stated. Treatment was UV irradiation. Allocation was said to be randomised but method unclear
Husstedt 1993	No GBS cases included in a trial of Gingko biloba extract
Li 1998	Not stated whether it was randomised. UV irradiation. Time from onset differed between irradiation and control groups
Li 2007	A randomised trial of lymphoplasmapheresis versus supportive treatment alone in 66 participants: the treatment tested included plasma exchange which is the subject of another Cochrane Review
Meythaler 2000	Treatment started > 1 year after disease onset. Cross-over design RCT of 4-aminopyridine
NCT03773328	Not started and start suspended
Ostronoff 2008	Not RCT. Single case report of improvement following rituximab in 1 person with GBS following haematopoietic stem cell transplantation. Treatment with rituximab started after the acute phase (40 days after onset of neurological signs).

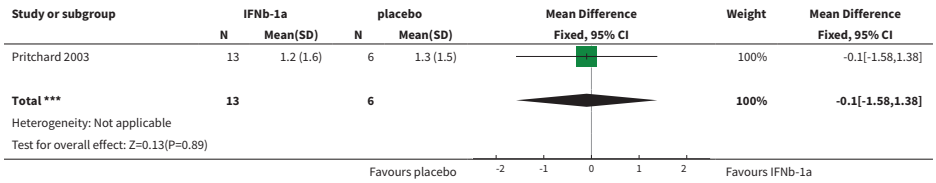
Palmer 1965	Not in GBS. Single case of CIDP treated with 6 mercaptopurine
Palmer 1966	Not in GBS. Single case of CIDP treated with 6 mercaptopurine
Rosen 1976	Not RCT. Case series treated with cyclophosphamide. See Discussion and Table 2
Schaller 2001	Not RCT. Single case of GBS treated with IFNb-1a
Sendhilkumar 2013	Excluded because not a pharmacological treatment and not conducted in the acute phase (RCT of pranayama (yoga) and meditation in rehabilitation)
Tzachanis 2014	Not RCT. Single case report of improvement following alemtuzumab in 1 person with GBS that presented 6 months after treatment for chronic lymphocytic leukaemia. The exact time point when alemtuzumab was started is not noted in the paper, but can be estimated based on the other treat-ments that were provided as after 20 days from onset of neurological signs.
Umapathi 2014	Proposed RCT of azithromycin in GBS associated with diarrhoea. Not yet started or funded as at 1 March 2015 (personal communication from author)
Wang 2006	Not a pharmacological treatment, but acupuncture. 25 participants were randomised to electroacupuncture for 14 days and 24 to IVIg 0.4 g/kg daily for 5 days. Sequence generation was unclear, allocation concealment was done, blinding was not done, outcome data were complete, selective outcome reporting and other sources of bias were unclear. Mean improvement with acupuncture after 4 weeks was 1.58 (0.33) grades and with IVIg 1.68 (0.21) grades. Median (95%CI) time to unaided walking was 79.5 (58.7 to 100.3) and 81.2 (59.8 to 102.6) grades. There were no deaths. Adverse events were not described
Warembourg 1967	No GBS cases and not a RCT. See Discussion and Table 2
Yuill 1970	Not RCT. Single case report of use of azathioprine
Zagar 1995	Review not a RCT

CI: confidence interval; **CIDP:** chronic inflammatory demyelinating polyradiculoneuropathy; **GBS:** Guillain-Barré syndrome; **IFNb-1a:** interferon beta-1a; **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **RCT:** randomised controlled trial; **UV:** ultraviolet

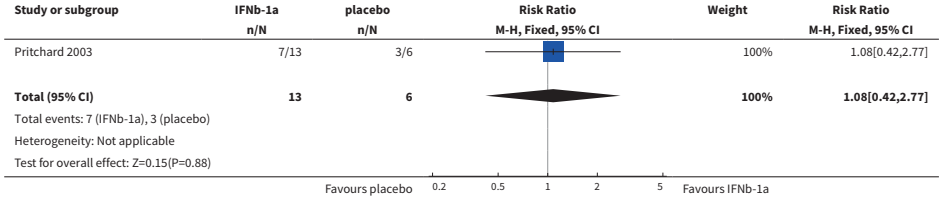
DATA AND ANALYSES

Comparison 1. IFNb-1a versus placebo

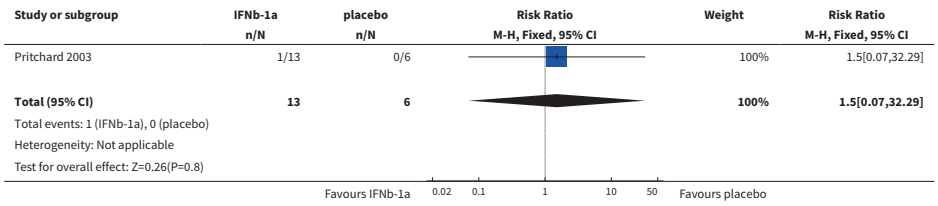
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	1	19	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.58, 1.38]
2 Improvement by 1 or more grades after 4 weeks	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.42, 2.77]
3 Death	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.07, 32.29]
4 Participants with 1 or more serious adverse events	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.23, 3.72]



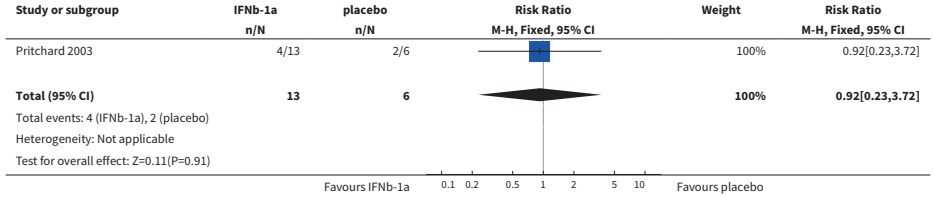
Analysis 1.1. Comparison 1 IFNb-1a versus placebo, Outcome 1 Improvement in disability grade aAer 4 weeks.



Analysis 1.2. Comparison 1 IFNb-1a versus placebo, Outcome 2 Improvement by 1 or more grades aAer 4 weeks.



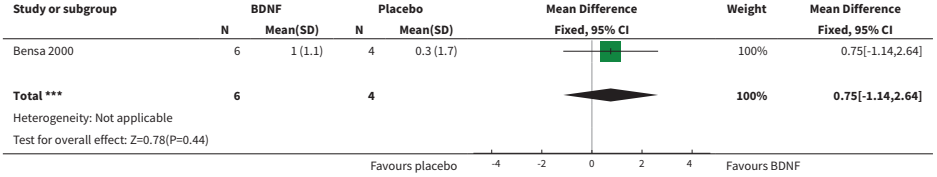
Analysis 1.3. Comparison 1 IFNb-1a versus placebo, Outcome 3 Death.



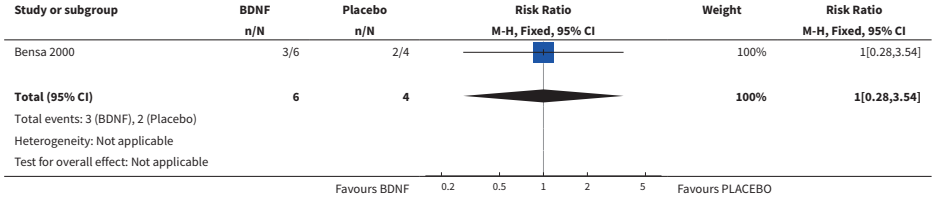
Analysis 1.4. Comparison 1 IFNb-1a versus placebo, Outcome 4 Participants with 1 or more serious adverse events.

Comparison 2. BDNF versus placebo

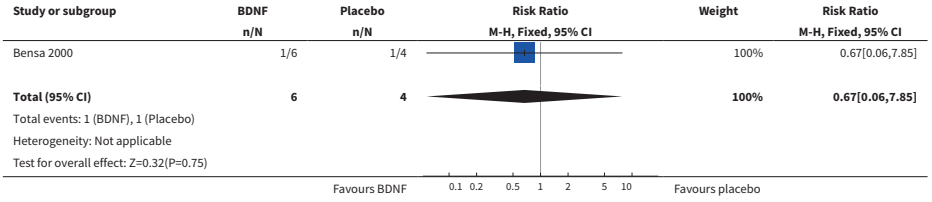
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	1	10	Mean Difference (IV, Fixed, 95% CI)	0.75 [-1.14, 2.64]
2 Improvement by 1 or more grades after 4 weeks	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.28, 3.54]
3 Death	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.06, 7.85]
4 Participants with 1 or more serious adverse events	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.17, 10.25]
5 Serious adverse events	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.28, 3.54]



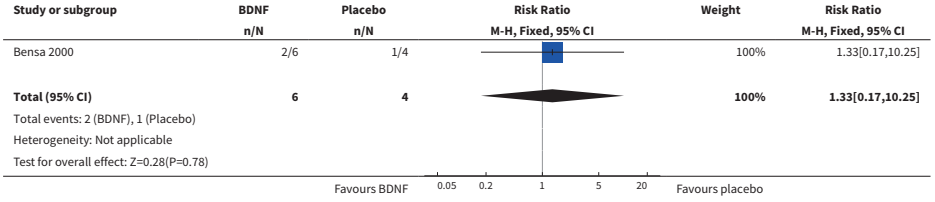
Analysis 2.1. Comparison 2 BDNF versus placebo, Outcome 1 Improvement in disability grade after 4 weeks.



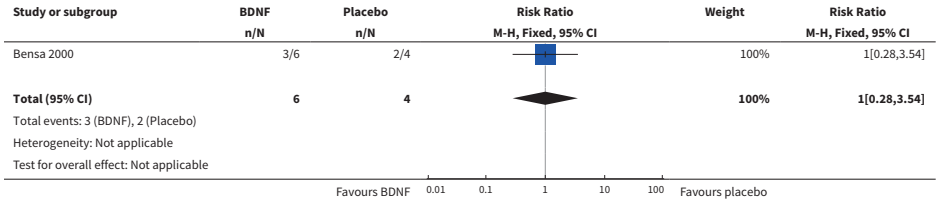
Analysis 2.2. Comparison 2 BDNF versus placebo, Outcome 2 Improvement in disability grade by one or more points after 4 weeks.



Analysis 2.3. Comparison 2 BDNF versus placebo, Outcome 3 Death.



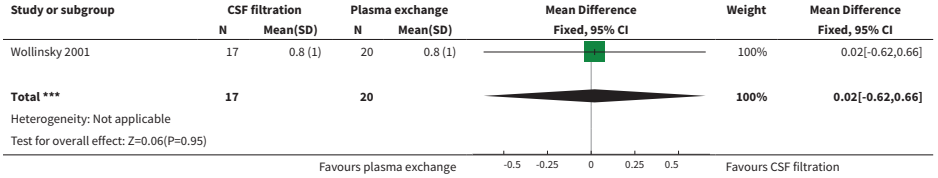
Analysis 2.4. Comparison 2 BDNF versus placebo, Outcome 4 Death or disability after 12 months.



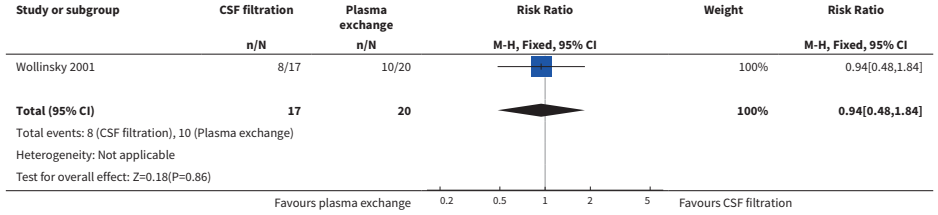
Analysis 2.5. Comparison 2 BDNF versus placebo, Outcome 5 Serious adverse events.

Comparison 3. CSF filtration versus plasma exchange

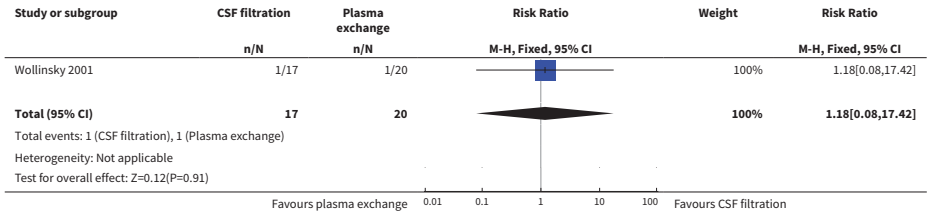
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	1	37	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.62, 0.66]
2 Improvement by 1 or more grades after 4 weeks	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.84]
3 Death	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.08, 17.42]
4 Participants with 1 or more serious adverse events	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.25]
5 Serious adverse events	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.08, 17.42]



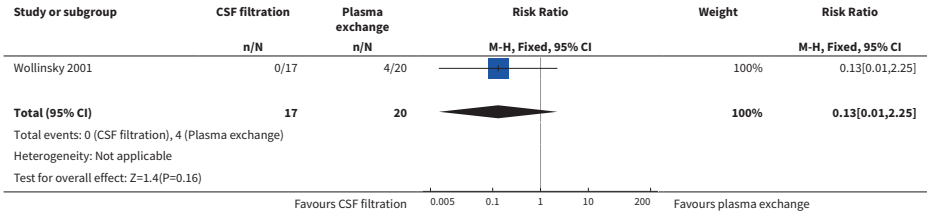
Analysis 3.1. Comparison 3 CSF filtration versus plasma exchange, Outcome 1 Improvement in disability grade after 4 weeks.



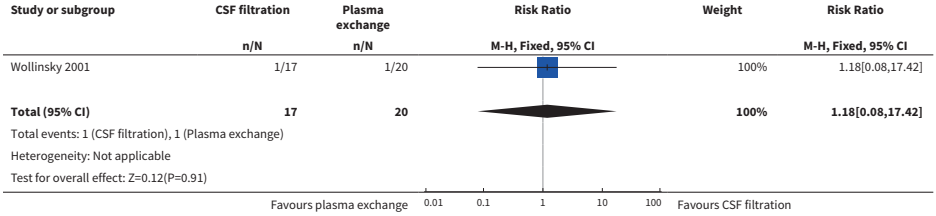
Analysis 3.2. Comparison 3 CSF filtration versus plasma exchange, Outcome 2 Improvement by 1 or more grades after 4 weeks.



Analysis 3.3. Comparison 3 CSF filtration versus plasma exchange, Outcome 3 Death.



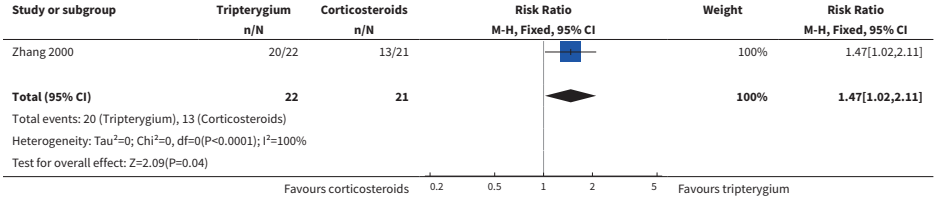
Analysis 3.4. Comparison 3 CSF filtration versus plasma exchange, Outcome 4 Serious adverse events.



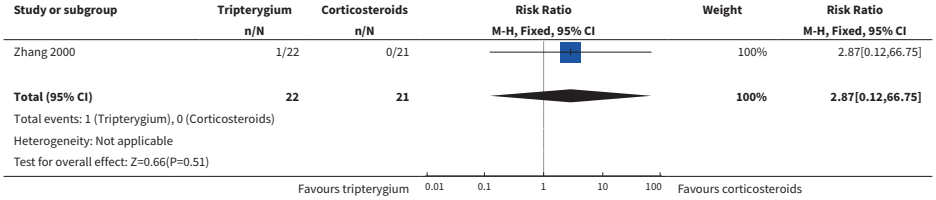
Analysis 3.5. Comparison 3 CSF filtration versus plasma exchange, Outcome 5 Adverse events leading to cessation of treatment.

Comparison 4. Tripterygium polyglycoside versus corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade by one or more points after 8 weeks	1	43	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.02, 2.11]
2 Adverse events	1	43	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.12, 66.75]



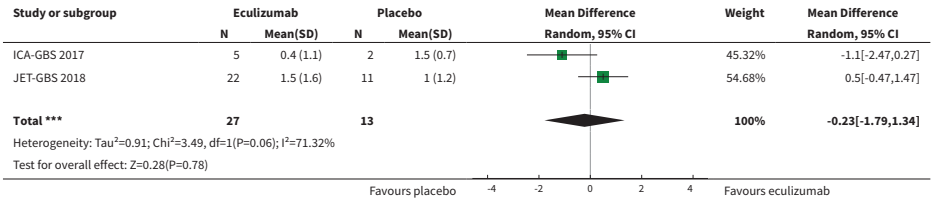
Analysis 4.1. Comparison 4 Tripterygium polyglycoside versus corticosteroids, Outcome 1 Improvement in disability grade by one or more points after 8 weeks.



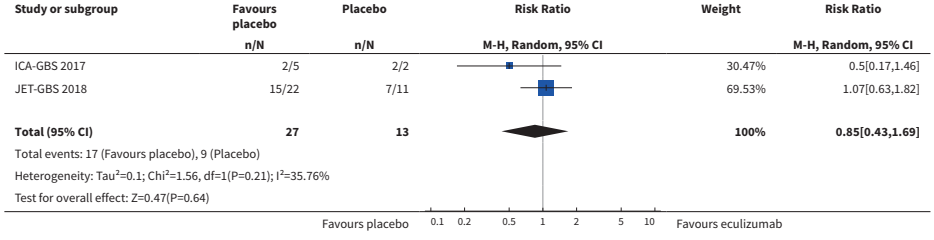
Analysis 4.2. Comparison 4 Tripterygium polyglycoside versus corticosteroids, Outcome 2 Adverse events.

Comparison 5. Eculizumab versus placebo

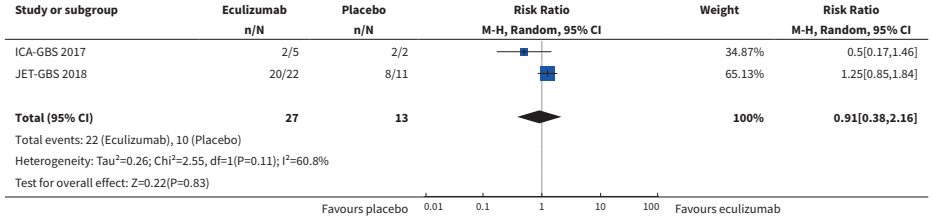
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	2	40	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.79, 1.34]
2 Improvement by 1 or more disability grades after 4 weeks	2	40	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.43, 1.69]
3 Improvement by 6 or more points on the I-RODS score after 4 weeks	2	40	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.38, 2.16]
4 Death	2	38	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.08, 26.86]
5 Improvement in disability grade after 6 months	2	38	Mean Difference (IV, Random, 95% CI)	-0.75 [-3.88, 2.37]
6 Improvement by 1 or more grades after 6 months	2	38	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.36]
7 Improvement by 6 or more points on the I-RODS score after 6 months	2	37	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.83, 1.17]
8 Death or disability after 6 months	2	38	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.15, 10.11]
9 Participants with adverse events	2	41	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.88, 1.14]
10 Participants with serious adverse events	2	41	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.34, 10.50]



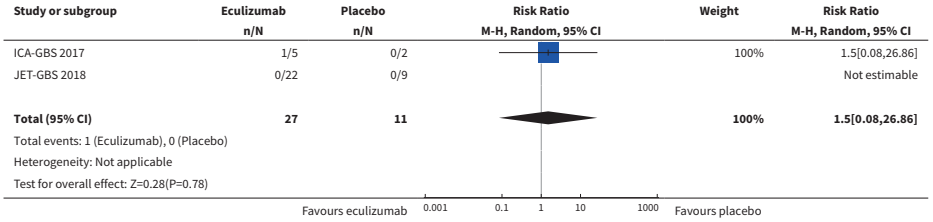
Analysis 5.1. Comparison 5 Eculizumab versus placebo, Outcome 1 Improvement in disability grade after 4 weeks.



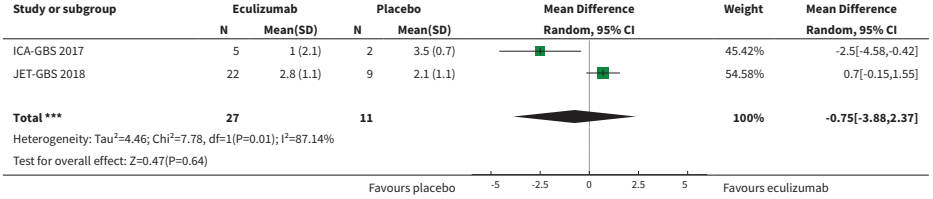
Analysis 5.2. Comparison 5 Eculizumab versus placebo, Outcome 2 Improvement by 1 or more disability grades after 4 weeks.



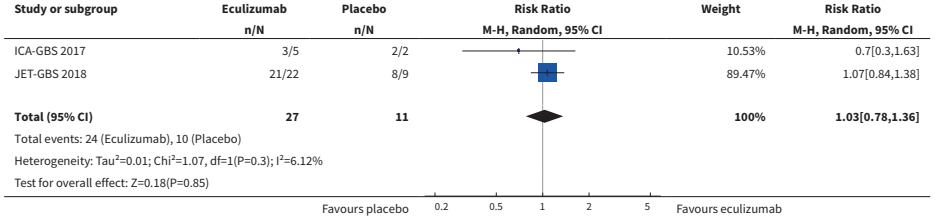
Analysis 5.3. Comparison 5 Eculizumab versus placebo, Outcome 3 Improvement by 6 or more points on the I-RODS score after 4 weeks.



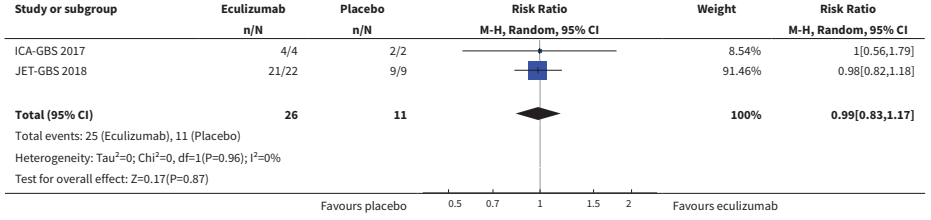
Analysis 5.4. Comparison 5 Eculizumab versus placebo, Outcome 4 Death.



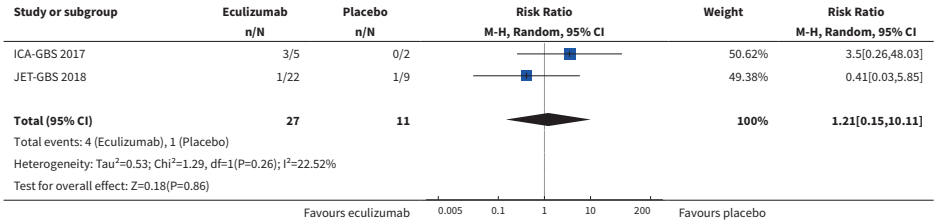
Analysis 5.5. Comparison 5 Eculizumab versus placebo, Outcome 5 Improvement in disability grade after 6 months.



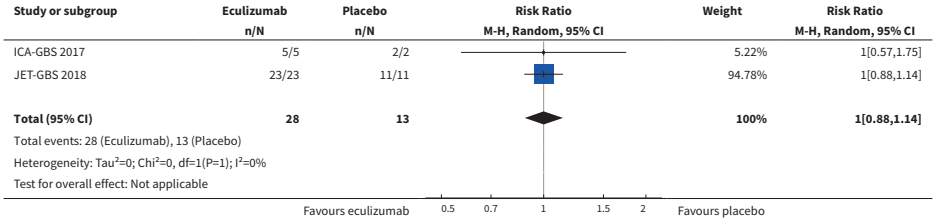
Analysis 5.6. Comparison 5 Eculizumab versus placebo, Outcome 6 Improvement by 1 or more grades after 6 months.



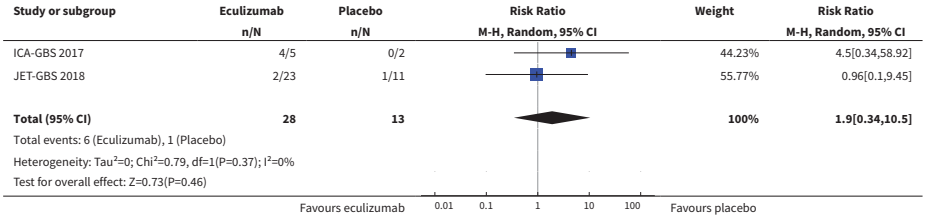
Analysis 5.7. Comparison 5 Eculizumab versus placebo, Outcome 7 Improvement by 6 or more points on the I-RODS score after 6 months.



Analysis 5.8. Comparison 5 Eculizumab versus placebo, Outcome 8 Death or disability after 6 months.



Analysis 5.9. Comparison 5 Eculizumab versus placebo, Outcome 9 Participants with adverse events.



Analysis 5.10. Comparison 5 Eculizumab versus placebo, Outcome 10 Participants with serious adverse events.

5

Discussion

The studies in this thesis aimed to address the following objectives:

1. To define the variability in clinical presentation, diagnostic features, subtypes, and clinical outcome between GBS patients from various geographical regions.
2. To describe the variability in CSF protein level and cell count in relation to demography, disease severity, subtype and outcome of GBS, in order to get more insight into the clinical utility of CSF examination for diagnosing GBS.
3. To validate and improve the clinical prognostic models for GBS that predict the risk of respiratory insufficiency and the inability to walk independently.
4. To identify novel predictors for respiratory insufficiency in GBS.
5. To define the variability in the current treatment practice of GBS among countries.
6. To evaluate the efficacy of treatments other than IVIg, plasma exchange and corticosteroids for GBS.

In this chapter, we will discuss the main findings of the studies described in this thesis in relation to the existing literature on GBS. We will describe the practical implications, discuss methodological considerations and provide directions for future research.

CLINICAL CHARACTERISTICS AND DIAGNOSIS

Regional variation of GBS: clinical presentation, disease course and outcome

In **Chapter 2.1** we have described the clinical characteristics, disease course and outcome for the first 1000 patients included in IGOS, an observational, prospective cohort study collecting data from GBS patients from 21 countries, across five continents. We compared GBS patients from three geographical regions: Europe/Americas, Asia and Bangladesh. This study demonstrated a marked worldwide variation of GBS, showing differences in the disease severity, outcome, and in the prevalence of GBS subforms among regions. In European and American countries, the majority of patients presented with the sensorimotor variant of GBS. In Asia, the predominant clinical variant was also sensorimotor GBS, but more patients presented with the MFS or MFS-GBS overlap syndrome, representing about one-fifth of the Asian GBS patients. The Bangladesh population formed a separate subgroup with unique characteristics, including a younger age, a higher proportion reporting preceding gastro-intestinal illness, more severe disease and worse outcomes. The predominant clinical variant in Bangladesh was the pure motor variant, characterized by weakness in arms and legs without the involvement of sensory nerves. Although the demyelinating subtype was the predominant electrophysiological subtype in all three regions, a higher proportion of the GBS patients in Bangladesh had the axonal subtype[1]. These results show that GBS is a heterogeneous disease, constituting a range of clinical

severities and subforms. Furthermore, comparison of GBS patients from different regions shows a clustering of specific clinical variants and NCS subtypes, indicating that part of this heterogeneity may be attributed to regional differences. Regional variation of GBS was already suggested by the comparison of studies from single countries. Reports from Western countries showed a higher frequency of the demyelinating subtype, while in Asia and Central and South America higher prevalences of axonal GBS were reported[2-10]. Direct comparison between studies from single countries was however complicated by differences in study design, in- and exclusion criteria, or focus on specific subgroups. The IGOS has several advantages compared to previous studies for determining the regional variation of GBS, including: (i) a standard study protocol used by all centres, (ii) a prospective study design, (iii) collection of detailed clinical data, including well-defined clinical endpoints and previously identified prognostic factors for GBS, (iv) assessment of long-term outcome and (v) a much larger sample size[11].

What factors determine the regional variation of GBS?

Confirming the regional variation of GBS is important to better understand the pathogenesis and the role of region- and host-specific disease modifying factors. Multiple factors may play a role in defining this regional variation. In previous studies, preceding infections have been associated with specific clinical and electrophysiological subforms of GBS. Through the concept of molecular mimicry, it is hypothesized that antibodies directed against structures on the outer membranes of bacteria cross-react with gangliosides, ganglioside complexes or other glycolipids that are present on the peripheral nerves[12, 13]. The type of anti-ganglioside antibody may differ depending on the preceding infection, and may result in specific neurological complaints as the representation of these gangliosides is thought to vary throughout the peripheral nervous system[14]. *Campylobacter jejuni* is the most common preceding infection in GBS and has been associated with a pure motor axonal subtype, with severe muscle weakness and poor outcome[2, 5, 10, 15, 16]. Several studies have shown that this infection is more prevalent in Bangladesh, which corresponds to our findings in the IGOS cohort that the Bangladeshi patients more often reported symptoms of a preceding gastro-intestinal illness and more frequently presented with a severe axonal form of GBS[1]. Variation in local exposure to infections may provide an explanation for the regional differences in the distribution of these GBS subforms. To further investigate this hypothesis, all patients within the IGOS-1000 cohort for whom a serum sample was available (n=768) were tested for a recent infection with *C. jejuni, M. pneumoniae,* hepatitis E virus (HEV), cytomegalovirus (CMV) and Epstein Barr virus (EBV)[17]. The study did find a relation between preceding infections and the reported antecedent events, clinical and electrophysiological subforms, and outcome of GBS, however, the infections were not specific for one particular GBS phenotype, and more importantly, no differences were found in the frequency of these five

infections across the studied regions[17]. Although the results of this study argue against a potential role for infections in defining the regional variation of GBS, serological testing was only performed for the five infections that are most commonly associated with GBS and the triggering of an auto-immune response in GBS may be limited to specific strains of these bacteria and viruses[18, 19]. Another explanation for the regional variation of GBS may be provided by host susceptibility factors, as the study by Leonhard et al showed that Asian patients who tested positive for *C. jejuni* more often presented with an axonal subtype than European and American *C. jejuni*-positive patients [17]. Host genetic factors also may play a role in the observed differences in outcome between GBS patients, for example via genetic polymorphisms that influence the activity of the immune system or treatment response through IVIg pharmacokinetics[20, 21]. Finally, a form of selection bias may have occurred in IGOS, especially in the cohort from Bangladesh, which may have resulted in more profound differences in the observed outcome between the studied regions. Health resources and access to health care are limited in Bangladesh, and medical attention may only be sought by the more severely affected patients. In addition, the majority of the Bangladeshi patients was not treated and if they were treated the time to start of the first treatment was longer, which may have resulted in more profound axonal damage[1].

REGIONAL VARIATION OF GBS – summary of findings and clinical implications

1) The clinical presentation, disease course, subtypes and outcome of GBS differ between regions.
   a) In Western countries sensorimotor, demyelinating GBS is most prevalent.
   b) Miller Fisher and Miller Fisher overlap syndromes occur more frequently in Asia.
   c) In Bangladesh, GBS patients are younger, more frequently have preceding diarrhoea, a higher proportion present with a pure motor, axonal form of GBS, and outcome is worse.

CSF findings in GBS

In **Chapter 2.2** we described the CSF features, and the relation with demography, disease severity and clinical outcome for the IGOS-1500 cohort. The CSF protein level varied greatly among patients, and was related to the timing of lumbar puncture, the distribution of muscle weakness, and the GBS clinical variant and electrophysiological subtype. Most patients had a CSF cell count <50 cells/ul, but in a minority of cases, with an otherwise typical GBS phenotype, a cell count ≥50 cells/ul was observed. In these patients, diagnosis was not altered during follow up. Multivariate logistic regression analysis, corrected for known confounding factors, showed that the CSF protein level

was independently associated with walking ability at week 2, and the ability to run at weeks 2 and 4. The CSF protein level was not associated with long-term outcome of GBS or with the need for mechanical ventilation.

CSF protein level and diagnosis of GBS

The diagnosis of GBS mostly relies on the clinical examination but can be supported by CSF findings[22, 23]. The hallmark of CSF examination in GBS is the albuminocytological dissociation, which is almost fully determined by the protein level as most GBS patients have a normal cell count. An elevated CSF protein level was present in 70% of the IGOS patients, which was in line with results from previous studies that showed proportions ranging from 64% to 77%[24-26]. One study from Asia only found an elevated protein level in 56% of the patients, even though a larger proportion of the lumbar punctures was performed after 3 days and patients with MFS, who often have lower CSF protein levels, were analysed separately. The definition of an elevated CSF protein level in this study was based on normative values from the laboratories in the respective hospitals[27]. Previous studies also reported the relation between the CSF protein level and the timing of lumbar puncture[24, 26, 27], and the variation in CSF total protein among GBS subforms[27, 28]. One study found a two-fold increase in CSF protein after treatment with IVIg in patients with acute and chronic demyelinating diseases. This was considered to result from IVIg entering the CSF through the blood-nerve barrier[29], but we could not replicate this finding in our study. Although the CSF protein level is one of the few widely available biomarkers for GBS, its usefulness for diagnosing GBS can be debated, as at least 30% of the GBS patients have a normal protein level, and protein levels vary depending on multiple confounding factors. In addition, an elevated CSF protein level may not be specific for GBS, as similar findings have been reported in other demyelinating diseases, such as A-CIDP[30]. When the CSF protein level is used as a diagnostic criterion for GBS, these confounding factors should be taken into consideration, and it should be explicitly stated that a normal CSF protein level does not exclude a diagnosis of GBS.

Variation in CSF protein among GBS subforms

In our study of the IGOS-1500 cohort, patients with sensorimotor and demyelinating GBS had the highest CSF protein levels, while lower levels were found in patients with MFS and equivocal or normal NCS. Similar results have been found in previous studies[27, 28]. The variation in CSF protein level among GBS subforms may relate to the distribution of nerve damage. Patients with higher protein levels may have more prominent involvement of nerve segments that are in close contact to the CSF, such as the spinal nerve roots. A previous study that compared early nerve sonography patterns among patients with axonal and demyelinating GBS found that proximal nerve segments and cervical spinal nerves tended to be more frequently involved in patients with demyelinating

GBS, whereas patients with axonal GBS had more prominent involvement of distal nerve trunks[31]. In contrast, Berciano and colleagues proposed a new pathogenic mechanism for early GBS, stating that early clinical and electrophysiological changes could be traced back to severe inflammatory edema of proximal nerve segments, irrespective of the GBS subtype[32]. Further studies to assess the relationship between CSF total protein and GBS subtypes, also including NCS and imaging results, are therefore needed as these could provide more insight into the (early stage) pathophysiology of GBS.

CSF cell count and diagnosis of GBS

A CSF cell count <50 cells/ul is a typical finding for GBS and constitutes part of the diagnostic criteria[22, 23]. In our study, 13 patients had a cell count ≥50 cells/ul, and similar cases have been reported in previous literature[27, 33, 34]. High-dose IVIg treatment may be accompanied by aseptic meningitis in up to 10% of patients, which is characterized by a CSF pleocytosis and elevated total protein level. The symptoms of meningitis usually occur within hours to days after the IVIg infusion, and will resolve without sequel within 24 to 48 hours after cessation of treatment[35, 36]. Three of 13 IGOS patients with a CSF cell count ≥50 cells/ul received IVIg before the lumbar puncture, and in two of these patients an aseptic meningitis was suspected either by the local treating neurologist or based on symptoms of meningitis recorded in the IGOS case report forms. Studies on Bickerstaff's brainstem encephalitis (BBE), a subform of GBS that is characterized by ophthalmoplegia, ataxia and consciousness disturbances, report CSF pleocytosis in about one-third of patients[37, 38]. Despite the apparent involvement of the central nervous system in BBE, it is considered a subform of GBS due to the presence of anti-GQ1b antiganglioside antibodies in two-thirds of these patients. In IGOS, 1 (8%) of 13 patients with a CSF cell count ≥50 cells/ul was classified as having BBE by the local treating neurologist. As GBS often is regarded a disease spectrum, patients with a cell count ≥50 cells/ul may form one end of this spectrum. This implicates that the finding of an elevated CSF cell count in patients that are highly suspected of GBS based on clinical features necessitates additional investigations to exclude other diagnoses, but does not rule out the possibility of GBS. In the general population of GBS patients, the proportion with an elevated CSF cell count may be even higher than reported in IGOS, because clinicians may be reluctant to include a patient with an increased cell count in whom alternative diagnoses have not been ruled-out yet.

CSF FINDINGS IN GBS – summary of findings and clinical implications

I. The CSF protein varies in relation to the timing of lumbar puncture, and the GBS clinical variant and NCS subtype. A single cut-off value to define an elevated CSF protein in GBS is therefore not meaningful, and a normal protein level should not rule-out the diagnosis.

II. An elevated CSF cell count should prompt additional investigations to rule out infectious or neoplastic disorders, but it should not exclude a GBS diagnosis in patients with a high clinical suspicion.

PREDICTION OF OUTCOME

Validation of existing prediction models for GBS

In **Chapter 3.1 and 3.2** we validated the mEGOS and EGRIS prognostic models with data from the IGOS-1500 cohort. At hospital admission and day 7 of admission, clinicians can use the mEGOS to predict the risk that a patient with GBS will not be able to walk independently at 4 weeks, 3 months and 6 months after diagnosis[39]. The EGRIS uses clinical factors available at hospital admission to predict the need for mechanical ventilation within the first week after admission[40]. The mEGOS and EGRIS were developed with data from Dutch GBS patients and required validation in other countries to assess their performance in the globally diverse GBS population. We validated both models in the full IGOS-1500 cohort and in separate regions (Europe/North America and Asia), also including patients with variant forms of GBS. The mEGOS was also validated in Bangladesh separately, because of the unique characteristics of this cohort, and the results of these analyses were described in **Chapter 3.3**. The studies showed that both models could differentiate between patients with and without the outcome of interest, also in an international GBS cohort, with AUC-values above 0.7 for the mEGOS, and above 0.8 for the EGRIS. The accuracy of the mEGOS model, indicated by the correspondence between the predicted risks and observed outcomes, varied between regions, underestimating the risk of poor outcome in Europe/North America, while overestimating the risk of poor outcome in Asia. The EGRIS model overestimated the risk of respiratory failure in all regions. We used the IGOS data to improve both models and to develop a region-specific version of the mEGOS (mEGOS-Eu/NA) and EGRIS (EGRIS-Eu/NA) for GBS patients from European and North-American countries, which provide the most accurate predictions for patients from this region. In Bangladesh, the discriminative ability of the mEGOS was worse than in Western GBS patients, but this could be partially explained by the more homogeneous cohort in Bangladesh. The predicted probabilities based on the mEGOS model corresponded to the observed outcomes in Bangladesh, showing that the original mEGOS also can be used in GBS patients from Bangladesh. Furthermore, these results also may be extrapolated to other low- and middle-income countries with similar socio-economic status, health care system and prevalence of infections.

Validation of the mEGOS and EGRIS in previous studies

Both the mEGOS and EGRIS previously have been validated in two GBS cohorts from Japan and Malaysia[41, 42]. Results regarding the discriminative ability of the models were in line with the results from our studies. The two Asian studies did not assess model calibration, but based on the mean mEGOS and EGRIS we were able to calculate the mean predicted probabilities, and compared these with the observed outcomes. In the Japanese study, the mEGOS at admission accurately predicted outcome at 6 months (predicted and observed risk of poor outcome both 11%), but the risk of poor outcome was underestimated by the mEGOS at day 7 (predicted risk 6%, observed proportion with poor outcome 11%). The EGRIS model underestimated the risk of respiratory failure in GBS patients from Japan (predicted risk 13%, observed 17%). In the Malaysian cohort, differences between predicted and observed risks were more pronounced, and both models underestimated the risks of the outcomes of interest (mEGOS at admission – outcome at 6 months: predicted 13%, observed 31%; mEGOS at day 7 – outcome at 6 months: predicted 9%, observed 31%; EGRIS: predicted 23%, observed 44%). A prediction model similar to the mEGOS, the Erasmus GBS Outcome Score (EGOS), which uses age, preceding diarrhoea and the GBS disability score after 2 weeks to predict the inability to walk at 6 months, was validated in a GBS cohort from Northeast Brazil[43]. The authors found that 24% of the Brazilian GBS patients with an EGOS score of 5.5-7 were unable to walk independently at 6 months, while in the same subgroup of European patients from the EGOS development cohort, 52% were unable walk[43]. A limitation of this study was that the authors did not separately assess the discriminative ability of the EGOS in Northeast Brazil. Finally, the EGRIS was recently validated in a retrospective cohort from three Peruvian hospitals. The study only included patients who presented with the main GBS subtypes, AIDP and AMAN, and excluded clinical variants such as the pharyngeal-cervical brachial variant, MFS and Bickerstaff's encephalitis. The EGRIS was significantly higher in patients who required early ventilation compared to patients who did not, and the authors reported an AUC value of 0.63. Model calibration was assessed using the Hosmer-modified test, which showed good fit, but is often limited by power-issues. Surprisingly, the MRC sum score and bulbar weakness were not significant predictors of mechanical ventilation in this cohort from Latin America (although the odds ratio's did show a trend for a higher risk of mechanical ventilation with decreasing muscle strength and presence of bulbar weakness), and facial weakness was a protective factor[44].

Explaining differences in model performance

The various mEGOS and EGRIS validation studies show profound regional differences in model calibration, which are most likely explained by factors that are related to the outcome of interest, but are not included in the models itself. First, the in- and exclusion criteria of these studies differed. In our IGOS validation cohorts we included the

full spectrum of GBS clinical variants, while for the Malaysian study MFS patients were analysed separately, and clinical variants were excluded from the Peruvian cohort[41, 44]. As previous studies have shown that the disease severity and outcome vary between clinical subforms of GBS, differences in the distribution of these subforms may partly explain the variation in model calibration. Second, another explanation may be provided by differences in the electrophysiological subtypes. Previous studies have suggested that there are two types of axonal GBS cases: (i) patients with severe disability and poor outcome, and (ii) patients who initially have severe muscle weakness but show rapid clinical recovery. The latter subgroup is characterized by reversible conduction failure (RCF) or block on repeated NCS. At the molecular level this RCF seems to be caused by sodium-channel disruption and myelin detachment at the nodal and paranodal regions caused by antiganglioside antibodies and complement deposition, that is reversible in some cases and progresses to axonal degeneration in others. About one-third of the AMAN patients show RCF on repeated NCS[2]. The mEGOS and EGRIS models may perform differently in these axonal GBS cases with RCF, and the prevalence of this subtype may vary among the regional cohorts. Finally, other factors that also may have contributed to the regional differences in model calibration include variation in treatment or access to physiotherapy and rehabilitation[45]. In addition, for the EGRIS differences in the criteria for intubation among countries or differences in doctor's behaviour regarding intubation also may have played a role. It is important to get further insight into the factors that influence outcome of GBS, as outcome predictions may be improved by adding these factors to the existing models. An important lesson learned from previous validation studies, is that the accuracy of the model predictions may vary depending on the patient selection and the clinical setting to which the model is applied. Therefore, when the mEGOS and EGRIS are applied to new settings, clinicians should pay attention to differences in predicted and observed outcomes, and should be careful in using prediction-based cut-off values to guide clinical decision making.

Biomarkers in GBS

Most of the existing prediction models for GBS only include clinical factors that can be determined early in the disease course[39, 40, 43, 46]. The advantage of such models is that they are widely applicable and may guide treatment decisions. Nonetheless, there is a growing interest in potential biomarkers that could further improve diagnostic accuracy, outcome prediction, and monitoring of treatment response in GBS. In **Chapter 2.2** we discussed the prognostic value of the CSF protein level, and showed that a high protein level was independently associated with more severe disease in the acute phase. Several other potential biomarkers have been identified in previous studies. In a Dutch study, low serum ΔIgG levels were independently associated with higher disability, more severe muscle weakness and a worse outcome in GBS patients treated with a

standard dose of IVIg[20]. In addition, serum albumin is an easily accessible biomarker that has been established as a prognostic factor in various diseases[47-49]. A study in severely affected GBS patients from The Netherlands found that both pre- and posttreatment hypoalbuminemia were associated with an increased risk of respiratory insufficiency, and that posttreatment hypoalbuminemia also was associated with a smaller chance to walk unaided at 3 and 6 months, independent of other prognostic factors[50]. In addition, adding serum albumin levels to the EGRIS and mEGOS improved the discriminative ability of these models[50]. Neurofilament light chain (NfL) is an important marker for axonal damage that is extensively studied within the whole field of neurology. Several small studies showed that NfL levels in serum and CSF are increased in GBS and are related to poor outcome[51-54]. A recent Spanish study assessed the relation between serum and CSF NfL levels and clinical characteristics, electrophysiological subtypes and outcome of GBS. The study showed that patients with the pure motor variant or AMAN subtype had higher NfL levels than patients with typical GBS or AIDP, and that higher baseline serum NfL was associated with a worse clinical outcome, also when corrected for the mEGOS predictors[55]. In contrast to NfL, CSF sphingomyelin was proposed as a promising marker for active demyelination in patients with AIDP and CIDP. It was also shown to correlate with disease severity based on several established outcome scales[56], but further studies are needed to define the independent prognostic value of CSF sphingomyelin. Finally, in a subgroup of GBS patients anti-ganglioside antibodies can be detected in serum, which have been shown to be closely related to specific GBS clinical variants and NCS subtypes. A study from Japan found that patients with anti-GD1a antibodies more often had a poor outcome, especially when they also had a high mEGOS score[57]. Further studies will be performed within IGOS to confirm these findings and to determine the usefulness of these biomarkers in clinical practice.

In **Chapter 3.4** we used the IGOS-1500 cohort to identify factors associated with mechanical ventilation in GBS, including clinical factors, but also CSF features and NCS characteristics. In addition, we developed a more simplified clinical model which can be used to predict the risk of mechanical ventilation at different time points within the first two months from disease onset. In univariate logistic regression analysis clinical factors that were significantly associated with mechanical ventilation included higher age, decreased muscle strength, cranial nerve involvement, high disease progression rate, areflexia and autonomic dysfunction. A low forced vital capacity was associated with a higher risk of mechanical ventilation, also when corrected for the presence of facial and bulbar weakness. When we assessed the available raw NCS data we found that a demyelinating subtype and an early (< 1 week from study entry) conduction block of the peroneal nerve were both associated with a higher risk of mechanical ventilation. We did not find an association between CSF features and mechanical ven-

tilation (except for a lower risk of mechanical ventilation in patients with a mild CSF pleocytosis, 5-10 cells/µl), nor did we find an association with positive serology for *C. jejuni*, *M. pneumoniae,* EBV, CMV or HEV. We used Cox regression to develop a simplified clinical model to predict the risk of mechanical ventilation, which eventually included bulbar weakness, time from onset of weakness to admission, neck flexor strength, and bilateral hip flexor strength, and had a similar AUC value (0.84) as compared to the original EGRIS. Because of the small number of patients in whom a nerve conduction study was performed within the first week, we were unable to include NCS variables in the multivariate model. However, we did assess the independent predictive value of an early conduction block of the peroneal nerve when corrected for our final multivariate clinical model, which remained significant. Our novel multivariate model was both internally validated, and internally-externally validated by geographic cross-validation, which demonstrated that the model performed well across different regional settings. In line with previous reports, our study found a strong association between mechanical ventilation and the disease progression rate, facial and bulbar weakness, and disease severity of GBS[40, 46]. In multivariate analysis, it was shown that the inclusion of only three individual muscle MRC scores provided similar discriminative ability as including the full MRC sum score, which facilitates the use of this new model in clinical practice. The role of nerve conduction studies in daily practice is to support the diagnosis of GBS, especially in atypical cases. The optimal time point to perform these studies, as often advised in clinical guidelines, is one to two weeks after symptom onset, as this increases the likelihood of finding abnormalities. The current study however shows that it also may be useful to perform NCS at an earlier time point (within the first week), as this may provide important prognostic information. Our study did not find an association between positive infection serology and mechanical ventilation, although a previous study found an increased risk of mechanical ventilation in GBS patients with a serologically confirmed preceding CMV-infection[58]. This may be related to the limited number of patients within the IGOS cohort in whom a preceding infection was identified. An important conclusion from this study was that the prediction of mechanical ventilation in GBS could not be further improved by adding more or distinct clinical factors. Future studies should therefore investigate the additive prognostic value of NCS characteristics and biomarkers for the prediction of GBS outcome.

PREDICTION OF OUTCOME – summary of findings and clinical implications

I. The mEGOS and EGRIS can be used in the full spectrum of GBS clinical variants, and are also internationally generalizable.

II. A more accurate, region-specific version is available for patients from European and North-American countries: mEGOS-Eu/NA and EGRIS-Eu/NA. For patients from other regions the original mEGOS and EGRIS can be used.
III. Clinical decision making should not be fully driven by prediction models. Instead, prediction models can be used to support clinical decisions.
IV. We developed a more simplified clinical model to predict the risk of mechanical ventilation in GBS (modified Erasmus GBS Respiratory Insufficiency Score, mEGRIS), including: bulbar weakness, time from onset of weakness to admission, neck flexor strength, and bilateral hip flexor strength.
V. NCS do not only support the diagnosis of GBS, but also may provide important prognostic information.

TREATMENT

Current treatment practice of GBS worldwide

In daily practice, dilemmas commonly occur on whether or not to provide treatment in specific subgroups of GBS patients, as most treatment trials have focussed on the subgroup with "classic" GBS, who have lost the ability to walk. At present, evidence for the efficacy of treatment in mildly affected patients is limited, it's currently unknown whether treatment improves outcome in patients with GBS variants, and there's no general consensus on how to treat GBS patients who haven't responded to the first treatment or who continue to deteriorate. In absence of an international treatment guideline, this lack of evidence for treatment efficacy in certain GBS subgroups may lead to varying treatment practice among hospitals and countries. In **Chapter 4.1** we described the variation in treatment practice of GBS by using data from first 1300 patients included in the IGOS. This study showed that the frequency of different types of treatment – i.e. IVIg, PE, corticosteroids – varied among countries, and that even in situations where evidence for treatment efficacy was lacking clinicians often decided to provide treatment.

Treatment related fluctuations (TRF)

Five percent of the patients in the IGOS-1300 cohort experienced a TRF, of whom only two-thirds were re-treated with a second course of immunotherapy. Previous studies have reported TRFs in 6-10% of patients with GBS[30, 59-61]. The low proportion of TRFs in the IGOS cohort may be related to the definition that was used for a TRF. Most previous studies defined a TRF by a secondary deterioration of five or more points on the MRC sum score or one or more grades on the GBS disability scale, while in IGOS TRFs were reported at the discretion of the treating physician. In addition, because IGOS

used a standardized study protocol with visits at fixed time points, TRFs that occurred in between subsequent study visits may have been missed. Although the underlying mechanism causing TRFs is not yet fully unravelled, TRFs are considered to result from a transient effect of the first treatment in patients who still have active disease. Therefore, consensus-based guidelines often advice to provide a second course of treatment in patients with a TRF[62]. In IGOS one-third of the GBS-TRF patients were not re-treated. The decision to provide a second treatment depended on the timing of the TRF, the severity of symptoms, and the type of hospital. Patients who were re-treated had lower muscle strength and a larger proportion was unable to walk independently around the time of the TRF, they were more often admitted to a university hospital and the TRFs occurred at an earlier time point after the start of the first treatment than in patients who were not re-treated for the TRF. In previous studies, the proportion of GBS-TRF patients who were re-treated varied from 72-81%[59, 61]. In about half of these patients, a second treatment was not provided because the deterioration was considered to be mild[61].

Mild GBS and MFS

In the IGOS-1300 cohort, about three-quarters of the patients with mild GBS and MFS received treatment, even though it is often recommended that these patients do not require immunotherapy because of the favourable clinical course. Most trials that investigated the efficacy of PE and IVIg in GBS only included patients who were unable to walk independently. One RCT assessed the efficacy of PE in GBS cases with mild disease and found that the time to hospital discharge and the onset of motor recovery was significantly shortened in the patients who were treated with 2 PE sessions compared to patients who received supportive care only[63]. The mild GBS cases in IGOS who were treated with immunotherapy more often had involvement of the autonomic nervous system, which may have prompted the decision to start treatment. IgG antibodies to GQ1b have been found in 83-100% of typical MFS patients and are considered to play an important role in the pathogenesis as GQ1b is highly expressed in the oculomotor nerves and in the muscle spindles in arms and legs[38]. Nonetheless, no difference was found in the time to recovery from ataxia or ophthalmoplegia between MFS patients who were treated with PE or supportive care only[64]. In addition, in a study that compared the clinical recovery from ataxia and ophthalmoparesis among MFS patients treated with IVIg, PE or supportive care only, IVIg seemed to slightly hasten recovery, although outcome after one year was not different between the treatment arms[65]. Even though these findings were based on retrospective data, it is generally considered that MFS patients do not require immunomodulating treatment because of the good natural recovery. An exception is provided by MFS patients with complicated disease, who show overlap with GBS, for whom treatment with either IVIg or PE is recommended[38]. In our IGOS study cohort, we did not find any differences between the MFS patients who did

and did not receive treatment, except for the proportion of patients with pain, which was higher in the treated group. However, because we only determined the presence of ataxia or bulbar weakness in IGOS and did not assess the severity of these symptoms, we cannot exclude the possibility that the severity of symptoms may have played a role in the decision to treat patients with MFS. In addition, if the decision to treat was prompted by changes in the clinical status that occurred in between IGOS visits, these may have been missed.

GBS patients who show no clinical response to treatment with IVIg or PE

Some patients with GBS show no response to treatment with IVIg or plasma exchange, or even continue to deteriorate. In the IGOS-1300 cohort, one-third of the 743 severely affected GBS patients showed no clinical improvement after the first treatment, and in one-third (n=82/235) of these patients a second course of immunotherapy was administered even though there was no evidence to substantiate this decision. Within IGOS, a substudy was performed to determine the efficacy of a second course of IVIg in GBS patients with a poor prognosis, which was defined by an mEGOS score of 6 to 12 at day 7 of the study (I-SID). Patients who received a second IVIg course were subdivided into an early second-IVIg group (i.e. second course within 2 weeks from the start of the first IVIg course) and a late second-IVIg group (i.e. second course within 2-4 weeks from the start of the first IVIg), and were compared to patients who received only one IVIg course. Results were not in favour of a second IVIg course, and outcome was often worse in the patients treated with a second course. However, the number of patients in the second IVIg groups was small, and although the authors corrected for subgroup imbalances and potential confounding factors, confounding by indication may still have played a role[66]. In 2021, the results of the Second IVIg Dose in GBS (SID-GBS) trial were published, a double-blind randomized placebo-controlled trial that investigated the efficacy of an early second IVIg course in GBS patients with a poor prognosis. In this trial, the second IVIg course was administered within 7-9 days after the start of the first IVIg course, and the primary endpoint was the GBS disability score at 4 weeks. The study showed that a second IVIg course did not result in a better outcome than placebo, and was potentially more harmful as illustrated by the higher proportion of patients with thromboembolic complications in the second-IVIg group[67].

Novel pharmacological treatments

In **Chapter 4.2** we have provided the results of an update of a systematic review and meta-analysis that evaluated the efficacy of pharmacological treatments other than IVIg, plasma exchange and corticosteroids for GBS. Previous versions of this review already evaluated the efficacy of four different interventions for GBS: interferon beta-1a (IFNb-1a) versus placebo, brain-derived neurotrophic factor (BDNF) versus placebo,

CSF filtration versus plasma exchange, and tripterygium polyglycoside versus intravenous high-dose corticosteroids. A potential beneficial effect was only observed for tripterygium polyglycoside, a Chinese herbal medicine. However, all trials (including the tripterygium trial) were small and of very low-certainty evidence, and therefore no definitive conclusions could be drawn. With the update of this review, the results of two RCTs that evaluated the safety and efficacy of eculizumab, a complement factor 5 inhibitor, for GBS were included: the ICA-GBS and the JET-GBS study[68, 69]. Complement inhibiting therapies as treatment for GBS have gained more interest after clinicopathological and animal model studies showed evidence for a role of the complement cascade in the induction of nerve damage in GBS[70]. In the ICA-GBS and JET-GBS trials, eculizumab combined with IVIg was compared to IVIg and placebo, but no clear benefit or harm was observed with eculizumab. In the JET-GBS trial a larger proportion of patients treated with eculizumab was able to run after 24 weeks, but further studies with larger sample sizes are required to confirm these results. Furthermore, a recent phase 1b trial with a complement factor 1 inhibitor (ANX005) conducted in a GBS cohort from Bangladesh showed an early, dose-dependent improvement of muscle strength. Authors defined muscle strength by the MRC sum score, which is an important predictor of functional outcome in GBS that also correlated with the GBS disability score at 8 weeks in the same study (PNS abstract, poster no. 204). The safety and tolerability, and drug-drug interactions of ANX005 in combination with IVIg in GBS patients are currently being assessed in a multicentre open-label study (ClinicalTrials.gov Identifier: NCT04035135).

TREATMENT FOR GBS – summary of findings and clinical implications

I. The treatment practice of GBS varies among countries and hospitals.
II. Patients who show no clinical improvement after the first treatment were often provided a second treatment, while at the time of the study there was no evidence to support this decision. A recent RCT has shown that an early second IVIg course in GBS patients with a poor predicted outcome is not effective.
III. One-third of the patients with a TRF are not re-treated for their TRF. The decision to either or not treat patients with a TRF depends on the severity of the TRF, the timing of the TRF and the type of hospital.
IV. Patients with mild GBS and MFS were treated in about 75% of cases, while this is not advised by consensus-based guidelines because on the favourable natural course.
V. Complement factor inhibitors may be effective treatments for GBS when combined with IVIg, but larger studies are required.

METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS OF IGOS

Most of the studies described in this thesis were performed with data from the IGOS study. The IGOS is the first large scale, prospective cohort study on GBS, collecting longitudinal data on the full spectrum of GBS patients. Since the start of the study in 2012, 2000 patients have been included in more than 150 centres, in 21 countries, across five continents[11]. The observational study design and broad inclusion criteria of IGOS have the advantage of providing real-world data on the full spectrum of GBS patients, which reflects the true variability seen in current clinical practice. Because of the multicentre and standardized study design, IGOS is the first study to enable a direct comparison between GBS patients from different countries and regions. By using the IGOS data we have been able to confirm the regional variation of GBS, which is of great importance as it provides a basis for further research on the underlying pathophysiological mechanism, and for identifying novel predictors of disease course and outcome in individual patients with GBS.

Nevertheless, the IGOS has several limitations. First, the rather flexible and observational nature of the study at times resulted in highly variable data, especially among hospitals and countries, which complicated the analyses. For example, the IGOS study protocol did not include specified time points for the ancillary investigations. Examination of the CSF and NCS could be performed at any time during the disease course, at the discretion of the treating neurologist. In addition, NCS were not performed according to a prespecified protocol, but by use of local guidelines, and the criteria used to classify these studies also varied between centres. To increase the comparability of the NCS results among the IGOS participating centres, we generated a computer algorithm that classified all NCS according to the criteria of Hadden and colleagues, by using raw data from the first NCS and local reference values. Nevertheless, previous studies have shown that the electrophysiological classification may differ depending on the timing of the investigation and the criteria set that is used for classification. In addition, the NCS classification may change after repeated studies, as was illustrated for GBS patients with reversible conduction failure[2, 71, 72]. Therefore, if we want to improve the diagnostic utility of NCS for GBS a more standardized protocol, including serial NCS and different criteria sets, will be required. Second, the majority of the IGOS patients were included in Europe and North America, while patients from Asia, South America and Africa are relatively underrepresented. Third, tertiary care medical facilities with specific expertise in neuromuscular diseases represent the majority of participating centres in IGOS, which may have favoured the inclusion of more severe, complicated GBS cases[1]. This also was illustrated by a study from Al-Hakem et al which compared a population-based cohort of Danish patients with GBS to the Danish patients included in IGOS and showed that the

IGOS patients were more severely affected[73]. Whether differences in referral bias among countries may have contributed to the regional differences in disease severity and outcome that were observed in IGOS is unknown. Fourth, although detailed information on clinical characteristics and ancillary investigations were collected in IGOS during a follow up of minimum one year, additional, more specified data may be required to study specific subgroups of GBS patients or specific 'topics' within the field of GBS research[11]. For example, clinical examination and outcome assessment in children with GBS require a different approach than in adults, especially for very young children. In addition, various studies have assessed the sensitivity of different clinical features and biomarkers for GBS diagnosis, but little is known about their specificity, which would require data collection in patients with other neurological diseases or GBS mimics. The recent Zika virus epidemic and SARS-Cov-2 pandemic have increased our interest in infections that can precede GBS, but to establish a causal relation a case-control design is needed. Furthermore, there is a need for better treatments for GBS, but the performance of sufficiently powered RCTs is limited by the low disease incidence. This poses the question what alternative study designs could be used to study treatment effects, and how the IGOS data could contribute to this.

FUTURE RESEARCH

GBS Diagnosis

As GBS constitutes a disease spectrum of variants and subtypes with a highly variable clinical presentation, the differential diagnosis is comprehensive which may complicate early disease recognition and diagnosis. In order to minimize (secondary) axonal nerve damage it is important to have an accurate diagnosis and to start treatment as soon as possible. Currently, a prospective study is being conducted in academic and regional hospitals in The Netherlands that aims to improve the diagnosis of GBS by comparing the clinical presentation and diagnostic test results in patients with GBS and patients with other diseases mimicking GBS ("GBS Mimics Study"). This study will describe the actual differential diagnosis in current (Dutch) clinical practice and provides the opportunity to determine the specificity of clinical features and diagnostic test findings. This study will probably further show the limitations of the 'albuminocytologic dissociation' as a diagnostic marker for GBS, which may be found equally in patients with mimics of GBS. However, the IGOS and GBS Mimics Study also provide the possibility to identify novel positive and negative predictive diagnostic markers, including the serum/CSF albumin ratio, serum NfL and CSF sphingomyelin. The latter may provide a promising marker for active inflammation and demyelination that could be useful to monitor disease activity and treatment efficacy, also in patients with a transition to CIDP.

Prediction of outcome

The mEGOS and EGRIS prognostic models for GBS, including the region-specific versions for patients from European countries and North America, do not provide the "gold standard" for outcome prediction in GBS. Differences in model performance may still be observed depending on the clinical setting and patient population to which the models are applied. Continuous validation of these models will be needed to confirm their validity in regions that are currently underrepresented in IGOS, but also in light of the evolving new therapies for GBS which may be applied to specific subgroups of patients and may influence prognosis and outcome. Efforts also should be made to recalibrate the mEGOS and EGRIS in a larger Asian GBS cohort, to develop a region-specific version for Asian GBS patients. Furthermore, studies should be performed to assess the independent prognostic value of specific biomarkers in GBS, such as serum albumin and ΔIgG level, anti-ganglioside antibodies, serum and CSF NfL levels, and electrophysiological markers. Inclusion of the validated and recalibrated mEGOS and EGRIS models in international guidelines for GBS will enhance their implementation in clinical practice, but their use in specific countries will also depend on factors such as resource availability and cost-effectiveness issues. Decision curve analysis can help to define and optimize clinical usefulness of prognostic models by weighting risks of false positive and false negative results, also taking into account factors such as treatment costs and availability of resources. Most prognostic modelling studies and treatment trials in GBS have used the GBS disability score as the primary outcome measure. Whilst the widespread use of the GBS disability score facilitates comparison among studies, a limitation of this score is that it focuses on walking ability and negates the importance of other clinical features of GBS (i.e. weakness of upper limb muscles, cranial nerve involvement, sensory disturbances and pain) and their impact on functional ability and patient well-being. Efforts have been made to develop patient reported outcome measures with optimal clinimetric qualities that encompass a broader range of symptoms, such as the I-RODS [74]. But before these measures can be used in prognostic models and RCTs further validation and adjustment to improve their generalizability are required, for which the IGOS provides the ideal platform.

Treatment

New and more effective treatments are required to improve outcome and reduce residual disability of GBS. The progress made in understanding the pathogenesis of GBS could be used as an inspiration to identify targets for new treatments. Antibody-mediated nerve damage is considered an important disease mechanism in GBS, and therapies that target these antibodies or down-stream effector mechanisms such as complement activation may inhibit further nerve damage and improve functional outcome of patients with GBS. Imlifidase is an IgG-degrading enzyme that is currently being studied in GBS patients

in a multicentre open-label phase II trial. GBS patients will be treated with Imlifidase followed by a standard course of IVIg. Each patient will be matched to a number of control patients within IGOS for comparative studies to determine the relative safety and efficacy of Imlifidase. Matching will be performed based on geographical location, age, preceding diarrhea and disease severity (ClinicalTrials.gov Identifier: NCT03943589). In addition, results are awaited of a multicentre open-label study investigating the safety and tolerability, and drug-drug interactions of a complement factor 1 inhibitor (ANX005) when combined with a standard course of IVIg in patients with GBS (ClinicalTrials.gov Identifier: NCT04035135). Patients in low-income countries often cannot afford treatment with IVIg or PE, or the required equipment and infrastructure is not available in the hospitals. Small volume plasma exchange (SVPE) may provide a simple and less expensive alternative for conventional plasma exchange, which was already shown to be safe and feasible in 20 severely affected patients with GBS from Bangladesh[75]. A phase III trial will have to be performed to determine the efficacy of SVPE in comparison to conventional treatments for GBS. IVIg and plasma exchange have been proven effective in RCTs for severely affected GBS patients who have lost the ability to walk, while guidelines for treatment of specific subgroups of GBS patients – i.e. mild GBS, GBS-TRF or MFS – are only based on results from smaller, non-randomized studies or solely on expert consensus. Additional studies should be performed to assess treatment efficacy in these specific subgroups of GBS patients. Because performing RCTs in GBS is complicated by the rare nature of the disease, observational comparative effectiveness research that uses matched (historical) controls from observational studies – as will be dome for the Imlifidase trial – may provide a suitable alternative. Finally, all evidence regarding treatment of GBS will need to be combined in an international treatment guideline. A joint task force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS) is currently working on an international guideline for the management of GBS, which is expected in 2022.

IGOS 2.0

In the past years the IGOS database has proven itself as an inexhaustible source of 'real world' data and biosamples, that has helped us in answering many of our research questions but has created even more new questions that cannot be addressed by the current IGOS study design. These include questions regarding outcome prediction and measurement in children with GBS, but also the development of novel outcome measures for adult GBS patients, and investigating the causal relationship between specific infections and GBS. Future GBS studies will focus more on selected subgroups of GBS patients, which will require more detailed data and a more specified study protocol. On the other hand it will remain important to compare data among hospitals and countries, and to increase the sample size of currently underrepresented regions. The IGOS could

stimulate such research by providing a template study protocol with different modalities:

i. 'basic' study protocol with a minimum number of assessments to answer basic questions and compare GBS patients among countries and regions. By limiting the number of assessments and additional investigations this also provides developing countries with limited resources the opportunity to participate in IGOS.
ii. template for more specific substudies, for example on preceding infections (which will also require the collection of data on control subjects), nerve conduction studies (performed at fixed time points, according to a prespecified protocol, using different criteria sets for classification), biomarkers, children (using outcome measures that can be applied in children), treatment efficacy (comparative effectiveness research), etc.

Each participating centre may decide for themselves in which study module they would like to participate, also based on the availability of resources. The established IGOS network can subsequently be used to stimulate and facilitate collaboration among centres that are participating in similar modules.

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6

Summary

SUMMARY

Guillain-Barré syndrome is the most common cause of acute flaccid paralysis worldwide. In typical cases, the disease presents with a rapidly progressive symmetrical limb paresis and hypo- or areflexia, and the peak severity is reached within four weeks. Patients with GBS show substantial variability in presenting symptoms and severity, subtype, clinical course and outcome. Part of this variability may be explained by regional differences, as indicated by comparing studies from single countries. However, as these single country studies used different study designs, diagnostic criteria or focused on selected subgroups of GBS patients, an extensive, international study, with standardized data collection was required for a more systematic comparison between regions. The current standard treatment for GBS consists of either intravenous immunoglobulins (IVIg) or plasma exchange and the same regimen is used for all patients, despite substantial variability in disease severity and clinical course. Several prognostic models have been developed that can be used in individual patients with GBS to predict the risk of respiratory insufficiency (Erasmus GBS Respiratory Insufficiency Score, EGRIS) or the risk of being unable to walk independently (modified Erasmus GBS Outcome Score, mEGOS). As new treatments are being developed, these models may provide a means to select those patients who may benefit most from additional or more vigorous treatment. However, both prognostic models were based on data from Dutch GBS patients and only limited data is available on the applicability of these models in other countries.

These knowledge gaps are addressed in the research described in this thesis. The main aims of the studies were: (I) to describe the variability in clinical presentation, diagnostic features, subtype, disease course, treatment and clinical outcome among GBS patients in general, and among patients from various regions, (II) to validate the mEGOS and EGRIS clinical models in GBS patients from countries outside The Netherlands, (III) to further improve outcome prediction in GBS by making region-specific adjustments to the mEGOS and EGRIS, and (IV) to identify novel predictors of respiratory insufficiency in GBS. Most of the studies in this thesis were based on data from the International GBS Outcome Study (IGOS), a prospective, observational, multicentre, cohort study on GBS that used a standardized study protocol to collect clinical and electrophysiological data and biomaterial from GBS patients from 21 countries, across five continents.

Chapter 2 is based on several studies that investigated the variability in symptoms, signs and diagnostic features of GBS. In chapter 2.1 data from the IGOS-1000 cohort was used to compare the presenting symptoms, disease course and clinical outcome among GBS patients from three main regions: Europe/Americas, Asia (without Bangladesh) and Bangladesh. This study demonstrated the variation of GBS between geographical re-

gions. GBS patients in Western countries (Europe, North-America) most often presented with a sensorimotor and demyelinating subform, while in patients from Asia pure motor forms and the Miller Fisher syndrome occurred more frequently. GBS patients in Bangladesh more often had an axonal subtype with involvement of motor nerves only, and had a more severe disease course and worse outcome. Factors that may play a role in defining this regional diversity that need to be studied further include differences in local exposure to infections, treatment and health care infrastructure, and host factors, including genetic and immunological characteristics. In the study described in chapter 2.2 we evaluated the variation in cerebrospinal fluid (CSF) protein level and cell count among GBS patients included in the IGOS-1500 cohort. The CSF protein level varied in relation to the timing of the lumbar puncture, the distribution of limb muscle weakness, the clinical variant and electrophysiological subtype. Our study showed that most GBS patients have a normal CSF cell count, but in a minority of cases more than 50 cells/μL were found, despite otherwise typical clinical features of GBS. This study showed that a normal CSF protein level does not exclude the diagnosis of GBS, especially early in the disease course. Furthermore, an increased CSF cell count requires additional diagnostic work-up to exclude other causes, but does not rule-out GBS.

Chapter 3 focuses on the prediction of clinical outcome in GBS. The mEGOS and EGRIS are prediction models for GBS that are commonly used in clinical practice. The mEGOS predicts the risk of being unable to walk independently in the first six months from disease onset, while the EGRIS predicts the risk of respiratory insufficiency within the first week from admission. In chapter 3.1 and 3.2 both models were validated in the IGOS-1500 cohort. Model performance, as expressed by the discriminative ability and calibration, was assessed in the full IGOS cohort and in subgroups from Europe/North America and Asia. These studies showed that the mEGOS and EGRIS can be used in the full spectrum of GBS, including mild forms and clinical variants, and are also valid in countries outside The Netherlands. The models are especially useful to distinguish patients with a high and low risk of the clinical outcomes of interest, which was illustrated by the area under the receiver operating characteristic curve (AUC) values: >0.7 in all subgroups for the mEGOS, and >0.8 in all subgroups for the EGRIS. Model calibration varied between regions, which may reflect differences in the prevalence of GBS subtypes or differences in treatment or health care resources. We developed a region-specific version of the mEGOS and EGRIS for GBS patients from European and North American countries, to improve the accuracy of the predictions for patients from this region. For GBS patients from countries outside Europe and North America the original mEGOS and EGRIS can be used to retrieve valid outcome estimations. In chapter 3.3 the mEGOS was validated in a subset of IGOS patients from Bangladesh. The discriminative ability of the mEGOS was worse in Bangladesh compared to other regions, although this may be

partially explained by the homogeneity of the cohort from Bangladesh. The predicted probabilities as estimated by the mEGOS model corresponded well to the observed outcomes in Bangladesh, indicating that the original mEGOS also can be used in Bangladesh and possibly in other low- and middle-income countries with a similar socio-economic status and health care infrastructure. In chapter 3.4 we developed a new model to predict the risk of mechanical ventilation in GBS based on a simplified EGRIS. We found that a model based on only three individual muscle groups provided similar discriminative ability as a model that used the full MRC sum score, which facilitates the applicability in clinical practice. Another advantage of this simplified EGRIS compared to the original model is that it can be used to predict the risk of respiratory insufficiency at multiple time point during the disease course. Furthermore, we found that adding more clinical factors to the model did not improve the discriminative ability. An early conduction block of the peroneal nerve was found to be an independent predictor of respiratory insufficiency in GBS. This implicates that, to improve outcome prediction in GBS more emphasis should be put on the prognostic value of electrophysiological characteristics and biomarkers, rather than adding more clinical factors.

In chapter 4.1 we compared the treatment practice of GBS among different countries from the IGOS-1300 cohort. Overall, IVIg was the most commonly provided first-line treatment, but the frequency of the various treatments (e.g. IVIg, plasma exchange or other immunomodulatory treatments) differed among countries. In one-third of the severely affected patients who showed no clinical improvement after the first treatment, a second cycle of immunomodulatory treatment was provided, although at the time of the study there was no evidence for the efficacy of an early second treatment course. Patients with a treatment-related fluctuation (TRF) were re-treated in only two-thirds of cases. GBS-TRF patients were more often treated if they had severe limb muscle weakness or were unable to walk independently, if the TRF occurred at an early time point during the disease course, and if they were admitted to a university hospital. Finally, despite the favourable disease course, patients with mild GBS and MFS were treated in about 75% of cases. Except for a higher proportion of patients with autonomic disturbances and pain in the treated group, we did not identify any other differences between the treated and untreated MFS and mild GBS cases. These differences in treatment practice of GBS highlight the importance of an international treatment guideline, to standardize and thereby optimize treatment worldwide. A joint task force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS) is currently working on an international guideline for the management of GBS, which is expected in 2022. Furthermore, many studies are being performed to assess the safety and efficacy of novel treatments for GBS, as morbidity and mortality still remain substantial. In chapter 4.2 we present the results of a systematic review and meta-

analysis that investigated the safety and efficacy of pharmacological treatments other than IVIg, plasma exchange and corticosteroids for GBS. None of the studies included in this reviews had sufficient power to detect any significant harm or benefit from the assessed treatments. Two of the most recent studies included in this review assessed the efficacy of a complement factor 5 inhibitor – eculizumab – for GBS, which may be a promising treatment as the complement cascade was shown to play an important role in the induction of nerve damage in GBS. However, further studies, with larger numbers of patients, are warranted.

The final chapter (chapter 5) discusses the findings in this thesis in relation to the existing literature, elaborates on the limitations and methodological considerations, and provides directions for future research.

SAMENVATTING

Het Guillain-Barré syndroom is wereldwijd de meest voorkomende oorzaak van een snel progressieve (tetra)parese. In klassieke gevallen presenteert de ziekte zich met symmetrisch zwakte van de ledematen en hypo- of areflexie, waarbij het dieptepunt wordt bereikt in de eerste vier weken. Er is grote variatie in het type klachten waarmee GBS patiënten zich presenteren, de ziekte ernst, het subtype, ziektebeloop en ziekte uitkomst. Op basis van eerdere studies uit verschillende landen wordt verondersteld dat een deel van deze variatie kan worden verklaard door regionale verschillen. Door verschillen in studie design, diagnostische criteria of inclusie van specifieke subgroepen van GBS patiënten zijn de resultaten van deze studies onderling echter moeilijk te vergelijken. Voor een meer systematische vergelijking van GBS patiënten uit verschillende regio's is een internationale, multicenter studie met gestandaardiseerde dataverzameling een vereiste. Ondanks de verschillen in ernst van de symptomen en prognose worden alle patiënten met GBS op dezelfde manier behandeld, met plasmaferese of intraveneuze immuunglobulinen (IVIg). Voor individuele patiënten met GBS kan aan de hand van bestaande prognostische modellen voorspeld worden hoe groot de kans is dat zij aan de beademing raken (Erasmus GBS Respiratory Insufficiency Score, EGRIS) of niet meer zelfstandig kunnen lopen (modified Erasmus GBS Outcome Score, mEGOS). Deze modellen zouden ook een rol kunnen spelen bij de ontwikkeling van nieuwe behandelingen voor GBS, door patiënten te selecteren die mogelijk het meeste baat zullen hebben bij een meer intensieve behandeling. De mEGOS en EGRIS zijn echter ontwikkeld op basis van data van Nederlandse GBS patiënten en er is beperkt bewijs voor de validiteit van deze modellen in andere landen.

Het doel van het onderzoek in dit proefschrift was: (I) het beschrijven van de variatie in de klinische presentatie, diagnostische kenmerken, subtype, ziektebeloop en behandeling van GBS in het algemeen, en tussen patiënten uit verschillende regio's; (II) het valideren van de mEGOS en EGRIS in landen buiten Nederland; (III) het verbeteren van de mEGOS en EGRIS op basis van regio-specifieke karakteristieken; (IV) het identificeren van nieuwe voorspellers voor respiratoire insufficiëntie bij GBS. Het merendeel van de studies in dit proefschrift zijn gebaseerd op data van de "International Guillain-Barré Syndrome Outcome Study (IGOS)", een prospectieve, observationele, multicenter cohort studie waarin klinische en elektrofysiologische data, en biomateriaal worden verzameld van GBS patiënten, afkomstig uit 21 landen van 5 verschillende continenten, op basis van een gestandaardiseerd studieprotocol.

Hoofdstuk 2 is gebaseerd op studies naar de variatie in klinische symptomen, en bevindingen bij neurologisch en aanvullend onderzoek bij GBS. Data van het IGOS-1000

cohort zijn gebruikt in hoofdstuk 2.1 voor het vergelijken van de ziektesymptomen bij presentatie, het ziektebeloop en de prognose tussen GBS patiënten uit drie verschillende regio's: Europa/Amerika, Azië (zonder Bangladesh) en Bangladesh. Deze studie toonde de diversiteit van GBS, met uitgesproken verschillen tussen geografische regio's. GBS patiënten in Westerse landen (Europa, Noord Amerika) presenteerden zich vaker met het sensomotore en demyeliniserende subtype, terwijl bij Aziatische patiënten de puur motore variant en het Miller Fisher syndroom frequenter voorkwamen. GBS patiënten uit Bangladesh hadden vaker het axonale subtype, met betrokkenheid van alleen motore zenuwen, en deze patiënten waren vaak ernstiger aangedaan en hadden een slechtere prognose. Factoren die een rol kunnen spelen bij de regionale variatie van GBS, die verder bestudeerd moeten worden in toekomstig onderzoek, zijn: verschillen in de prevalentie van infecties, behandeling, structuur van de gezondheidszorg, en patiënt-specifieke kenmerken zoals genetische en immunologische karakteristieken. De studie in hoofdstuk 2.2 beschrijft de variatie van het totaal eiwit en celgetal in de liquor bij GBS patiënten uit het IGOS-1500 cohort. De eiwitconcentratie in de liquor varieerde in relatie tot de tijd tot de lumbaalpunctie, de verdeling van de spierzwakte in de ledematen, de klinische variant en het elektrofysiologische subtype. De meerderheid van de GBS patiënten had een normaal celgetal in de liquor, echter in enkele gevallen werd een celgetal >50 cellen/µL gevonden. Behoudens het verhoogde celgetal, presenteerden deze patiënten zich met de typische klinische karakteristieken van GBS. Deze studie laat zien dat een normale eiwitconcentratie in de liquor de diagnose GBS niet uitsluit. Een verhoogd celgetal in de liquor sluit de diagnose GBS eveneens niet volledig uit, maar maakt het wel noodzakelijk om aanvullend onderzoek te verrichten om alternatieve diagnoses uit te sluiten.

Hoofdstuk 3 richt zich op het voorspellen van de prognose bij GBS. De mEGOS en EGRIS zijn prognostische modellen voor GBS die frequent gebruikt worden in de klinische praktijk. Met de mEGOS kan voorspeld worden hoe groot de kans is dat een patiënt met GBS niet zelfstandig zal kunnen lopen in het eerste half jaar na stellen van de diagnose. De EGRIS voorspelt het risico op respiratoire insufficiëntie in de eerste week na ziekenhuisopname. Hoofdstuk 3.1 en 3.2 beschrijven de validatie van deze modellen in het IGOS-1500 cohort. Voor beide modellen werd gekeken naar het discriminerend vermogen en de calibratie, in het gehele IGOS cohort en in subgroepen uit Europa/Noord Amerika en Azië. Deze studies toonden dat de mEGOS en EGRIS gebruikt kunnen worden voor het voorspellen van de prognose bij alle patiënten met GBS, onafhankelijk van de ernst van de symptomen of de klinische variant, en dat de modellen ook toepasbaar zijn buiten Nederland. De modellen zijn vooral geschikt om een onderscheid te maken tussen patiënten met een laag en hoog risico op respiratoire falen (EGRIS) dan wel om niet zelfstandig te kunnen lopen (mEGOS). Dit wordt geïllustreerd aan de hand van de

“area under the receiver operating characteristic curve (AUC)” waarden: >0.7 voor de mEGOS en >0.8 voor de EGRIS. De calibratie, ook wel de nauwkeurigheid of precisie van de voorspellingen, verschilde per regio. Deze regionale verschillen kunnen mogelijk verklaard worden door verschillen in de prevalentie van GBS subtypen of verschillen in behandeling of beschikbaarheid van medische middelen. Voor zowel de mEGOS als de EGRIS werd een regio-specifieke versie ontwikkeld voor patiënten uit Europa en Noord Amerika, om hiermee de nauwkeurigheid van de voorspellingen voor patiënten uit deze regio te verbeteren. Voor het voorspellen van de prognose bij patiënten met GBS buiten Europa of Noord Amerika kunnen de originele mEGOS en EGRIS gebruikt worden. Hoofdstuk 3.3 beschrijft de validatie van de mEGOS in een subgroep van GBS patiënten uit Bangladesh. Het discriminerend vermogen van het model was minder goed in Bangladesh ten opzichte van andere regio’s, wat deels verklaard zou kunnen worden door de homogeniteit van het cohort uit Bangladesh. De voorspelde kansen om niet zelfstandig te kunnen lopen correspondeerden goed met de geobserveerde aantallen GBS patiënten die niet zelfstandig konden lopen in Bangladesh. Op basis van deze resultaten kan geconcludeerd worden dat de originele mEGOS ook gebruikt kan worden in Bangladesh, en mogelijk ook in andere landen met een laag- of midden inkomen met verglijkbare socio-economische klasse en gezondheidszorg. In hoofdstuk 3.4 hebben we een nieuw model ontwikkeld voor het voorspellen van beademing in GBS, gebaseerd op een vereenvoudigde versie van de EGRIS. De studie toonde dat een model gebaseerd op drie individuele spiergroepen een vergelijkbaar discriminerend vermogen had als een model dat gebruik maakt van de MRC sum score, wat de toepasbaarheid in de klinische praktijk verbetert. Een voordeel van het gesimplificeerde model ten opzichte van de originele EGRIS is dat het kan worden gebruikt voor de voorspelling van respiratoire insufficiëntie op verschillende tijdspunten gedurende het ziekte beloop. Tevens toonde de studie dat het toevoegen van extra klinische voorspellers aan het model niet leidt tot een verbetering van het discriminerend vermogen. Een vroegoptredende geleidingsblokkade van de nervus peroneus was een onafhankelijke voorspeller van beademing bij GBS. Dit impliceert dat voor het verbeteren van prognostische modellen voor GBS de nadruk moet liggen op het voorspellend vermogen van elektrofysiologische karakteristieken of biomarkers, en niet op het toevoegen van extra klinische factoren.

In hoofdstuk 4.1 wordt de behandeling van GBS vergeleken tussen verschillende landen uit het IGOS-1300 cohort. Gemiddeld genomen was IVIg de meest toegepaste eerstelijns behandeling, maar de frequentie van de verschillende behandelingen (IVIg, plasmaferese en andere immuun modulerende behandelingen) varieerde tussen de landen. Bij een derde van de ernstig aangedane GBS patiënten die geen verbetering lieten zien na de eerste behandeling, werd een tweede immuun modulerende behandeling gestart, ondanks het ontbreken van bewijs voor de effectiviteit hiervan. Slechts twee derde van

de patiënten met een "treatment-related fluctuation (TRF)" werd behandeld voor de TRF. GBS patiënten met een TRF werden vaker behandeld als ze ernstige spierzwakte hadden of niet meer in staat waren om zelfstandig te lopen, als de TRF op een vroeg tijdspunt in het ziekte beloop optrad, of als ze waren opgenomen in een universitair ziekenhuis. Ten slotte, ondanks het gunstige ziektebeloop werd drie kwart van de patiënten met milde GBS of het Miller Fisher syndroom behandeld. Behoudens een hoger percentage patiënten met autonome stoornissen en pijnklachten in de behandelde groep, werden geen verschillen tussen de behandelde en niet-behandelde milde GBS en MFS patiënten gevonden. Deze verschillen in de behandeling van GBS benadrukken het belang van een internationale richtlijn. De European Federation of Neurological Societies (EFNS) en de Peripheral Nerve Society (PNS) werken op dit moment samen aan een internationale richtlijn voor de behandeling van GBS, welke in 2022 verwacht kan worden. Ondanks de bestaande behandelingen is de morbiditeit en mortaliteit van GBS nog steeds aanzienlijk. Op dit moment zijn er verschillende studies gaande naar de veiligheid en effectiviteit van nieuwe behandelingen voor GBS. In hoofdstuk 4.2 worden de resultaten beschreven van een systematische review en meta-analyse naar de veiligheid en effectiviteit van farmacologische behandelingen anders dan IVIg, plasmaferese en corticosteroïden voor GBS. Geen van de geïncludeerde studies had voldoende power voor het aantonen van een significant effect (voordelig of schadelijk) van de bestudeerde behandeling. De twee meest recent geïncludeerde studies onderzochten de effectiviteit van een complement factor 5 remmer – eculizumab – voor de behandeling van GBS. Complement remmers zijn mogelijk een veelbelovende behandeling voor GBS, omdat studies hebben aangetoond dat de complement cascade een belangrijke rol speelt in het induceren van zenuwschade. Echter, meer studies met grotere aantallen patiënten zijn nodig om dit verder in kaart te brengen.

Het laatste hoofdstuk (hoofdstuk 5) bespreekt de bevindingen uit dit proefschrift in relatie tot de bestaande literatuur, beschrijft de limitaties en methodologische overwegingen, en bevat aanbevelingen voor nieuwe studies.

7

Epilogue

ACKNOWLEDGEMENTS - DANKWOORD

Het is bizar, maar het einde is nu toch echt in zicht. Vier jaar onderzoek, en nog wat zwoegen daarna. Dat had ik nooit allemaal in mijn eentje kunnen doen, en daarom wil ik een aantal mensen bedanken.

First of all, I would like to thank all patients who have participated in IGOS. Patients from 21 countries around the globe who were willing to share their medical information with us, fill out piles of questionnaires and pay extra visits to the hospital to help increase our knowledge on this rare disorder. Without your participation this all wouldn't have been possible and therefore I would like to express my sincere gratitude.

Second, all colleagues - clinicians and researchers - from The Netherlands and abroad. Your tremendous effort has brought us a step closer in improving the management of GBS. I immediately felt at home in "the IGOS-family" and will always remember the Peripheral Nerve Society (PNS) meetings where we got the chance to see each other in person, to give an update on the research projects, but also to have drinks, dance and go out until the late hours. Thank you all for this great collaboration!

Mijn eerste promotor, Prof. Jacobs, beste Bart. Het is eigenlijk allemaal begonnen in de ICK-week voorafgaand aan mijn coschap Neurologie waarin jij mijn docent was. Je wist me al snel te enthousiasmeren voor het onderzoek naar GBS en een jaar later startte ik als masterstudent bij de onderzoeksgroep. Ik heb heel veel geleerd in die 6 maanden, maar vooral ook veel plezier gehad en me altijd erg welkom gevoeld. Ik kon als student mee naar de PNS in Glasgow, mocht daar een presentatie geven en heb Ceilidh gedanst (met Schotse rokken) met alle congresgangers op de laatste avond. Een onvergetelijke ervaring! Toen ik de kans kreeg om een PhD te doen heb ik geen seconde getwijfeld. Wat ik altijd erg heb gewaardeerd is je vertrouwen in ons (PhDs), bijv. door ons de mogelijkheid te bieden om namens jou en IGOS een presentatie te geven in het buitenland. Daarnaast heb ik veel bewondering voor je enthousiasme voor de Neurologie, Immunologie en het onderzoek, en voor het feit dat je ondanks je drukke schema altijd bereid was om even tijd te maken voor een praatje. Bedankt hiervoor, en ik hoop dat we in de toekomst kunnen blijven samenwerken.

Mijn tweede promotor, Prof. Lingsma, beste Hester. We zijn nu vijf jaar en vele (zo niet duizenden) AUC-waarden en calibratiecurves verder. Ik heb ontzettend veel van je geleerd en zal me altijd de nuttige, efficiënte, maar vooral ook gezellige meetings herinneren die we hebben gehad. Je was altijd bereid om mee te denken over een project of advies te geven, soms in het Erasmus in het Na-gebouw, en soms via FaceTime terwijl

je onderweg was om je kinderen van school te halen. Waarbij ik er in de laatste situatie altijd van versteld stond hoe je uit je hoofd, soms fietsend, ook nog hele nuttige adviezen kon geven over berekeningen in R.

Prof. Dippel, beste Diederik. Hartelijk dank dat je zitting wilt nemen in mijn promotiecommissie. Ik kijk uit naar je bijdrage op gebied van zowel de klinische neurologie, alsook prognostische modellen, die een belangrijk onderdeel vormen van de grote Mr.Clean studies.

Prof. Steyerberg, ik heb veel gehad aan de NIHES-cursus die u gaf over prognostic modelling en heb regelmatig uw boek - *Clinical Prediction Models* - geraadpleegd voor mijn onderzoeksprojecten. Ik voel mij daarom ook vereerd dat u onderdeel wilt uitmaken van mijn promotiecommissie.

Dr. Van der Beek, beste Nadine. Ik heb de afgelopen jaren regelmatig met je mogen samenwerken, tijdens de neuromusculaire lunches op de woensdagmiddag, op verschillende congressen, en niet te vergeten tijdens de Rasch-cursus in het Erasmus gegeven door Prof. Pallant. Ik waardeer het heel erg dat je onderdeel wilt uitmaken van mijn promotiecommissie.

Prof. van Doorn, beste Pieter. Ondanks dat de neuromusculaire poli moest worden stilgelegd voor mijn verdediging was je bereid om zitting te nemen in mijn commissie. Dit waardeer ik ontzettend! Ik heb de afgelopen jaren heel veel van je geleerd en met veel plezier met je samengewerkt. Je was altijd beschikbaar voor overleg voor de GBS telefoon, ongeacht het tijdstip, en probeerde ons als arts-onderzoekers altijd zoveel mogelijk bij alles te betrekken, van patiëntencasus in de kliniek tot het bepalen van de locatie van de PNS. Bedankt daarvoor!

Dear Prof. Hughes, dear Richard. I was already very fortunate to collaborate with you on the Cochrane-project, and feel honored that you are willing to attend my thesis defense. You (and your gown) will definitely give more color to this day.

Dr. Drenthen, beste Judith. Je bent vanaf het begin af aan nauw betrokken geweest bij alle EMG-projecten van IGOS en ICOS en had altijd de tijd om ons wat meer uitleg te geven over EMGs. Mogelijk dat EMG-data in de toekomst, naast diagnostiek, ook een rol gaan spelen in het voorspellen van de prognose van GBS. Ik zou hierover graag met je van gedachte wisselen tijdens mijn verdediging. Bedankt dat je onderdeel wilt uitmaken van mijn commissie!

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PHD PORTFOLIO

Name PhD student: Alex Y. Doets
Erasmus MC Department: Neurology
Research School: MolMed en NIHES
PhD period: March 2017 – March 2021
Supervisors: Prof. dr. B.C. Jacobs (promotor), Prof. dr. H.F. Lingsma (promotor)

1. PhD training	**Year**	**ECTS***
General courses		
Patient Oriented Research: design, conduct and analysis (CPO) – Erasmus MC	2017	0.3
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK) – Erasmus MC	2017	1.5
Scientific Integrity – Erasmus MC	2017	0.3
Specific courses		
Rasch Analysis – Introductory course – University of Leeds	2017	1.0
Basic Course on R (MolMed) – Erasmus MC	2017	1.8
Biostatistical Methods I, part A – NIHES, Erasmus MC	2018	2.0
Advanced Analysis of Prognosis Studies – NIHES, Erasmus MC (grade: 8.8)	2018	0.9
Rasch Analysis – Intermediate course	2018	1.5
Biostatistical Methods II – NIHES, Erasmus MC (grade 9.0)	2019	4.6
Seminars and workshops		
Boerhaave and Hoytema Symposium on Neuromuscular Diseases	2018-2021	1.2
Muscles2Meet Young Talent Symposium on Neuromuscular Diseases	2017, 2019	1.0
Belgian – Dutch Neuromuscular Study Club (2x)	2017	0.3
Scientific presentations and conference attendance		
Annual Scientific Meeting of the Dutch Neurology Society (NVN) – 2 oral presentations	2017-2019	2.0
Peripheral Nerve Society Meeting Sitges, Spain – 1 poster presentation	2017	1.5
Peripheral Nerve Society Meeting Baltimore, USA – 1 oral presentation, 1 poster	2018	1.8
Peripheral Nerve Society Meeting Genova, Italy – 1 oral presentation, 1 poster	2019	1.8
Peripheral Nerve Society Meeting (Virtual) – 2 posters	2020, 2021	0.6

2. Teaching activities	**Year**	**ECTS***
Lectures		
Invited speaker: Spanish Neurology Society Meeting, Seville, Spain	2018	0.5
Invited speaker: GBS-CIDP Symposium	2019	0.3
Oral presentation (2x): Muscle Disease Conference (Spierziektencongres)	2017, 2018	0.7
Supervisor		
Master thesis of A.L. Bruijstens: Unexpected clinical deteriorations in patients with Guillain-Barré syndrome	2017-2018	4.0
Master thesis of H. Al-Hakem: Cerebrospinal fluid findings in Guillain-Barré syndrome: evaluating associations with clinical characteristics and prognosis	2020	3.0
Other		
Reviewing papers for international peer-reviewed journals	2018-present	1.0
Total		**33.6**

*1 ECTS (European credit transfer system)= 28 study hours

LIST OF PUBLICATIONS

1. **Doets AY**, Verboon C, van den Berg B et al. Regional variation of Guillain-Barré syndrome. *Brain*. 2018 Oct 1; 141(10): 2866-2877.
2. **Doets AY**, Jacobs BC, van Doorn PA. Advances in management of Guillain-Barré syndrome. *Current Opinion in Neurology*. 2018 Oct; 31(5): 541-550.
3. Verboon C, **Doets AY**, Galassi G et al. Current treatment practice of Guillain-Barré syndrome. *Neurology*. 2019 Jul 2; 93(1): e59-e76.
4. **Doets AY**, Hughes RAC, Brassington R, Hadden RDM, Pritchard J. Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews 2020*, Issue 1.
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6. Walgaard C, Jacobs BC, Lingsma HF, Steyerberg EW, van den Berg B, **Doets AY**, Leonhard SE, Verboon C, Huizinga R, Drenthen J, Arends S, Budde IK, Kleyweg RP, Kuitwaard K, van der Meulen MFG, Samijn JPA, Vermeij FH, Kuks JBM, van Dijk GW, Wirtz PW, Eftimov F, van der Kooi AJ, Garssen MPJ, Gijsbers CJ, de Rijk MC, Visser LH, Blom RJ, Linssen WHJP, van der Kooi EL, Verschuuren JJGM, van Koningsveld R, Dieks RJG, Gilhuis HJ, Jellema K, van der Ree TC, Bienfait HME, Faber CG, Lovenich H, van Engelen BGM, Groen RJ, Merkies ISJ, van Oosten BW, van der Pol WL, van der Meulen WDM, Badrising UA, Stevens M, Breukelman AJ, Zwetsloot CP, van der Graaff MM, Wohlgemuth M, Hughes RAC, Cornblath DR, van Doorn PA; Dutch GBS Study Group. Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2021 Apr;20(4):275-283.
7. Luijten LWG, Leonhard SE, van der Eijk AA, **Doets AY**, Appeltshauser L, Arends S, Attarian S, Benedetti L, Briani C, Casasnovas C, Castellani F, Dardiotis E, Echaniz-Laguna A, Garssen MPJ, Harbo T, Huizinga R, Humm AM, Jellema K, van der Kooi AJ, Kuitwaard K, Kuntzer T, Kusunoki S, Lascano AM, Martinez-Hernandez E, Rinaldi S, Samijn JPA, Scheidegger O, Tsouni P, Vicino A, Visser LH, Walgaard C, Wang Y, Wirtz PW, Ripellino P, Jacobs BC; IGOS consortium. Guillain-Barré syndrome after SARS-CoV-2 infection in an international prospective cohort study. *Brain*. 2021 Dec 16;144(11):3392-3404.
8. **Doets AY**, Lingsma HF, Walgaard C, et al. Predicting Outcome in Guillain-Barré Syndrome: International Validation of the Modified Erasmus GBS Outcome Score. *Neurology*. 2022 Feb 1;98(5):e518-e532.

9. **Doets AY**, Walgaard C, Lingsma HF, et al. International Validation of the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score. *Ann Neurol*. 2022 Apr;91(4):521-531.
10. Papri N, **Doets AY**, Mohammad QD, Endtz HP, Lingsma HF, Jacobs BC, Islam Z. Validation and adjustment of modified Erasmus GBS outcome score in Bangladesh. *Ann Clin Transl Neurol*. 2022 Aug;9(8):1264-1275.
11. Leonhard SE, van der Eijk AA, Andersen H, Antonini G, Arends S, Attarian S, Barroso FA, Bateman KJ, Batstra MR, Benedetti L, van den Berg B, Van den Bergh P, Bürmann J, Busby M, Casasnovas C, Cornblath DR, Davidson A, **Doets AY**, van Doorn PA, Dornonville de la Cour C, Feasby TE, Fehmi J, Garcia-Sobrino T, Goldstein JM, Gorson KC, Granit V, Dm Hadden R, Harbo T, Hartung HP, Hasan I, Holbech JV, Holt JK, Jahan I, Islam Z, Karafiath S, Katzberg HD, Kleyweg RP, Kolb N, Kuitwaard K, Kuwahara M, Kusunoki S, Luijten LWG, Kuwabara S, Lee Pan E, Lehmann HC, Maas M, Martín-Aguilar L, Miller JA, Mohammad QD, Monges S, Nedkova-Hristova V, Nobile-Orazio E, Pardo J, Pereon Y, Querol L, Reisin R, Van Rijs W, Rinaldi S, Roberts RC, Roodbol J, Shahrizaila N, Sindrup SH, Stein B, Cheng-Yin T, Tankisi H, Tio-Gillen AP, Sedano Tous MJ, Verboon C, Vermeij FH, Visser LH, Huizinga R, Willison HJ, Jacobs BC; IGOS Consortium. An International Perspective on Preceding Infections in Guillain-Barré Syndrome: The IGOS-1000 Cohort. *Neurology*. 2022 Aug 18.

ABOUT THE AUTHOR

Alex Y. Doets was born on the 24th of July, 1991 in Delft, The Netherlands. In 2008 she graduated at the Haags Montessori Lyceum in The Hague, The Netherlands. Before starting her medical education at the Erasmus University Medical Centre in Rotterdam in 2010, she studied Health Sciences at the Vrije Universiteit in Amsterdam for one year. In 2017 she obtained her medical degree, and one month later she started her PhD research that is described in this thesis, under supervision of prof. dr. B.C. Jacobs (promotor) and prof. dr. H.F. Lingsma (promotor). From May, 2021 to February, 2022, Alex worked as a resident at the Neurology department of the Franciscus Gasthuis & Vlietland Hospital, The Netherlands. As of March, 2022 she started working at the Neurology department of the Erasmus University Medical Center in Rotterdam, The Netherlands.