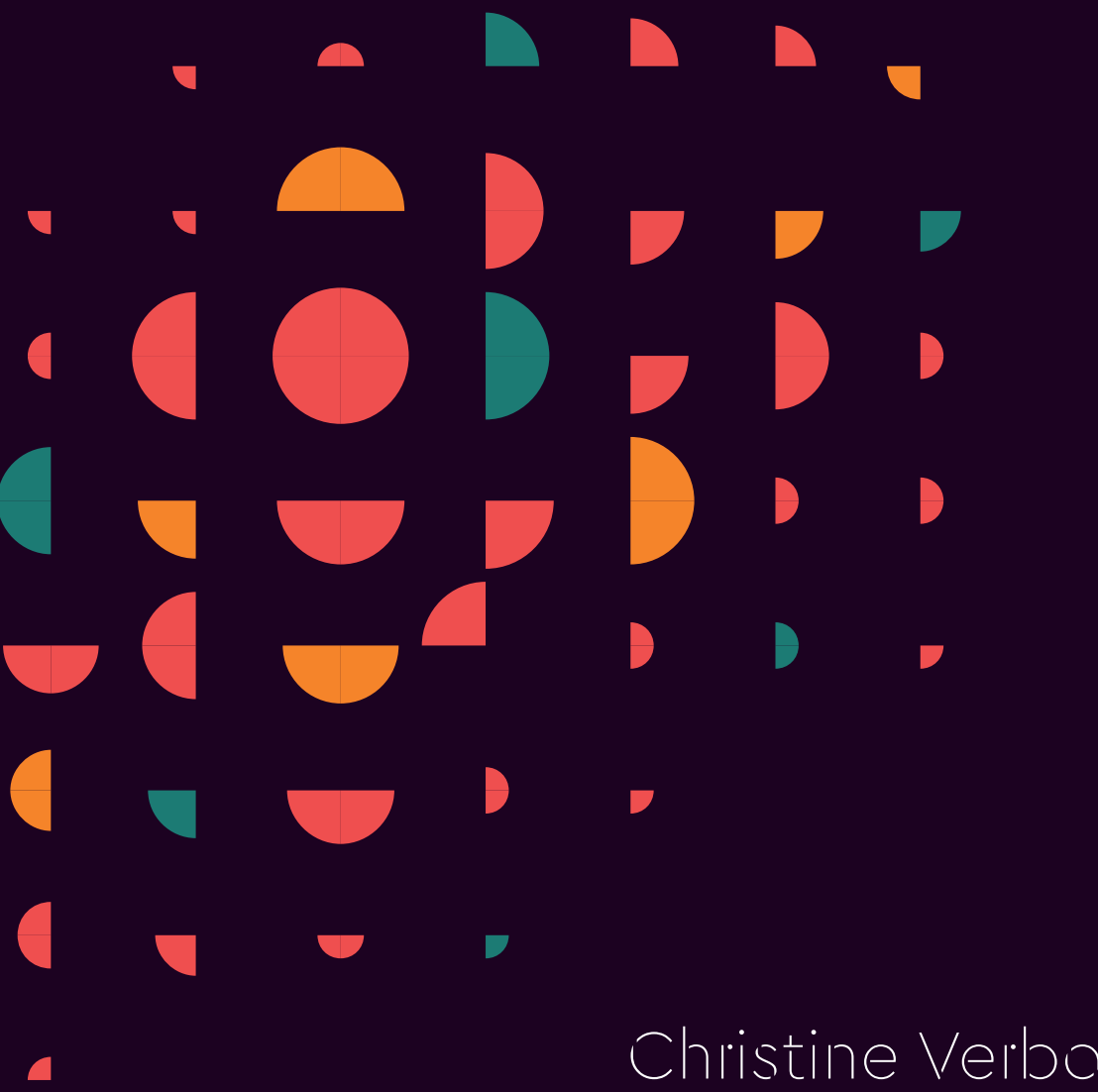
Guillain-Barré Syndrome in the Real World.

Observational studies of
clinical and treatment dilemmas.



Christine Verboon

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Guillain-Barré Syndrome in the Real World
Observational studies of
clinical and treatment dilemmas

Guillain-Barré Syndroom in de echte wereld
Observationele studies over
klinische en therapeutische dilemma's

Proefschrift

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1

Introduction

GUILLAIN-BARRÉ SYNDROME

In 1916, Georges C. Guillain, Jean-Alexandre Barré and Andre Strohl described two soldiers in the First World War who complained of tingling, reduced sensation and progressive weakness in arms and legs. At neurological evaluation, reduced and absent tendon reflexes were present. The cerebrospinal fluid (CSF) analysis showed elevated protein without a cellular reaction.[1] Despite severe generalized weakness in arms and legs at nadir, both patients showed a good clinical recovery.[2] This combination of features appeared to be a subacute, immune-mediated polyradiculoneuropathy, that was thereafter named "Guillain-Barré syndrome" (GBS). The incidence rate of GBS in North-American and European countries varies between 0.81 and 1.89 (median 1.11) cases per 100,000 per year, increases with age, and is 1.5 times higher in males than in females.[3] The disease presentation varies considerably among patients, and the clinical course and outcome is highly heterogeneous too, resulting in challenging clinical dilemmas regarding patient care and treatment.[4, 5]

Clinical symptoms

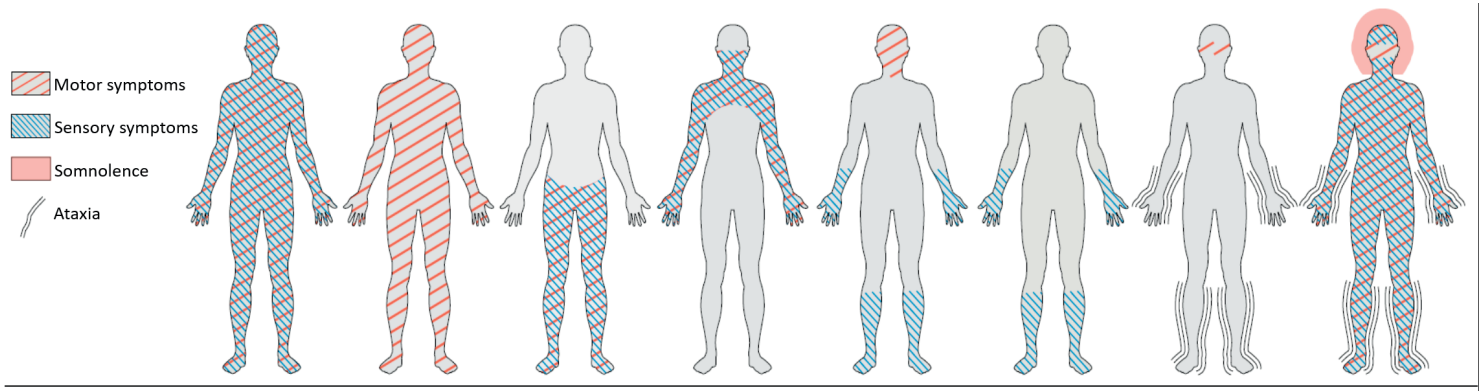
The core clinical symptoms of GBS are symmetrical flaccid weakness of the legs and arms, combined with decreased or absent deep tendon reflexes. Additional clinical features which are present in variable proportions of patients are cranial nerve palsies, paresthesias and sensory deficits, ataxia, and pain.[4, 6] Notably, autonomic dysfunction appears in up to 30% of patients, including cardiovascular dysregulation (such as arrhythmia and blood pressure irregularities), ileus or excessive sweating.[4] Various cranial nerves can be affected: most often bilateral facial nerve palsy but also ophthalmoparesis and bulbar weakness, resulting in problems with swallowing and speech. In addition, about one-fifth of the patients develop respiratory failure requiring ventilatory support.[4, 7]

Variant forms

The classical and predominant form of GBS is motorsensory, but several clinical variants of GBS have been described, including the Miller Fisher syndrome (MFS) with the typical triad of ophthalmoparesis, ataxia and areflexia, and the pure motor variant without sensory nerve deficits (although paresthesias may occur).[8] Other variants are the paraparetic variant where symptoms are exclusively present in the legs, or the pharyngocervicobrachial variant (PCB) (figure 1).[4, 9, 10] Bickerstaff brainstem encephalitis (BBE) is an exceptional variant in the GBS spectrum because of the coexisting involvement of both central and peripheral nervous system.[11-15]

According to most literature, MFS has a relatively benign disease course and a good clinical outcome.[13, 17] However, some patients may have a more severe illness and de-

Figure 1. Clinical, epidemiological, electrophysiological and serological features of GBS. Adapted with permission from reference.[4, 5, 9, 10, 16]



	Classic sensorimotor	**Pure motor**	**Paraparetic**	**Pharyngeal-cervical-brachial**	**Bilateral facial palsy with paresthesias**	**Pure sensory**	**Miller Fisher syndrome**	**Bickerstaff brainstem encephalitis**
Frequency	70%	15%	8%	1%	1%	<1%	5%	1%
NCS	Demyelinating or axonal	Predominantly axonal	Demyelinating or axonal	Unknown	Unknown	Sensory neuropathy	Normal or sensory axonal polyneuropathy	
Antibodies	GM1 or GD1a (10%)	GM1, GD1a, and GalNAc-GD1a (60%)	GM1, GD1a, GQ1b (5%)	GQ1b, GD1a, GT1a		GD1b (35%)	GQ1b (80-90%)	GQ1b (65-90%)

velop additional limb weakness or respiratory failure, which is called MFS-GBS overlap syndrome.[18, 19] Unfortunately, no prognostic factors have been identified that predict which patients may progress to MFS-GBS overlap syndrome. This is problematic for neurologists because early detection of MFS patients who are at risk of disease progression and poorer outcome would entail closer monitoring and initiating treatment.

Disease course

The disease course of GBS is monophasic although the duration of the active phase of disease may vary extensively between patients.[20] The progressive phase in practice usually takes one or two weeks, but may range from a period of days to four weeks (by definition).[21] After reaching the nadir of the disease, a plateau phase follows, with a highly variable duration of days to months.[4, 6] About 10% of patients experience a secondary clinical deterioration after initial stabilization or improvement, which has been defined as a treatment related fluctuation (TRF).[22, 23] This phenomenon is thought to be caused by ongoing disease activity while treatment effect wears off. A TRF is important to recognize as these patients may improve again after an additional course of the initial treatment (either IVIg or PE).[24] Finally, a recovery phase will commence, lasting months to several years.[4, 6] Hereafter, the outcome after GBS is highly variable, with 20% of GBS patients who are still not able to walk independently after six months of disease onset, 3-7% of patients die, and many patients experience long-term deficits and complaints, including reduced muscle strength, sensory deficits, pain and fatigue.[4, 6]

Pathophysiology

Two pathophysiological mechanisms may lead to polyradiculoneuropathy in GBS: demyelination and axonal degeneration of peripheral nerves and nerve roots, which can be identified by routine nerve conduction studies (NCS).[25] Some reports indicated that these pathophysiological mechanisms result in two distinct subtypes of GBS: a demyelinating and an axonal form of GBS. In a subgroup of patients with the axonal subtype of GBS, it has been shown that molecular mimicry between lipo-oligosaccharides in the outer membrane of *Campylobacter jejuni* and gangliosides on the axolemma of a peripheral nerve, results in the production of cross-reactive antibodies during preceding infection.[26] Binding of these antibodies to axolemmal gangliosides will result in complement activation and formation of membrane attack complexes (MAC) and ultimately in attracting macrophages that invade the nerve. Interestingly, the specificity of the anti-ganglioside antibodies in part is associated with the neurological deficits and reflects the distribution of these gangliosides along the peripheral nervous system. Axonal GBS is associated with antibodies against the gangliosides GM1a, GM1b, GD1a, GaINAc-GD1a. Most patients with axonal GBS subtype have the pure motor clinical variant, but some have the motorsensory form.[27, 28] The demyelinating subtype is most often

associated with motorsensory GBS, but the pathogenesis has been less clarified. Some patients with a demyelinating subtype of GBS have a preceding infection with *C. jejuni* and antibodies to gangliosides, similar as in axonal GBS. However, in the majority of patients with a demyelinating subtype of GBS, there is a preceding infection with a virus or no preceding event is reported. It is hypothesized that yet unidentified antibodies react against the myelin sheath of the peripheral nerve, leading to an immune reaction against the myelin.[27]

Antibodies against GQ1b, gangliosides located on oculomotor nerves, are present in more than 85% of patients with MFS, clinically characterized by ophthalmoplegia, ataxia and areflexia.[14, 27, 29]

Interestingly, the motorsensory and demyelinating type of GBS is reported to be predominant in Europe or North America (in 60-80% of the cases) while the pure motor and axonal GBS is more often found in Asia, Central and South America.[4] Until now, it is unclear whether this observation is truly signifying regional variation of the phenotype of GBS, or whether selection bias, differing study protocols and criteria sets of clinical variants and nerve conduction studies have led to this observation. Establishing the regional variation of GBS in various parts of the world is important to further understand the factors that determine the diversity and pathophysiology of the peripheral nerve damage and would serve as a basis for further research into efficacy of treatments for specific parts of the world.

Diagnosis and diagnostic criteria

The diagnosis of GBS mainly depends on clinical assessment and is supported by findings of additional investigations. Unfortunately, there is no unique diagnostic biomarker to ascertain the diagnosis of GBS. In 1981, Asbury founded the basis for the diagnostic criteria of GBS, which was revised in 1990 by Asbury and Cornblath into new criteria, which required the presence of progressive weakness and areflexia or hyporeflexia of the limbs.[21] Other clinical features which are strongly supportive of the diagnosis are the presence of a progressive phase of less than four weeks, relative symmetry of limb weakness, mild sensory symptoms or signs, cranial nerve involvement, onset of recovery after a plateau phase, occurrence of autonomic dysfunction, and absence of fever at onset.[21] Results of additional investigations are important to further support the diagnosis or exclude other causes. Important findings in support of the diagnosis GBS are the presence of the cytoalbuminological dissociation in the CSF, or demyelinating or axonal features on nerve conduction studies. However, the prototypical finding of a cytoalbuminological dissociation in the CSF is often not present in the acute phase.[20] Nevertheless, lumbar puncture is part of the routine diagnostic work-up of GBS with the

important purpose of excluding other causes, mainly infections, other causes of inflammation and malignancies. A CSF cell count of 11 to 50 leukocytes/mm^3 can be considered within the diagnostic criterion, but a cell count above 50 leukocytes/mm^3 is a red flag.[21] In 2011, the Brighton Collaboration introduced criteria for vaccine safety studies in response to the report of cases of GBS after vaccination to the H1N5 flu ('Mexican flu'), which added levels of diagnostic certainty to the results of clinical, electrophysiological and CSF investigations.[30]

Treatment

In accordance with the evidence of an immune-mediated pathogenesis of GBS, it was obvious that researchers commenced to improve disease course and outcome with immune-targeted therapies. Corticosteroids alone surprisingly proved to delay the onset of recovery.[24, 31] Plasma exchange (PE) was the first proven effective method in patients who were unable to walk independently, which should be started preferably within two, and a maximum of four weeks after onset of weakness.[32-37] In comparison to supportive treatment alone, PE shortened the median time to recovery (30 days vs. 44 days) and increased the proportion of patients able to walk with assistance after four weeks (RR 1.60, 95%CI 1.19-2.15).[34, 36, 37] In the nineties of the last century, intravenously administered immunoglobulin (IVIg) in a dosage of 2 gram per kilogram bodyweight over five days was shown to be not inferior to PE in patients who were unable to walk independently at study entry.[38, 39] Several subsequent comparison trials have shown that IVIg is equally effective as PE, however patients treated with IVIg seem to have less complications (pneumonia, atelectasis, thrombosis and haemodynamic difficulties) and treatment is less frequently discontinued than in patients treated with PE.[24, 39] Both PE and IVIg have pleiotropic effects on the immune system. PE diminishes the exposure to pathologic auto-immune antibodies by removing antibodies and other soluble inflammatory factors from the plasma and reinfusing the patients' cells with albumin or fresh frozen plasma.[37] IVIg consists mainly of IgG immunoglobulins, and also in lesser quantities of IgM and IgA type immunoglobulins, pooled together from 5,000-10,000 healthy blood donors.[40] Several possible targeting mechanisms have been postulated, including neutralization of pathogenic auto-antibodies and cytokines; inhibition of complement activation and formation of MAC; modulation of inhibitory and activating Fc receptors on macrophages; influencing the function and interaction of T-lymphocytes; and saturation of IgG recycling by the neonatal Fc receptor leading to accelerated degradation of auto-antibodies.[40-42] Which of these mechanisms of action explain the therapeutic effects of PE and IVIg in GBS and if these mechanisms of action are the same in all patients, is still unknown.

Prognosis

In most studies on the clinical course of GBS, a poor outcome is defined as being unable to walk independently after 6 months of onset.[4] Several clinical factors have been identified to be associated with poor outcome: increased age (above 40 years), preceding diarrhea, and higher disability at the nadir of the disease.[6] Other predictors of poor prognosis include low compound muscle action potential (CMAP) amplitudes on nerve conduction studies and a small rise in serum IgG levels 2 weeks after starting a standard IVIg course.[42, 43] Many of these factors are interrelated and the different results in previous reports from single countries indicate that the GBS type and prognosis may be influenced by the geographical region.

As of 2007, various prognostic models have been developed to predict the disease course and outcome in individual GBS patients, including the risk of respiratory insufficiency at the initial stage of the disease (Erasmus GBS Respiratory Insufficiency Score, EGRIS), and outcome after various time points, defined as being able to walk independently (modified Erasmus GBS Outcome Score, mEGOS).[44, 45] The EGRIS identifies patients with a high risk of respiratory insufficiency in the first week after hospital admission. A higher risk is identified in patients with a short duration between onset of weakness and hospital admission, who have a low Medical Research Council sum score, and who have facial and/or bulbar weakness.[44]

The mEGOS uses three clinical parameters to identify patients who have a high risk of a poor prognosis, i.e., being unable to walk independently after six months of disease onset. With higher age, presence of preceding diarrhoea and lower muscle strength (measured by the Medical Research Council sum score) at one week after hospital admission, the risk of a poor prognosis is increased.[45]

Treatment dilemmas in GBS

Despite tremendous progress in unraveling the pathophysiological processes leading to nerve damage in GBS and the discovery of effective immunotherapies, evidence about the best treatment regime for individual patients with GBS is still limited. Most treatment studies in GBS have been conducted in severely affected patients (often classified as being unable to walk independently) from Western countries, where the motorsensory variant and demyelinating subtypes predominate. This has resulted in evidence based guidelines and Cochrane reviews largely for patients with classic motorsensory GBS. However, since GBS is a heterogeneous disease with other clinical variants and subtypes, which may have differences in treatment response and disease course, many clinicians face dilemmas regarding the treatment of GBS patients who were previously excluded from randomized controlled trials (RCT). Two important treatment dilemmas are 1)

whether patients with a poor prognosis may benefit from a more aggressive treatment in the acute phase, and 2) whether patients with a relatively mild disease course would benefit from treatment.

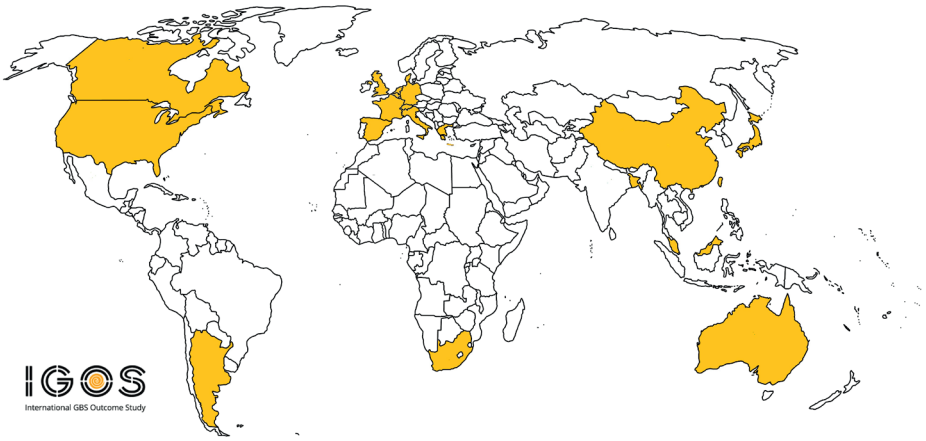
The standard treatment for all patients with severe GBS currently is one course of IVIg. However, patients who have a predicted high risk of a poor prognosis (defined as not being able to walk independently after six months predicted by the mEGOS) may benefit from a second IVIg course early after the first IVIg course, aiming to reduce further nerve damage. Until now, no studies have been performed to investigate the safety and efficacy of such a second IVIg course.

The other dilemma regarding the treatment of mild GBS faces also a lack of research data which is needed to justify treatment practice. Mild GBS has been defined as remaining able to walk independently at nadir and was always considered to have a benign disease course and prognosis. For this reason, and because treatment effect was likely largest in severely affected patients, patients with mild GBS were always excluded from the PE and IVIg RCTs. However, accumulating data provides evidence for the contrary; up to 40% of patients reported problems in motor function of the arms, fatigue and/or pain after six months in a study with mild GBS.[46] Therefore, mild patients might benefit from treatment too.

International GBS Outcome Study (IGOS)

In 2012, the research team at Erasmus Medical Center in Rotterdam, the Netherlands, initiated the conduct of an international study in collaboration with the Inflammatory Neuropathy Consortium. The International GBS Outcome Study (IGOS) is a prospective, observational cohort study aiming to identify factors that predict and determine the variation in the disease course and outcome in GBS and to facilitate the conduct of new treatment studies in GBS. All patients who fulfill the diagnostic criteria of Asbury and Cornblath (1990) can participate in the IGOS, regardless of age, disease severity, clinical variants, electrophysiological subtypes or treatment, if they are included within two weeks after onset of weakness (or other symptoms when weakness is absent).[21] The IGOS aims to include the whole spectrum of patients with GBS seen by neurologist attempting to approach the real world population of patients as much as possible, in contrast to the more selected cohorts of patients that are usually included in clinical trials. Data on demography, preceding infections, clinical features, results of CSF and electrophysiological testing, treatment, disease course and outcome are collected at standardized time points with a follow up of at least one year (and the option to extend the follow to two or three years). Countries from various world regions participate, including North and South-America, Europe, Asia, Australia and Africa (figure 2).

Figure 2. Participating countries in IGOS.



The aim was to include 2000 patients in IGOS and this number was reached in May 2021, while the last follow-up data are expected in May 2024. IGOS has already resulted in an extensive data/biobank consisting of (1) serially collected data on epidemiology, clinical presentation, course, treatment and outcome, (2) routine nerve conduction studies, and (3) serially collected biosamples (including serum, CSF and DNA). This data/biobank from a cohort of more than 2000 GBS patients from all world regions, gives the unique opportunity to conduct research focusing on specific topics in GBS, including epidemiology, diagnostic criteria, clinimetrics, electrophysiology, antecedent events, antibodies, genetics, prognostic modeling, treatment effects, and long-term outcome of GBS across various world regions.

Aims and objectives

The overall aim of the studies described in this thesis is to gain more insight into the diversity of the phenotype of GBS and to describe the variety of the current treatment practice of GBS based on real-world data from the IGOS. The first part of the thesis focusses on the clinical variability of GBS and elaborates on the following specific objectives:

1. To describe the spectrum of clinical GBS variants with ocular motor nerve dysfunction, which includes GBS with ophthalmoparesis, MFS, MFS-GBS overlap syndrome and BBE. In addition, to identify early predictors for disease progression in MFS.
2. To determine the regional diversity of GBS and to compare the clinical presentation, electrophysiological subtypes, disease course and outcome among patients from various geographical regions around the world.

The second part of the thesis encompasses various aspects with respect to the treatment of GBS. More specifically, the objectives of this part are:

3. To identify the most important treatment dilemmas of GBS in current clinical practice.
4. To describe the current treatment practice of patients with GBS from countries participating in IGOS.
5. To compare the disease course of GBS patients with a poor prognosis who have been treated with one or with two IVIg courses.

6. To investigate whether one IVIg course has a beneficial effect on disease course in GBS patients with a relatively mild form of GBS (patients being able to walk independently).

Outline

Chapter 1 provides a general introduction of GBS and the aims and scope of this thesis. **Chapter 2** describes the study design and methods of the International GBS Outcome Study (IGOS). **Chapter 3** comprises clinical aspects of GBS. First, the variation of MFS and the risk of developing MFS-GBS overlap syndrome will be described (Chapter 3.1). Next, the regional variation of GBS is being examined by investigating the relationship between geographical origin and clinical and electrophysiological phenotype, disease course and outcome (Chapter 3.2). **Chapter 4** focusses on the treatment aspects of GBS, by firstly discussing treatment dilemmas of GBS. Subsequently, an overview of the current treatment practice of GBS around the world is provided (Chapter 4.2). In addition, two studies will address the two most important treatment dilemmas: whether a second IVIg course is potentially beneficial in GBS patients with a poor prognosis (Chapter 4.3), and whether IVIg improves disease course in patients with a relatively mild form of GBS (Chapter 4.4). Finally, **chapter 5** provides a general discussion where the main findings of this thesis will be discussed in view of contemporary knowledge of GBS, together with recommendations about future research.

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International Guillain-Barré Syndrome Outcome Study (IGOS): Protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome in Guillain-Barré syndrome

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ABSTRACT

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy with a highly variable clinical presentation, course, and outcome. The factors that determine the clinical variation of GBS are poorly understood which complicates the care and treatment of individual patients. The protocol of the ongoing International GBS Outcome Study (IGOS), a prospective, observational, multi-centre cohort study that aims to identify the clinical and biological determinants and predictors of disease onset, subtype, course and outcome of GBS is presented here. Patients fulfilling the diagnostic criteria for GBS, regardless of age, disease severity, variant forms, or treatment, can participate if included within two weeks after onset of weakness. Information about demography, preceding infections, clinical features, diagnostic findings, treatment, course and outcome is collected. In addition, cerebrospinal fluid and serial blood samples for serum and DNA is collected at standard time points. The original aim was to include at least 1000 patients with a follow-up of 1-3 years. Data are collected via a web-based data entry system and stored anonymously. IGOS started in May 2012 and by January 2017 included more than 1400 participants from 143 active centres in 19 countries across 5 continents. The IGOS data/biobank is available for research projects conducted by expertise groups focusing on specific topics including epidemiology, diagnostic criteria, clinimetrics, electrophysiology, antecedent events, antibodies, genetics, prognostic modelling, treatment effects and long-term outcome of GBS. The IGOS will help to standardize the international collection of data and biosamples for future research of GBS.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy clinically characterized by a rapidly progressive symmetrical flaccid weakness of the limbs.[1, 2] The clinical presentation, course and outcome of GBS are variable. Some patients have mild weakness of the lower legs only, while others develop complete tetraplegia and respiratory failure requiring mechanical ventilation.[1, 2] Patients may have variant forms of GBS, including Miller Fisher syndrome (MFS), pure motor, paraparetic, or pharyngeal-cervical-brachial forms.[1-3] The electrophysiological findings are equally heterogeneous with subgroups of patients showing features of either demyelination or axonal degeneration.[4-6] The clinical recovery also varies: some patients recover spontaneously with no residual limitations, while others require mechanical ventilation for months and remain wheel chair bound for the rest of their lives or even die despite treatment.[1, 2] Independent of the GBS subtype, severity, or predicted outcome, the standard treatment regimen for the past two decades has consisted of intravenous immunoglobulin (IVIg) or plasma exchange (PE).[7-9] Despite treatment, outcome of GBS is frequently poor because 2%-5% of the patients die and 10%-20% of patients remain severely disabled.[2, 7, 10] Outcome is even worse in low-income countries: in Bangladesh, for example, 85% of patients receive no treatment, 15% die, and 30% remain severely disabled.[11] These findings show the need for more effective, personalized, and accessible treatments worldwide.

The factors that determine the heterogeneity of GBS and that could provide a basis to personalize treatment are largely unknown. Previous studies observed an association between the clinical course in patients and the acute phase clinical characteristics or biomarkers such as electrophysiological subtype, preceding infections, anti-ganglioside antibodies, serum levels of IgG, and albumin and genetic polymorphisms.[12-19] However, most of these studies were retrospective, and the findings were derived from relatively small series or selected groups of patients with a short follow-up period using a limited set of suboptimal outcome measures. In addition, the variety in inclusion criteria and methods used in these studies complicates comparing or combining collected data. Moreover, GBS varies considerably between geographical regions.[2, 20, 21] Solving these problems requires a prospective study design with standardized collection of clinical data and biomaterials from a large group of well-defined GBS patients with a long follow-up period. The International GBS Outcome Study (IGOS) was initiated to collect the required clinical data and biosamples. After several organizational meetings, a final study protocol was prepared, and local investigators were invited to participate. IGOS is being conducted in collaboration with the Peripheral Nerve Society and Inflammatory Neuropathy Consortium (INC) (www.pnsociety.com/inflammatory-neuropathy-consortium/), an international organization of clinical neurologists and scientists involved in the investigation and care of patients with GBS.

Study aim and objectives

The overall aim of IGOS is to determine the clinical and biological determinants and predictors of the clinical course and outcome of GBS. The objectives are: (1) to define the variation in clinical presentation, subtypes, progression, and recovery of GBS in patients from a broad range of geographical areas, (2) to describe the current practice of diagnosis, treatment, and care for GBS, (3) to identify environmental and host factors that determine the disease onset and the variation in clinical course, treatment response, and outcome, (4) to develop improved prognostic models to predict the clinical course and outcome in individual patients, and (5) to facilitate the collection of standardized and relevant data and biosamples for future studies of GBS.

METHODS AND MATERIALS

Study design

IGOS is an international, prospective, observational, multi-center cohort study. It uses a predefined protocol to collect data regarding baseline characteristics, clinical presentation and course, electrophysiology, diagnosis, treatment, and outcome during a follow-up of 1 year with the possibility to extend the follow-up to 2 or 3 years (Figure 1). The protocol specifies the timing of the collection of biosamples, including blood for DNA and serum studies and cerebrospinal fluid (CSF). Predictive models for the clinical course and outcome will be based on results collected in the first two weeks. The first 1,000 participants will constitute a derivation cohort. The next 500 or more patients will provide a validation cohort.

Inclusion and exclusion criteria for patients

Inclusion requires fulfilling the following criteria:

1. The diagnostic criteria for GBS of the National Institute of Neurological Disorders and Stroke (NINDS) (see table S1, Supplement), or one of the variants of GBS, including the MFS and overlap syndromes.[3, 22, 23]
2. Entry within two weeks of onset of weakness (or other symptoms attributed to GBS).
3. Opportunity to continue a follow-up for at least one year.
4. Informed consent of the participant or, for children, the parents or legal guardians.
5. The aim is to enroll patients representing the full spectrum of GBS. There are no exclusion criteria, and all patients with GBS or its variants, including MFS and overlap forms, may participate, regardless of age, disease severity, or treatment.

IGOS data- and biobank

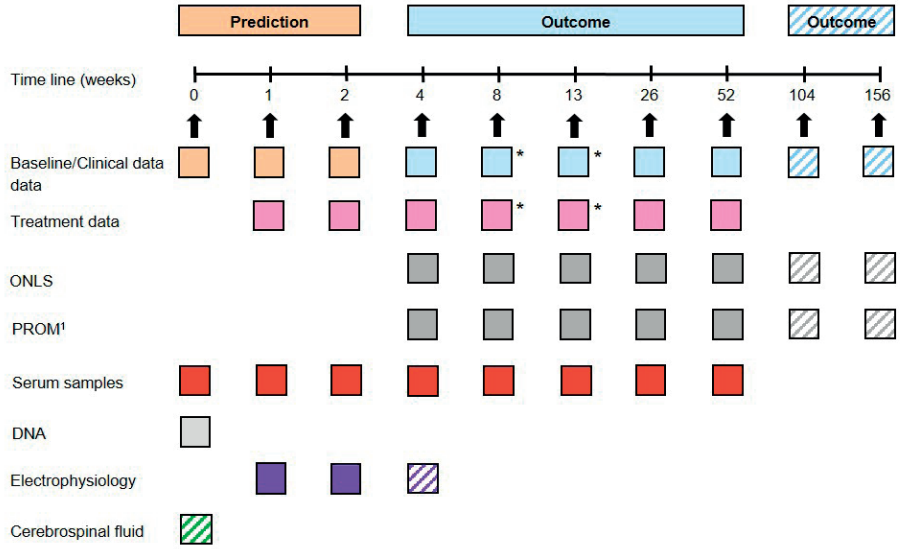
Baseline, clinical and treatment data

We collect baseline data about the patients' demography, co-morbidity, family history and antecedent events. In addition, we record the first clinical symptoms and signs of GBS, the timing and key features of the diagnosis, hospital transfers, neurological examination findings and the clinical course. The severity and distribution of clinical manifestations of GBS will be documented in detail, including cranial nerve deficits, limb weakness using the Medical Research Counsil (MRC) sum score[24] and Rasch-built MRC score[25], sensory deficits, ataxia, limb tendon reflexes, GBS disability scale[26], pain, autonomic dysfunction, respiratory failure, and associated medical complications. In addition, we record the occurrence of treatment related fluctuations and transitions to chronic inflammatory demyelinating polyneuropathy (CIDP).[27] From 4 weeks onward, we collect the following clinical outcome measures: Overall Neuropathy Limitation Scale (ONLS)[28], Rasch-built Overall Disability Score (R-ODS)[29], Fatigue Severity Scale (FSS) (and Rasch-built FSS)[30] and the EuroQol EQ-5D health questionnaire[31] (Figure 1). A complete neurological examination will be performed at study entry and after 1, 2, 4, 26 (± 2), and 52 (± 4) weeks. Participants still in hospital at 8 (± 1) and 13 (± 1) weeks will be examined but those who have been discharged have only a telephone assessment of the GBS disability scale, ONLS, R-ODS, FSS, and EuroQoL EQ-5D. All patient reported outcome measures have been translated (and back translated) into the language of the participants. We collect detailed information about the treatment for GBS including the type, timing, regimen and side-effects of treatment, admission to intensive care, and start and end of mechanical ventilation. If a patient dies, we document the timing and cause of death.

Electrophysiology data

We collect the results of the routine diagnostic electrophysiological examinations, including the raw data and the local investigators' interpretation and classification of the subtype, including acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor-sensory axonal neuropathy, inexcitable nerves, and equivocal or normal results. The study protocol recommends performing electrophysiological studies according to a predefined standard format (see table S2, Supplement). Some clinics routinely perform a second diagnostic nerve conduction study and we collect these results when available. We document locally used normative values and standard electrophysiology protocols.

Figure 1. Time schedule of research protocol for the IGOS database and biobank.



The filled blocks refer to obligatory studies, the striped to optional substudies. The timeline represents the follow-up period after study entry in weeks. The first 2 weeks focus on collecting data and biomaterials to predict the clinical course and outcome in the period after 2 weeks. Blood samples are obtained as indicated for serial serological studies and for DNA extraction. Routine diagnostic electrophysiology will be conducted in the first or second week, and as an optional study at 4 weeks. * At 8 weeks and 13 weeks patients admitted at the hospital will have a full examination and serum sampling but discharged patients will have telephone assessment only and no serum sampling.
[1] Patient reported outcome measures (PROM) used are Rasch-built Overall Disability Score (R-ODS), Fatigue Severity Scale (FSS), Rasch-FSS, EuroQol EQ-5D.

Blood samples

We collect blood and CSF samples according to a predefined schedule (Figure 1). Blood samples provide serum and DNA. The protocol specifies that the first serum sample is to be collected before the start of treatment, although in some patients treatment is being initiated before study entry (e.g., when patients transfer to a center participating in IGOS after treatment at a local community hospital). Blood samples are frozen and stored at -80◦C (or initially stored -20◦C for a maximum of 6 months) at the local center or at the center of the country coordinator, and transported on dry ice to a central biobank, at Erasmus MC in Rotterdam, the Netherlands, with a reserve biobank at the University of Glasgow, Scotland, UK.

Cerebrospinal fluid samples

If participants have a routine lumbar puncture to examine CSF for diagnostic studies, we keep an aliquot for biomarker studies. In centers participating in an advanced proteomics study, an extra aliquot is sampled[32]. This study requires centrifugation of the CSF sample within one hour after the lumbar puncture. The supernatant (without pellet) is removed and immediately stored in a polystyrene tube at -20◦C until being transferred

to the country coordinating center and stored at -80◦C. This optional research module requires additional informed consent.

Extended follow-up of two and three years

The time course of nerve regeneration and clinical recovery in GBS is unclear. Some patients continue to improve even after one year.[33, 34] To determine the further recovery and long-term residual deficits, there is an optional long-term follow-up research module with a telephone assessment at 2 years (104 ± 4 weeks) and 3 years (156 ± 4 weeks) after onset. The data collected then include the GBS disability score, ONLS, R-ODS, FSS (and Rasch-FSS), and EuroQoL EQ-5D. Severely affected patients may have more extensive evaluation including neurological examination at each visit. The long-term follow-up requires additional informed consent.

Children with GBS

Children with GBS differ from adult patients regarding their preceding infections, clinical features, GBS subtype, treatment, and outcome.[35, 36] In children, it is more difficult to obtain biosamples and the adult outcome measures have not all been validated. For this reason we are using an adapted protocol for children with age-dependent sampling of biomaterials and clinical assessment scales.

Data collection

We have developed a web-based data entry system that meets the standards of security and privacy of Erasmus MC, the host institution. The local investigators use this website to enter the data. The information stored is strictly anonymous. All participants have a unique code for use throughout the study. The quality of the collected data is controlled regularly by the IGOS Coordinating Center according to protocol and additional controls will be conducted by the IGOS Expertise Groups.

Sample size

The extent of the clinical variation of GBS in the world is currently unknown and limits the possibility to conduct a power calculation. There is only circumstantial evidence available to estimate the required size of the study. It is recommended for the development of predictive logistic regression models that the smallest outcome group should include at least 100 patients.[37] Previous therapeutic trials with GBS defined poor outcome as a GBS disability score of >2 (not being able to walk unaided or worse).[26] In treatment trials about 10%-15% of participants have had a poor outcome after one year.[7, 15] If we aim to include at least 100 participants with a poor outcome defined in this way, the whole study will need at least 1,000 participants. Therefore, this is the minimum size of the derivation cohort to identify new clinical and biological markers to predict poor

outcome or evaluate previously described prognostic factors. In addition, we collect an independent validation cohort of at least 500 patients to validate any new clinical or biomarkers that emerge from the derivation cohort.

Statistical analyses

Descriptive statistics are used to analyze the clinical data. We will develop prognostic models to evaluate the use of biomarkers and clinical characteristics to predict outcome in clinical practice according to our previously published statistical approaches.[15-17] The association between putative prognostic factors and outcome variables will be analyzed using univariate and multivariable logistic regression models. If two similar variables are equally associated with outcome, the variable most easily obtainable in clinical practice will be selected. We will quantify model performance with respect to discrimination (area under receiver operating characteristic curve). Multivariable regression coefficients will be used to develop new prognostic models for GBS.

IGOS Consortium and IGOS Research Policy Agreement

IGOS is conducted by the IGOS Consortium which consists of (1) the members of the Steering Committee, (2) the staff of the Coordinating Center at Erasmus MC, Rotterdam, the Netherlands, (3) the Country Coordinators, and (4) their networks of local investigators. To be able to participate in IGOS and to become a member of the IGOS Consortium all participants signed the IGOS Consortium Agreement, which defined the conduct of the study. All members of the IGOS Consortium can apply to the Steering Committee to use the IGOS data/biobank to address specific research questions. Research projects are also being conducted by the Expertise Groups, consisting of members of the IGOS Consortium and additional researchers if external expertise is required.

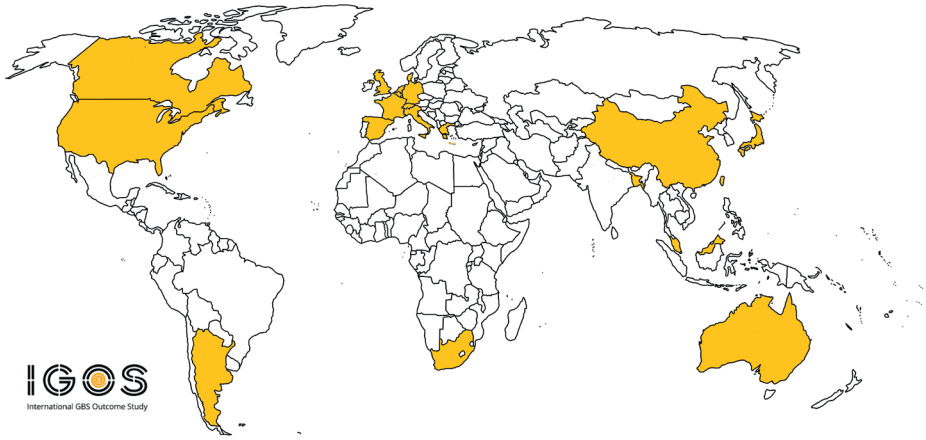
Ethical regulations

The IGOS received approval from the Medical Ethics Review Committee of the Erasmus MC Medical University Rotterdam in 2012. Each participating center also had approval from their local Institutional Review Board (IRB). The IGOS is being conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and the Medical Research Involving Human Subjects (WMO). The procedures set out in this protocol were designed to ensure that the investigators abide by the principles of the GCP guidelines of the European Community (ICH topic E6, CPMP/ICH/135/95, Directive 2001/20/EC) in the conduct, evaluation and documentation of this study. Inclusion in IGOS requires informed consent from each participant or their legal representative. IGOS was registered before the start of the study at ClinicalTrials.gov (NCT01582763).

DISCUSSION

IGOS started in May 2012 and in June 2015 IGOS had enrolled 1,000 patients who will form the derivation cohort (Figure 2). By January 2017, more than 1,400 patients with GBS had been included in IGOS by 143 active sites from 19 countries across five continents (Figure 3). We are continuing to recruit more patients to complete the independent validation cohort, and anticipate enrollment of 1,500 patients by July 2017.

Figure 2. Countries with hospitals participating in IGOS.

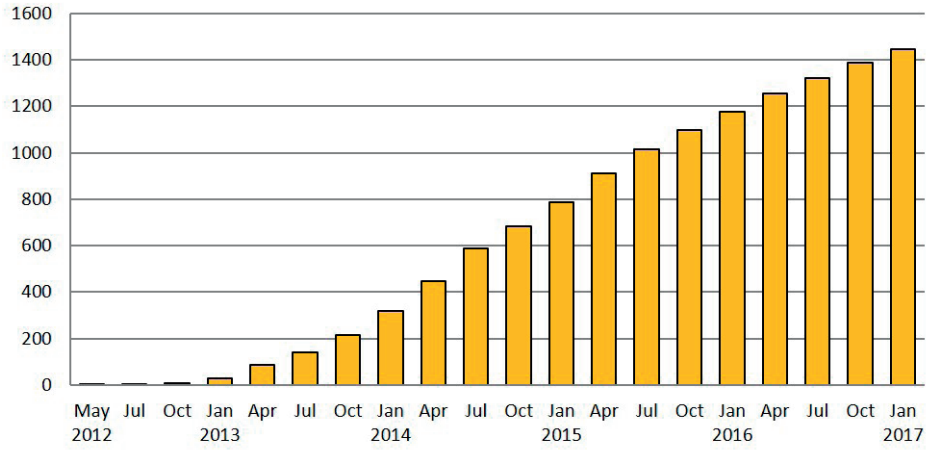


Wordwide representation of IGOS in 19 countries (indicated in orange) including Argentina, Australia, Bangladesh, Belgium, Canada, China, Denmark, France, Germany, Greece, Italy, Japan, Malaysia, Netherlands, South Africa, Spain, Taiwan, United Kingdom and United States of America.

IGOS has important advantages over previous observational studies of GBS. First, IGOS already includes the largest number of prospectively collected patients with a confirmed diagnosis of GBS. Second, there was no selection of patients based on age, clinical subtype, or severity, aiming to investigate the full range of variants within the spectrum of GBS. Third, we collected data from patients from various geographical regions, including high- and low-income countries using the same protocol and will be able to compare and contrast various attributes of the condition worldwide. Fourth, IGOS has a long follow-up period and uses several well-defined and validated outcome measures to assess the long-term outcome of GBS. Fifth, we are collecting biosamples prospectively according to the protocol at recruitment and follow-up visits coinciding with clinical assessments. We will use these samples to study preceding infections, antibodies to peripheral nerves and other immunological factors, pharmacokinetics, genetic factors, and other potential biomarkers for correlation with clinical features. Because of these advantages, IGOS will provide the most extensive research data- and biobank of GBS

patients collected so far. This will enhance our understanding of the pathogenesis and the individual clinical course, prognosis, treatment response, and outcome. The overall aim is to develop more effective personalized treatment regimens based on a better understanding of the variation of the disease.

Figure 3. Quarterly number of patients included in International Guillain-Barré Syndrome Outcome Study (IGOS).



IGOS has already enhanced international collaboration in research into the cause and treatment of GBS by strengthening international networks. Expertise Groups will be formed on various topics including (1) emerging preceding events related to GBS, (2) diagnostic criteria and protocols for GBS, (3) electrophysiological subtypes of GBS, (4) biological determinants including genetic polymorphisms, preceding infections, and serum antibodies in the pathogenesis of GBS and its subtype, (5) biomarkers for monitoring treatment, pharmacokinetics, and disease activity, (6) validating and improving outcome measures, (7) long-term outcome, (8) prediction of prognosis, and (9) improving treatment.

By providing an infrastructure for standardized collection of data and biomaterials, IGOS will facilitate international research projects on emerging infections associated with GBS, such as the recent outbreak of Zika virus infection.[38, 39] This infrastructure will also help to record other emerging preceding events that have been previously related to the development of GBS, including vaccinations. Our aim is also to use the international expertise involved in IGOS and the collected materials to compare and standardize assays for relevant biomarkers in GBS including preceding infections, antibodies, genetic polymorphisms, and pharmacokinetic analysis. The extensive recording of the clinical course and outcome at serial visits during long-term follow-up provides a unique oppor-

tunity for international validation of outcome measures that so far have been developed in limited regions only. The IGOS data- and biobank provide an easily accessed source of control natural history data for modelling studies and comparison with patients treated with novel treatment regimens. One ongoing study is already comparing one with two courses of IVIg in patients with a poor predicted outcome (International Second IVIg Dose GBS Study). A second observational study within IGOS is comparing IVIg treatment with supportive care alone for patients with initially mild GBS. IGOS provides an exciting opportunity to support future clinical trials. The consortium is open to collaboration with other academic partners and with pharmaceutical companies interested in improving the treatment of GBS.

Funding

The IGOS study protocol was developed without external financial support. The development of a web-based data entry support was supported by funding from the GBS-CIDP Foundation International (https://www.gbs-cidp.org/). Additional funding to support the conduct of IGOS for specific countries or projects was received from gain (http://www.gaincharity.org.uk/), Erasmus MC, Rotterdam, The Netherlands, University of Glasgow, Glasgow, United Kingdom, Grifols, CSL Behring, Shire Pharmaceuticals and Annexon. IGOS is scientifically independent, and the funding agencies have no influence on the study and infrastructure design of IGOS, nor on the collection, statistical analysis and interpretation of the data collected in IGOS, nor on the writing, publication of manuscripts or other presentations based on these data.

SUPPLEMENTARY MATERIAL

Supplement Table 1: Diagnostic criteria for Guillain-Barré syndrome (GBS)

Features required for diagnosis	Progressive weakness in both arms and legs (might start with weakness only in the legs)
	Areflexia (or decreased tendon reflexes)
Features that strongly support diagnosis	Progression of symptoms over days to 4 weeks
	Relative symmetry of symptoms
	Mild sensory symptoms or signs
	Cranial nerve involvement, especially bilateral weakness of facial muscles
	Autonomic dysfunction
	Pain (often present)
	High concentration of protein in CSF
	Typical electrodiagnostic features
Features that should raise doubt about the diagnosis	Severe pulmonary dysfunction with limited limb weakness at onset
	Severe sensory signs with limited weakness at onset
	Bladder or bowel dysfunction at onset
	Fever at onset
	Sharp sensory level
	Slow progression with limited weakness without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or CIDP)
	Marked persistent asymmetry of weakness
	Persistent bladder or bowel dysfunction
	Increased number of mononuclear cells in CSF (>50×10E6/L)
	Polymorphonuclear cells in CSF

Adapted from Asbury and Cornblath et al.[22]

Supplement Table 2: Recommended protocol for routine diagnostic electrophysiology

Motor nerve conductions studies										
		Responsive (yes/no)	DML (ms)	Distal CMAP amplitude (baseline-peak) (mV)	Prox. CMAP ampl. I (baseline-peak) (mV)	Prox. CMAP ampl. II (baseline-peak) (mV)	NCV I (m/s)	NCV II (m/s)	Minimal F-wave latency(>10)(ms)	H-M latency (ms)
1.	Median nerve –APB (nd)	X	x	x	x		x		x	
2.	Ulnar nerve- ADM (nd)	X	x	x	x	x	x	x	x	
3.	Peroneal nerve-EDB (nd))	X	x	x	x	x	x	x	x	
4.	Other nerve*	X	x	x	x	x	x	x	x	
5.	H-reflex m. soleus (nd)	X								x

Sensory nerve conductions studies									
		Responsive (yes/no)	DSL (ms)	Distal SNAP amplitude (baseline-peak) (µV)	Prox. SNAP ampl. I (baseline-peak) (µV)	Prox. SNAP ampl. II (baseline-peak)(µV)	NCV I (m/s)	NCV II (m/s)	NCV III (m/s)
1.	Median nerve- dig II (nd)	X	x	x	x		x	X	
2.	Ulnar nerve- dig V (nd)	X	x	x	x	x	x	x	X
3.	Sural nerve (nd)	X	X	X			X	X	
4.	Optional radial nerve(nd)	X	X	X	X		X	X	

Optional needle EMG						
		Fibrilations (yes/no)	Positive sharp waves (yes/no)	Polyphasic MU (yes/no)	Increased size MU (yes/no)	Decreased MU recruitment (yes/no)
1.	Dorsal Interosseus I muscle					
2.	Anterior tibial muscle					
3.	Proximal arm muscle (deltoid or biceps muscle)					
4.	Proximal leg muscle (vastus lateralis muscle)					

Local investigators are free to conduct the nerve conduction studies according to their local routine standards but recommended in IGOS is to perform a complete electrophysiological examination at two separate time points: the first within 7 days of admission or registration in IGOS, and the second at four weeks after admission or registration in IGOS. The collected data should include sensory studies in legs and arms (3-4 nerves), motor studies with F waves (3-4 nerves), tibial H-reflexes and EMG of a proximal and distal muscle in an arm and leg. Normative data and pictures of the waveforms will also be included in the report. nd = non-dominant side. * = other nerve (median, ulnar or peroneal nerve on dominant-side or tibial nerve on dominant side)

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3

Clinical aspects of Guillain-Barré syndrome

3.1

Prediction of disease progression in Miller Fisher and overlap syndromes

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ABSTRACT

Patients with Miller Fisher syndrome (MFS) may have a relatively mild clinical course or progress to Guillain-Barré syndrome (GBS) with limb weakness (MFS-GBS overlap syndrome). Other variants in this spectrum are GBS with ophthalmoparesis and Bickerstaff's Brainstem encephalitis (BBE). We aimed to compare the clinical course of MFS and overlap syndromes and to identify predictors of disease progression. In a prospective study of 170 patients with GBS and variant forms, 37 (22%) had a MFS, MFS-GBS overlap syndrome, ophthalmoplegic GBS or BBE. The clinical, serological, and electrophysiological features were compared. Twenty-three patients presented with MFS, of which 10 (43%) developed limb weakness (MFS-GBS overlap syndrome). All these transitions occurred in the first week after onset of symptoms. There were no differences in the clinical, electrophysiological and serological features at entry between MFS and MFS-GBS. Twelve patients had ophthalmoplegic GBS and the disease severity at nadir and outcome was worse than in the patients with a MFS-GBS overlap syndrome. No early predictors for progression from MFS to MFS-GBS overlap syndrome were found. All transitions occurred in the first week. This finding implicates that all patients with MFS need careful monitoring for at least 1 week.

INTRODUCTION

Ophthalmoparesis is a distinctive clinical feature in patients with Miller Fisher syndrome (MFS) and Guillain-Barré syndrome (GBS). Patients with MFS have ophthalmoparesis with additional ataxia and areflexia without limb weakness, and usually have a relatively benign clinical course requiring no specific treatment.[1, 2] Some patients presenting with MFS may deteriorate and develop additional limb weakness (MFS-GBS overlap syndrome) or bulbar or respiratory failure.[3-5] Ophthalmoplegia could also occur later on in patients presenting with GBS with limb weakness and sensory deficits ('ophthalmoplegic GBS'). Other patients in this related spectrum of disorders have GBS and may later on develop consciousness disturbances and pyramidal tract signs and are diagnosed as Bickerstaff's brainstem encephalitis (BBE).[6] The clinical course and outcome of these subtypes may vary considerably.

At present, no early characteristics have been identified that can be used to predict whether a patient initially diagnosed as MFS is at risk for progression to MFS-GBS overlap syndrome [3]. We aimed to determine risk factors for progression to MFS-GBS overlap syndrome and compared the clinical course and outcome of these variant forms.

MATERIALS AND METHODS

Data were derived from a prospective, multicenter cohort study in 170 Dutch patients with GBS, MFS or variant forms, who were included within 2 weeks after onset of symptoms (GRAPH study).[7] The study was approved by an ethical standards committee on human experimentation, and informed consent was obtained from all patients.

For the current study, we selected patients with ophthalmoparesis and divided them into 4 groups: 1) patients without limb weakness (MFS), 2) patients who developed bilateral limb weakness during disease course (MFS-GBS overlap syndrome), 3) patients with limb weakness as presenting symptom, who later on developed ophthalmoplegia (ophthalmoplegic GBS), and 4) patients with disturbance of consciousness diagnosed as BBE.[6].

Data were collected from study entry and after six months follow-up. Potential risk factors for disease progression in MFS to MFS-GBS overlap syndrome analyzed were gender, age, antecedent event, presenting neurological features at entry (including facial weakness, sensory deficits, pain, MRC sum-score, GBS disability score), results of CSF and nerve conduction studies (NCS), and presence of serum anti-GQ1b antibodies.

Information on ataxia was collected retrospectively from patient records and defined as presence of coordination problems, positive test of Romberg or ataxic gait.

Cerebrospinal fluid (CSF) was tested for white blood cell count and protein level. Serum was tested for IgM and IgG antibodies to GQ1b (IgM and IgG) by ELISA.[8]

Statistical analysis

We used SPSS (version 21) for statistical analyses. Categorical data were presented as proportions and differences were analyzed using the Fisher's exact test or Chi-squared test. Continuous data were presented as medians and interquartile ranges (IQR) and compared using the Mann-Whitney *U* test. A two-sided p-value of < 0.05 was considered to be statistically significant.

RESULTS

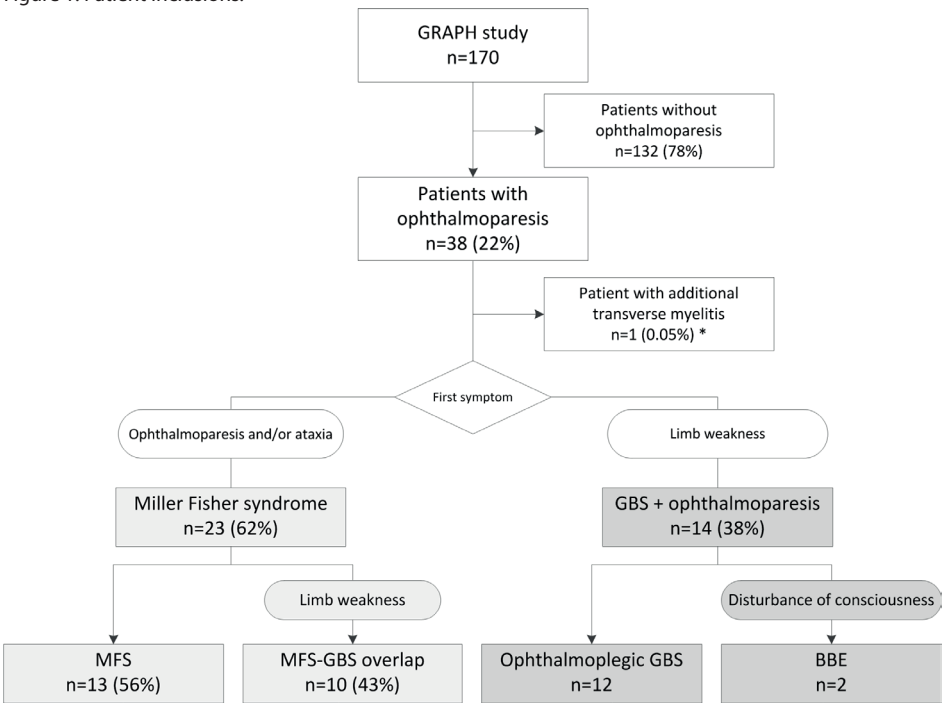
In the cohort of 170 patients, 38 (22%) had ophthalmoparesis at entry or during disease. One patient was excluded because of an additional transverse myelitis, resulting in 37 patients included in this study. Twenty-three patients presented with MFS, of whom 10 (43%) later on developed limb weakness (MFS-GBS overlap). Twelve patients (32%) had ophthalmoplegic GBS and 2 patients (5%) BBE (Figure 1 and Table 1).

Limb weakness occurred in all MFS-GBS patients within one week after onset of symptoms (median 1 day, range 0-6 days). No significant differences were found in the clinical features at entry that could be used to predict progression from MFS to MFS-GBS overlap syndrome (Table 1).

At entry, patients with ophthalmoplegic GBS had more severe limb weakness (MRC sum score 39, IQR 27-43) than MFS-GBS overlap (MRC sum score 53, IQR 44-58) (p=0.02) and a worse median GBS disability score (median 4 (IQR 4-5) versus 3 (IQR 3-4)) (p=0.04) (Table 1). Two MFS patients had bulbar weakness at presentation and another patient with MFS developed bulbar weakness after one week. None of them required mechanical ventilation.

The two BBE patients had the most severe clinical picture, being completely paralyzed and ventilated. Both developed disturbances in consciousness within 12 days after onset of weakness.

Figure 1. Patient inclusions.



BBE = Bickerstaff brainstem encephalitis, GBS = Guillain-Barré syndrome, GRAPH = GBS Research about Pain and Heterogeneity, MFS = Miller Fisher syndrome. * This patient was diagnosed with atypical GBS with transverse myelitis (demyelinating lesion in thoracic spine).

A cyto-albuminologic dissociation in CSF was more often found in ophthalmoplegic GBS patients (67%) than in the other groups (MFS 18% and MFS-GBS overlap 20%) (p=0.02). NCS revealed that patients with MFS most often had sensory nerve involvement only (44%), whereas ophthalmoplegic GBS and patients with MFS-GBS overlap most often had both sensory and motor involvement (respectively 100% and 70%, MFS 33%, p=0.007). All patients with ophthalmoplegic GBS had evidence of motor nerve involvement on NCS: 33%-67% had reduced distal compound muscle action potentials (dCMAP's) or unresponsive nerves, 22%-50% had prolonged distal motor latencies (DML), 34%-67% had decreased motor conduction velocity (MCV), and 50%-100% had abnormal F-waves. In the MFS-GBS overlap group, motor involvement consisted of abnormal dCMAP amplitudes in 0%-75% of the patients, prolonged DML in 13%-38%, decreased MCV in 0%-38%, and prolonged or absent F-waves in 30%-50%. In contrast, MFS patients showed more often sensory nerve involvement (0%-28% abnormal sensory nerve action potential (SNAP), 43%-75% prolonged distal sensory latency (DSL), and 0%-57% decreased sensory conduction velocity (SCV)) and less frequent motor nerve involvement (0%-13% abnormal dCMAP amplitudes, 0%-33% prolonged DML, 0%-34% decreased MCV, and 0% abnormal F-waves).

Serum anti-GQ1b IgG antibodies were more often present in patients with MFS (85%) or MFS-GBS overlap (63%) than in patients with ophthalmoplegic GBS (8%) ($p<0.001$). One patient with BBE was positive for IgM to GQ1b, but negative for IgG to GQ1b. The other patient with BBE was negative for both IgM and IgG to GQ1b.

Univariate analysis did not reveal any features at entry which were significantly associated with progression to MFS-GBS overlap (defined as an odds ratio > 1.0 and calculated for sensory deficits, facial weakness, GBS disability score at entry, CSF examination, results of NCS, and presence of GQ1b antibodies).

None of the patients with MFS developed respiratory failure, while 1 patient (10%) of the MFS-GBS overlap group and 7 (58%) of the ophthalmoplegic GBS patients and both BBE patients needed ventilatory support at some time during the disease course (p-value MFS-GBS overlap versus GBS group=0.03). In the patient with MFS-GBS overlap syndrome, respiratory failure occurred within one day after onset of symptoms.

At nadir, the MRC-sum score was lower in the ophthalmoplegic GBS group than in the MFS-GBS overlap group (median 24 (IQR 4-39) versus 51 (IQR 44-58)) ($p=0.002$).

These patients also had a worse GBS disability score than the MFS-GBS overlap patients (median 5 (IQR 4-5) versus 3 (IQR 3-4) ($p=0.01$).

Five MFS patients (39%) were treated with IVIg of whom two (40%) had residual symptoms or signs after six months follow-up. Of the eight untreated MFS patients, five patients had residual symptoms or signs (63%). All patients in the MFS-GBS overlap, ophthalmoplegic GBS and BBE group were treated with IVIg.

After 6 months, limb weakness was still present in 10% of the MFS-GBS overlap syndrome patients, 55% of the ophthalmoplegic GBS patients and in both BBE patients. Sensory deficits were found in 38% of the MFS patients, 56% of the patients with MFS-GBS overlap syndrome, 82% of the patients with ophthalmoplegic GBS, and in both BBE patients. Cranial nerve involvement (oculomotor or facial weakness) was observed in 20% of the MFS patients, 44% of the MFS-GBS overlap syndrome patients, 50% of the ophthalmoplegic GBS patients and in both BBE patients.

The median time to independent walking was not significantly different between patients with MFS and MFS-GBS overlap (7 versus 14 days) but was longer in patients with ophthalmoplegic GBS (91 days, p-value MFS-GBS overlap versus ophthalmoplegic GBS=0.03). This observation was confirmed in Kaplan-Meijer analysis between the

Table 1. Demographical features and clinical course of MFS and overlap syndromes.

	MFS (n=13)	MFS-GBS overlap (n=10)	Ophthalmoplegic GBS (n=12)
Gender (male), n (%)	9/13 (69%)	7/10 (70%)	9/12 (75%)
Age, years (median, IQR)	51 (37-55)	58 (50-64)	47 (39-61)
Antecedent event			
Diarrhoea, n (%)	2/13 (15%)	-	3/12 (25%)
Upper respiratory infectious symptoms, n (%)	5/13 (39%)	7/10 (70%)	4/11 (36%)
Clinical features at entry			
Clinical triad[1], n (%)	8/13 (62%)	6/9 (67%)	2/10 (20%)
Ophthalmoparesis (at least 1 nerve), n (%)	13/13 (100%)	9/10 (90%)	7/9 (78%)
Ataxia, n (%)	8/13 (62%)	6/8 (75%)	2/10 (20%)
Decreased reflexes or areflexia, n (%)	12/13 (92%)	9/10 (90%)	9/10 (90%)
Paresthesias, n (%)	9/13 (69%)	6/9 (67%)	11/11 (100%)
Pain, n (%)	7/12 (58%)	3/10 (30%)	7/10 (70%)
Sensory deficits, n (%)	5/13 (39%)	7/10 (70%)	10/11 (90%)
Facial weakness, n (%)	5/13 (39%)	5/10 (50%)	6/10 (60%)
MRC-sum score, median (IQR)	60 (60-60)	53 (44-58)	39 (27-43)
GBS-disability score, median (IQR)	3 (2-3)	3 (3-4)	4 (4-5)
Ventilator dependency, n (%)	-	1/10 (10%)	7/12 (58%)
Additional investigations			
Time from onset until LP (days), median, IQR	3 (2-7)	2 (1-4)	4 (1-5)
Cyto-albuminologic dissociation in CSF, n (%)	2/11 (18%)	2/10 (20%)	8/12 (67%)
Time from onset until NCS (days), median (IQR)	5 (3-11)	6 (3-10)	8 (7-24)
Results nerve conduction studies			
Normal, n (%)	2/9 (22%)	-	-
Sensory abnormalities, n (%)	4/9 (44%)	3/10 (30%)	-
Motor (+/- sensory) abnormalities, n (%)	3/9 (33%)	7/10 (70%)	10/10 (100%)
GQ1b-IgG positive in serum, n (%)	11/13 (85%)	5/8 (63%)	1/12 (8%)
GQ1b-IgM positive in serum, n (%)	2/13 (15%)	3/8 (38%)	-

[1] Clinical triad: involvement of ≥ 1 ocular nerve (oculomotor, trochlear or abducens), ataxia and decreased reflexes or areflexia without limb weakness. LP: lumbar puncture. NCS: nerve conduction study. MFS: Miller Fisher syndrome. MFS-GBS overlap: MFS patients later on developing limb weakness. Ophthalmoplegic GBS: GBS patients (with limb weakness) later on developing ophthalmoparesis.

three groups, with a log rank p-value of 0.002. The proportion of patients walking independently at six months however was the same for MFS-GBS overlap (80%) and ophthalmoplegic GBS patients (83%), and in addition all MFS patients were able to walk independently.

DISCUSSION

In our study, 43% of the patients with MFS developed limb weakness and one MFS-GBS overlap patient developed respiratory failure. This disease progression occurred in the first week of onset of symptoms in all these cases. We identified no early characteristics to determine which MFS patients are at risk for progression to MFS-GBS overlap syndrome. These findings indicate that at present there are no predictors of disease progression for MFS and that all these patients need careful monitoring of the clinical course for at least one week.

Previous studies reported variable proportions of patients with MFS who developed limb weakness ranging from 26% to 50%.[1, 3, 5, 9-12] These varying proportions can be explained in part by different definitions of weakness and disease progression. Our study, conducted in the Netherlands, confirmed the findings of a recent study from Japan, showing that about half of the patients with MFS developed limb weakness after the first week of onset of symptoms.[3] Respiratory insufficiency in the Japanese MFS-GBS overlap syndrome requiring ventilatory support occurred within the first week after onset of symptoms.[3] This is comparable with another study in 45 patients with MFS-GBS overlap syndrome, in whom respiratory insufficiency occurred within one week (median 2 days, range 1 to 6 days).[5] The current study shows that the same disease dynamics occur in a prospective and unbiased cohort of Dutch patients. Together, these studies demonstrate that patients presenting with MFS have a considerable risk of disease progression but that this occurs predominantly early in the disease course.

In the current study we defined two subtypes in the MFS-GBS spectrum; the MFS-GBS overlap syndrome and ophthalmoplegic GBS. Both subtypes are characterized by weakness of the limbs and eye muscles, but the sequence in which these symptoms develop differs. Interestingly, our patients with ophthalmoplegic GBS were more severely affected at nadir and had poorer outcome than patients with MFS-GBS overlap syndrome. Apparently, the site weakness appears initially, usually is most severely affected at nadir and shows the slowest and incomplete recovery. This finding also gives further support to the hypothesis that GBS and MFS form a continuous spectrum in which the MFS-GBS overlap syndrome and ophthalmoplegic GBS are intermediate forms.[6]

Although MFS is considered to have a benign course, we found that 63% of untreated and 40% of the IVIg treated MFS patients had residual symptoms and signs after six months follow-up. No randomized controlled trial has been performed investigating the efficacy of IVIg or plasma exchange in MFS or MFS-GBS overlap syndrome.[2]

The main limitation of the study is the limited number of patients of specific subtypes that has influenced the study power to demonstrate risk factors for disease progression. The Japanese study investigating the difference between the subtypes in 60 patients, also did not identify such risk factors for MFS.[3]

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3.2

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 1,000 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 or 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 con-

tinuous 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.

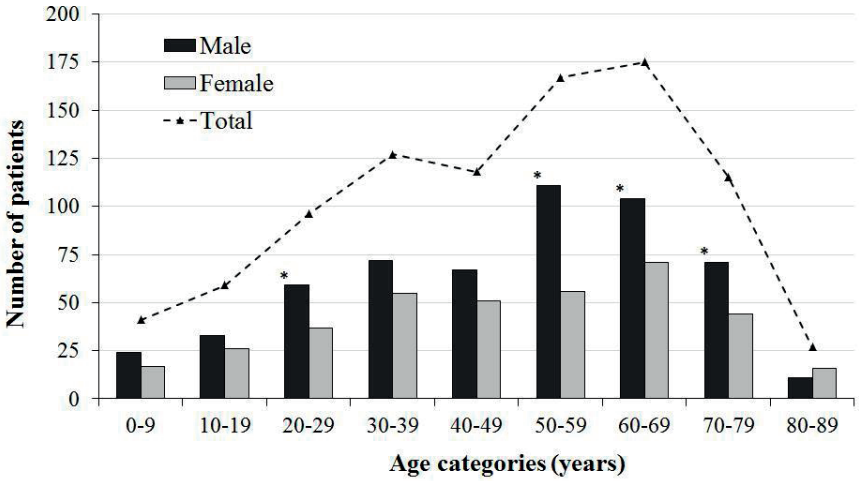
Cohort description and heterogeneity of GBS

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.

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.

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.

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

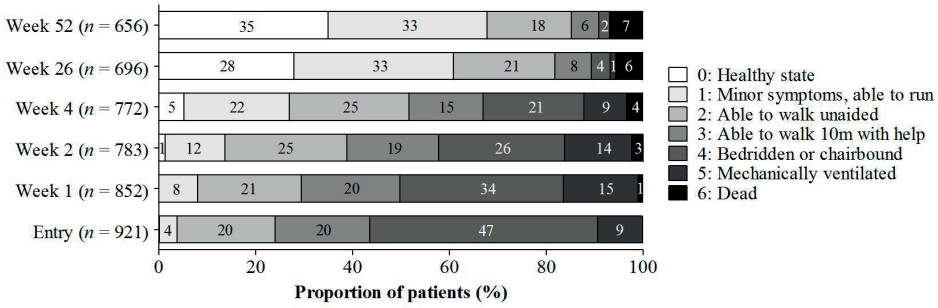


Table 1. Demography and clinical features of IGOS cohort (*n* = 925)

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%)
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%)

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

Demographics	
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.

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.

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).

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**
Other[b]	6/715 (1%)	0/69 (0%)	1/125 (1%)	0.75

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

	Regions			
	Europe/ Americas (*n* = 715)	**Asia (*n* = 69)**	**Bangladesh (*n* = 125)**	***P-value***
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.

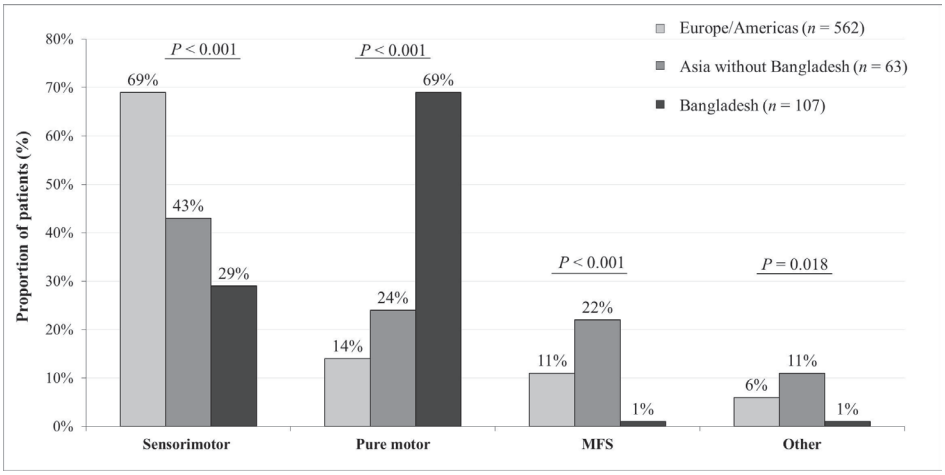
Patients from Bangladesh were significantly younger (age 28 years, IQR 16-40) than patients from Europe/Americas (55 years, IQR 37-67, $P < 0.001$) and Asia (50 years, IQR 34-60, $P < 0.001$). An upper respiratory tract infection was the most common reported antecedent event in Europe/Americas (38%) 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%, $P = 0.003$).

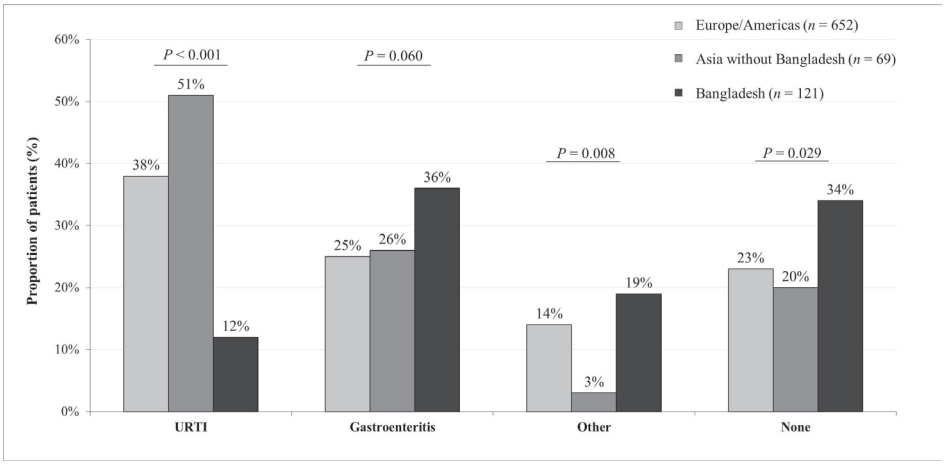
The predominant clinical pattern of GBS in Europe/Americas and Asia was sensorimotor (Europe/Americas: $n = 387$, 69%; Asia $n = 27$, 43%), whereas in Bangladesh most patients had pure motor GBS ($n = 74$, 69%). MFS or MFS-GBS overlap occurred more frequently in Asia ($n = 14$, 22%) than in Europe/Americas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

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

A



B

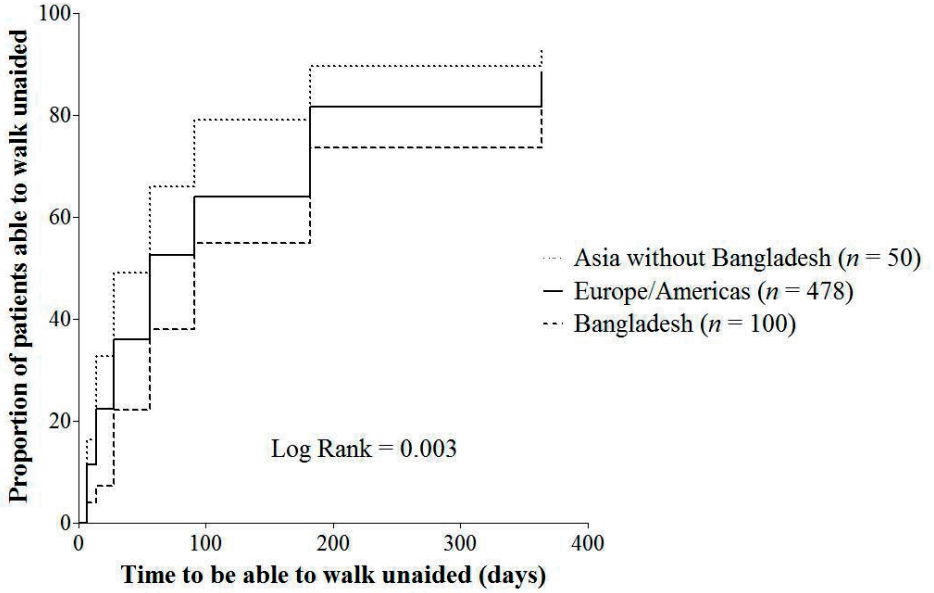


MFS: Miller Fisher and Miller Fisher GBS overlap syndromes. Other: Pharyngeal-cervical-brachial, pure sensory, ataxic and other clinical variants. GBS = Guillain-Barré syndrome, MFS = Miller Fisher syndrome. Other: Urinary tract infection, vaccination, surgery and other antecedent events. URTI = upper respiratory tract infection.

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%

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 3 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

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).

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.[31http://data.un.org] 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.

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
Other	1.00	1.000	1.00

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**
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.

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4

Treatment aspects of Guillain-Barré syndrome

4.1

Treatment dilemmas in Guillain-Barré syndrome

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ABSTRACT

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy with a highly variable clinical course and outcome. Intravenous immunoglobulin and plasma exchange are proven effective treatments, but the efficacy has been demonstrated mainly on motor improvement in adults with a typical and severe form of GBS. In clinical practice, treatment dilemmas may occur in patients with a relatively mild presentation, variant forms of GBS, or when the onset of weakness was more than two weeks ago. Other therapeutic dilemmas may arise in patients who do not improve or even progress after initial treatment. We provide an overview of the current literature about therapeutic options in these situations, and additionally give our personal view that may serve as a basis for therapeutic decision making.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a rapidly progressive and potentially life-threatening polyradiculoneuropathy that requires early diagnosis, monitoring and treatment.[1, 2] Plasma exchange (PE, usually 200-250 mL/kg in five sessions) and intravenous immunoglobulin (IVIg, 0.4 g/kg for 5 days) are proven effective treatments for GBS.[3, 4] IVIg may be considered first choice treatment because it is relatively easy to administer, widely available and has less side effects.[3-5] Despite the proven effectiveness of these treatments in GBS, the care of patients in clinical practice is often complex. First, outcome in many patients is still poor: 2-10% may die, 20% are still unable to walk after 6 months and many patients suffer from residual complaints, including pain and severe fatigue.[1, 3, 4, 6-8] Second, the patients in whom the therapeutic effects have been demonstrated frequently represent a selected proportion of the patients (symptoms < two weeks and who are walking with aid, bed bound or in need of artificial ventilation (GBS disability grade ≥ 3, table 1)).

Table 1.GBS disability scale. Adapted from: Hughes et al, 1978 and PSGBS group 1997.[9, 10]

Grade	
0	Healthy
1	Minor symptoms and capable of running
2	Able to walk 10 m without assistance but unable to run
3	Able to walk 10 m across an open space with help
4	Bedridden or chair bound
5	Requiring assisted ventilation for at least part of the day
6	Dead

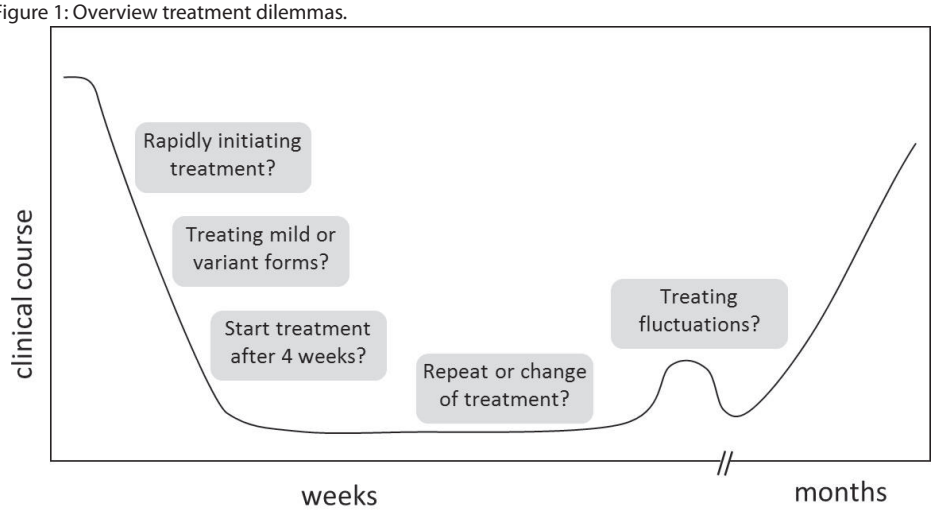
Third, the efficacy of PE and IVIg has primarily been demonstrated related to improvement on the GBS disability scale 4 weeks after the start of treatment. However, this scale focuses on walking and does not take into account other consequences of GBS that are important in daily life, such as arm function, facial weakness, sensory deficits, pain and fatigue. Finally, as a consequence of this, the Cochrane reviews about treatment of GBS are restricted to the specific inclusion and outcome criteria of the trials being focused on the GBS disability scale.[3, 4, 11-14] In clinical practice, clinicians are facing various situations that are not covered by the existing therapeutic studies and other literature (figure 1).

In this review, we will address two main issues that may result in dilemmas in the treatment of patients with GBS:

1. Start of (standard) treatment
    a. Therapeutic time window

   b. Mild form of GBS
   c. Clinical variants and electrophysiological subtypes of GBS
   d. Children
2. Change or repeat of treatment
   a. Insufficient clinical response
   b. Add-on treatment
   c. Other treatments than PE or IVIg
   d. Treatment-related fluctuations (TRFs)

Figure 1: Overview treatment dilemmas.



We give a summary of the current evidence of treatment in these specific clinical situations. Furthermore, we provide a personal view for each dilemma, in order to support clinicians in their decision-making, as long as evidence from clinical trials is lacking. The level of evidence of the treatment effect ranges from 1 to 4 (table 2).

Table 2. Levels of evidence.[15, 16]

Level 1	≥ 1 (meta-analysis of) RCTs with appropriate number of patients, intervention and outcome measures
Level 2	Controlled trial without randomization or RCT with low number of patients
Level 3	Uncontrolled trials
Level 4	≥ 1 case reports

Abbreviation: RCT = randomized controlled trial.

START OF (STANDARD) TREATMENT

Therapeutic time window

Time is nerve?

All randomized controlled trials (RCTs) with IVIg and PE in GBS were conducted in the acute phase of disease, within 2 (in case of IVIg) to 4 weeks (in case of PE) after onset of weakness. One may assume that treatment is most effective when started as soon as possible in order to prevent further nerve damage, similar to the concept 'Time is brain' in ischemic cerebrovascular accidents. Some support for this hypothesis comes from the PE trials, where PE in patients randomized within 7 days after onset of symptoms had a more pronounced effect (on time to improve one clinical grade, median time to walk without assistance), than in patients randomized between 8 to 28 days after onset.[3, 17, 18] Furthermore, IVIg has pleiotropic immune modulatory effects that may inhibit Fc-mediated activation of macrophages, prevent binding of antibodies to neural targets, and prevent complement activation which would otherwise lead to further nerve damage.[4, 19, 20] These effects of IVIg and the potential ongoing nerve injury, in the absence of results of properly controlled trials, may implicate that treatment should be initiated as soon as possible.

Current personal view: Based on limited evidence we recommend to start treatment as soon as possible in patients who walk with aid, are bedbound or ventilated (level of evidence: 3). In patients who are still able to walk unaided but show rapid progression of symptoms one likely should aim to prevent further nerve damage and not wait for further clinical deterioration (level of evidence: 4).

How long after onset of weakness can treatment still be effective?

The progressive phase in the vast majority of patients with GBS takes less than four weeks, and most patients will present within a few days to weeks after onset of symptoms.[21] However, about 3% of patients show deterioration during a period of 4 to 8 weeks that in part may be due to an ongoing immune-mediated injury of the nerves (subacute idiopathic demyelinating polyneuropathy, SIDP).[22] For these cases, no evidence is available regarding treatment effect of IVIg or PE.

Presentation 4 weeks after onset of symptoms can be a demonstration of a relatively mild disease course with a good natural prognosis which does not necessitate treatment. When there is still progression after 4 weeks, especially in patients who are not that severely disabled and who show clear signs of demyelination on nerve conduction studies, acute onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) should be considered. Especially when progression persists after 8 weeks, chronic in-

flammatory demyelinating polyneuropathy (CIDP) should be considered and then (re-) treatment with IVIg or even a switch to corticosteroids is indicated.[23]

Current personal view: There is no information available on the effect of treatment in patients with GBS presenting 4 weeks or later after onset of weakness. Subacute GBS or A-CIDP should be considered in patients who present after 4 weeks of onset. We suggest to start IVIg when there is clear clinical progression or a 'wait and see' policy in case of relatively mild and stable disease (level of evidence: 4).

'Mildly affected' patients

Although there is no consensus about the definition of mild GBS, one may consider a patient who is still able to walk unaided to be mildly affected, although it can imply that the patient has severe other neurological deficits. In this paper, like in some other publications, we use the term mild GBS when the patient is still able to walk without help (GBS disability score 1 or 2).[24] Previous studies indicate that about one-third of patients have a mild form of GBS, although the actual proportion may be underreported due to selection bias.[25] Some studies have indicated that the clinical course in these patients may not be as mild as expected. Up to 38% of patients with a mild form of GBS-reported problems in hand function and running after six months follow-up even despite the fact that 22% of them received treatment.[26]

Most RCTs were conducted in patients with a severe form of GBS, defined as walking with aid or worse (table 1). The primary end point in these trials was usually based on the proportion of patients regaining the capacity to walk unaided or improvement by at least one grade on the GBS disability scale. In part because of these endpoints, mildly affected patients were usually not included in the RCTs, which limits the evidence whether treatment will be effective in this subgroup of patients.

The Cochrane reviews on PE and IVIg provide no direct advice for the treatment of mild GBS.[3,4] The therapeutic effect of IVIg has not been evaluated in adult patients with mild GBS. However in a small group of children with mild GBS, a shorter time to improvement and a lower GBS disability grade at four weeks were observed in the IVIg group.[27]

One RCT investigated the effect of PE on time to onset of motor recovery in patients being able to stand unaided, or walk 5 meters with or without assistance.[24] In this study, it was shown that treatment with two PE sessions significantly shortened the time to onset of motor recovery (4 days) than supportive care (8 days) and shortened the time to hospital discharge (13 versus 18 days).[24] Long-term outcome (defined as full muscle-strength recovery after one year) was not significantly different, but this outcome

measurement may lack specificity to demonstrate a difference. Moreover, spontaneous full recovery is possible due to the mild course of the disease, and it would possibly be more informative to investigate whether treatment hastens full recovery in the context of cost-effectiveness and risk-benefit analysis.

Current personal view: Patients with mild GBS may have long-term functional impairment, but only a beneficial effect of treatment with PE has been demonstrated (level of evidence: 2). This effect has not been demonstrated for IVIg in adult patients. Based on the effect of PE in mild cases and of IVIg in severe cases, IVIg likely may be effective in mild GBS too. We propose that treatment (either PE or IVIg) should be considered especially in mildly affected patients who develop additional features such as autonomic dysfunction, bulbar or facial weakness (level of evidence: 4). New treatment trials preferentially should study the effect of treatment not only restricted to severely affected GBS patients.

Clinical variants and electrophysiological subtypes of GBS

Miller Fisher syndrome (MFS)

MFS, characterized by ophthalmoplegia, ataxia and areflexia, is considered to be a variant form of GBS because of the common underlying pathogenesis and the presence of overlap forms with GBS.[28] Patients with typical MFS (ie, without limb weakness) in general have a benign natural course with complete recovery in 60-100% of the patients after six months.[14, 29, 30] Two retrospective studies (total n=142) found no difference in time to complete recovery in patients treated with IVIg or PE versus supportive care, but IVIg slightly hastened the time to onset of amelioration of symptoms.[30, 31]

According to the Cochrane review, there is currently not enough evidence that immunotherapy could hasten recovery of MFS and that patients suffering from typical MFS are likely to improve completely with a conservative approach.[14]

However, 25-50% of patients presenting with MFS will develop limb weakness (MFS-GBS overlap syndrome) and 40% of patients will develop additional bulbar weakness and swallowing disorders that may require intubation.[28, 32, 33] There currently are no prognostic models available to predict which patients are prone to progress to MFS-GBS overlap syndrome. According to the Cochrane review, results of therapeutic trials in GBS may be extrapolated to patients with a MFS-GBS overlap syndrome because it is part of the GBS spectrum.[14]

Current personal view: Evidence from retrospective studies indicates that typical MFS might require supportive care only because of the relatively benign natural course (level

of evidence: 3). In patients with additional limb weakness, swallowing disorders, facial weakness or respiratory failure treatment with IVIg or PE should be considered (level of evidence: 4).

Bickerstaff's brainstem encephalitis (BBE)

BBE is considered to be a rare variant within the GBS spectrum.[34] Patients with BBE usually have ophthalmoplegia, ataxia, and sometimes limb weakness, but in addition they show symptoms of brainstem involvement including alterations in consciousness or long tract signs.[35] No RCT has been conducted in BBE, and only case reports and series have been published describing the clinical course after various forms of treatment. The largest study was a retrospective study in 62 cases of BBE, which reported different combinations of treatment regimens (PE, IVIg, steroids, combinations of these, and supportive care).[36] Six months after onset of symptoms, two-third of all patients had completely recovered, with the highest recovery in the IVIg group. Residual symptoms in the other patients were limb weakness, cognitive changes, diplopia, gait disturbance, dysaesthesia and dysphagia. Five percent (3 patients) died during the six month follow-up period. Other smaller series have reported full recovery of neurological symptoms in 67% to 100% of the patients after six months.[14]

Current personal view: Although the effect of treatment has not properly been studied in BBE, the clinical severity of BBE in the acute phase and overlap with GBS suggest that treatment with IVIg or PE in the acute phase is justifiable (level of evidence: 4).

Other clinical variants of GBS

Other variants within the GBS spectrum are the pure motor, pharyngeal-cervical-brachial (PCB), pure ataxic, pure sensory and paraparetic variant. No RCT has been performed specifically in any of these variants.

One post-hoc subgroup analysis reported that significantly more patients with pure motor GBS regained the capacity to walk unaided after treatment with IVIg compared with PE (87% versus 45%, p=0.02).[37] Three other retrospective studies showed evidence that patients with anti-GM1 antibodies (associated with pure motor GBS) might do better after IVIg compared with PE.[38-42]

Current personal view: Based on the results of four retrospective studies with small numbers of patients, we consider to recommend IVIg over PE in patients with pure motor GBS (level of evidence: 3). Patients with PCB, ataxic and sensory GBS might never become eligible for treatment when only the GBS disability scale is taken into account

and therefore treatment should be initiated when symptoms are seriously disabling or rapidly progressing (level of evidence: 4).

Electrophysiological subtypes of GBS

Based on nerve conduction studies, GBS can be classified into acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor (sensory) axonal neuropathy (AMAN, AMSAN). The proportion of patients with axonal GBS varies between geographical areas, with a higher frequency in Asian and South-American countries.[1] Most therapeutic studies were conducted in Western countries where the frequency of axonal GBS is relatively low (<10%). Patients with AMAN or AMSAN were included in these trials but only one study performed a posthoc analysis in this subgroup which showed no difference in outcome of these patients treated with either IVIg or PE, although patient numbers were small (total n=32).[43]

Current personal view: No RCT has been performed exclusively in patients with axonal forms of GBS, but until such studies have demonstrated otherwise, we recommend to treat these patients similarly as the patients with a demyelinating form of GBS (level of evidence: 4).

Children with GBS

GBS may occur at all ages, although the incidence of GBS in children is lower than in adults. Three prospective randomized trials have investigated the effect of IVIg versus supportive care in children and one investigated the effect of IVIg versus PE in ventilated children (table 3). The first three studies showed that IVIg had a significant effect on shortening the time to improvement and total recovery than dexamethasone or supportive care. [4, 27, 44, 45] It was also found that in 51 severely affected children, there was no difference in effectiveness when IVIg was administered over 2 days or 5 days (total 2 g/kg), although there were more relapses (TRFs) in the group with a short treatment regimen.[27] The effect of PE has not been investigated extensively in large randomized trials in children. One prospective randomized trial in 41 ventilated children found that PE slightly but significantly shortened the duration of mechanical ventilation compared with IVIg treated children, but there was no significant effect on hospital stay or the proportion of children able to walk unaided at four weeks.[46] Important to bear in mind, is that PE in children can have more adverse events and complications than in adults because of citrate toxicity, higher relative vascular volume shifts and the need for safe vascular access.[47]

Current personal view: There currently is no indication to treat children with GBS differently than adults. IVIg seems to be effective in children with GBS (level of evidence: 2)

and is preferred over PE because it is easier administered and possibly better tolerated in small children (level of evidence: 3).

Table 3. Overview of RCTs in children

Study	Number of patients	Design	Inclusion criteria	Results
Gürses et al 1995 [44]	18	*Single center quasi-randomized parallel group* Supportive care versus 2 g/kg IVIG over 2 days	Resembling GBS criteria of Asbury 1990	The interval from onset to nadir, from nadir to improvement and duration of hospitalization was significantly shorter in the IVIg group than in the controls.
Wang et al 2001 [4]	54	*Single center parallel group* Dexamethasone alone versus dexamethasone and IVIg (0.2 to 0.3 g/kg daily for five to six days) versus dexamethasone and PE	Unknown	Significant earlier and better recovery in IVIg + dexamethasone group compared with dexamethasone alone and the PE group
Korinthenberg et al 2005 [27]	21	*Multicenter randomized parallel group* Supportive care versus IVIg (1 g/kg over 2 days)	Children able to walk without aid for ≥ 5 meter	No difference in maximum disability grade but significantly earlier onset of improvement and lower GBS disability grade at four weeks
	51	*Multicenter randomized parallel group* IVIg 2 g/kg over 2 days versus 2 g/kg over 5 days	Children unable to walk 5 meter unaided	No differences in both primary and secondary outcome measures but more often TRFs observed in short regimen group
El-Bayoumi et al 2011 [46]	41	*Single center randomized parallel group* IVIg (2 g/kg over 5 days) versus PE	Children who were ventilated	Children treated with PE had slightly but significant shorter time of mechanical ventilation

GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; PE, plasma exchange; RCT, randomized controlled trial; TRFs, treatment related fluctuations

CHANGE OR REPEAT OF TREATMENT

Insufficient clinical response after initial treatment

Patients with GBS may show no signs of clinical recovery after initial treatment and may even further deteriorate. Previous trials have shown that about 40-50% of patients treated with either PE or IVIg show no improvement on the GBS disability scale at four weeks (table 4).[17, 18, 48, 49] At present it is only possible to evaluate the effect of treatment on a clinical basis. Whether a patient would benefit from a second course or a change to another treatment cannot be determined yet.

Table 4. Overview of PE or IVIg RCTs with outcome measures based on GBS disability scale.

Study	Number of patients	Design	Inclusion criteria	Improvement by ≥ 1 functional grades at 4 weeks	Time to onset of motor recovery	Time to recover walking with aid	Time to recover walking without aid	Ventilatory assistance
Greenwood et al 1984 [50]	29	Supportive care vs PE	- Age > 3 years - Disability grade ≥ 3 - Onset ≤ 30 days	40% vs 50% p=NS				80% vs 57% p=NR
Osterman et al 1984 [51]	38	Supportive care vs PE	- Adults < 80 years - Disability grade ≥ 3	30% vs 78% p<0.025	17 vs 9 days P<0.05			
GBS study group et al 1985 [17]	245	Supportive care vs PE	- Age > 12 years - Disability grade ≥ 3 - Onset ≤ 30 days	39% vs 59% p<0.01			83 vs 53 days p<0.001	42% vs 47% p=NR
French group et al 1987 [18]	220	Supportive care vs PE	- Age > 16 years - Regardless severity - Randomization ≤ 17 days after onset of motor signs	37% vs 61% p=NR	13 vs 6 days p<0.011	44 vs 30 days p<0.01	111 vs 70 days p<0.001	43% vs 21% p<0.005
Van der Meché et al 1992 [48]	147	PE vs IVIg	- Age > 4 years - Disability grade ≥ 3 - Onset ≤ 14 days	34% vs 53% p=0.024			69 vs 55 days p=0.07	42% vs 27% p<0.05
Bril et al 1996 [49]	50	PE vs IVIg	- Age ≥ 14 years - Disability grade ≥ 2	61% vs 69% p=NS				

Table 4. Overview of PE or IVIg RCTs with outcome measures based on GBS disability scale. (*continued*)

Study	Number of patients	Design	Inclusion criteria	Improvement by ≥ 1 functional grades at 4 weeks	Time to onset of motor recovery	Time to recover walking with aid	Time to recover walking without aid	Ventilatory assistance
French group et al 1997 [24]	91	Supportive care vs 2 PE sessions	- Age > 16 years - Onset ≤ 30 days - Mildly affected patients	28% vs 58% p=NR	8 vs 4 days p=0.0002	14 vs 12 days p=0.8	28 vs 15 days p=0.40	13% vs 2% p=0.11
	304	2 PE vs 4 PE sessions	- Moderately affected patients		6 vs 5 days p=0.1	24 vs 20 days p=0.04	64 vs 52 days p=0.13	28% vs 26% p=1.00
	161	4 PE vs 6 PE sessions	- Severely affected patients		8 vs 8 days p=0.11	56 vs 60 days p=0.89	113 vs 103 days p=0.64	100% vs 100%
PSGBS group et al 1997 [10]	379	PE vs IVIg vs PE followed by IVIg	- Age > 16 years - Disability grade ≥ 3 - Onset ≤ 14 days				49 vs 51 vs 40 days p=NS	23% vs 22% vs 16% p=NS
Diener et al 2001 [52]	76	PE vs immune-adsorptionvs IVIg	- Age unknown - Regardless severity - Onset ≤ 14 days	71% vs 80% p=NS				
Raphael et al 2001 [53]	39	IVIg 3 versus 6 days	- Age > 16 years - Regardless severity - Onset ≤ 30 days - Contra-indications to PE	22% vs 44% p=0.27		131 vs 84 days p=0.08	152 vs 97 days p=0.39	67% versus 33% p=0.004
Van Koningsveld et al 2004 [54]	225	IVIg with or without methylprednisolone (or placebo)	- Age > 6 years - Disability grade ≥ 3 - Onset < 14 days	68% vs 56% p=0.06			28 vs 56 days p=0.37	21% vs 23% p=0.77

Data are shown as medians or proportions with p-values; ns = not significant, nr = not reported

GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; NR, not reported; NS, not significant; PE, plasma exchange; RCT, randomized controlled trial.

Switch to another therapy

Some neurologists may switch to the other treatment after either IVIg or PE as initial treatment if there is no clinical response. The rationale is that these treatments probably have different immune-modulatory effects that may influence the treatment efficacy in individual patients. One randomized trial compared the efficacy of PE, IVIg, or PE followed immediately by IVIg in 379 severely affected patients, but did not find significant differences between the three treatment modalities in any of the outcome measures.[10] Thus IVIg after PE was not significantly better than IVIg or PE alone. However, all patients receiving the combination switched to IVIg regardless of recovery after PE. No trial has been conducted to show whether patients who truly do not respond to one of these two treatments, may respond after switching to the other treatment.

Whether PE after IVIg should be considered, remains unclear. One small retrospective study in 46 patients reported that treatment with IVIg followed by PE was not better than IVIg alone. On the contrary, the patients who received both treatments had a worse GBS disability grade at discharge and were longer hospitalized.[55] The researchers conclude that this could reflect a more severe disease course in the patients receiving two treatments, but it could also suggest that PE washes out IVIg, thus preventing the therapeutic effects of IVIg.

Repeat treatment

Another option for patients who continue to deteriorate after initial treatment is to repeat the same regimen of treatment, being either PE or IVIg. Most studies on PE have investigated the effect of five exchanges. One trial showed that six plasma exchanges were not superior over four in already ventilated patients but the sixth course was given as part of the study protocol and not because of lack of improvement.[24]

A second course of IVIg may be beneficial in patients who rapidly metabolize the administered IgG. Previous studies showed that a low serum IgG increase two weeks after treatment, is associated with more severe disease course and poor outcome in comparison with patients who have a high IgG increase after treatment.[56] Four severely affected GBS patients who did not show recovery after a first course of IVIg started to improve after a second course of IVIg.[57] However this study was not controlled and for these patients it was not possible to determine whether the second course contributed to clinical recovery. A double-blind placebo RCT evaluating the effect of a second course of IVIg (administered shortly after the first IVIg course) in GBS patients with a poor prognosis is currently being conducted in the Netherlands, the Second IVIg Dose in GBS trial (SID-GBS). The results of this study are awaited in 2018.

Current personal view: At present there is no evidence that outcome is improved by repeating treatment (either IVIg or PE) or switch to another type of treatment (level of evidence: 2). PE after IVIg should probably be avoided (level of evidence: 4).

Add-on treatment to IVIg

Various trials have shown that treatment with corticosteroids alone does not improve recovery in GBS and some studies even suggest that oral corticosteroids may delay recovery.[12] One large RCT indicated that intravenous methylprednisolone (500 mg/day for 5 days) when added to IVIg has a small effect at 4 weeks after a post-hoc correction for known prognostic factors, but there was no improvement of long-term outcome.[54]

Studies in patients and animal models have established the crucial role of complement activation in the pathogenesis of GBS, at least in the subgroup of patients with complement fixing anti-ganglioside antibodies.[58] Eculizumab, a humanized monoclonal recombinant antibody to complement factor 5, prevents the formation of membrane attack complex and nerve injury in an animal model for GBS.[59] This complement inhibitor is therefore a promising new treatment for GBS that is currently being investigated in two RCTs (the Inhibition of Complement Activation (Eculizumab) in GBS study (ICA-GBS) in the UK and the Japanese Eculizumab Trial for GBS (JET-GBS) in Japan).[60, 61]

Current personal view: Corticosteroids as single treatment strategy should be avoided (level of evidence: 1). Methylprednisolone when added to IVIg does not improve long-term outcome but may have a limited effect on short-term outcome (level of evidence: 2).

Treatment other than PE and IVIg

Two small placebo randomized controlled safety studies have reported a non-significant effect of brain-derived neurotrophic factor (BDNF) or interferon beta-1a (IFNb-1a) on disability grade or rate of improvement respectively.[62, 63] A third small parallel randomized controlled study found a significant effect on improvement of disability grade eight weeks after onset of symptoms when patients were treated with the Chinese herbal medicine tripterygium polyglycoside compared to high-dose corticosteroids.[64] Another small, open parallel-group study found a similar effect when comparing PE to filtration of cerebrospinal fluid.[65] According to the Cochrane review, the numbers in the IFNb-1a and BDNF studies were too small to exclude clinical relevance and sequential larger RCTs might be more promising.[11]

Current personal view: At present there is no evidence for the effect of alternative treatments.

Treatment-related fluctuation (TRF)

Patients with GBS who have received treatment may show a secondary deterioration after initial clinical stabilization or improvement. This treatment-related fluctuation (TRF) is generally defined as a worsening of at least 1 grade on the GBS disability scale, or a decrease in Medical Research Council (MRC) sum-score after initial stabilization or improvement within the first 8 weeks after treatment.[66] TRFs have been reported in 8-16% of patients with GBS treated with either IVIg or PE.[66, 67] At present it is not possible to predict who may develop a TRF or how long and severe a TRF will be. In a study in children, more TRFfs were observed in the two-day IVIg treatment group (1 g/kg for 2 days) than in the five-day treatment group (0.4 g/kg for 5 days).[27] This may suggest that a shorter treatment regimen is associated with an increased chance to develop a TRF. Clinical deteriorations occurring 8 or more weeks after onset of weakness or for a third time should lead to considering the diagnosis A-CIDP.[67]

The mechanism of a TRF has not been elucidated but it has been hypothesized that the effect of treatment is transient while disease activity continues.[66] TRFs therefore provide evidence that a treatment in a specific patient is effective, although not lasting long enough, and that the patient will probably respond again after repeating the same treatment. Therefore, it is rational to treat a patient with a TRF with a second course of either IVIg or PE but no RCTs have been conducted to demonstrate the effect.[5] The Dutch GBS trial[48] showed that the clinical course of patients with a TRF who did not receive a second course, was comparable to those who did, indicating a relatively benign course of a TRF, but the numbers were very small (n=14).[66] The current treatment policy often is to retreat these patients.

Current personal view: We recommend to repeat treatment with IVIg or PE after a TRF, although the effect has not been determined in controlled studies (level of evidence: 4).

CONCLUSIONS

Treatment of GBS is complicated by the limited amount of evidence for the treatment effect in various clinical conditions that may frequently occur in GBS. Probably for some of these conditions it will not be possible to determine the effect of treatment in RCTs. Based on the existing evidence from therapeutic studies and our personal experience we have made recommendations for clinical practice (table 5). Future evidence should come from RCTs and from carefully conducted prospective cohort studies in considerable numbers of patients comparing the outcome after various treatment regimens.

Table 5. Summary of treatment dilemmas in GBS and recommendations.

Dilemma		Current personal view
Start of treatment	Time window	Treatment should be initiated as soon as possible after diagnosis to prevent further nerve damage (LOE: 3). The effect of IVIg started after two weeks and of PE after four weeks onset of weakness is unknown (LOE: 4).
	Mild forms	Consider treating mildly affected patients with a rapidly progressive course or with additional features such as autonomic dysfunction, bulbar or facial weakness (LOE: 2).
	Variants	Patients with typical MFS likely require supportive care only (LOE: 3). In complicated MFS (limb weakness, bulbar weakness) and BBE, treatment with IVIg or PE should be considered (LOE: 4). Other GBS variants should be treated according to local guidelines until results of specific treatment trials show otherwise (LOE: 4).
	Children	Treatment with IVIg is beneficial in children and IVIg is preferred over PE because it is easier to administer (LOE: 2).
Repeat or change of treatment	Insufficient clinical response	There is not enough evidence that switching to IVIg after PE is effective in patients who are severely affected (LOE: 2). IVIg followed by PE should probably be avoided (LOE: 4). The effect of a 2nd IVIg course in patients with a poor prognosis is currently investigated.
	TRF	Although there are no RCTs, there is some rationale to retreat patients who experience a TRF with either IVIg or PE (LOE: 4). When a patient develops three or more TRFs or deteriorates 8 weeks after onset, A-CIDP should be considered.

Abbreviations: A-CIDP = acute onset chronic inflammatory demyelinating polyneuropathy, BBE = Bickerstaff's brainstem encephalitis, GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, LOE = level of evidence, MFS = Miller Fisher syndrome, PE = plasma exchange, RCT = randomized controlled trial.

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4.2

Current treatment practice of Guillain-Barré syndrome

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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 compared 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

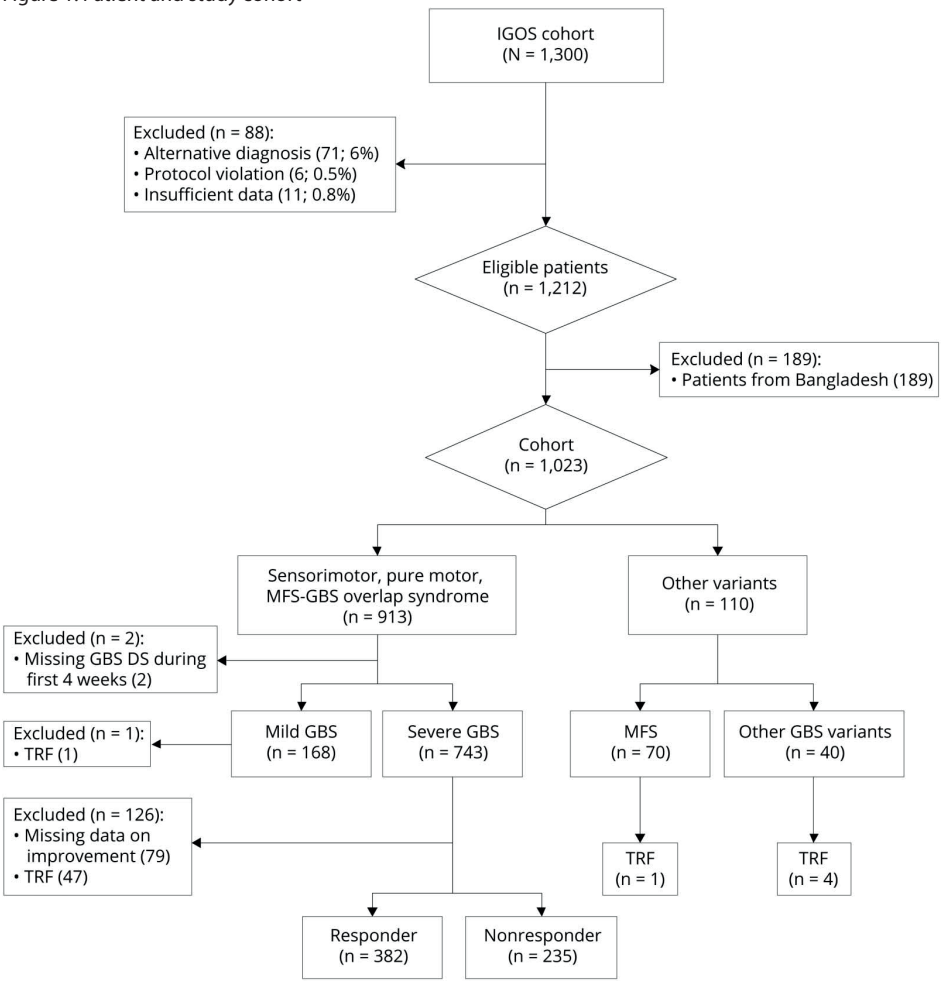
Study cohort

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.

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

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).

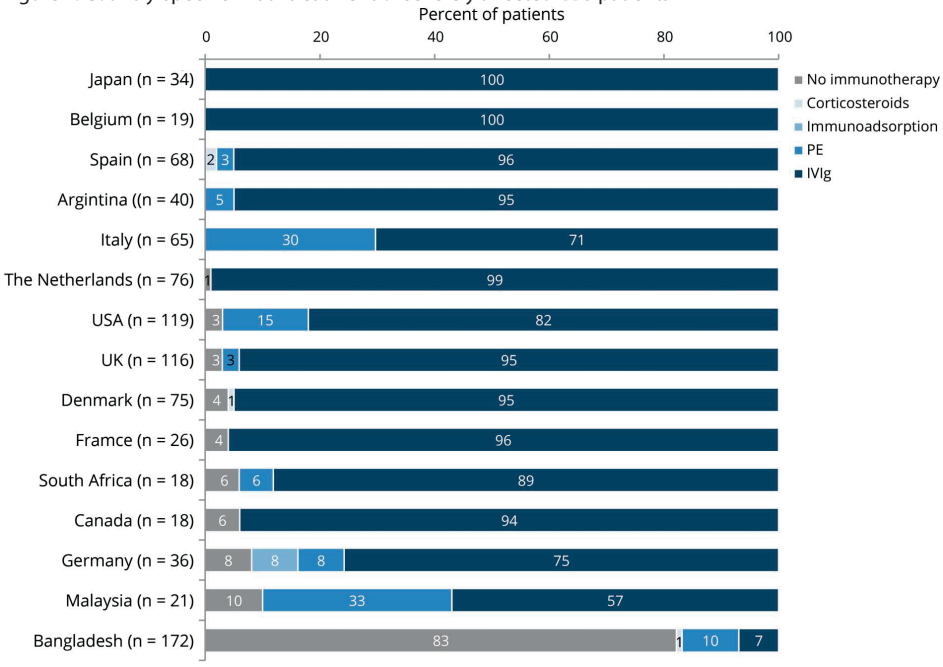
Eight (1%) patients were initially treated with other treatments, such as monotherapy with corticosteroids (n=5) or immunoadsorption (n=3). Of the five patients initially treated with corticosteroids only, one received an additional course of IVIg, and one received two additional courses of IVIg with 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).

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).

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

Clinical situation	Treatment	Full cohort (n=1023)	Europe (n=664)	America (n=238)	Asia* (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**	82 (35%)	50 (31%)	26 (47%)	6 (40%)
TRF		**n=53**	**n=45**	**n=7**	**n=0**
	Second immunotherapy[2]**	36 (68%)	30 (67%)	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%)

* Asia not including Bangladesh

** Consisting of IVIg, PE, or corticosteroids alone

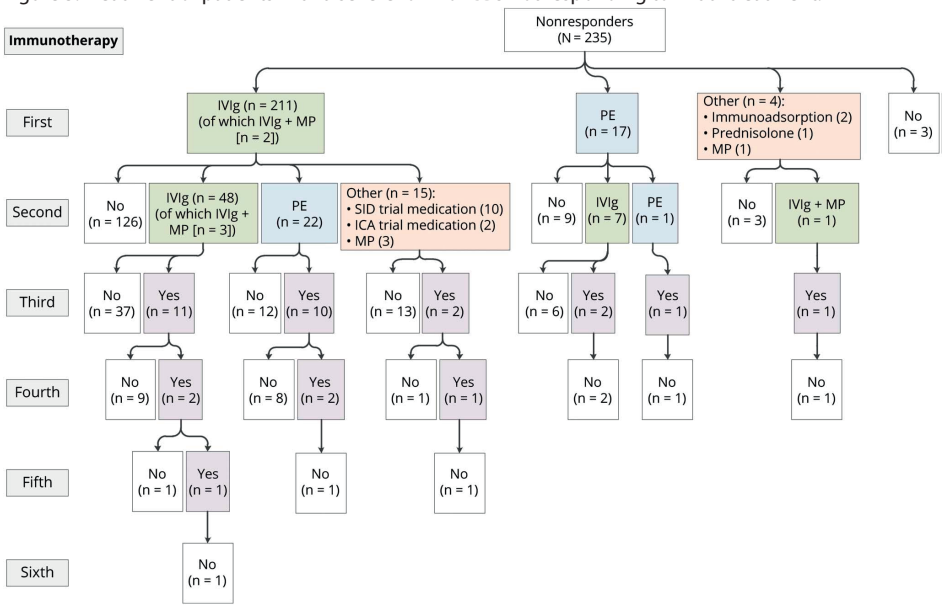
Abbreviations: GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, MFS = Miller Fisher syndrome, PE = plasma exchange, TRF = treatment related fluctuation

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 immuno-

therapy. 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).

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 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 inde-

pendently 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).

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).

Treatment of MFS and other variants

In the study cohort, 70 (7%) patients had MFS, and 40 (4%) patients had another distinct variant form 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.[19] 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, 20] 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, 21, 22] 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.[23, 24] Some patients were treated with corticosteroids only, even though this treatment is considered ineffective for GBS.[25] 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.[26]

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.[21] 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.[27] 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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4.3

Second IVIg course in Guillain-Barré syndrome with poor prognosis: the non-randomised ISID study

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ABSTRACT

Objective

To compare disease course in patients with Guillain-Barré syndrome (GBS) with a poor prognosis who were treated with one or with two intravenous immunoglobulin (IVIg) courses.

Methods

From the International GBS Outcome Study (IGOS), we selected patients whose modified Erasmus GBS Outcome Score (mEGOS) at week 1 predicted a poor prognosis. We compared those treated with one IVIg course to those treated with two IVIg courses. The primary endpoint, the GBS disability scale at 4 weeks, was assessed with multivariable ordinal regression.

Results

Of 237 eligible patients, 199 patients received a single IVIg course. Twenty patients received an 'early' second IVIg course (1-2 weeks after start of the first IVIg course) and 18 patients a 'late' second IVIg course (2-4 weeks after start of IVIg). At baseline and one week, those receiving two IVIg courses were more disabled than those receiving one course. Compared to the one course group, the adjusted odds ratio for a better GBS disability score at 4 weeks was 0.70 (95%CI 0.16-3.04) for the early group and 0.66 (95%CI 0.18-2.50) for the late group. The secondary endpoints were not in favor of a second IVIg course.

Conclusions

This observational study did not show better outcomes after a second IVIg course in GBS with poor prognosis. The study was limited by small numbers and baseline imbalances. Lack of improvement was likely an incentive to start a second IVIg course. A prospective randomized trial is needed to evaluate whether a second IVIg course improves outcome in GBS.

INTRODUCTION

A standard course of intravenous immunoglobulin (IVIg, 2 g/kg in 2-5 days) shortens time to recovery in Guillain-Barré syndrome (GBS) when administered within the first two weeks.[1-4] However, approximately 20% of patients are unable to walk independently at six months.[5] Evidence-based treatment options to improve outcome are currently lacking.[6] One small, uncontrolled series of 'treatment unresponsive' patients suggested that a second IVIg course was more effective than one course.[7] In addition, patients with a large increment in serum IgG level after IVIg treatment recovered more quickly than those with a small increment.[8] There are however reasons not to treat all GBS patients with a second IVIg course. First, approximately 80% of GBS patients treated with one IVIg course recover relatively well.[5] Second, serious side effects may occur, including anaphylaxis, acute kidney injury, thromboembolic events or hemolytic anemia.[9, 10] Third, IVIg is an expensive and relatively scarce blood product.

Therefore, careful selection of patients who might benefit from a second course of IVIg is important. The modified Erasmus GBS Outcome Score (mEGOS) identifies patients who are more likely to have a poor prognosis, defined as being unable to walk independently.[11] These patients in particular might benefit from a second course of IVIg if administered within the first weeks after onset of disease, when nerve damage is most likely reversible. We used the database of the prospective, observational International Guillain-Barré Syndrome study (IGOS) to compare disease course in patients treated with one IVIg course versus two IVIg courses and we aimed to assess whether a second IVIg course in patients with GBS and a predicted poor prognosis improved functional outcome.[12]

METHODS

Study design

IGOS is an ongoing, prospective, observational cohort study which includes patients with GBS within the first two weeks of onset. The IGOS study protocol has been published previously.[12]

Study population and treatment

From patients in IGOS, we identified those treated with a standard course of 2 g/kg IVIg over 2-5 consecutive days. As mEGOS has not been validated in young children, patients aged under 6 were excluded.[11] We excluded patients who had died or were lost to follow up in the first 7 days from study entry, or who received a second IVIg course because of

a reported treatment related fluctuation (TRF) observed by the local physician.[13] We also excluded patients who participated in a randomized controlled study (Second Immunoglobulin Dose in GBS patients (SID-GBS) trial[14, 15] or Inhibition of Complement Activation in GBS (ICA-GBS) trial).[16]

Multiple imputation was used for patients with missing age (n=9/1300) or MRC sum score at week 1 (n=120/1300).[17] Based on a standard set of five imputation samples, medians were calculated for age and MRC sum score. In this way, mEGOS could be calculated for all patients, using age, preceding diarrhea, and MRC sum score at week 1. We further identified patients with mEGOS 6-12 at one week who considered to have a poor prognosis (35% probability or higher of not being able to walk independently at 6 months).[11]

IVIg groups

From the group of patients with poor prognosis treated with at least one IVIg course, we selected those treated with a second course of IVIg. Because of the observational nature of IGOS, the decision to administer two IVIg courses was made by the local treating investigators. As a result, the second IVIg course was not given at a standardized time point. In the analysis, we separated patients treated with a second IVIg course early (started within two weeks after start of the first IVIg course) from those treated late (started after two weeks but within three to four weeks after start of the first IVIg course and completed before the assessment of week 4). Patients who received one standard course of IVIg before the 4-week assessment were considered controls. Other additional treatments such as corticosteroids and plasma exchange were ignored.

Assessments

Demographic and clinical data including GBS disability score[18, 19], MRC sum score[20], sensory deficits, facial weakness, previous diarrhea, and clinical variants were collected at entry, and subsequently at week 1, 2, and 26 (GBS disability score, MRC sum score)[12]. According to the IGOS protocol[12], study entry should coincide with the first day of treatment, even if informed consent was obtained after start of treatment. Due to ethical regulations in some countries, study entry was set by the date of informed consent. Results of the first nerve conduction study (NCS) were classified according to the criteria of Hadden and colleagues into demyelinating, axonal, inexcitable, equivocal or normal.[21] Treatment information was collected regarding dates of start and end of treatment, treatment type (IVIg, PE, other), treatment regimen, and side effects after IVIg.

Deterioration at the time of starting the second IVIg course was determined by worsening at least one MRC sum score point on the visits prior to and after the moment of starting the second IVIg course.

Study endpoints

The primary endpoint was improved functional outcome on the GBS disability scale after 4 weeks. Secondary endpoints were GBS disability score at 26 weeks, improvement of ≥ 1 score on the GBS disability scale at 4 and 26 weeks, median change in the MRC sum score at 4 and 26 weeks, being able to walk independently at 26 weeks, requiring ventilation at any time during follow up, time admitted to the intensive care unit (ICU), time on a ventilator, GBS related mortality at 6 months, treatment related fluctuation (TRF), and complications (not further specified).

Statistical analysis

Statistical analyses were performed using SPSS software (version 21.0 and 24.0). Data were expressed as medians with interquartile ranges (IQR) or as proportions. Mann-Whitney *U* tests were used to compare continuous variables across 2 groups, and one-way ANOVA or Kruskal Wallis tests (if variances differed significantly) were used to compare continuous variables across 3 groups. Chi-square or Fisher's exact tests were performed to compare proportions. Reported p-values were calculated between the three groups unless stated otherwise. A two-sided p-value <0.05 was considered to be significant. Treatment effect on the GBS disability scale at 4 and 26 weeks was evaluated for the early and late second IVIg groups using multivariable ordinal regression analysis, adjusting for prognostic factors and disease severity (age, GBS disability score at entry and week 1, MRC sum score at entry and week 1, occurrence of diarrhea, electrophysiological axonal or inexcitable pattern) and country of residence. The reported odds ratios (OR) express the odds of having a better outcome (i.e. a lower GBS disability score).

Sub-analysis: propensity score matching

We recognized that the non-randomized study design could have caused confounding by indication due to observed and unobserved confounders. To correct for the effect of confounders, we developed a multivariable regression model and performed a propensity score matched analysis. With this method, propensity scores for receiving treatment were calculated for each individual, given an individual's covariates.[22] We calculated the propensity scores for each individual in a multivariable logistic regression model with independent variables: age, gender, time to enter the study, time to start first IVIg course, GBS disability score at entry and week 1, MRC sum score at week 1, GBS variant at entry, preceding diarrhea and country of residence. Variables with missing values would result in a lower number of matched controls and were therefore not added in the model (e.g.

electrophysiological classification, deterioration or improvement at starting the second course). In our model, the calculated propensity scores expressed the probability of receiving a second IVIg course. The propensity score was subsequently used to match controls to patients in both the early and late second IVIg group (nearest neighbor matching 1:1 with a caliper of 0.1). After propensity score matching, we performed a new unadjusted ordinal regression analysis.

RESULTS

Patients

In January 2017, 1300 patients with a follow-up period of 6 months had been enrolled in IGOS. Seventy-one patients (5%) were excluded because of alternative diagnosis, 6 (0.5%) because of protocol violation, 34 (3%) because of young age and 29 (2%) because of insufficient data.

Of the remaining 1165 patients, 831 (71%) were initially treated with IVIg. Seventeen patients were lost to follow-up at the first week and seven died before 7 days after study entry, so that prognosis could be predicted in 807 patients based on the mEGOS. Poor prognosis (mEGOS 6-12) was predicted in 260 patients (32%), of whom 23 were excluded because they participated in a randomized controlled trial (RCT, SID-GBS trial 11; ICA-GBS trial 1) or because they received the second IVIg course because of a TRF (11). Ultimately, 237 patients with a poor prognosis fulfilled the entry criteria for this study (Figure 1).

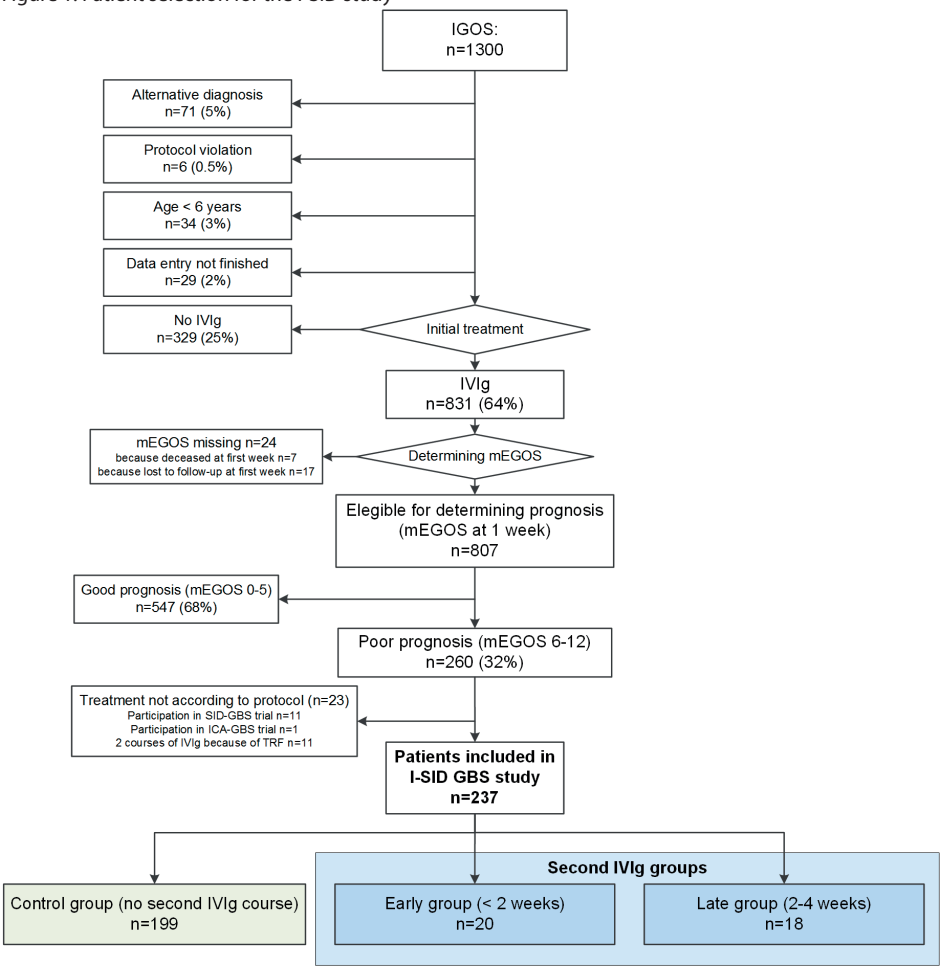
Control group

The primary endpoint of this study concerned improvement at four weeks. Therefore, the control group included the 199 patients treated with one IVIg course within the first four weeks from study entry irrespective of other treatments before or after four weeks. Of the 199 patients, 160 (80%) received standard treatment only (1 IVIg course within four weeks of study entry), 31 patients were additionally treated with PE before or after 4 weeks, and 6 patients were treated with additional IVIg after four weeks. One additional patient received IVIg within 4 weeks, followed by IVIg after 4 weeks and was thereafter treated because of vasculitis. Another patient received IVIg and 7 PE sessions within 4 weeks and was after his GBS diagnosed with granulomatous polyangiitis.

Early second IVIg group

Twenty patients were treated with a second IVIg course that started within fourteen days after start of the first IVIg course and were included in the 'early second IVIg group'.

Figure 1. Patient selection for the I-SID study



Abbreviations: GBS = Guillain-Barré Syndrome, mEGOS = modified Erasmus GBS Outcome Score, ICA-GBS = Inhibition of Complement Activation in GBS, IGOS = International GBS Outcome Study, I-SID GBS study = International Second Immunoglobulin Dose in GBS patients, Inhibition of complement activation in GBS, IVIg = Intravenous immunoglobulin, SID-GBS trial = Second Immunoglobulin Dose in GBS patients, TRF = treatment related fluctuation

Sixteen (80%) were treated with only one additional IVIg course and 4 were treated with various combinations of IVIg and PE.

Late second IVIg group

Eighteen patients were treated with a second IVIg course two to four weeks after start of the first IVIg course and were included in the 'late second IVIg group'. Fourteen (78%) were treated with only one additional IVIg course while 4 patients were treated with various combinations of IVIg and PE.

Data completeness

At week 4, the primary endpoint was available in 167/199 (84%) patients in the control group (eight patients lost to follow-up and 24 missed the visit). In both the early and the late second IVIg group one patient was lost to follow-up and one patient had a missed visit. Therefore, the primary endpoint was available in 90% (18/20 and 16/18) in the two IVIg groups.

Patient characteristics

At baseline, there were no significant differences between the three treatment groups regarding age, gender, MRC sum score at entry, sensory deficits, preceding diarrhea or GBS variant (table 1). There were significant differences in the proportion of patients already ventilated at study entry in the early second IVIg group (n=9, 45%) and in the late second IVIg group (n=6, 33%) compared to in the control group (n=36, 18%) (3-way p-value, p=0.01).

One week after study entry, patients in the early and late second IVIg group had significantly lower MRC sum scores (10, IQR 0-26, and 6, IQR 1-32) than controls (25, IQR 8-35) (p=0.004) and were thus more severely affected. This was also reflected by higher GBS disability scores (Figure 2).

Patients in the control group were often already improving at least one point on the MRC sum score between the first to the second study week (n=102, 63%). However, patients in the second IVIg groups were often still deteriorating at least one point in MRC sum score at the time of starting their second IVIg course (n=13, 81% in the early group and n=8, 47% in the late group).

Primary endpoint

Treatment with a second IVIg course made no significant difference to the GBS disability score 4 weeks after study entry. The adjusted OR for a lower GBS disability score was 0.70 (95% confidence interval (CI) 0.16-3.04) for the early second IVIg group, and 0.66 (95% CI 0.18-2.50) for the late group (Figure 2, table 2).

Secondary endpoints

There was also no significant difference in the GBS disability score at 26 weeks. The adjusted OR for a lower GBS disability score was 0.89 for the early group (95% CI 0.22-3.53) and 0.40 (95% CI 0.10-1.62) for the late group (Figure 2, table 2).

Fifty-one (31%) patients in the control group improved at least one point on the GBS disability scale 4 weeks after study entry, compared with only 3 (17%, p=0.22) of the

Table 1. Demographic and clinical characteristics at entry and during disease course

	Control group (1x IVIg) n=199	Early second IVIg group (2x IVIg) n=20	Late second IVIg group (2x IVIg) n=18	*p*-value among 3 groups[1]
Demographics				
Males, n (%)	109 (55)	12 (60)	12 (67)	0.58
Age, years, median (IQR)	59 (43-70)	65 (54-70)	59 (53-71)	0.54
Clinical features at entry				
Time from onset to study entry, days, median (IQR)	5 (3-8)	4 (2-8)	5 (2-8)	0.68
Time from onset to first IVIg course, days, median (IQR)	3 (2-6)	2 (1-3)	2 (1-5)	0.11
Antecedent diarrhoea, n (%)	73 (37)	4 (20)	5 (28)	0.27
Facial weakness, n (%)	71 (36)	8 (40)	9 (50)	0.47
MRC sum score, median (IQR)	32 (18-42)	27 (5-42)	30 (3-46)	0.56
Sensory deficits, n (%)	113 (57)	13 (65)	7 (39)	0.47
GBS variant, n (%) No	141 (71)	15 (75)	12 (67)	0.85
Pure motor	46 (23)	3 (15)	6 (33)	0.41
Miller Fisher (overlap)	10 (5)	2 (10)	0 (0)	0.37
Other	2 (1)	0 (0)	0 (0)	*
Clinical features after one week follow up				
MRC sum score, median (IQR)	25 (8-35)	10 (0-26)	6 (1-32)	0.004†[§]
mEGOS, median (IQR)	10 (8-11)	11 (9-11)	10 (8-11)	0.10
Clinical features at nadir				
MRC sum score, median (IQR)	21 (4-33)	4 (0-20)	2 (0-16)	<0.001†[§]
GBS disability score, n, (%) Unable to run (2)	1 (1)	0 (0)	0 (0)	0.03†
Unable to walk independently (3)	7 (4)	0 (0)	0 (0)	
Bedridden or chairbound (4)	107 (54)	4 (20)	6 (33)	
Ventilated (5)	84 (42)	16 (80)	12 (67)	
Electrophysiological classification, n (%)				
Demyelinating	87/154 (57)	9/12 (75)	9/17 (53)	*
Axonal	18/154 (12)	1/12 (8)	5/17 (29)	
Inexcitable	8/154 (5)	0 (0)	1/17 (6)	
Equivocal	40/154 (26)	2/12 (17)	2/17 (12)	
Normal	1/154 (1)	0 (0)	0 (0)	
Time until NCS, days, median (IQR)	6 (4-10)	2 (2-10)	7 (4-9)	0.52

† p-value < 0.05 for control group versus early second IVIg group

[§] p-value < 0.05 for control group versus late second IVIg group

* not calculated because of small patient numbers

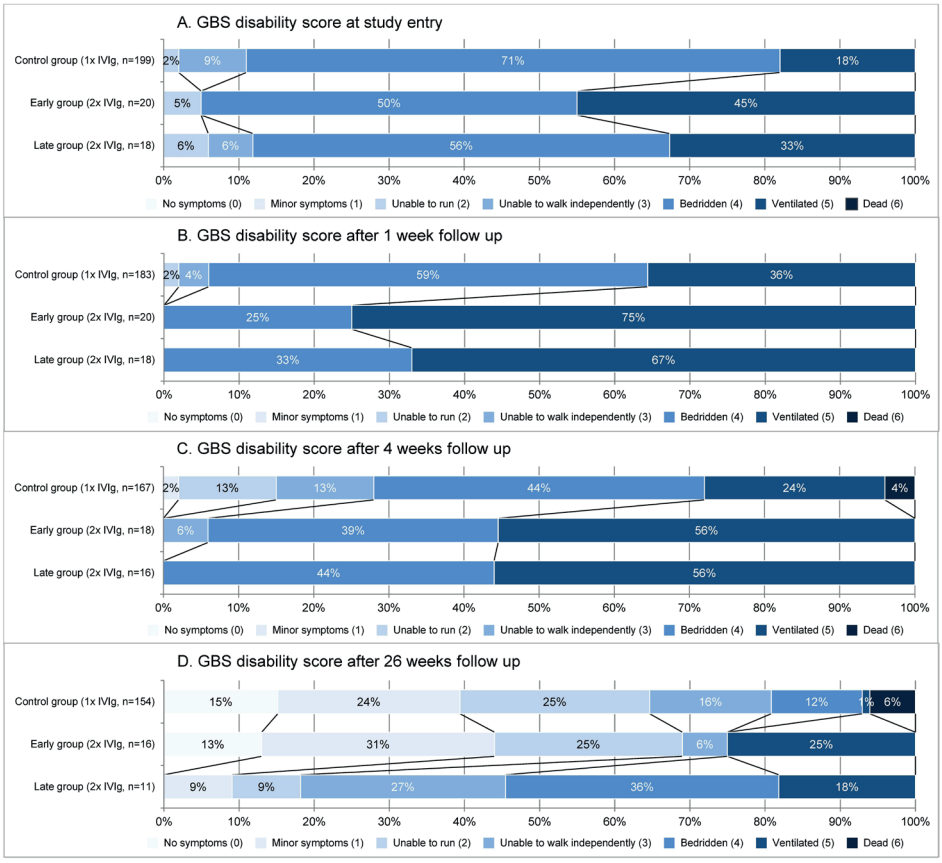
[1]There were no significant differences between the early and late second IVIg group

Abbreviations: GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, IQR = interquartile range, mEGOS = modified Erasmus GBS Outcome Score, MRC = medical research council, NCS = nerve conduction study.

early group and none (p=0.01) of the late group (table 3). At 26 weeks, 127 of 145 (88%) patients in the control group improved at least one point on the GBS disability scale compared to 12/16 (75%, p=0.16) in the early and only 4/11 (36%, p<0.001) in the late IVIg group (table 3).

In the control group, patients improved by a median of 4 points on the MRC sum score (IQR -8 to 12) from entry to 4 weeks. The MRC sum score decreased by 2 points (IQR -23 to 10) in the early group (p=0.14) and by 4 points (IQR -36 to 2) in the late group (p<0.001). After 26 weeks, the patients in the early second IVIg group improved more on the MRC sum score (median change 27, IQR 3-48) than the control group (18, IQR 12-32, p=0.43) and the late group (11, IQR -4 to 21, p=0.05).

Figure 2. GBS disability score at study entry (A), 1 (B), 4 (C) and 26 weeks (D).



Abbreviations: GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin

Treatment related fluctuations were reported, but not treated with a second IVIg course, in 4 of the control patients, 2 of the early group patients and in 1 patient of the late group.

ICU admission was longest in patients after late treatment (64 days, IQR 33-144), whereas the controls (30 days, IQR 13-55) and patients in the early group (31 days, IQR 18-82) had similar ICU admission stays. Patients in the late group required longer ventilatory support (76 days, IQR 33-239) than the controls (27 days, IQR 15-61) and early group (55 days, IQR 26-220).

Table 2. Odds ratios for a lower GBS disability score at 4 and 26 weeks.

	N	Unadjusted OR (95% CI)	*p*-value	N	Adjusted OR* (95% CI)	*p*-value
Week 4:						
Treatment						
Control	167	Ref.		125	Ref.	
Early second IVIg	18	0.31 (0.12-0.78)	0.01	10	0.70 (0.16-3.04)	0.63
Late second IVIg	16	0.28 (0.11-0.76)	0.01	14	0.66 (0.18-2.50)	0.54
Week 26:						
Treatment						
Control	154	Ref.		105	Ref.	
Early second IVIg	16	0.98 (0.39-2.44)	0.97	8	0.89 (0.22-3.53)	0.87
Late second IVIg	11	0.23 (0.08-0.70)	0.01	8	0.40 (0.10-1.62)	0.40

* Adjusted for age, preceding diarrhoea, GBS disability score at entry and week 1, MRC sum score at entry and week 1, axonal or inexcitable NCS, country of residence.
Abbreviations: CI = confidence interval, IVIg = intravenous immunoglobulin, OR = odds ratio

Serious complications of the second IVIg courses were not reported. Six control patients experienced headache, shivering, nausea or vomiting, and/or blood pressure changes after their first IVIg course. In the early group, one patient had hallucinations/psychosis and in the late group, one patient experienced headache after the first IVIg course. Headache was reported in one patient after the second full IVIg course.

Nine patients in the control group died within six months (6%) while in the second IVIg groups, no patients died. Causes of death were: cardiac arrest as a consequence of multi-organ system failure (2), respiratory failure (n=2, of whom one chose to have ventilator support withdrawn after 2 weeks), pneumonia and sepsis (n=2), and other (n=3).

Table 3. Endpoints at 4 and 26 weeks

	Control group (1x IVIg) n=199	Early second IVIg group (2x IVIg) n=20	Late second IVIg group (2x IVIg) n=18	p-value
Secondary endpoints				
Improving ≥ 1 score on GBS disability sore, n (%) at:				
4 weeks	51/167 (31)	3/18 (17)	0 (0)	0.002[2§]
26 weeks	127/145 (88)	12/16 (75)	4/11 (36)	0.001[2§]
Able to walk independently, n (%) at:				
26 weeks	99/154 (64)	11/16 (69)	2/11 (18)	0.01[2§¶]
Change in MRC sum score (median, IQR) at:				
4 weeks	4 (-8-12)	-2 (-23-10)	-4 (-36-2)	<0.001
26 weeks	18 (12-32)	27 (3-48)	11 (-4-21)	0.06
Requiring ventilation, n (%)	88 (44)	16 (80)	12 (67)	0.003†
GBS related mortality at 6 months, n (%)[3]	9/154 (6)	0 (0)	0 (0)	0.44
TRF[3], n (%)	4 (2)	2 (10)	1 (6)	0.11
Complications after first IVIg course, n (%)				
Headache	3 (2)	0 (0)	1 (6)	
Shivering	1 (1)	0 (0)	0 (0)	
Nausea/vomiting	1 (1)	0 (0)	0 (0)	
Hallucinations/psychosis	0 (0)	1 (5)	0 (0)	
Hypo/hypertension	1 (1)	0 (0)	0 (0)	
Complications after second IVIg course, n (%)				
Headache	0 (0)	0 (0)	1 (6)	

[1] p-value derived from unadjusted ordinal regression analysis
[2] p-value derived from unadjusted binary logistic regression analysis
[3] The second IVIg course in the early and late groups was not given because of the TRF
† p-value < 0.05 for control group versus early second IVIg group
§ p-value < 0.05 for control group versus late second IVIg group
¶ p-value < 0.05 for early versus late second IVIg group
Abbreviations: GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, IQR = interquartile range, MRC = medical research council, TRF = treatment related fluctuation.

Sub-analysis: ordinal regression analysis after propensity score matching

Patients from the early and late second IVIg group were matched separately to controls by propensity scores. The unadjusted odds ratio for a lower GBS disability score was calculated for the early and late group separately. The highest OR for a lower GBS disability score was found at 26 weeks for the early group (1.26, 95%CI 0.35-4.60) but this was not statistically significant. The other ORs were also not in favor of a second IVIg course (table 4).

Table 4. Odds ratios for a lower GBS disability score at 4 and 26 weeks after propensity score matching.

	N	Unadjusted OR (95% CI)	*p*-value
Week 4:			
Treatment			
Control	18	Ref.	
Early second IVIg	18	0.74 (0.21-2.64)	0.64
Control	16	Ref.	
Late second IVIg	16	1.03 (0.26-4.13)	0.97
Week 26:			
Treatment			
Control	16	Ref.	
Early second IVIg	16	1.26 (0.35-4.60)	0.73
Control	12	Ref.	
Late second IVIg	11	0.42 (0.09-1.90)	0.26

Abbreviations: CI = confidence interval, IVIg = intravenous immunoglobulin, OR = odds ratio

DISCUSSION

This is the first prospective study evaluating outcome after a second course of IVIg in patients with GBS. We did not observe a benefit from a second course of IVIg in GBS patients with a poor prognosis as defined by the mEGOS prognostic model. Severe complications such as hemolytic anemia or thromboembolism were not reported after the second course of IVIg.

After one week, patients in the second IVIg groups were significantly more disabled (lower MRC sum scores and higher GBS disability scores) than the IVIg controls. These patients also were deteriorating more often at the start of their second IVIg course compared with the one IVIg course group (deteriorating at least one point on the MRC sum score: 13/16, 81% in the early group, 8/17, 47% in the late group). Conversely, patients treated with one IVIg course were often already improving when a second course was administered in the second IVIg groups (i.e., 102/163, 63% improving from the first to the second IGOS study week, and 112/151, 74% improving from the second to the fourth IGOS study week). Continued deterioration was therefore the most likely reason for the treating physicians to start a second IVIg course, whereas improvement probably prevented starting a second course. The unbalanced disease severity likely caused confounding by indication because a poor neurological condition may have influenced the investigators' decision to initiate a second IVIg treatment but likely also resulted

in a worse outcome. Despite correcting for disease severity in a multivariable ordinal regression model, the data did not show a beneficial effect from a second course of IVIg.

Duration of ICU stay and ventilation were secondary endpoints. These situations however also may have prompted the decision to administer a second course of IVIg; a higher proportion of patients who received a second IVIg course had longer ICU admission and required assisted ventilation. The median time on a ventilator was longer than the time admitted to the ICU in all groups because in some countries patients were discharged to rehabilitation centers with mechanical ventilation facilities.

In addition to observed confounding factors, unbalanced unobserved confounders likely played a role too. This is demonstrated by the difference between unadjusted and adjusted ORs. One of the unobserved confounders could be IgG or albumin levels.[8, 23] In this study we did not have data on IgG and serum albumin concentrations. Other unobserved confounders could have been insurance status, availability of IVIg, and other unknown patient, physician or hospital related factors. In our attempt to mitigate the effect of confounders, we conducted a secondary analysis in which we matched patients on propensity scores, defined as the probability of receiving an early or late second IVIg course. Even with this analysis, the data did not show positive odds ratios for a better outcome.

In order to prevent further nerve damage, treatment might be most effective in the early stage of GBS. In our study, only eight patients received a second IVIg course within 9 days after start of the first IVIg course, while the other patients received the second IVIg course later, possibly because they were in a poor neurological condition. Furthermore, 20% of the patients in all three IVIg groups were also treated with PE, or with more than two IVIg courses or combinations of PE and IVIg. Approximating the preferred analysis of a randomized controlled trial, we conducted an 'intention-to-treat' analysis. Therefore, we did not exclude patients treated with IVIg combined with other treatments and also not the two patients in the control group who later on were diagnosed with vasculitis and granulomatous polyangiitis. A large RCT showed that IVIg administered immediately after PE was not better than IVIg or PE alone.[1] No randomized trials have been performed to evaluate the effect of PE after IVIg. However, since PE removes IVIg, this sequence of treatment should logically be avoided, or used only at least two weeks after IVIg. By that stage however any treatment is likely to have only marginal effects as nerve damage has already occurred.[6]

We selected patients with a poor prognosis because we expected that these patients might benefit most from a second IVIg course. These patients have previously been iden-

tified to have a probability of 35% or greater of not being able to walk independently.[11] This does not mean that all patients with a high mEGOS score have poor outcome. The predictive value of the mEGOS has been validated recently in another cohort of 177 patients where a significant correlation was found between higher mEGOS and poor outcomes.[24]

Next to the major limitation of the observational nature of this study, other limitations can be pointed out. First, the four-week endpoint was chosen as the primary outcome because it corresponds to the primary endpoint in previous randomized controlled trials. However, it may be that this time point was not best suited for this observational study, especially in the late group, since the GBS disability score was usually recorded less than 1 week after the completion of the second IVIg course. Second, in ordinal regression analysis the treatment effect ideally should be the same across all cut-off values of the outcome scale (the proportional odds assumption), but in this study the treatment effect was not similar across the GBS disability scale (Figure 2). However, it has been argued in the statistical literature that the proportional odds model is still valid when the proportional odds assumption is not met.[25] Lastly, despite starting with a large group of GBS patients and using multiple imputation to increase the number of eligible subjects, we ultimately had small numbers in the second IVIg groups (n=20 in the early group and n=18 in the late group).

In conclusion, the observational design of this large prospective multicenter international study introduced bias by observed and unobserved confounding factors. This study however reflects current daily practice in GBS patients with a poor prognosis, and showed no positive effect of a second IVIg course on functional outcome. The second IVIg course was often started late, and this was likely because of severe neurological impairment after a standard IVIg course. A positive effect of a second IVIg course cannot be ruled out but needs to be investigated further as is being done in the SID-GBS RCT.[14 15]

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4.4

Intravenous immunoglobulin treatment for mild GBS: an international observational study

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ABSTRACT

Objective

To compare the disease course in patients with mild Guillain-Barré syndrome (GBS) who were treated with intravenous immunoglobulin (IVIg) or supportive care only.

Methods

We selected patients from the prospective observational International GBS Outcome Study (IGOS) who were able to walk independently at study entry (mild GBS), treated with one IVIg course or supportive care. The primary endpoint was the GBS disability score four weeks after study entry, assessed by multivariable ordinal regression analysis.

Results

Of 188 eligible patients, 148 (79%) were treated with IVIg and 40 (21%) with supportive care. The IVIg group was more disabled at baseline. IVIg treatment was not associated with lower GBS disability scores at four weeks (adjusted odds ratio [aOR] 1.62, 95%CI 0.63-4.13). Nearly all secondary endpoints showed no benefit from IVIg, although the time to regain full muscle strength was shorter (28 versus 56 days, p=0.03) and reported pain at twenty-six weeks was lower (n=26/121, 22% versus n=12/30, 40%, p=0.04) in the IVIg treated patients. In the sub-analysis with persistent mild GBS in the first two weeks, the aOR for a lower GBS disability score at four weeks was 2.32 (95%CI 0.76-7.13). At one year, 40% of all patients had residual symptoms.

Conclusion

In patients with mild GBS, one course of IVIg did not improve the overall disease course. The certainty of this conclusion is limited by confounding factors, selection bias and wide confidence limits. Residual symptoms were often present after one year, indicating the need for better treatments in mild GBS.

INTRODUCTION

Approximately 20-40% of patients with Guillain-Barré syndrome (GBS) do not lose the ability to walk unaided during their disease course, which has been called 'mild GBS'.[1-3] In contrast to what its name suggests, mild GBS may have an unfavorable clinical course and poor outcome after supportive care alone. Patients who initially have mild GBS can deteriorate later on during the progressive phase of the disease. Dilemmas about whether and when to start treatment arise during the first weeks after onset of GBS because currently it is not possible to predict at presentation who is at risk of further deterioration, while postponing treatment until after further deterioration might result in more severe and possibly irreversible nerve damage.[4, 5] In addition, the differentiation between mild and severe GBS is based on the GBS disability scale, which is mainly driven by motor function of the legs and ignores involvement of the arms as well as cranial, sensory and autonomic nerves or non-motor function; up to 38% of mildly affected patients report residual fatigue, pain or persistent neurological deficits after six months.[6]

Both plasma exchange (PE) and intravenous immunoglobulin (IVIg) are equally effective in GBS patients who are unable to walk independently (severe GBS).[7-10] One trial showed that the time to onset of motor recovery in patients still able to walk was shortened after two sessions of PE[1], but no randomized controlled trials have been performed to evaluate the efficacy of IVIg in mild GBS.[7, 11] Reasons not to treat mild GBS patients may include spontaneous recovery in a large proportion of patients due to the self-limiting nature of the disease, side effects including allergic reactions or thromboembolic events, and the fact that IVIg is expensive[12].

A previous study of patients recruited in the International GBS Outcome Study (IGOS) showed that 75% of those with mild GBS at entry were treated with IVIg.[13] We have taken advantage of this variation in current treatment practice to compare the clinical course and outcome in patients with mild GBS treated with either supportive care or supportive care and IVIg.

METHODS

IGOS

IGOS is an international, observational, prospective cohort study enrolling patients with GBS from participating centers within two weeks of disease onset.[14] The Institutional Review Boards from all participating centers approved IGOS and all patients gave written informed consent.

Study population

From the first 1300 patients enrolled in IGOS (IGOS-1300 cohort), we selected all patients with a GBS disability score of 2 or lower (able to walk independently) at study entry who had been included up until January 2017, with the following exceptions. We excluded patients from low-income countries (i.e., Bangladesh) because the current treatment practice differs substantially from other IGOS-participating countries.[2] We also excluded patients who had Miller Fisher syndrome and other GBS variants without limb weakness because these variant forms may not affect the GBS disability score or the Medical Research Council (MRC) sum score. We also excluded those who were treated with plasma exchange only.

We selected patients with mild GBS at presentation because in clinical practice, the dilemma of whether and when to start treatment is most pressing at the time of initial diagnosis.

Patient groups

We divided patients into those receiving supportive care alone and those receiving supportive care and one standard course of IVIg (2 g/kg in 2-5 days) within the first four weeks after study entry. Patients who received additional IVIg courses or PE sessions were not excluded.

We first analyzed patients with mild GBS at entry. However, this analysis might have included patients who presented early, but were destined to progress to severe GBS. Therefore, to assess the effect of IVIg in patients with truly persistent mild GBS, we conducted a second analysis in the subgroup of patients whose GBS disability score remained 2 or less during the first 2 weeks after study entry.

Assessments

We prospectively collected data regarding age, gender, reported antecedent events and the following clinical features: cranial nerve involvement, sensory deficits, MRC sum score, ataxia, GBS disability score, GBS clinical variant, and autonomic dysfunction at entry and after 1, 2, 4, 8, 13, 26 and 52 weeks. The GBS disability score measures disability, and ranges from 0 (healthy) to 6 (dead).[15] The MRC sum score measures strength in 6 bilateral muscle pairs and ranges from 60 (full muscle strength) to 0 (complete paralysis).[16] The presence of autonomic dysfunction was determined by the treating physician, and was defined as cardiac, blood pressure, gastro-enterological, bladder, pupil, or other autonomic dysfunction. We classified the first nerve conduction study (NCS) according to Hadden's criteria into the categories demyelinating, axonal, inexcitable, equivocal or normal nerve conduction.[17] Treatment information included treatment type (IVIg, PE, other), treatment regimen, dates of start and end of treatment, and adverse events.

Study endpoints

The primary endpoint was functional outcome, defined as a lower GBS disability score after four weeks in patients treated with one IVIg course compared to patients not treated with IVIg. This endpoint has often been used in previous trials and enables comparisons between studies.[7, 11, 18, 19] Secondary endpoints were: GBS disability score at 26 weeks, MRC sum score, Rasch-Built Overall Built Disability Score (R-ODS), fatigue severity scale (FSS) and the EuroQol Visual Analogue Scale at 4 and 26 weeks, time to regain full muscle strength (MRC sum score of 60), time to reach full disability recovery (GBS disability score of 0)[20, 21], and the frequency of hospital admission, progression to GBS disability score 3 or higher, progression to mechanical ventilation, and the presence of pain and cranial nerve deficits at 4 and 26 weeks.[22] The R-ODS raw score was transformed into the R-ODS centile metric score to calculate the median R-ODS centile metric.[20] A mild course during the four weeks of follow-up was defined as a GBS disability score of 2 or lower at study entry and after one, two and four weeks. The time needed to regain full muscle strength (MRC sum score of 60 points) and full recovery on the GBS disability scale (a score of 0 points) were derived from the study assessment dates. Residual symptoms were defined as the presence of pain (muscle, joint, radicular, neuropathic pain, painful paresthesias), cranial nerve involvement, sensory deficits, ataxia or an MRC sum score < 60 after one year follow-up. Complications (not further specified), number of treatment related fluctuations (TRFs) and mortality were also recorded.

Statistical analysis

For statistical analyses we used SPSS software (version 21.0 and 24.0). Data were expressed as medians with interquartile range (IQR) or as proportions. We used Mann-Whitney U test to compare continuous variables across two groups, and Chi-square or Fisher's exact tests to compare proportions. A two-sided p-value <0.05 was considered statistically significant. We assessed the effect of IVIg on the GBS disability scale at 4 and 26 weeks by a multivariable ordinal regression model, where we corrected for known prognostic and imbalanced factors (age, ataxia, autonomic dysfunction, GBS disability score and MRC sum score at entry, preceding diarrhea, electrophysiological subtype and geographical region). We additionally corrected for the presence of early improvement, which for the supportive care group was defined as improving at least two points on the MRC sum score from entry to the first visit after one week, and for the IVIg group as improving at least two points on the MRC sum score during the visits prior to and after start of IVIg. The reported odds ratios (ORs) expressed the odds of having a lower GBS disability score (hence a better outcome). A Kaplan-Meier curve was calculated for patients reaching full muscle strength recovery, defined as an MRC sum score of 60 points.

RESULTS

By January 2017, 1300 patients were enrolled in IGOS with a follow-up period of at least 12 months. We excluded 391 patients (30%): 71 (5%) with an alternative diagnosis, 6 (0.4%) with a protocol violation, 10 (1%) with incomplete data, 189 (15%) from Bangladesh and 115 (9%) who had a variant form of GBS without limb weakness (figure 1). Of the remaining 909 patients, 11 (1%) had a GBS disability score higher than 2 before study entry, and 705 (78%) had a score greater than 2 at study entry, and they were also excluded. The remaining group of 193 patients who presented with a mild form of GBS were treated as follows: 40 (22%) with supportive care alone, 148 (77%) with IVIg, and 5 (3%) with PE. Patients who underwent PE only were excluded from this study. Thus 188 patients altogether were included (figure 1). The 148 IVIg treated patients received their IVIg course of 2 g/kg in 2 to 5 days before or at entry of the study (n=112, 76%) or in the first week after study entry (n=36, 24%).

Patient characteristics

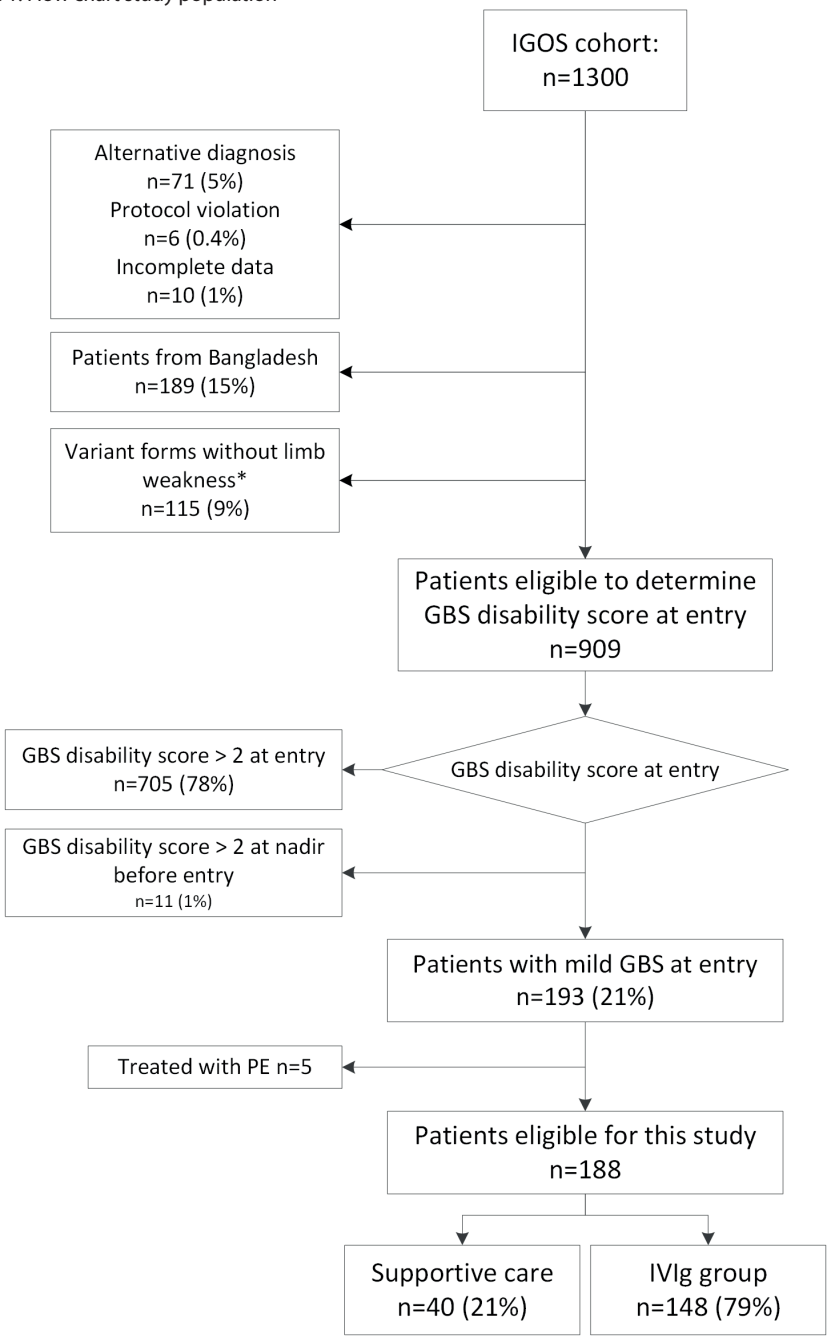
There were no differences between the groups in age, gender, reported antecedent events, GBS disability score, MRC sum score, GBS variants, cranial nerve involvement or pain at entry (table 1).

Compared to the untreated patients, the IVIg group more often had ataxia (50/139, 36% versus 7/39, 18%, p=0.03) and autonomic dysfunction (25/142, 17% versus 1/39, 3%, p=0.02). The MRC sum score after one week of follow-up did not differ between the groups (IVIg group 56, IQR 50-59 versus the supportive care group 56, IQR 54-58, p=0.51). However, few patients in the IVIg group improved two points on the MRC sum score prior to and after the start of their IVIg (23/132, 17%), whereas improvement from study entry to one week often occurred in the supportive care group (14/31, 45%, p=0.001). The GBS disability scores deteriorated slightly after one week in the IVIg group in which 41/135 (30%) of the patients had deteriorated at least one point compared with only 5/34 (15%) of the supportive care alone patients (p=0.07, figure 2).

Primary endpoint

Treatment with one IVIg course made no difference to the GBS disability score four weeks after study entry (figure 2). After correction for prognostic confounders and unbalanced patient characteristics, the adjusted odds ratio (aOR) for a better outcome at 4 weeks in the IVIg group was 1.62 (95% confidence interval (CI) 0.63-4.13, p=0.32) (table 2).

Figure 1. Flow chart study population



* Variant forms without limb weakness (n=115): pure MFS n=66, sensory ataxic GBS n=24, other variant forms without limb weakness n=25.

Abbreviations: GBS = Guillain-Barré syndrome, IGOS = International GBS Outcome Study, IVIg = intravenous immunoglobulin, MFS = Miller Fisher syndrome, PE = plasma exchange

Table 1. Baseline and clinical patient characteristics.

	Supportive care group n=40	IVIg group n=148	*p*-value
Male, n (%)	23 (58)	100 (68)	0.24
Age, y, median (IQR)	49 (32-58)	46 (34-59)	0.79
Duration from onset to study entry (days), median (IQR)	6 (4-10)	6 (3-9)	0.26
Duration from onset to start treatment (days), median (IQR)	na	5 (3-9)	na
Duration from start treatment to study entry (days), median (IQR)	na	0 (0-0)	na
Region, n (%)			na
Europe	29 (73)	101 (68)	
Americas	5 (13)	32 (22)	
Asia	3 (8)	13 (9)	
Africa	3 (8)	0 (0)	
Australia	0 (0)	2 (1)	
Antecedent event, n (%)			
URTI	20/39 (51)	57 (39)	0.15
Diarrhoea	7/39 (18)	43 (29)	0.16
Other	4/39 (10)	19 (13)	0.66
None	8/39 (21)	29 (20)	0.90
CHARACTERISTICS AT ENTRY			
Cranial nerve involvement, n (%)	12 (30)	52 (35)	0.54
Oculomotor	2 (5)	8 (5)	1.00
Facial	10 (25)	39 (26)	0.86
Bulbar	2 (5)	17 (12)	0.23
MRC sum score, median (IQR)	54 (52-57)	54 (50-57)	0.41
GBS disability score, n (%)			0.19
1: Minor symptoms and capable of running	6 (15)	12 (8)	
2: Able to walk 10 meters or more without assistance but unable to run	34 (85)	136 (92)	
GBS clinical variant, n (%)			
Sensorimotor	26 (65)	111 (75)	0.21
Pure motor	12 (30)	25 (17)	0.06
MFS-GBS-overlap	1 (3)	9 (6)	0.69
Pharyngeal-cervical-brachial	1 (3)	3 (2)	1.00
Sensory deficits, n (%)	21 (53)	85 (57)	0.58
Ataxia, n (%)	7/39 (18)	50/139 (36)	0.03
Autonomic dysfunction, n (%)	1/39 (3)	25 (17)	0.02
Pain, n (%)	22/39 (56)	78 (53)	0.68
ADDITIONAL INVESTIGATION			
Electrophysiological classification (n, %)			
Demyelinating	13/32 (41)	63/121 (52)	0.25

Table 1. Baseline and clinical patient characteristics. (*continued*)

		Supportive care group n=40	IVIg group n=148	*p*-value
	Axonal	1/32 (3)	3/121 (3)	1.00
	Inexcitable	0/32 (0)	0/121 (0)	na
	Equivocal	16/32 (50)	45/121 (37)	0.19
	Normal	2/32 (6)	10/121 (8)	1.00

Abbreviations: GBS = Guillain-Barré syndrome, IQR = interquartile range, IVIg = intravenous immunoglobulin, MFS = Miller Fisher syndrome, MRC = Medical Research Council, na = not applicable, URTI = upper respiratory tract infection

Table 2. Unadjusted and adjusted odds ratio for an improved GBS disability score at 4 and 26 weeks.

WEEK 4						
	N	Unadjusted OR (95% CI)	p-value	N	Adjusted OR* (95% CI)	p-value
Treatment						
Supportive care	34	1.0 (ref.)		27	1.0 (ref.)	
IVIg	129	0.69 (0.33-1.43)	0.32	98	1.62 (0.63-4.13)	0.32
WEEK 26						
	N	Unadjusted OR (95% CI)	p-value		Adjusted OR* (95% CI)	p-value
Treatment						
Supportive care	30	1.0 (ref.)		25	1.0 (ref.)	
IVIg	121	0.75 (0.35-1.62)	0.47	97	0.65 (0.24-1.78)	0.41

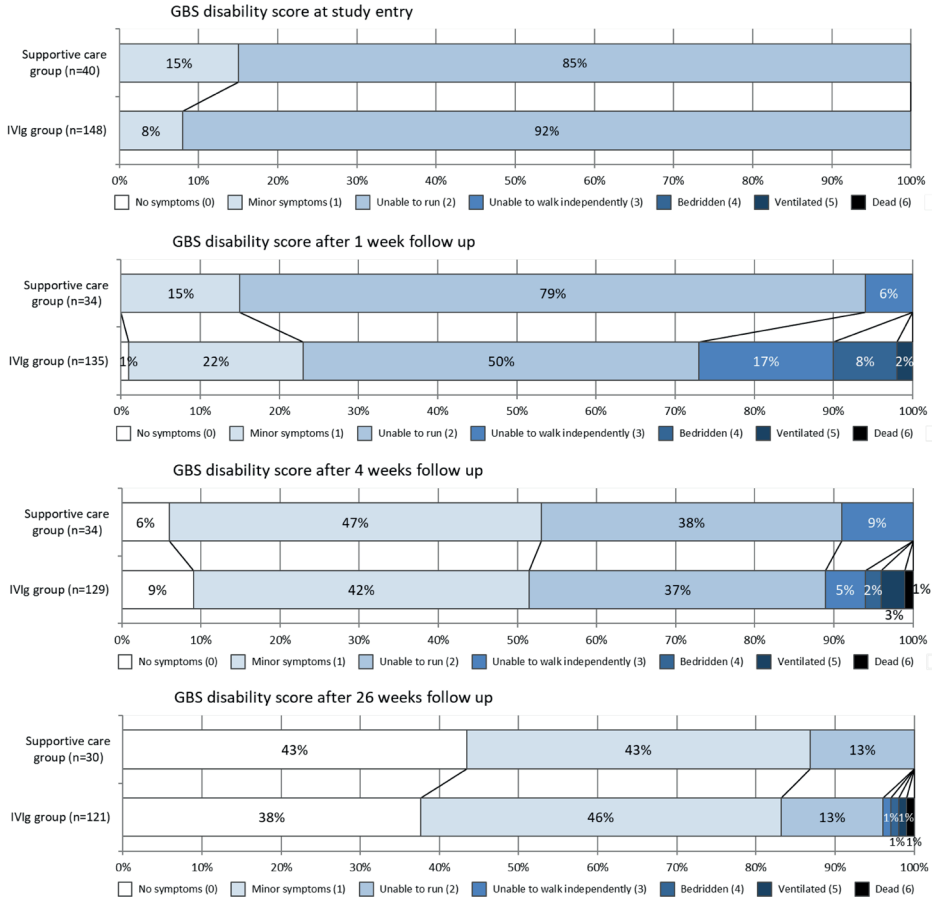
* Adjusted for: age, ataxia at entry, autonomic dysfunction at entry, diarrhea, region, GBS disability score at entry, MRC sum score at entry, axonal subtype, improvement on the MRC sum score.

Secondary endpoints

There was no effect on the GBS disability scale at 26 weeks after IVIg. The aOR for a lower GBS disability score at 26 weeks was 0.65 (95% CI 0.24-1.78, p=0.41) (table 2). There was also no favorable effect on any of the other secondary endpoints, although fewer IVIg treated patients reported pain after 26 weeks (26/121, 22%) compared to supportive care patients (12/30, 40%), p=0.04, table 3).

The median R-ODS centile metric score did not differ between the two groups at four weeks (table 3). The time to complete muscle strength recovery was shorter in the IVIg group (28 days, IQR 14-56) than in the supportive care group (56 days, IQR 14-182, p=0.03). However, the Kaplan-Meier analysis at one year follow-up did not differ significantly (p log rank = 0.26, figure 3a).

Figure 2. GBS disability score during various time points.



Few side effects of IVIg were reported; these included headache (n=8), nausea/vomiting (n=4), venous puncture hazards (n=1), eczema (n=1), blood pressure fluctuations (n=1) and thrombo-embolism (n=1). Ten patients (7%) experienced a treatment related fluctuation of whom six were treated with either a second IVIg course or PE. Five other patients (3%) received a second IVIg course or additional PE, probably because of ongoing disease progression despite IVIg. One patient in the IVIg group died four weeks from presentation. He was 64 years old, had no medical history, presented with a mild sensorimotor GBS but continued to deteriorate to severe GBS in the first weeks. He received 2 g/kg IVIg in 5 days after admission and was re-treated with IVIg 0.8 g/kg in 2 days after two weeks, and died two weeks later from bilateral pulmonary thromboembolism and a recent left ventricular myocardial infarction.

Table 3. Clinical outcome at 4 weeks and 26 weeks in patients with an initial mild form of GBS treated with supportive care alone or additional IVIg.

	Supportive care group	IVIg group	*p*-value
WEEK 4	**n=34**	**n=129**	
GBS disability score, n (%)			0.66*
Healthy (0)	2 (6)	12 (9)	
Minor symptoms (1)	16 (47)	54 (42)	
Able to walk independently (2)	13 (38)	48 (37)	
Able to walk with help (3)	3 (9)	7 (5)	
Bedridden or chairbound (4)	0 (0)	3 (2)	
Ventilated (5)	0 (0)	4 (3)	
Dead (6)	0 (0)	1 (1)	
Improving to GBS disability score = 0, n (%)	2 (6)	12 (9)	0.74
Time needed to reach GBS disability score = 0 (days), median (IQR)	91 (91-274)	91 (56-365)	0.64
Deteriorating to GBS disability score ≥ 3 during first 4 weeks, n (%)	3/30 (10)	42/118 (36)	0.01
MRC sum score, median (IQR)	59 (58-60)	60 (56-60)	0.74
Recovered muscle strength, n (%)	13/31 (42)	75/128 (59)	0.09
Time needed to reach full muscle strength (days), median (IQR)	56 (14-182)	28 (14-56)	0.03
Admitted to hospital or rehabilitation center, n (%)	1 (3)	31/128 (24)	0.01
Cranial nerve deficits, n (%)	8/32 (25)	33/127 (26)	0.91
Sensory deficits, n (%)	13/31 (42)	54/127 (43)	0.95
R-ODS centile metric, median (IQR)[1]	71 (55-93)	69 (52-83)	0.59
Pain, n (%)	14/33 (42)	36/128 (28)	0.11
FSS, median (IQR)	44 (18-57)	41 (27-54)	0.96
EuroQol VAS, median (IQR)	80 (60-90)	70 (51-83)	0.38
WEEK 26	**n=30**	**n=121**	
GBS disability score, n (%)			0.47*
Healthy (0)	13 (43)	46 (38)	
Minor symptoms (1)	13 (43)	55 (46)	
Able to walk independently (2)	4 (13)	16 (13)	
Able to walk with help (3)	0 (0)	1 (1)	
Bedridden or chairbound (4)	0 (0)	1 (1)	
Ventilated (5)	0 (0)	1 (1)	
Dead (6)	0 (0)	1 (1)	
Improving to GBS disability score = 0, n (%)	13 (43)	46 (38)	0.59
MRC sum score, median IQR	60 (60-60)	60 (60-60)	0.29
Recovered muscle strength, n (%)	24/28 (86)	92/117 (79)	0.60
Admitted to the hospital/rehab, n (%)	0 (0)	3/121 (3)	1.00

Table 3. Clinical outcome at 4 weeks and 26 weeks in patients with an initial mild form of GBS treated with supportive care alone or additional IVIg. (*continued*)

	Supportive care group	IVIg group	*p*-value
Cranial nerve deficits, n (%)	2/28 (7)	11/118 (9)	1.00
Sensory deficits, n (%)	8/28 (29)	30/118 (25)	0.73
R-ODS centile metric, median (IQR)[2]	93 (75-100)	93 (74-100)	0.96
Pain, n (%)	12 (40)	26/121 (22)	0.04
FSS, median (IQR)	22 (9-52)	22 (10-42)	0.76
EuroQol VAS, median (IQR)	90 (83-99)	90 (75-98)	0.28
Requiring ventilation, n (%)	0 (0)	6 (4)	0.35
Mortality, n (%)	0 (0)	1 (1)	1.00
OTHER ENDPOINTS	**n=40**	**n=148**	
Residual symptoms after one year, n (%)	11/29 (38)	44/107 (41)	0.76

* p-value retrieved from unadjusted ordinal regression analysis

[1] Patients having at least 1 answer 'not applicable' on R-ODS at 4 weeks: n=57/140 (29%)

[2] Patients having at least 1 answer 'not applicable' on R-ODS at 26 weeks: n=34/139 (25%)

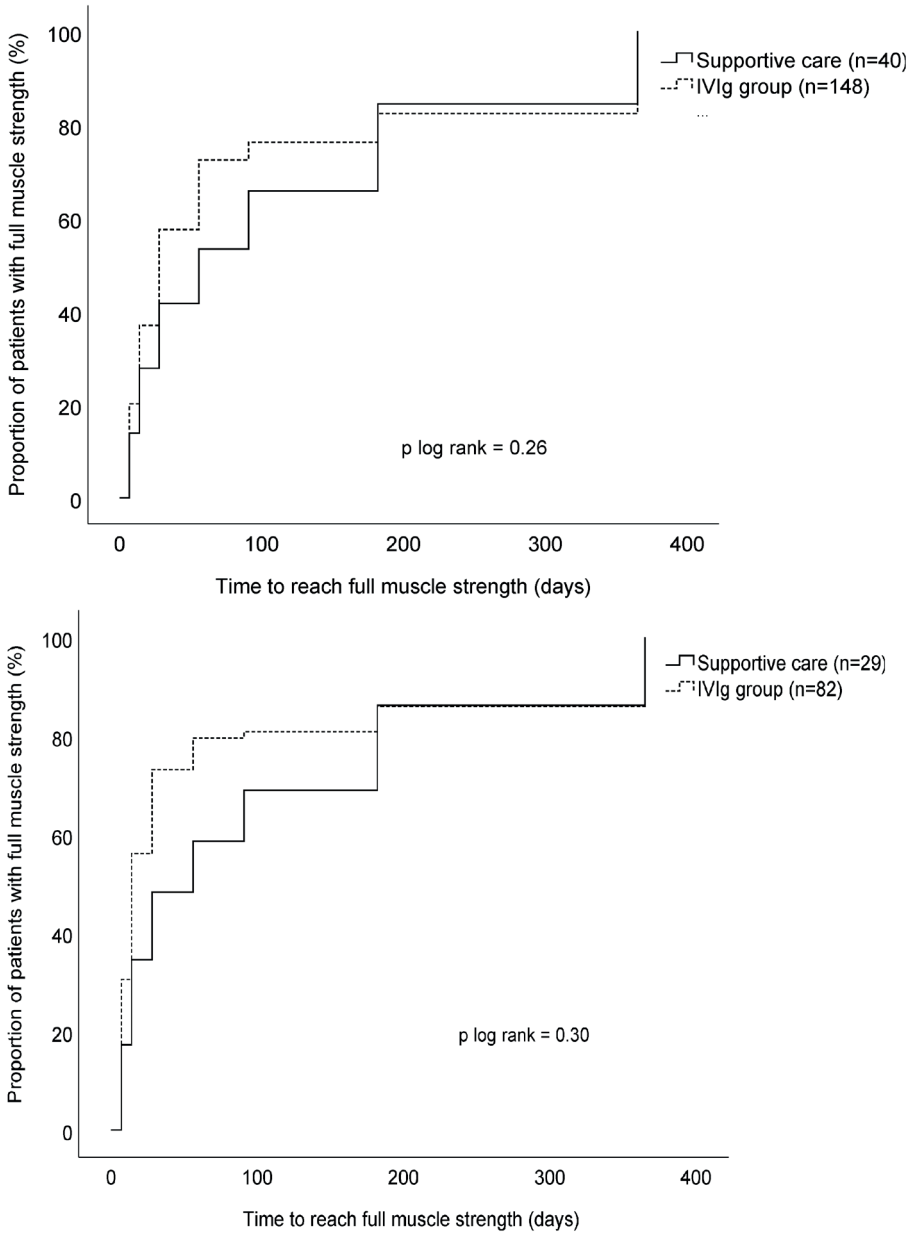
Abbreviations: FSS = fatigue severity scale, GBS = Guillain-Barré syndrome, IVIg = intravenous immunoglobulin, MRC = medical research council, rehab = rehabilitation centre, R-ODS = Rasch-built Overall Disability Scale, VAS = visual analogue scale.

After one year follow-up, the frequency of residual symptoms was similar in both groups, occurring in 44/107 (41%) of the IVIg treated patients and in 11/29 (38%) of the untreated patients (p=0.76). In the total group, residual symptoms most frequently consisted of pain (32/137, 23%), sensory deficits (31/135, 23%), cranial nerve involvement (11/136, 8%) and limb weakness (11/136, 8%).

SUBGROUP ANALYSIS OF PATIENTS WITH PERSISTENT MILD GBS

A further analysis was conducted in those patients with persistent mild GBS for the first 2 weeks (GBS disability score 2 or lower), including 29 patients in the supportive care group and 82 patients in the IVIg group. The baseline characteristics were comparable between the two groups and did not differ from the characteristics of the whole group of patients with mild GBS at study entry (supplementary appendix table 1). With a multivariable ordinal regression model, the aOR for an improved GBS disability score at four weeks was 2.32 in favor of IVIg, but this was not significant (95% CI 0.76-7.13, p=0.14). Most of the secondary endpoints did not improve after IVIg. However, more IVIg treated patients regained full muscle strength after four weeks (54/77, 70% versus 12/25, 48%, p=0.04) and the time to regain full muscle strength was shorter in the IVIg treated patients (14 days, IQR 7-28) than in the untreated patients (56 days, IQR 14-182, p=0.01).

Figure 3. Time to regain full muscle strength in mild GBS patients treated with supportive care versus IVIg in the complete cohort (3a) and in the subgroup with persistently mild GBS patients (3b).



However, the Kaplan-Meier curves of the two groups displaying the time to regain full muscle strength after four weeks were not different (figure 3b). Residual symptoms were

frequently and equally present in both groups (supportive care group 9/26 (35%) and IVIg group 20/64 (31%), p=0.76).

DISCUSSION

This observational study showed no benefit from IVIg on functional outcome in GBS patients who were able to walk independently at presentation or during the first two weeks after study entry. Up to 41% of IVIg treated and untreated patients showed residual symptoms at one year.

We have conducted the first comparative study to estimate the efficacy of IVIg in mild GBS. Because of the observational nature of the study, treatment was offered at the discretion of the study investigator. Approximately three quarters of patients with persistent mild GBS were treated with IVIg, despite the lack of any controlled trial data providing evidence for efficacy of IVIg in mild GBS. Arguments to treat this group in an early phase are that it is currently not possible to predict who is at risk for further deterioration, early treatment may prevent further nerve damage, and the fact that side effects of a standard IVIg course (2 g/kg in 5 days) are infrequent and generally mild. In the sub-analysis of persistent mild GBS, the baseline characteristics were comparable, and so the question arises whether clinicians were inclined to treat mild GBS whatever the circumstances or if there were other unobserved factors that resulted in confounding by indication. This phenomenon occurs when a worse disease course is both an indication to start treatment and also a predictor for poor outcome. Another likely confounder is disease progression, which would have been more likely to lead to IVIg treatment compared to those with a stable course or improvement. Of the untreated patients, 14/31 (45%) were already improving in the first week after study entry, whereas only 23/132 (17%) of the IVIg treated patients were improving at the time of starting the IVIg course (p=0.001). Finally, various electrophysiological parameters including compound muscle action potential (CMAP) amplitude have been identified as prognostic factor.[23, 24] Although we have corrected for electrophysiological subtypes in the multivariable regression analysis, we have not assessed individual NCS parameters because there was no standardized NCS protocol in IGOS.

We observed that IVIg appears to hasten full muscle strength recovery. This result should be interpreted with care, since this was one positive finding among many secondary endpoints examined. However, it might be argued that the time needed to recover strength is a more responsive endpoint in patients with mild GBS. Previously, a randomized controlled trial showed that two sessions of PE hastened the onset of motor recov-

ery in patients with mild GBS compared to untreated patients.[1] Clinical deterioration was less frequent in the PE group (4% versus 39%, p=0.0001) in that study, but this was also influenced by the fact that patients who deteriorated were re-grouped into a moderate GBS group, receiving 2 or 4 PE sessions. The design of that PE trial was suitable for patients with mild GBS, as deterioration would regroup them into a PE group with more PE sessions. For IVIg, this is problematic, because IVIg is given in one standard course over 2 to 5 days. Unfortunately, we are not able to predict which patients with mild GBS at presentation will deteriorate. Until prognostic markers are identified that predict deterioration in mild GBS patients, a well-designed prospective trial evaluating the efficacy of IVIg in mild GBS remains problematic, primarily because of ethical constraints.

This is the first study evaluating the one year outcome in mildly affected GBS patients. Previously, problems with hand and arm function and mobility have been reported in up to 38% of mild GBS patients at 6 months, irrespective of treatment.[6] We also found that despite the presumed benign course and good outcome, approximately 40% of patients with mild GBS, regardless of IVIg treatment, had residual symptoms at a year. In the subset of those with persistent mild GBS, residual symptoms were present in 35% of patients. This demonstrates the unmet need for more effective treatment even for those considered mildly affected.

The most important limitation of our study is its observational nature resulting in selection bias and confounding by indication. In addition, the most responsive primary endpoint for patients with mild GBS is unknown. As discussed above, onset of motor recovery might be a responsive endpoint, but the IGOS database did not document the date of onset of motor recovery so we could only estimate the time of onset of motor recovery by using the study visit dates. Another possible endpoint might be time to hospital discharge, especially in studies including cost-effectiveness analysis. However, discharge policies differ widely between hospitals and the date of hospital discharge was not recorded in IGOS. For this study, we used the GBS disability scale because it is widely known and most often used in therapeutic trials for GBS. However, the scale may not be sensitive enough for patients with mild GBS. In 2013, a group of inflammatory neuropathy experts reached agreement and recommended using the activity and participation level measured by the 24-item Rasch-built Overall Disability Scale (R-ODS) for all future therapeutic GBS studies.[20, 25] However, the R-ODS scale contains items which are not always applicable, especially in different regions of the world, diminishing its reliability and applicability.[26] Lastly, although IGOS has collected a very large cohort of GBS patients, the patient numbers in this study, and especially in the sub-study of patients with persistent mild GBS, were small, and the study could be underpowered.

Although this observational study did not identify significant benefit from adding IVIg to supportive care in initially mild GBS, confounding factors may have masked the possible positive effect of such treatment. IVIg may shorten time to full recovery of muscle strength and PE has previously been proven to hasten recovery in mild GBS[1].Since other trials in severe GBS have shown that IVIg and PE have similar efficacy[7], it would be premature to conclude that PE is more efficacious than IVIg in mild GBS. Because this study has shown that 40% of patients with mild GBS have persistent symptoms at one year regardless of treatment status, other more effective treatments are needed. Ideally, future studies would use more responsive clinical outcome measures appropriate for mild GBS, measure prognostic biomarkers of ongoing inflammation and nerve damaging, which predict disease progression, and include more participants in a randomized controlled design.

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5

Discussion

Patients diagnosed with Guillain-Barré syndrome (GBS) face an uncertain future. Some patients experience mild tingling and weakness in hands and feet only, while others develop a peripheral 'locked-in syndrome' with tetraplegia, ophthalmoplegia, and respiratory insufficiency. In addition, some patients quickly recover completely even without specific therapy, while others rapidly deteriorate during treatment, require ventilation for months, recover poorly and may even die from GBS. The clinical diversity and limited number of treatment trials conducted in GBS highly complicates the treatment of individual patients. A better understanding of the factors influencing the treatment response, clinical course and outcome is required to develop more effective treatments and to optimize the treatment for individual patients.

The overall aim of the studies described in this thesis was to gain more insight into the clinical diversity of GBS and consequences for the treatment of patients with GBS. Most studies in the thesis were based on the real-world data collected in the International GBS Outcome Study (IGOS). The results are discussed in three sections. The first section describes the clinical variation and variant forms of GBS in the IGOS cohort, and investigates the difference between geographical regions. The second section focusses on the dilemmas in the treatment of GBS that result from the clinical diversity. This parts starts with a description of the variation in the treatment of patient with GBS in current clinical practice, followed by an analysis of two specific treatment dilemmas: (1) whether a second intravenous immunoglobulin (IVIg) course improves outcome in GBS patients with a poor prognosis and (2) whether one IVIg course improves outcome in relatively mildly affected patients. The findings of the two studies will be discussed in the light of current available literature, altogether with strengths and limitations of the studies and theoretical considerations on how to study treatment effectiveness in observational studies. In the third section, suggestions for future research will be explored.

International GBS Outcome Study (IGOS)

The IGOS is a prospective, observational cohort study aiming to define the clinical course and outcome of GBS and to identify prognostic factors that predict and influence disease course (chapter 2). Previously, several studies have investigated the clinical variability of GBS, but most of these studies were retrospective, restricted to a single center or multiple centers from a single country, and based on treatment trial cohorts that are biased towards the inclusion criteria. These studies frequently showed inconsistent or variable results, which in part could be explained by the limited power of smaller studies and the diversity in study design between studies. These limitations inspired the GBS research group at Erasmus MC to initiate an extensive international cohort study in collaboration with the Inflammatory Neuropathy Consortium (INC). The IGOS was conducted in more than 160 hospitals from 21 countries from 5 continents and attempted to include the full

spectrum of GBS (chapter 2).[1] All GBS patients can be included in IGOS, regardless of age, clinical variant, subtype or disease severity, resulting in an unselected group of GBS patients, thus a real-world GBS study population. IGOS aimed to include 2000 patients with GBS, a number that was reached in May 2021, but for most studies in the thesis a cohort of the first included 1000, 1300 or 1500 patients was used. Comparative studies across geographical areas including comparisons between high- and low-income countries is possible because all participating centers use the same study protocol. Lastly, the extensive follow-up period in IGOS is at least one year (extension studies until three years) which is important because most recovery likely occurs in the first years after onset and a large proportion of patients report considerable residual complaints and limitations. Practical advantages of IGOS are that the databank of IGOS may be used to match GBS controls to trial subjects, and that extensive collaboration within the IGOS Consortium through expertise groups provides unique research opportunities for both senior and junior researchers across the world. A limitation of IGOS is that despite the conduct in 21 countries in 5 continents, some areas currently remain underrepresented including eastern Europe, eastern Asia, central America and most parts of Africa. This is largely due to decreased access to research facilities and lack of infrastructure for research, including access to the internet and storage of biosamples. Furthermore, IGOS aims to include the full spectrum of GBS but some selection bias cannot be prevented as mild cases may not come under the attention of an IGOS collaborator and atypical cases may never enter the study. A recent nationwide Danish study reported that the group of GBS patients participating in IGOS were more severely affected than the other GBS patients.[2] Lastly, tertiary medical care or university hospital centers are overrepresented in IGOS where the patient population and care may differ from other hospitals. Keeping these limitations in mind, IGOS still provides the largest standardized data- and biobank on a large number of GBS patients from many parts of the world, which serves as a strong base to address many research questions including the ones specified in this thesis.

Clinical variability of GBS

The classic 'textbook' form of GBS consists of a typical clinical picture with progressive limb weakness, reduced deep tendon reflexes with or without limb sensory symptoms and signs.[3] In practice, however, not all patients present with this classical picture. Many variant forms of GBS have been identified, including the Miller Fisher syndrome (MFS), pure sensory GBS, paraparetic GBS, pharyngo-cervical-brachial GBS, and Bickerstaff encephalitis.[4, 5] Some patients may have 'formes frustes' of GBS, for example patients with bilateral facial nerve palsy and limb areflexia but without other neurological deficits of GBS. Other patients may have overlap syndromes as may occur in patients that initially present with MFS, but subsequently develop limb weakness and progress to a MFS-GBS

overlap syndrome (chapter 3.1). Apart from the variation in clinical presentation, the disease course, clinical severity and outcome differ widely too.

Which factors contribute to the clinical variation of GBS?

The diversity in clinical phenotype and severity of GBS still remains elusive but two sets of contributing factors have been identified in previous studies.

1. Antecedent events

About two-third of GBS patients report symptoms of a preceding infection including upper respiratory infections or gastroenteritis in the four weeks prior to the onset of GBS.[6, 7] The most important infectious trigger of GBS is *Campylobacter jejuni*, which can be demonstrated in 25-50% of the adult GBS patients.[6] Other microbial agents which have been linked to GBS are cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*.[7] A *C. jejuni* infection usually results in a pure motor variant of GBS (no sensory deficits) with more severe limb weakness and poor clinical outcome, whereas CMV or EBV infections usually result in the classic motorsensory form of GBS.[7, 8] *C. jejuni* infections can trigger the immune system to produce antibodies to the bacterial lipo-oligosaccharides that cross-react to gangliosides like GM1 or GD1a because of molecular mimicry. These cross-reactive antibodies then bind to GM1 and GD1a residing in the membranes of peripheral nerve axons and myelin sheets.[6, 7, 9] Binding of these antibodies will lead to complement activation, formation of membrane attack complexes and binding of macrophages resulting in axonal degeneration and demyelination. Although the molecular mimicry theory has been substantiated with robust evidence in relation to *C. jejuni*, the GM1 or GD1a antibodies, and pure motor GBS with an axonal neuropathy on nerve conduction studies, no such direct evidence has been found for motorsensory demyelinating GBS or MFS. Instead, only a small proportion of patients with motorsensory GBS have antibodies in their serum (including GM1, GM2 or GD1a, and more recently anti-Gal-C and anti-LM1 antibodies) and various – but no unique – antecedent events for motorsensory GBS have been described including the ones specified above.[10, 11] The majority of patients with MFS have anti-GQ1b antibodies (90%) and an upper respiratory tract infection occurs in approximately 75% of patients, but also no unique antecedent event has been found.[7, 11-13] These findings imply that the type of antecedent event plays a role in triggering a specific phenotype of GBS, but as discussed, it is not all-encompassing in understanding the clinical variability of GBS.

2. Host-susceptibility factors

In case of gastroenteritis due to *C. jejuni,* only one out of 1000 patients will develop GBS, which indicates that host-susceptibility factors have to play a role too.[14] Even within families, not all who contract gastroenteritis after *C. jejuni* infection will develop GBS.[15] One case report described that two days after a barbecue party, a father and his two sons developed gastroenteritis but the mother did not.[15] Five days after start of gastroenteritis, only one of the sons, a previously healthy ten-year-old boy, developed a pure motor form of GBS. This was accompanied by the presence of anti-ganglioside antibodies in his serum whereas his father, mother and brother did not have any neurological symptoms or signs nor had elevated serum antibody levels. Initially, these observations led to the hypothesis that the human leucocyte antigen system would play a major role by triggering immune responses by antigen presentation to T-lymphocytes. However, many subsequent studies did not establish the pathogenic role for the HLA system in GBS.[16, 17]

Other studied host-susceptibility factors are Cluster of Differentiation (CD)1A and CD1E genes, Fas ligands, Fc gamma receptors, Intercellular adhesion molecule-1, different interleukins, nucleotide oligomerization domain proteins, Toll-like receptor 4, tumor necrosis factor-α, and polymorphisms of mannose-binding lectin 2 genes.[16, 18] However, there are also contradictory reports on these host-susceptibility factors assumedly because of small studies, so that the controversies in the pathogenic role of these host-susceptibility factors continue to exist. Another possible explanation for the conflicting study results on the role of genes in contracting GBS, might be interacting mechanisms with differences regarding genotypes among populations in combination with particular microorganisms triggering GBS.

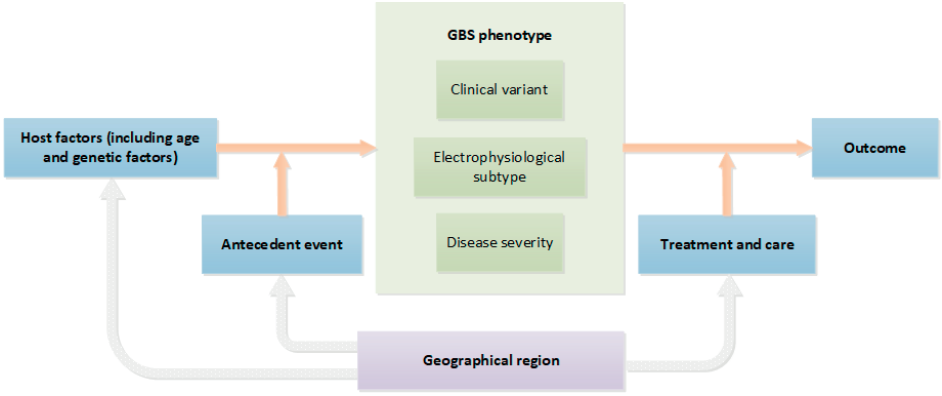
Which general factor influences antecedent event and host-susceptibility factors?

The type of antecedent event and the host-susceptibility factors which contribute to the GBS phenotype may be influenced by the geographical origin of patients (figure 1).

Studying regional variation of GBS is required to further investigate the effect of environmental factors on the heterogeneity of GBS. To investigate the regional variation we used the IGOS-1000 databank (chapter 3.2).[19] In this study, we divided the patients into three regions: Europe/Americas, Asia and Bangladesh (chapter 1, figure 2). Europe and Americas were combined as one region because interim results showed that the phenotype of GBS was similar. The reason for separating Bangladesh from other Asian countries (Japan, Malaysia and Taiwan) was the difference in socio-economic status and related hospital and treatment facilities, and the relative high number of patients from Bangladesh (n=125) in comparison to the other patients from Asia (n=69). Regional variation was confirmed with respect to clinical variants, severity, electrophysiological subtypes,

and outcome. Our study showed that there was a variation in antecedent infections among the regions. Gastro-enteritis was the most commonly reported antecedent event in Bangladesh (36%) whereas symptoms of an upper respiratory tract infection occurred most often in Europe/Americas (38%) and Asia (51%). Concordantly, the predominant clinical variant in Bangladesh was pure motor (69%, versus 14% in Europe/Americas and 24% in Asia). In addition, patients from Bangladesh had a worse clinical course and outcome than patients from Europe/Americas and Asia. Other factors associated with poor outcome were axonal subtype, more severe disease course in the acute stage and lack of immunotherapy. In our study, we observed that the far majority of patients from Bangladesh did not receive immunotherapy (86%) despite severe disability. This finding substantiates the major differences in medical infrastructure, availability of treatments in the world that also affects the medical care of patients with GBS (figure 1).

Figure 1. Factors related to the phenotype of GBS.



The GBS phenotype is influenced by antecedent event and host-susceptibility factors, and clinical outcome is influenced by the GBS phenotype and the treatment and medical care being provided. Treatment and care refer to the availability of relatively expensive treatments (IVIg, plasma exchange (PE), intensive care facilities) and rehabilitation which largely depend on the presence of financial resources. In turn, host-susceptibility factors, antecedent events and treatment and care are overarching influenced by geographical region.

Our study confirmed findings of previous single-country studies around the world reported varying dominating subtypes, with motorsensory GBS as predominant subtype in North-America and Europe (60-80%) and pure motor variant in northern China and Bangladesh (30-65%).[20-24] The frequency of MFS was reported to occur in only 1-5% of patients from Western countries compared to 20-25% in patients from Japan or Taiwan.[7, 13, 23]

Another argument for a role of regional antecedent infections influencing GBS phenotype, comes from two studies in China, reporting the axonal subtype in Northern China in the nineties of the previous century, while in contrast a recent study reported a domi-

nating demyelinating subtype of GBS in southern China.[25, 26] One possible explanation is that the socio-economic status of China has evolved in the last two decades and that improved hygienic circumstances diminish campylobacteriosis and the related axonal forms of GBS.[27]

In conclusion, geographical origin is presumably a major factor in explaining the variation in clinical variants, subtypes, clinical course and outcome of GBS. The geographical regions may determine the type of antecedent events and host-susceptibility factors that influence the specificity of the immune response to nerves and thereby the GBS phenotype. In addition, the variation in treatment facilities for GBS in high- versus low-income countries will in part determine the clinical course and outcome (figure 1.)

Treatment of GBS

Lack of efficacy of corticosteroids in GBS

When considering novel treatment strategies in GBS, some historical aspects on treatment trials in GBS may be recapitulated. Following the emerging evidence for the involvement of the immune system in the pathogenesis of GBS, the first randomized controlled trial (RCT) evaluating the efficacy of 60 mg oral prednisolone in tapering dose in 40 patients with GBS was performed in 1978.[28] Surprisingly, patients treated with prednisolone improved less well than patients with supportive care. Even more, prednisolone treated patients who entered the study early (within one week of onset) had significant worse outcomes than control patients. These findings suggested that oral prednisolone delays recovery. Fifteen years later, another RCT found that intravenous methylprednisolone (500 mg for 5 days) did not improve outcome compared to placebo.[29] Other studies also failed to identify positive effects of intravenous corticosteroids in GBS patients.[30] Finally, intravenous methylprednisolone when added to IVIg was also not improving outcome when compared with IVIg alone.[31] These findings were remarkable, considering that corticosteroids are effective in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which may be considered the chronic form in the spectrum of peripheral nerve inflammatory diseases including GBS. In addition, high-dose corticosteroids had been shown to temper clinical deficits and hasten recovery in the experimental autoimmune neuritis, considered by some an animal model for GBS.[30] Several mechanisms have been proposed to explain the lack of effect of corticosteroids in GBS. First, at the time when most patients are admitted, nerve damage may be more dependent on immune-mediated processes that are not influenced by corticosteroids, including the binding of antibodies to structures on nerves and local activation of complement. At that time, suppressing the cellular immune system alone is insufficient. Second, the immune suppressing mechanisms of corticosteroids might prevent activation of suppressor T-cell and B-cells, which are needed to terminate the immune response to nerves. In addi-

tion, corticosteroids might also interfere with the remyelination processes, especially by inhibiting macrophages clearing the myelin debris in order to start remyelination processes, and by suppressing Schwann cell proliferation.[28-30]

Intravenous immunoglobulin (IVIg)

After ascertaining a beneficial effect of 5 sessions of PE in GBS patients who were unable to walk independently in the late eighties, IVIg was introduced as treatment for GBS after various comparative RCTs of IVIg and PE showing similar improvement after either therapy.[32-34] IVIg dosage (2 g/kg over 5 days) was historically adopted from the first trials ever with IVIg, which were performed in patients with idiopathic thrombocytopenic purpura.[35] All RCTs with IVIg in GBS have initially included patients with typical forms who presented early after onset of symptoms, and were severely affected (GBS disability score 3 or more, unable to walk independently). In these patients, a possible treatment effect of IVIg was expected most explicitly, considering that the inflammation occurs only early in the disease onset and that severely affected patients will show only limited spontaneous recovery. However, as we have indicated in our review on treatment dilemmas in GBS (chapter 4.1), GBS is a heterogeneous disorder that includes various clinical phenotypes with a range of disease severities. In clinical practice, not all patients fulfil the criteria used in the treatment trials in GBS, resulting in various dilemmas on the treatment of individual patients in clinical practice. We hypothesized that these treatment dilemmas and the absence of international guidelines for the management of GBS could result in a diverse treatment practice. Indeed, our study on treatment practice revealed a high diversity in the treatment of GBS in specific situations (chapter 4.2). In the subsequent studies in this thesis, we have focused on investigating two important dilemmas including (1) whether patients with a poor prognosis benefit from a second IVIg course (chapter 4.3), and (2) if one course of IVIg improves recovery in patients with a mild form of GBS (chapter 4.4).

A second IVIg course in patients with poor prognosis

The IGOS cohort was used to conduct the International Second Immunoglobulin Dose (I-SID) study, in which we compared the clinical course of patients with poor predicted outcome in the group treated with a standard single dose of IVIg with the group treated with two dosages of IVIg. In this observational study we selected a subgroup of patients from the IGOS database who had a predicted poor prognosis, which was defined as a high risk of not being able to walk independently six months after onset of symptoms (chapter 4.3). Of these 237 patients, 38 (16%) patients received a second IVIg course. Those who received a second IVIg course, were more disabled at baseline than those receiving a single IVIg course, for which we corrected in the multiple regression analysis model. We found that the disease course in GBS patients with a predicted poor prognosis

was not better after a second IVIg course instead of one course.[36] Despite the limitations about the study design (i.e. a high risk of selection bias due to the observational nature of the study) and the relatively low numbers of patients that could be included, the results of this study were later confirmed by an RCT comparing a standard single course of IVIg and placebo with a double course of IVIg.[37] In addition, the RCT reported higher number of serious adverse events in the second IVIg group.[37] Thrombo-embolic events were significantly more present in the second IVIg group which may be attributed to a dose-dependent increase of plasma viscosity. In our observational study, no such serious adverse events were reported which is probably attributable to the less strict documentation of adverse events compared to the RCT.

Although the RCT also showed no benefit of a second IVIg course, some differences between the RCT and the observational study described in this thesis should be pointed out. First and most importantly, the patients of the observational study received the second IVIg course rather late, which was inherent to the real-world-data nature of the study, whereas the RCT where all patients received the second IVIg within 7 days after start of the first IVIg in accordance with the study protocol. Second, although the patients from the observational study were selected from the IGOS database with pre-specified criteria, this differs from the strict inclusion criteria for the RCT.

The explanation for the lack of efficacy of a second IVIg course might be that timing of the second course is probably too late to prevent further nerve damage. Other possible explanations could be that all treatments based on IVIg alone have the limitation of targeting only a part of the immunological mechanisms that contribute to the nerve damage in severe GBS. In conclusion, the observational I-SID study and SID GBS trial both indicate that a second IVIg course does not contribute to a better disease course in GBS patients with a predicted poor prognosis. Therefore, a second course of IVIg should be avoided in clinical practice, especially now that it is known that it can be harmful to the patient.

Treatment of mild GBS

In our study regarding IVIg in patients with relative mild motorsensory GBS (chapter 4.4), we selected 188 patients who were mildly affected (i.e. being able to walk independently at entry of the study), of which the majority was treated with IVIg (79%) and the rest (21%) received supportive care. The IVIg treated patients were more disabled at baseline than the supportive care treated patients. We found that the disease course of patients with mild GBS at entry was not improved by one standard course of IVIg (2 g/kg) based on a comparison of most clinical endpoints. Nevertheless, the time to recover full muscle strength was shorter in patients treated with IVIg compared with supportive care. In the

end, the data of this observational study were considered not robust enough to either prove or to rule out with certainty a beneficial effect of IVIg in mild GBS. This result is most unrewarding, because mild GBS patients, in contrast to what its name suggests, may experience long term deficits and complaints such as fatigue or pain. Previously, French researchers found that two PE sessions significantly shortened the time to onset of motor recovery in patients with mild GBS compared to supportive care.[38, 39] It is an interesting finding that in our study with mild GBS patients, the majority of patients were already being treated with immunotherapy (80%), being PE in only 3% of patients and IVIg in 77% of patients.

One may hypothesize that considering that PE is beneficial in mild GBS and that PE and IVIg are similarly efficacious in severe GBS, IVIg might be efficacious in mild GBS too. However, drawing this conclusion is premature in the absence of study results to support the hypothesis, especially in this era of evidence-based medicine. In addition, the availability of IVIg is relatively scarce and costs are high, which should also be taken into account. At the same time, one may ask why not to treat all patients with motorsensory or motor GBS, regardless of severity. Adverse events after one course of IVIg may occur but are generally mild and reversible, including fever, myalgia, headache, hypotension, meningism, and allergic reactions. Rarely, renal tubular necrosis, thromboembolic events or anaphylaxis are observed but the risk is probably dose-dependent and therefore not very high in patients receiving only one course of IVIg.[33] Why wait for further deterioration when early treatment might result in a larger therapeutic effect and prevention of irreversible nerve damage? In other diseases with a mild presentation and potential full recovery, such as a transient ischemic attack, neurologists will not wait for further deterioration or spontaneous recovery of the neurological deficits. On the contrary, to prevent further nerve injury all patients with an acute ischemic event are treated in the earliest phase. For patients with GBS, nerve damage is likely still reversible in the most acute phase, so the expression "time is brain" might be extrapolated to "time is nerve".

In conclusion, one course of IVIg did not seem to improve disease course in patients with mild GBS. Previously two sessions of PE has been proven to hasten onset of recovery in mild GBS and IVIg may shorten time to full muscle strength recovery. Since the patients with mild GBS represent about 20-35% of all GBS patients and may experience long-term symptoms and signs, they should not be overlooked and the threshold for the decision to start treatment should be low.

Remarks on the I-SID and IVIg in mild GBS studies

The results of these two studies must be interpreted in the context of their study design. Both studies had an observational study design in which patients were not randomized

and the data were collected in a real-world setting. Local neurologists participating in IGOS were free to treat the patients according to their own local protocols, in absence of an international guideline about the treatment of GBS. Although IGOS provides a good representation of the treatment of GBS in current practice, the diversity in treatment practice complicated a straightforward comparison of groups of patients (chapter 4.2). Selection bias was expressed by more disability and deterioration in the study groups compared to the control groups. In the two studies, deterioration or lack of improvement must have influenced the decision to start the intervention whereas at the same time, outcome is also influenced by a worse nadir.

Observational studies are valuable to estimate a predefined outcome after a particular exposure. When it comes to estimate the effect of treatment, there is much debate regarding the additive value of observational studies when compared to randomized controlled trials. In the light of the abovementioned obstacles, how should the results of observational studies evaluating treatment effect be interpreted and can observational studies be of additive value for meta-analyses and guidelines?

The value of observational studies for estimating treatment efficacy

In epidemiology, several major discoveries are on the account of observational studies, with the association of smoking and lung cancer as an important example.[40, 41]

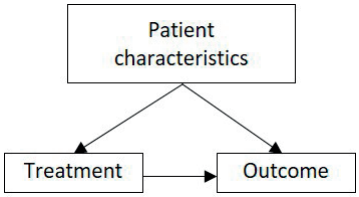
Three important issues regarding evaluating treatment effect in observational studies can be pointed out. First, the major limitation with observational studies is selection bias, because subjects are assigned to the study arms based on patient characteristics and not on randomization processes.

The second major issue is that unobserved confounders cannot be used in multiple regression analyses because these patient characteristics are not recorded in the study. Unobserved confounders also exist in RCTs but after randomization it can be assumed that they are evenly distributed among the study groups. Examples of unobserved confounders in our studies may include insurance status, worried patients or their relatives who ask for an extra treatment, and level of expertise of the treating physician.

The third problem is confounding by indication, where patient characteristics (observed and unobserved) influence both the indication for treatment and the outcome. In our studies, confounding by indication is very likely present, because GBS patients who are more disabled will more likely receive treatment than patients who are less severely disabled or who are already improving. Simultaneously, a more severe disease course is predictive for a worse outcome in GBS (figure 2).

In observational cohort studies, the risk of confounding (by indication) may be reduced by new study analysis approaches which are called causal inference techniques, including propensity score matching, a method where subjects are matched not only based on sex or age, but also on features of disease severity.[42] Taking a closer and more theoretical look on observational studies and causal inference, one may consider observational studies as conditionally randomized experiments.

Figure 2. Confounding by indication.



Observational studies as conditionally randomized experiments

In an observational study, the individuals may be split into groups based on a baseline characteristic (stratification). Within these strata, individuals are better exchangeable with each other, and they have or have not received the intervention. This is a way of regarding observational studies as conditionally randomized experiments, but it is only possible under the following three conditions. First, the two interventions (or more) should be well-defined. Second, the probability of an individual to receive either intervention is based only on the observed confounders. Lastly, the probability to receive either intervention is greater than zero.[43] When all these three conditions are met, we may use standardization processes or causal inference techniques to increase the exchangeability of subjects to estimate treatment effects in these assumed conditionally randomized experiments.

Can observational studies be used to estimate treatment effect?

The main critical problem with large observational cohort studies is that the assumption about the probability of receiving treatments cannot be met, since it is impossible to know all confounders.[42, 44] So how should treatment effectiveness be evaluated in observational studies? In 2014, a Cochrane systematic review compared the estimated effect measures of RCTs with observational studies.[45] This quantitative analysis showed no significant differences between the effect estimates in 79% (11 of 14) of the reviews, but a substantial heterogeneity for this estimate (I^2 = 73%). They concluded that there was little evidence for significant differences in effect estimates between RCTs and observational studies. A recent systematic literature review comparing relative treatment effects from RCTs and observational studies, also reported no significant difference in the relative risk ratios of 80% of the included RCTs and observational studies comparisons, and a significant variation (even with opposite directions) in about 20% of the comparisons.[46] If an observational study reports different effect estimates compared to an RCT, other factors then study design alone should be considered (such as underlying risk of bias which is always higher in observational studies) given the high heterogeneity.[45]

In conclusion, taking all the above mentioned considerations into account, a precise observational study can be considered a controlled trial without randomization. It may serve as a starting point for setting up a well-designed RCT because it produces insight in the clinical course and practice of treatment based on real-world data. RCTs have powerful benefits over observational studies but when RCTs are not feasible, an observational study can be of additive value in evaluating treatment effectiveness. The observational study should be well set-up and meet the following conditions: meticulous documentation and description of all possible confounders, a careful statistical analysis plan with pre-specified endpoints and usage of additional statistical methods for confounder correction, and an interpretation of the results with care given the unceasing higher risk of bias. The observational studies carried out according to these conditions, may be deemed reliable and considered for meta-analysis.

Future perspectives

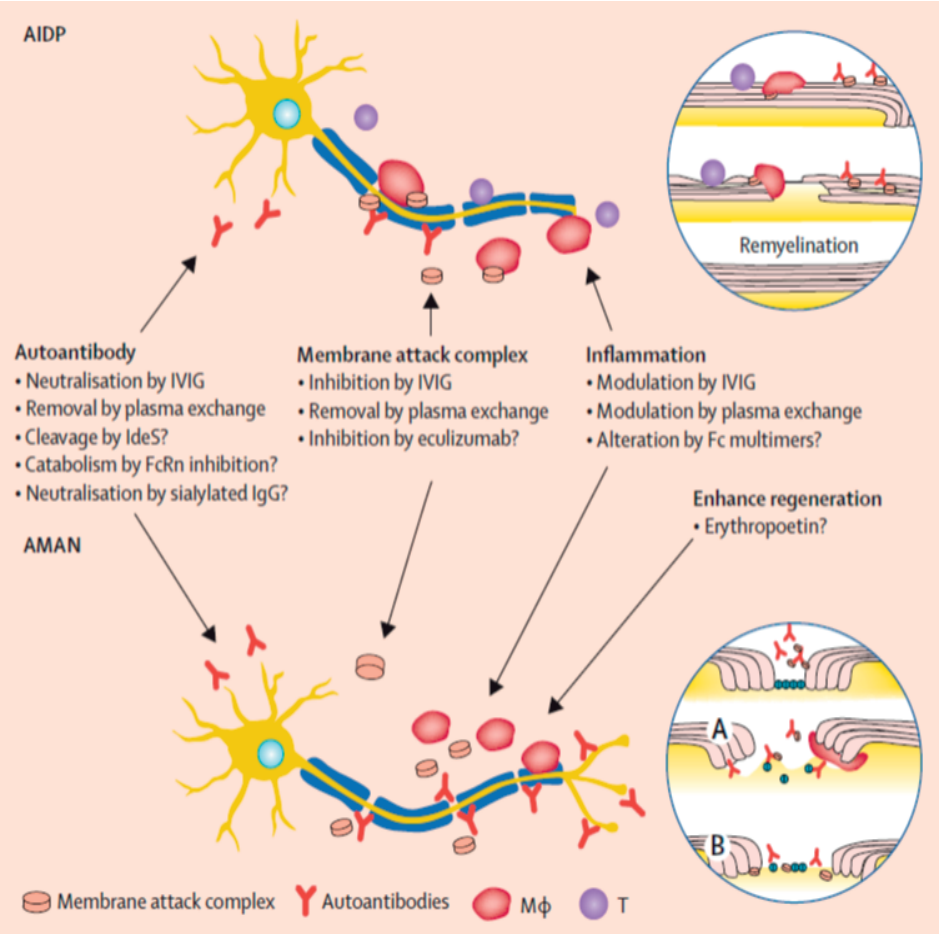
From better understanding the pathophysiology to better targeted treatment

One of the most eminent knowledge gaps in GBS is our lack of understanding the immunopathogenesis of the AIDP. It is important to recognize the possible different immunopathogenic ways for demyelinating and axonal GBS, because it might require different therapeutic approaches. Up to now, various subgroup analyses in the treatment trials have not shown different outcomes of demyelinating versus axonal GBS patients but these subgroup analyses were frequently post-hoc and relatively small, especially for axonal GBS. Based on the current information there is no evidence to treat demyelinating GBS differently from axonal GBS.[33]

In addition to differing targeted therapies of demyelinating versus axonal GBS, two other therapeutic strategies can be pointed out. The first strategy would aim to prevent immune-mediated damage of myelin, Schwann cells and primary or secondary axonal degeneration of the peripheral nerves in the earliest phase of disease. The second strategy would aim to promote remyelination and regeneration of the peripheral nerves. Aiming to prevent demyelination and secondary axonal damage is probably the most attractive option for finding better therapeutic options since promoting remyelination has been disappointing in various neurological diseases and no therapeutic agent which lead to remyelination or axonal regeneration currently exists. The first step in preventing as much nerve damage as possible is raising awareness of GBS and stimulate the early diagnosis and start of treatment. Based on IGOS, the medium delay from onset of weakness to the first hospital visit is 3 days (IQR 2-6), and treatment is started approximately one day later (IQR 2-7).[19] In young children, the delay (both patient and doctor) is even longer because establishing the diagnosis in young children is complicated and the disease might be missed because of the rarity in children.[47] At that time however,

all immune processes leading to nerve demyelination have already been activated. Therefore, treatment should be started early and should cause fast immunomodulatory mechanisms (figure 3).

Figure 3. Pathogenesis and therapeutic agents (with permission from reference 6).[7]



Novel treatments that interfere with early immunomodulatory mechanisms

Two small studies have investigated whether Eculizumab, an intravenously administered agent, could prevent demyelination of the peripheral nerves.[48, 49] Eculizumab is a humanized monoclonal antibody which prevents formation of membrane attack complex by direct binding and inhibition of complement factor C5. The first study was underpowered due to patients declining participation in the study, but – importantly – reported that Eculizumab was well-tolerated and safe when applied in conjunction with IVIg.[48] The second study attained pre-calculated power and showed no benefit of

Eculizumab when added to IVIg on many study endpoints, including time to improve one functional grade on the GBS disability scale, but more people were able to run after 24 weeks when treated with IVIg and Eculizumab.[49] Therefore, these two neutral studies do not rule out a potential benefit of Eculizumab because the first was underpowered and the second study was also relatively small. Furthermore, the pathogenesis of demyelinating GBS might be different to axonal GBS, and complement C5 may not be a relevant therapeutic target in all these forms of GBS. Until further understanding of the immunopathogenesis of GBS is established, Eculizumab or other complement inhibitors should be evaluated in large, well set-up trials.

Another complement inhibitor which is currently under investigation in two trials is ANX005 which was developed by Annexon biosciences (NCT0403513 and NCT04701164). This novel intravenously administered treatment targets complement C1q and the entire classical complement pathway.

A novel potential treatment which targets even possibly earlier immunopathogenic processes in GBS is Imlifidase, an enzyme derived from the Streptococcus pyogenes bacterium capable of cleaving IgG very effectively. The enzyme has a rapid onset of action and cleaves virtually all IgG antibodies within hours after administration. The medicine has been shown to be effective in rare IgG-mediated auto-immune conditions, rejection of organ transplants and cancer.[50, 51] Currently, a phase II open-label study is evaluating the safety and efficacy of imlifidase administered at the first day after inclusion in the study, followed by a standard course of IVIg (2 g/kg in 5 days) starting on day 3 (NCT03943589).

Study design

In addition to the search on identifying novel therapeutic targets and agents, the design of future treatment trials needs to be reconsidered. Three components are essential for a good study: the right patient, the right clinical endpoint and the right study design.

1. The right patient

In order to set up new treatment trials in the future, the right patient should be included but this is not as easy as it may seem. For a treatment trial in mild GBS, prognostic markers are needed which enable early selection of patients with a persistent mild form of GBS and that exclude patients with initial mild GBS who deteriorate to severe GBS anyway. Currently, some prognostic factors have been identified that predict a poorer outcome including high age, presence of preceding diarrhoea, severity of muscle weakness (MRC sumscore) and disability (GBS disability score) and serum biomarkers such

as high albumin levels and small increase in IgG after IVIg treatment, but these do not sufficiently predict a mild or severe disease course in an individual patient.

Serum neurofilament light chain (sNfL) is a biomarker for axonal damage and becoming increasingly important for predicting disease course in many neurological diseases such as multiple sclerosis and frontotemporal dementia.[52, 53] Recent evidence suggests that sNfL might serve as a prognostic biomarker for disease severity in patients with GBS.[54] This study showed that patients with GBS had higher sNfL levels than healthy controls. More importantly, higher sNfL levels at entry were correlated with increased disease disability at nadir but cut-off points to discriminate between mild and severe GBS have yet to be established. In absence of such prognostic markers and the inability to identify truly mild GBS patients, a large, non-exclusionary RCT in all patients with mild GBS at entry may be the only way of evaluating whether IVIg is also beneficial in mild GBS.

The same considerations may be applied to other forms of GBS, such as MFS or pharyngo-cervico-brachial variant, and all the other less severe variants that form the spectrum of GBS. No randomized controlled trial has ever been performed in these variants so it is still unknown if these patients might benefit from immunotherapy too. In addition to the expected issues with inclusion criteria for such an RCT, determining which outcome measure would also be quite challenging.

2. The right clinical outcome

Many RCTs in GBS have randomized patients into a treatment and a placebo arm, with functional disability at four weeks as primary endpoint (most often dichotomized into being able to walk independently or not). Reasons to do so, are that GBS is a self-limiting disease with nadir at 2-4 weeks. Thus, the largest treatment effect is expected at that time point, assuming a less severe nadir compared to controls. For severely affected patients, this endpoint might be sensitive for research purposes but it does not take into account many other important disabling symptoms in GBS patients, such as arm function, cranial nerve deficits, pain, fatigue, time to onset of recovery, time to hospital discharge, and time to resume normal daily activities. In addition, for patients with mild motorsensory GBS, measuring treatment effect is challenging as being able to walk or not is not informative. For these patients, exclusive primary endpoint have yet to be established. During the 2013 international workshop of neuropathy experts, the Rasch-built Overall Disability Scale (R-ODS) was proposed as a sensitive endpoint for GBS at the activity and participation level.[55, 56] Although the R-ODS is a patient reported outcome measure and in that aspect is subjective, it includes many forms of daily activities and weighs the incapacities per item which should result in a better representation of the

patients' performance. However, the scale has not been validated in specific forms of GBS, nor in other world regions such as Asia. For milder forms of GBS, a sensitive endpoint might be time to onset of motor recovery (which could be defined as the time needed to recover at least one grade on the GBS disability score, or at least two points in MRC sum score), such as was being used in the PE trial with mild GBS.[38] Other sensitive endpoints for mild GBS might be time to full muscle strength recovery, or time to full recovery of all symptoms and signs (which would partly be subjective). Therefore, more research on sensitive and easily applicable study endpoints is needed.

3. The right study design

Another point which needs to be addressed here is what study designs may be used to answer research questions in GBS. In general, RCTs are considered the gold standard for evaluating treatment effectiveness because the randomization process reduces the risk of imbalances or bias.[42] However, RCTs are not always the holy grail due to flawed study design, stringent inclusion criteria, and imprecise interpretation of the results, which may lead to conflicting reports.[42, 44] In addition, they are expensive, time consuming and may be burdensome for the patients. An alternative solution might be an observational cohort study, which is especially applicable in case of low numbers of patients in rare diseases (such as GBS variants), or no consensus on the intervention.[42] The extent to which observational studies contribute to measure treatment efficacy has been discussed before.

Final remarks

In conclusion, after the report by Georges C. Guillain, Jean-Alexandre Barré and Andre Strohl in 1916, tremendous progress on the understanding of the pathophysiology of GBS and disease outcome has been made in the last century. With every major breakthrough and discovery, new research questions have been launched. Observational studies based on real-world data provide important insights and may pave the way for further research. Personalized medical care and a better prediction of disease course and outcome are two important research subjects among many others including further unravelling the pathophysiology of GBS. Because GBS is a rare disease, international collaboration among researchers and patient organizations is vital to address these continuing exciting research subjects.

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6

Summary & Samenvatting

SUMMARY

The Guillain-Barré syndrome (GBS) is a heterogeneous disease regarding etiology, clinical presentation, treatment response, disease course, and outcome. Factors that cause this heterogeneity are still poorly understood. This thesis contains studies on the diversity of the clinical picture of GBS and the variability on the treatment of GBS. These studies are largely based on real-world data collected in the International GBS Outcome Study (IGOS).

In **Chapter 1**, the introduction, the current existing literature about the heterogeneity of GBS is reviewed. In addition, practical issues regarding the diagnosis and treatment of GBS are explored. Furthermore, the IGOS is introduced. Lastly, the aims and research questions of this thesis are being formulated.

In **Chapter 2**, the study protocol of the IGOS is being described in detail. The IGOS is a large-scale observational cohort study on GBS, aiming to describe the heterogeneity of disease presentation, response on treatment, disease course and outcome. All patients diagnosed with GBS or a variant form of GBS can participate, irrespective of age, severity, variant, treatment and disease course, provided that the patient participates within two weeks after onset of weakness (or other symptoms in case of absence of weakness). In IGOS, detailed data are being collected regarding demography, medical history, antecedent events, disease presentation and course, treatment, and results of additional investigations (including results of cerebrospinal fluid analysis and nerve conduction studies). In addition, blood samples at study entry are being collected for genetic and serologic factors. The follow-up period is 1-3 years and during set time points, clinical data and serological samples are being collected. Approximately 160 hospitals from 21 countries (from 5 continents) collaborate on IGOS.

The studies on the clinical picture of GBS are described in **Chapter 3**. First, a study on the Miller Fisher syndrome (MFS) is reported (**Chapter 3.1)**. MFS is thought to be a variant of GBS, where patients can develop a classical triad of ataxia, areflexia and ophthalmoplegia without limb weakness. According to the literature, the prognosis of MFS is generally excellent. However, a proportion of MFS patients develops weakness of limb, bulbar and respiratory muscles causing respiratory insufficiency and need for ventilator assistance. It is not yet known which MFS patients are at risk of developing such an MFS-GBS overlap syndrome. In **Chapter 3.1** the results of the research on the course of MFS, the progression to an MFS-GBS overlap syndrome and the prognostic factors that could predict the clinical course are described. In this multicenter, observational study which 170 Dutch patients with (variants of) GBS, 23 (14%) had MFS. Of these, 10 patients (43%) developed

muscle weakness in the limbs and in all patients this occurred within the first week after the onset of symptoms. One of the 10 patients with the MFS-GBS overlap syndrome developed respiratory failure requiring ventilation. This also happened early in the course (first day after the onset of symptoms). No prognostic predictors for the development of MFS-GBS overlap syndrome were identified. Furthermore, it was observed that 39% of the MFS patients were treated with intravenous immunoglobulins (IVIg) and 61% were not. After 6 months of follow-up, residual complaints and symptoms were common; in 40% of the IVIg treated MFS patients and in 63% of the untreated MFS patients. These findings indicate that all patients with MFS are at risk of worsening in the first week after symptom onset and should therefore be monitored during that period. Furthermore, research should be performed on the best treatment strategy for MFS patients.

The variation in clinical presentation and course in GBS is large, but it is unknown which factors determine this variation. Publications from different countries suggest that GBS may vary by region. However, the published studies differ greatly in study design, inclusion criteria and diagnostic criteria, which makes it difficult to compare them. In **Chapter 3.2** we present the results of the first study on regional differences in the clinical presentation, diagnostic findings, subtypes and course of GBS using the same study protocol of the IGOS for all patients. Of the first 1000 patients in the IGOS, 91 had to be excluded due to a different diagnosis, insufficient data or violations of the study protocol, resulting in 909 patients who were divided into three regions; 715 patients in Europe/Americas, 69 in Asia (excluding Bangladesh) and 125 in Bangladesh. In Europe/America and in Asia the most common form of GBS was the motorsensory variant (69 and 43% respectively) while in Bangladesh the pure motor variant was most common (69%). It also appeared that the MFS variant and MFS-GBS overlap variant were most common in Asia (22%) and less common in Europe/America (11%) and Bangladesh (1%). Furthermore, nerve conduction studies showed that the subtypes of GBS also differed by region. Although the demyelinating variant was the most common variant of GBS in all regions, the axonal subtype was observed more often in Bangladesh (36%) compared to Europe/Americas (6%) and Asia (6%). We observed that independent of the region of origin, patients with the axonal subtype were younger, had less sensory impairment and recovered less well than patients with the demyelinating subtype. The rate of recovery at one year after diagnosis varied widely by region, with the percentage of people able to walk independently after one year ranging from 91% in Asia to 83% in Europe/Americas and 69% in Bangladesh. Compared to the other regions, death rate was highest in Bangladesh (17%), followed by Europe/Americas (5%) and Asia (2%). This study with the IGOS-1000 cohort confirmed the worldwide variation of GBS in terms of clinical variants, severity, electrophysiological subtypes, clinical course and recovery. The study showed

that this variation is likely partly influenced by regional differences in demographics, prior infections and treatment.

Chapter 4 focusses on the treatment of GBS. In **Chapter 4.1**, an overview of treatment dilemmas is given altogether with a treatment advice based on the available literature and expert-opinion. **Chapter 4.2** provides an overview of current treatment practice in GBS, based on the first 1,300 patients enrolled in the IGOS, of whom 1,023 patients could be used for the study. The results showed a striking variability in the current treatment of GBS. Of the patients who failed to improve after the first treatment, 35% was treated by their physician with a second therapy (IVIg or plasmapheresis or another therapy). Also striking was that 75% of patients with mild GBS were treated with IVIg or plasmapheresis. A significant proportion of the patients in these two specific situations were therefore treated although evidence for this treatment practice is currently lacking. Thus, with this study we have shown that there is significant variation in the treatment of specific situations in GBS. We can use this variation in treatment to compare the clinical course after different treatments.

In **Chapter 4.3** we investigated the possible effect of a second course of IVIg compared to one standard course of IVIg (2 g/kg in 5 days) on the disease course in patients with GBS who had a predicted poor prognosis. A poor prognosis was defined in this study as a high probability of not being able to walk independently after six months. Of the 237 patients eligible for this observational study, 199 patients received a single course of IVIg and 38 received a second course of IVIg, of which 20 in the early phase (within 1-2 weeks of starting the first course of IVIg) and 18 in late stage (started after 2-4 weeks). Patients treated with a second course were more severely affected at the start of the study and after one week than people treated with a single course. After adjusting for various prognostic factors as well as disease severity, the odds ratios for a better outcome were not increased in the second IVIg course groups (adjusted OR for the early group 0.70, 95%CI 0.16-3.04 and 0.66, 95%CI 0.18-2.50 for the late group group). The secondary endpoints also showed no positive effects of a second course of IVIg. Thus, this study showed no positive effect of a second course of IVIg on the disease course in GBS patients with a poor prognosis, although the study was limited by a treatment bias resulting in a greater probability of a second course in more severely affected patients. The study results are therefore not robust enough to exclude a positive effect of a second IVIg course.

In **Chapter 4.4** the disease course is compared in patients with mild GBS treated with one course of IVIg compared to patients who received supportive treatment. From the IGOS-1300 cohort, 188 patients with a mild form of GBS at entry (able to walk indepen-

dently) could be selected. Of these, 148 (79%) patients were treated with IVIg and 40 (21%) with supportive care. The patients in the treatment group were more severely affected than the other people at the start of the study. The adjusted odds ratio for a better outcome was not higher in the IVIg-treated group compared to the untreated group (1.62, 95% CI 0.63-4.13). The secondary endpoints also showed no positive effects of IVIg for the mild GBS patients. A subgroup analysis in patients who remained able to walk independently during the entire course of the disease also showed no difference between the two treatment groups. Interestingly, however, the time to full recovery of muscle strength was shorter in the IVIg group (28 days versus 56 days, p=0.03) but this was the only positive effect observed among many other negative endpoints. Finally, we found in this study that despite the assumption that mild GBS has a favorable course compared to the severe group, up to 40% of patients had residual symptoms after one year. Thus, this observational study showed no positive effect of IVIg in GBS patients who were relatively mildly affected. Further analyses are needed on sensitive outcome measures for patients with mild GBS. It is important to develop a better treatment for mild forms of GBS.

In **Chapter 5**, the main findings of this thesis are discussed in the context of the current literature of GBS, and is concluded with recommendations for future research.

SAMENVATTING

Het Guillain-Barré syndroom (GBS) is een heterogene aandoening wat betreft de oorzaken, presentatie van de ziekte, respons op behandeling, klinisch beloop en herstel. Tot op heden is nog niet goed bekend waar deze heterogeniteit door wordt veroorzaakt. Dit proefschrift bevat studies die de diversiteit van het klinisch beeld van GBS en de variabiliteit van de behandeling in GBS onderzoeken. Deze studies zijn grotendeels gebaseerd op real-world data die werden verzameld in de International GBS Outcome Study (IGOS).

In **Hoofdstuk 1**, de inleiding, wordt een overzicht gegeven van de bestaande kennis over de heterogeniteit van GBS en komen de huidige praktische problemen ten aanzien van de diagnose en behandeling van GBS aan bod. Tevens wordt de IGOS geïntroduceerd. Ten slotte worden de onderzoeksvragen behorende bij de studies in dit proefschrift geformuleerd.

Hoofdstuk 2 beschrijft in detail het studieprotocol van de IGOS. De IGOS is een grootschalige observationele cohortstudie naar GBS, met als doel de variatie in de klinische presentatie, behandeling, ziektebeloop en -uitkomst te beschrijven. Alle patiënten met de diagnose GBS of een variant van GBS kunnen meedoen ongeacht de leeftijd, ernst van de ziekte, variant van GBS, behandeling en beloop, zolang de patiënt toestemming heeft gegeven om aan de studie mee te doen en binnen 2 weken na het ontstaan van de zwakte (of andere uitval) kan worden geïncludeerd. In de IGOS worden gedetailleerde gegevens verzameld over de demografie, voorgeschiedenis, voorafgaande infecties, klinische klachten en verschijnselen bij presentatie en gedurende het ziektebeloop, behandeling en diagnostische kenmerken (waaronder het onderzoek naar de liquor cerebrospinalis en zenuwgeleiding). Daarnaast wordt er bij studie-entry bloed afgenomen voor onderzoek naar genetische en serologische factoren, en liquor cerebrospinalis. De patiënten blijven na de diagnose 1-3 jaar in follow-up en op vaste tijdstippen worden er klinische gegevens en serum samples verzameld. Ongeveer 160 ziekenhuizen uit 21 landen (van 5 continenten) doen mee aan de IGOS.

In **Hoofdstuk 3** worden de studies naar de kliniek van GBS beschreven. In Hoofdstuk 3.1. wordt verslag gedaan van het onderzoek gedaan naar het Miller Fisher syndroom (MFS), dat wordt beschouwd als een variant van GBS, waarbij patiënten volgens de oorspronkelijke beschrijving het klassieke trias ontwikkelen van ataxie, areflexie en ofthalmoplegie maar zonder zwakte van de ledematen. Volgens de literatuur is de prognose van MFS over het algemeen goed. Echter, bij een deel van de MFS patiënten breidt de zwakte zich uit naar de spieren van de ledematen, slikspieren en de ademhalingsspieren waardoor sommige patiënten moeten worden geïntubeerd en beademd. Het is tot nu toe niet

bekend welke MFS patiënten risico lopen om een dergelijk MFS-GBS overlap syndroom te ontwikkelen. In **Hoofdstuk 3.1** worden de resultaten van het onderzoek beschreven naar het beloop van MFS, de progressie naar een MFS-GBS overlap syndroom en naar de prognostische factoren die het klinische beloop zouden kunnen voorspellen. In deze multicenter, observationele studie waarin 170 Nederlandse patiënten met (varianten van) GBS waren geïncludeerd, kwamen 23 (14%) patiënten met het MFS voor. Hiervan ontwikkelden 10 patiënten (43%) spierzwakte van de ledematen en bij alle patiënten gebeurde dit in de eerste week na het ontstaan van de symptomen. Eén van de 10 patienten met het MFS-GBS overlap syndroom, werd respiratoir insufficiënt waardoor hij beademd moest worden. Ook dit gebeurde al vroeg in het beloop (eerste dag na ontstaan van symptomen). Er werden geen prognostische voorspellers voor het ontwikkelen van MFS-GBS overlap syndroom worden geïdentificeerd. Deze bevindingen wijzen erop dat alle patiënten met MFS het risico lopen om in de eerste week na het ontstaan van symptomen te verslechteren en daarom gedurende die periode gemonitord moeten worden. Verder werd gezien dat 39% van de MFS patiënten behandeld werden met intraveneuze immunoglobulinen (IVIg) en 61% niet. Na 6 maanden follow-up kwamen restklachten en -symptomen vaak voor; in 40% van de IVIg behandelde MFS patiënten en in 63% van de niet-behandelde MFS patiënten. Deze bevindingen impliceren dat er onderzoek gedaan moet worden naar de beste behandelstrategie voor MFS patiënten.

De variatie in de klinische presentatie en het beloop bij GBS is groot maar onbekend is welke factoren deze variatie bepalen. Publicaties uit verschillende landen suggereren dat GBS kan verschillen per regio. De gepubliceerde studies verschillen echter sterk in studie-opzet, inclusiecriteria en diagnostische criteria, waardoor deze niet goed met elkaar vergeleken kunnen worden. In **Hoofdstuk 3.2** presenteren wij de resultaten van het eerste onderzoek naar regionale verschillen in de klinische presentatie, diagnostische bevindingen, subtypes en het beloop van GBS waarbij voor alle patiënten hetzelfde studieprotocol van de IGOS werd gebruikt. Van de eerste 1000 patiënten in de IGOS moesten er 91 worden geëxcludeerd vanwege een andere diagnose, onvoldoende beschikbare data of schendingen van het studieprotocol, waardoor er 909 patiënten konden worden ingedeeld in drie regio's; 715 patiënten in Europa/Amerika's, 69 in Azië (zonder Bangladesh) en 125 in Bangladesh. In Europa/Amerika en in Azië was de meest voorkomende vorm van GBS de motorsensore variant (respectievelijk bij 69 en 43%) terwijl in Bangladesh de puur motore variant het vaakst voorkwam (69%). Ook bleek dat de MFS variant en MFS-GBS overlap variant het vaakst voorkwamen in Azië (22%) en minder vaak in Europa/Amerika (11%) en Bangladesh (1%). Verder werd in zenuwgeleidingsonderzoek aangetoond dat ook de subtypen van GBS verschilden per regio. Hoewel de demyeliniserende variant de meest voorkomende variant van GBS was in alle regio's, werd het axonale subtype vaker gezien in Bangladesh (36%) in vergelijking

met Europa/Amerika's (6%) en Azië (6%). We zagen dat onafhankelijk van de regio, de mensen met het axonale subtype jonger waren, minder sensibele stoornissen hadden en minder goed herstelden dan patiënten met het demyeliniserende subtype. De mate van herstel op één jaar na de diagnose verschilde sterk per regio, waarbij het percentage van mensen dat weer zelfstandig kon lopen na een jaar uiteenliep van 91% in Azië naar 83% in Europa/Amerika's en 69% in Bangladesh. In vergelijking met de andere regio's overleden in Bangladesh de meeste mensen aan de gevolgen van GBS (17%), gevolgd door Europa/Amerika's (5%) en Azië (2%). Deze studie met het IGOS-1000 cohort bevestigde de wereldwijde variatie van GBS wat betreft klinische varianten, ernst, neurofysiologische subtypen, klinisch beloop en herstel. De studie toonde aan dat deze variatie waarschijnlijk deels wordt beïnvloed door regionale verschillen in demografie, voorafgaande infecties en behandeling.

Hoofdstuk 4 richt zich op de behandeling van GBS. In **hoofdstuk 4.1** wordt een overzicht gegeven van behandeldilemma's en wordt er behandeladvies gegeven op basis van de beschikbare literatuur en expert opinie. **Hoofdstuk 4.2** geeft een overzicht van de huidige behandelpraktijk bij GBS, gebaseerd op de eerste 1.300 patiënten die deelnamen aan de IGOS, van wie 1.023 patiënten konden worden gebruikt voor het onderzoek. De resultaten toonden een opvallende variabiliteit in de huidige behandeling van GBS. Van de patiënten die niet verbeterden na de eerste behandeling, werd 35% door hun arts behandeld met een tweede therapie (IVIg of plasmaferese of een andere therapie). Opvallend was ook dat 75% van de patiënten met milde GBS werd behandeld met IVIg of plasmaferese. Een aanzienlijk deel van de patiënten in deze twee specifieke situaties werd daarom behandeld, hoewel bewijs voor deze behandelpraktijk momenteel ontbreekt. Met deze studie hebben we dus aangetoond dat er significante variatie is in de behandeling van specifieke situaties bij GBS. Deze variatie in behandeling kunnen we gebruiken om het klinisch beloop na verschillende behandelingen te vergelijken.

In **Hoofdstuk 4.3** hebben we onderzocht wat het effect is van een tweede IVIg kuur in vergelijking met één IVIg kuur (2 g/kg in 5 dagen) op het ziektebeloop bij patiënten met GBS die een voorspelde slechte prognose hadden. Een slechte prognose werd in deze studie gedefinieerd als een hoge kans om niet zelfstandig te kunnen lopen na zes maanden. Van de 237 patiënten die in aanmerking kwamen voor deze observationele studie, hadden 199 patiënten een enkele IVIg kuur gekregen en 38 een tweede IVIg kuur, waarvan 20 in de vroege fase (binnen 1-2 weken na het starten van de eerste IVIg kuur) en 18 in de late fase (gestart na 2-4 weken). Mensen die met een tweede kuur waren behandeld, waren ernstiger aangedaan aan het begin van de studie en na één week dan mensen die met een enkele kuur waren behandeld. Na correctie voor verschillende prognostische factoren alsook de ernst van de ziekte, bleek dat de odds ratio's op een

betere uitkomst niet verhoogd waren in de tweede IVIg kuur groepen (adjusted OR voor de vroege groep 0.70, 95%CI 0.16-3.04 en voor de late groep 0.66, 95%CI 0.18-2.50). Ook de secundaire eindpunten lieten geen positieve effecten zien van een tweede IVIg kuur. Deze studie toonde dus geen positief effect van een tweede IVIg kuur op het ziektebeloop bij GBS patiënten met een slechte prognose, al werd de studie beperkt door een behandelbias waarbij patiënten met een ernstiger beloop een grotere kans hadden op een tweede kuur dan patiënten met een beter beloop. De studieresultaten zijn dus niet robuust genoeg om een positief effect van een tweede IVIg kuur uit te sluiten.

In **Hoofdstuk 4.4** wordt het ziektebeloop vergeleken van patiënten met een milde vorm van GBS, die werden behandeld met één IVIg kuur of alleen ondersteunende behandeling. Uit het IGOS-1300 cohort konden 188 patiënten worden geselecteerd met een milde vorm van GBS, die zelfstandig konden lopen op het moment dat ze mee gingen doen aan de studie. Hiervan werden 148 (79%) patiënten behandeld met IVIg en 40 (21%) met ondersteunende therapie. De patiënten in de behandelde groep waren ernstiger aangedaan dan de andere mensen aan het begin van de studie. De gecorrigeerde odds ratio op een betere uitkomst was niet hoger in de IVIg-behandelde groep ten opzichte van de onbehandelde groep (1.62, 95% CI 0.63-4.13). De secundaire eindpunten lieten ook geen positieve effecten van IVIg zien voor de milde GBS patiënten. Ook een subgroep analyse bij patiënten die gedurende het gehele ziektebeloop in staat bleven om zelfstandig te blijven lopen toonde geen verschil tussen de twee behandelgroepen. Deze observationele studie toonde dus geen positief effect van IVIg in GBS patiënten die relatief mild waren aangedaan. Opvallend was echter, dat de tijd tot volledig herstel van spierkracht korter was in de IVIg-groep (28 dagen versus 56 dagen, p=0.03). Deze bevinding laat zien dat IVIg mogelijk de duur tot herstel verkort. Eén van de conclusies van deze studie was dan ook dat er verdere analyses nodig zijn naar gevoelige uitkomstmaten voor patiënten met een milde GBS. Ten slotte vonden we in deze studie dat ondanks de veronderstelling dat een milde GBS een gunstig beloop kent ten opzichte van de ernstige groep, tot wel 40% van de patiënten restverschijnselen had na één jaar. Ook voor milde vormen van GBS is het dus van belang om een betere behandeling te ontwikkelen.

In **Hoofdstuk 5** worden de belangrijkste bevindingen van dit proefschrift besproken in de context van de hedendaagse kennis van GBS, waarna er wordt afgesloten met aanbevelingen voor toekomstig onderzoek.

7

Epilogue

DANKWOORD

Dit proefschrift was nooit tot stand gekomen zonder de hulp van velen, van wie ik een aantal mensen persoonlijk wil bedanken.

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ABOUT THE AUTHOR

Christine Verboon was born on November 28th 1985 in Dirksland, the Netherlands. She studied Medicine and Philosophy of Medicine at the Erasmus University in Rotterdam. After she obtained her medical degree in 2011, she started her neurology training at the Neurology department of the Erasmus medical center in Rotterdam (head: prof. dr. P.A.E. Sillevis Smitt and dr. J.E.C. Bromberg). One year later, she started a PhD trajectory under supervision of prof. dr. B.C. Jacobs. She was awarded with the John W. Griffin price for the presentation on immunoglobulin treatment for patients with mild Guillain-Barré syndrome at the conference of the Inflammatory Neuropathy Consortium in Glasgow, 2016. After finishing her neurology training in December 2021, she works as neurologist at the Albert Schweitzer hospital in Dordrecht. She lives in Rotterdam with her husband Matthijs van der Burg and their two sons Quint and Dorus.

PHD PORTFOLIO

Courses	Year	ECTS
Scientific Integrity	2014	0.3
Biostatistics for Clinicians (NIHES)	2014	4.5
Regression Analysis for Clinicians (NIHES)	2014	4.5
Basiscursus Regelgeving en Klinisch Onderzoek (BROK)	2015	1.4
Biomedical English writing and communication	2016	3.0
Introduction in GraphPad Prism Version 6	2017	0.5
Oral presentations		
GBS workshop (1 presentation)	2014	1.0
Inflammatory neuropathy consortium congress (4 presentations)	2014, 2016	4.0
Peripheral nerve society congress (5 presentations)	2017, 2018	5.0
Muscle disease congress (2 presentations)	2016, 2017	2.0
Referaat afdeling neurologie, Erasmus MC (2 presentations)	2014, 2018	2.4
Poster presentations		
Wetenschappelijke vergadering (NVN) (2 posters)	2014, 2016	2.0
Peripheral nerve society congress (4 posters)	2015, 2017, 2019, 2020	4.0
(Inter)national conferences		
Boerhaave neuromuscular courses	2014, 2015, 2017, 2018, 2021	1.5
Teaching		
Teaching nurses	2012-2017	0.5
Teaching medical students (vaardigheidsonderwijs Spierzwakte)	2014, 2021	0.5
Supervising Master students (2 students)	2014, 2016	3.0
Other		
Article reviews (3 articles)	2017-2021	0.5
Total		**40.6**

LIST OF PUBLICATIONS

1. **Verboon C**, van Doorn, PA, Jacobs, BC. Treatment dilemmas in Guillain-Barré syndrome. Journal of Neurology, Neurosurgery and Psychiatry 2016;0:1-7.

2. **Verboon C**, van Berghem, H, van Doorn, PA, Ruts, L, Jacobs, BC. Prediction of disease progression in Miller Fisher and overlap syndromes. Journal of the Peripheral Nervous System 2017; 22:446-450.

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4. Doets AY*, **Verboon C***, van den Berg B*, Harbo T, Cornblath DR, Willison HJ, Islam Z, Attarian S, Barroso FA, Bateman K, Benedetti L, Van den Bergh P, Casasnovas C, Cavaletti G, Chavada C, Claeys KG, Dardiotis E, Davidson E, van Doorn PA, Feasby TE, Galassi G, Gorson KC, Hartung HP, Hsieh ST, Hughes RAC, Illa I, Islam B, Kusunoki S, Kuwabara S, Lehmann HC, Miller JAL, Mohammad QD, Monges S, Nobile Orazio E, Pardo J, Pereon Y, Rinaldi S, Querol L, Reddel SW, Reisin RC, Shahrizaila N, Sindrup SH, Waqar W, Jacobs BC, the IGOS consortium. Regional variation of Guillain-Barré syndrome. Brain 2018, 141; 2866-2877.

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8. 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.

9. **Verboon C**, van den Berg B, Cornblath DR, Venema E, Gorson KC, Lunn MP, Lingsma H, Van Den Bergh P, Harbo T, Bateman K, Péréon Y, Sindrup SS, Kusunoki S, Miller J, Islam Z, Hartung HP, Chavada G, Jacobs BC, Hughes RAC, van Doorn PA, the IGOS Consortium. Second IVIg course in Guillain-Barré syndrome with poor prognosis: the non-randomised ISID study. Journal of Neurology, Neurosurgery and Psychiatry 2019;0:1–9.

10. **Verboon C**, Harbo T, Cornblath DR, Hughes RAC, van Doorn PA, Lunn MP, Gorson KC, Barroso F, Kuwabara S, Galassi G, Lehmann HC, Kusunoki S, Reisin RC, Binda D, Cavaletti G, Jacobs BC, the IGOS consortium. Intravenous immunoglobulin treatment for mild Guillain-Barré syndrome: an observational prospective international study. Journal of Neurology, Neurosurgery and Psychiatry. 2021 Oct;92(10):1080-1088.

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.

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13. Peeters LEJ, van Oortmerssen JAE, Derks LH, den Hertog H, Fonville S, **Verboon C**, Rietdijk WJR, Boersma E, Koudstaal PJ, van den Meiracker AH, Versmissen J. Comparison of automated office blood pressure measurement with 24-hour ambulatory blood pressure measurement. Blood Press. 2022 Dec;31(1):9-18.

14. Doets AY, Lingsma HF, Walgaard C, Islam B, Papri N, Davidson A, Yamagishi Y, Kusunoki S, Dimachkie M, Waheed W, Kolb N, Islam Z, Mohammad QD, Harbo T, Sindrup SS, Chavada G, Willison HJ, Casasnovas C, Bateman K, Miller JAL, van den Berg B, **Verboon C**, Roodbol J, Leonhard SE, Benedetti L, Kuwabara S, Van den Bergh P, Monges S, Marfia GA, Shahrizaila N, Galassi G, Péréon Y, Bürmann J, Kuitwaard K, Kleyweg RP, Marchesoni C, Sedano Tous MJ, Querol L, Illa I, Wang Y, Nobile Orazio E, Rinaldi S, Schenone A, Pardo J, Vermeij FH, Lehmann HC, Granit V, Cavaletti G, Gutiérrez-Gutiérrez G, Barrosso FA, Visser LH, Katzberg HD, Dardiotis E, Attarian S, van der Kooi AJ, Eftimov F, Wirtz PW, Samijn JPA, Gilhuis J, Hadden RDM, Holt JKL, Sheikh KA, Karafiath S, Vytopil M, Antonini G, Feasy TE, Faber CG, Gijsbers CJ, Busby M, Roberts RC, Silvestri NJ, Fazio R, van Dijk GW, Garssen MPJ, Chiara SM, Gorson KC, Jacobs BC, IGOS consortium. Predicting Outcome in Guillain-Barré Syndrome: International Validation of the Modified Erasmus GBS Outcome Score. Neurology. 2022 Feb 1;98(5):e518-e532.