

# 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 1,300 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) variant 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. IV immunoglobulin (IVIg), plasma exchange (PE), or other immunotherapy was provided in 941 (92%) of the remaining 1,023 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 1,023 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.

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## Glossary

**GBS** = Guillain-Barré syndrome; **IGOS** = International GBS Outcome Study; **IQR** = interquartile range; **IVIg** = IV immunoglobulin; **MFS** = Miller Fisher syndrome; **MP** = methylprednisolone; **MRC** = Medical Research Council; **PCB** = pharyngeal-cervical-brachial weakness; **PE** = plasma exchange; **RCT** = randomized controlled trial; **SID-GBS** = Second Immunoglobulin Dose in GBS trial; **TRF** = treatment-related fluctuation.

Plasma exchange (PE) and IV 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.<sup>1,2</sup> 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.<sup>1–3</sup> 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).<sup>4,5</sup> 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.<sup>6</sup> In some patients, there can be subsequent deterioration after initial stabilization or recovery, a phenomenon referred to as treatment-related fluctuation (TRF).<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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 1,300 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 electrophysiologic subtype (demyelinating vs 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.<sup>9–11</sup>

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  $\geq 3$ ) and mild GBS as being able to walk independently at nadir (GBS disability score  $< 3$ ).<sup>12</sup> 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. Electrophysiologic subtypes were defined by the first nerve conduction study based on local reference values and the Hadden et al.<sup>13</sup> criteria.

### Data collection

We collected data on demographics (age, sex, country of residence) and clinical characteristics including disease severity (GBS disability score, limb weakness, sensory deficits, facial, bulbar, and oculomotor weakness, pain, and autonomic dysfunction) at entry and 1, 2, and 4 weeks follow-up. Documentation 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).<sup>14</sup> The disability caused by GBS was defined by the highest GBS disability score in the first 4 weeks after study entry (nadir), ranging from 0 (healthy) to 6 (dead).<sup>15</sup> 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 trial [SID-GBS]<sup>16</sup> and Inhibition of Complement Activation in GBS trial [ICA-GBS]<sup>17</sup>) 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 2 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 (SPSS Inc., Chicago, IL). 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  $\chi^2$  or Fisher exact tests. A 2-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 1,300 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 1,212 (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 PE, 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 1,023 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 2 weeks in 18 (2%) patients, and after 4 weeks in 5 (1%) patients. A total IVIg dosage of 2 g/kg body weight 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 1,001 administered IVIg courses, methylprednisolone (MP) was used as add-on treatment. Sixty-seven patients (7%) were initially treated with PE within a median of 6 days (IQR 3–9) after onset of symptoms. Most

patients underwent 5 PE sessions (*n* = 47, 70%). Others received 2 sessions (*n* = 2, 3%), 3 sessions (*n* = 2, 3%), 4 sessions (*n* = 9, 13%), 6 sessions (*n* = 6, 9%), or 7 sessions (*n* = 1, 1%). The PE sessions were performed during a median of 8 days (IQR 6–9, range 2–16).

Eight (1%) patients were initially treated with other treatments, such as monotherapy with corticosteroids (*n* = 5) or immunoadsorption (*n* = 3). Of the 5 patients initially treated with corticosteroids only, one received an additional course of IVIg, and one received 2 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 MFS or another local variant (sensory ataxic GBS, *n* = 6; pharyngeal-cervical-brachial variant, *n* = 1).

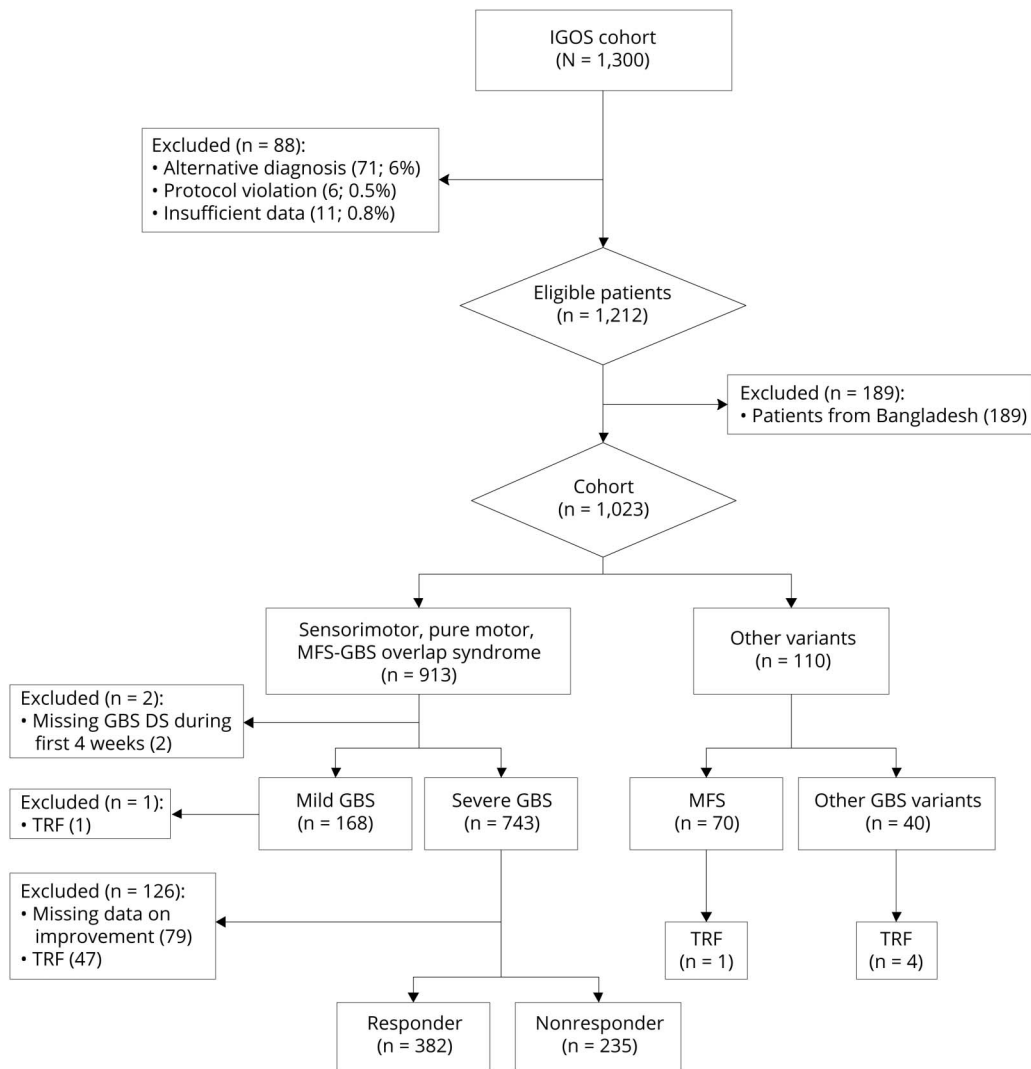
### Treatment of severe GBS

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 the United States (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 vs 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 4 weeks as compared to demyelinating GBS.

### 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). The proportion of patients who received a second immunotherapy did not differ between university (*n* = 59/179, 33%) and non-university hospitals (*n* = 23/56, 41%, *p* = 0.27). Of the 211 IVIg-treated patients without initial clinical improvement, 73 (35%) received additional immunotherapy. Most patients received a second course of IVIg (*n* = 48, 66%), which was started at median 12 days (IQR 8–17) after completing the first IVIg course. In other IVIg-treated patients, the treating physician switched to PE (*n* = 22, 30%), which was started within 2 weeks after completing IVIg in 17 (77%) of the 22 patients (median 6

**Figure 1** Patient and study cohort



Nonresponder was defined as worsening or failure to improve by at least one grade on the Guillain-Barré syndrome (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).<sup>27</sup> Other GBS variants = pharyngeal-cervical-brachial, sensory ataxic, Bickerstaff brainstem encephalitis, and bilateral facial weakness. GBS DS = GBS disability score; IGOS = International GBS Outcome Study; MFS = Miller Fisher syndrome; TRF = treatment related fluctuation.

days, IQR 3–13). Three other IVIg-treated patients received other forms of immunotherapy. Twenty-three (11%) of 211 IVIg-treated patients received a third, fourth, or fifth immunotherapy (figure 3).

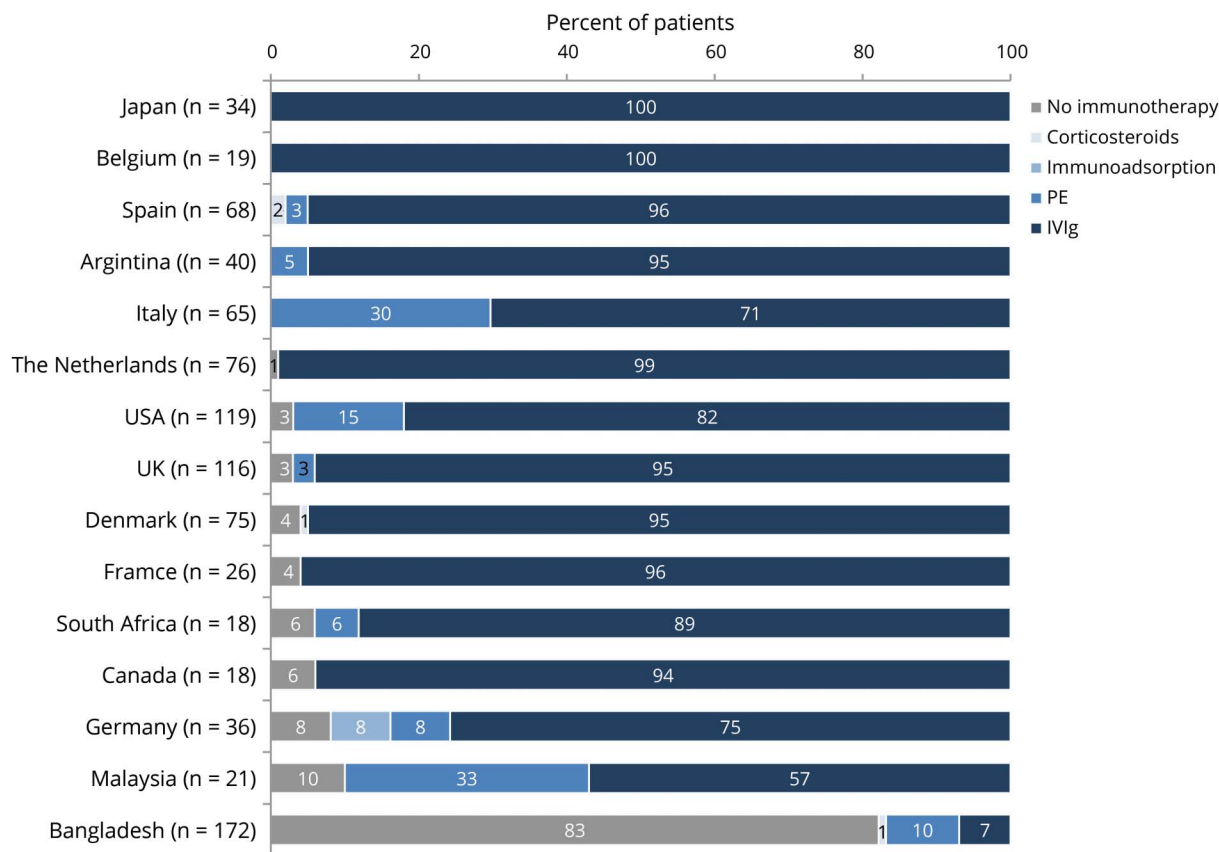
Of the 17 PE-treated patients not showing clinical recovery in the first 4 weeks, 8 (47%) received additional immunotherapy. In 7 (41%) of these, the treating physician switched to IVIg after a median time of 2 days (IQR 1–4) after completing PE. One (6%) patient was re-treated with a second round of PE sessions. Three (18%) of 17 PE-treated patients received a third immunotherapy (figure 3).

### Treatment of TRFs

A TRF occurred in 53 (5%) of 1,023 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 4 (8%) other patients, the physician switched treatment from IVIg to PE. Of the 3 patients initially treated with PE, one was retreated with IVIg. The remaining 17 (32%) patients received no treatment for their TRF. In patients who were re-treated for their TRF, the TRF occurred at an earlier time point than in untreated patients (median time to TRF after start of initial treatment [IQR]: treated 21 days [14–27], untreated 32 days [25–54],  $p = 0.008$ ). In addition, a higher proportion of treated patients was unable to walk independently around the time of the TRF (treated  $n = 33/36$  [92%], untreated  $n = 10/17$  [59%];  $p = 0.008$ ), and the MRC sum score was lower (median MRC sum score [IQR]: treated 41 [18–51], untreated 49 [43–60];  $p = 0.019$ ). Finally, patients admitted to a university hospital were more often re-

**Figure 2** Country-specific initial treatment of severely affected patients with Guillain-Barré syndrome (GBS)



This figure contains data from countries that have included at least 10 patients in the International GBS Outcome Study (IGOS). IVIg = IV immunoglobulin; PE = plasma exchange.

treated for their TRF (n = 31/39, 80%) 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) (Americas vs Europe  $p = 0.32$ , Americas vs Asia  $p = 0.68$ ). The subgroup of patients with mild GBS receiving immunotherapy more often had autonomic dysfunction in the first 4 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 vs 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 4 weeks after study entry. There was no difference in treatment provided by university (n = 97/132, 74%) vs 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 vs Asia  $p = 0.03$ , America vs 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 pharyngeal-cervical-brachial weakness [PCB], 2 Bickerstaff

**Table** Regional differences in treatment of subgroups of patients with Guillain-Barré syndrome (GBS)

Clinical situation and treatment	Full cohort (n = 1,023)	Europe (n = 664)	America (n = 238)	Asia <sup>a</sup> (n = 88)
<b>Severe GBS</b>	n = 743	n = 485	n = 177	n = 57
<b>IVIg</b>	662 (89)	442 (91)	152 (86)	46 (81)
<b>PE</b>	56 (8)	27 (6)	20 (11)	9 (16)
<b>Other</b>	6 (1)	5 (1)	0 (0)	0 (0)
<b>None</b>	19 (3)	11 (2)	5 (3)	2 (4)
<b>Nonimproving</b>	n = 235	n = 159	n = 55	n = 15
<b>Second immunotherapy<sup>b</sup></b>	82 (35)	50 (31)	26 (47)	6 (40)
<b>TRF</b>	n = 53	n = 45	n = 7	n = 0
<b>Second immunotherapy<sup>2,b</sup></b>	36 (68)	31 (69)	5 (71)	na
<b>Mild GBS</b>	n = 168	n = 112	n = 39	n = 12
<b>IVIg</b>	121 (72)	80 (71)	31 (79)	8 (67)
<b>PE</b>	5 (3)	3 (3)	1 (3)	1 (8)
<b>None</b>	42 (25)	29 (26)	7 (18)	3 (25)
<b>MFS</b>	n = 70	n = 38	n = 18	n = 11
<b>IVIg</b>	49 (70)	30 (79)	12 (67)	6 (55)
<b>PE</b>	2 (3)	1 (3)	1 (6)	0 (0)
<b>Other</b>	2 (3)	2 (5)	0 (0)	0 (0)
<b>None</b>	17 (24)	5 (13)	5 (28)	5 (46)

Abbreviations: IVIg = IV immunoglobulin; MFS = Miller Fisher syndrome; PE = plasma exchange; TRF = treatment-related fluctuation. Values are n (%).

<sup>a</sup> Asia not including Bangladesh.

<sup>b</sup> Consisting of IVIg, PE, or corticosteroids alone.

brainstem encephalitis, 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% vs adults n = 31/775, 4%) than a 5-day regimen (children n = 24/54, 44% vs 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.

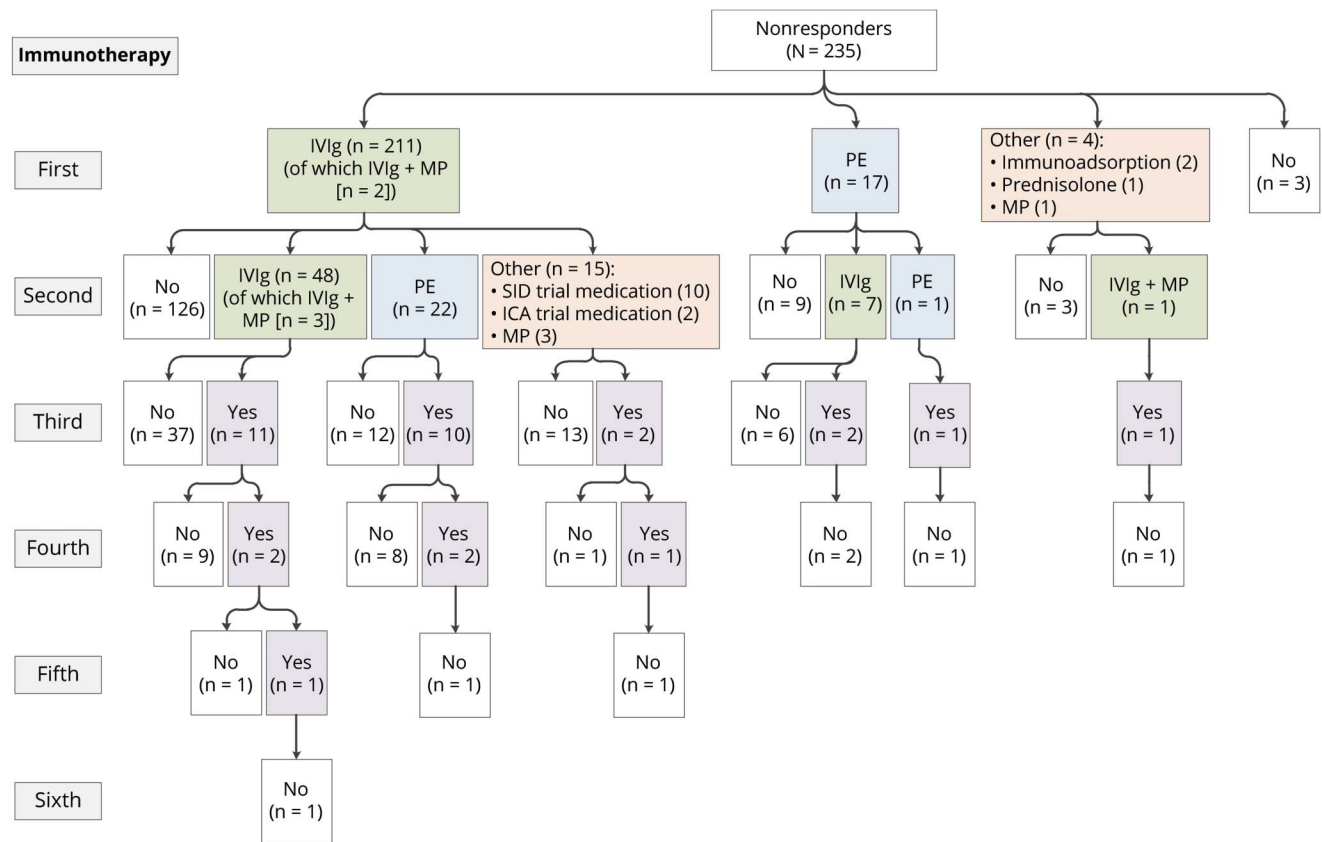
### Discussion

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 (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 2 g/kg body weight 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- and 2-day regimen in children indicated that a 2-day regimen is equally effective, but is more frequently followed by a TRF.<sup>18</sup> Methylprednisolone was provided as

**Figure 3** Treatment of patients with a severe form of Guillain-Barré syndrome (GBS) not responding to initial treatment



Treatment of 235 patients with a severe form of GBS who showed no improvement after initial treatment. ICA-GBS = Inhibition of Complement Activation in GBS trial; IVIg = IV immunoglobulins; MP = methylprednisolone; PE = plasma exchange; SID-GBS = Second Immunoglobulin Dose in GBS trial.

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.<sup>7,19</sup> 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 contraindications to IVIg, the availability of resources, health care insurance, or protocols.<sup>1-3,20,21</sup> 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 4 sessions were better than 2, but equally effective to 6 sessions in relation to time to walk with aid and time on a ventilator.<sup>12</sup> Immunoabsorption was instituted only in Germany, where 2 immunoabsorption trials were conducted. This may explain why the use was limited to German centers, in addition to reimbursement differences and costs.<sup>22,23</sup> Some patients were treated with corticosteroids only, even though this treatment is considered ineffective for GBS.<sup>24</sup> 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.<sup>9,10</sup> Low-cost alternative treatments for GBS are required and small volume plasma exchange is currently under investigation.<sup>25</sup>

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% 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.<sup>11</sup> The efficacy of a second course of IVIg is yet unknown, but is currently investigated in SID-GBS trial.<sup>16</sup> In some of these patients initially treated with IVIg, the treating physician switched to PE, which was often started within 2 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 of this early secondary treatment with PE is that IVIg is washed out and cannot further contribute to the recovery.<sup>7</sup> Other patients were treated with PE followed by IVIg. Previously, an RCT comparing PE or IVIg alone to PE

followed by IVIg showed no difference in outcome.<sup>20</sup> This trial was 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.<sup>11</sup> 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 vs 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.<sup>3,7</sup> 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 patients with GBS 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.<sup>12</sup> Moreover, more than three-quarters 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.<sup>26</sup> 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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## Disclosure

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scientific or medical advice to Johnson & Johnson, Janssen Vaccines AG, Syntimmune, Hansa Medical, and Minnetronix, and received funding to support meeting costs from Baxalta, CSL Behring, Grifols, Kendrion SpA, LFB Biomedicaments, Octapharma, TEVA, Buhlmann Laboratories, and Syntimmune. D. Cornblath is a consultant for Acetylon, Alcobra Pharma, Alnylam Pharmaceuticals, Annexon Biosciences, Akros Pharma, Biotest Pharmaceuticals, Boehringer Ingelheim, Cigna Health Management, CSL Behring, DP Clinical, Grifols, Hansa Medical, Karos Pharmaceuticals, Neurocrine Biosciences, Novartis, Octapharma, Pharnext, Seattle Genetics, Sun Pharmaceuticals, and Syntimmune; is on the data and safety monitoring board for Sanofi, Pledpharma, Pfizer, Johnson & Johnson, Ionis Pharmaceuticals, GlaxoSmithKline, and Axovant Sciences; has licensed technology for the Total Neuropathy Score for Acetylon, AstraZeneca, Calithera Biosciences, Genentech, Neurocrine Biosciences, Merrimack Pharmaceuticals, Seattle Genetics, and Shire Development Inc.; and is on the Board of Directors for the Peripheral Nerve Society. B. Jacobs has received funding for research projects from Prinses Beatrix Spierfonds, Horizon 2020, GBS-CIDP Foundation International, Grifols, CSL Behring, and Annexon; is on the Medical Advisory Board for the GBS-CIDP Foundation International; and is a member of the Inflammatory Neuropathy Consortium. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

## Publication history

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## Appendix 1 Authors

Name	Location	Role	Contribution
<b>Christine Verboon, MD</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content, member of the IGOS Coordinating Centre, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Alex Y. Doets, MD</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content, member of the IGOS Coordinating Centre, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Giuliana Galassi, MD</b>	University Hospital of Modena, Italy	Author	Interpreted the data, revised the manuscript for intellectual content, patient inclusion, acquisition of data

## Appendix 1 (continued)

Name	Location	Role	Contribution
<b>Amy Davidson, MD</b>	University of Glasgow, UK	Author	Interpreted the data, revised the manuscript for intellectual content, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Waqar Waheed, MD</b>	University of Vermont Medical Center, Burlington	Author	Interpreted the data, revised the manuscript for intellectual content, patient inclusion, acquisition of data
<b>Yann Péreon, MD, PhD</b>	Reference Centre for NMD, Nantes University Hospital, France	Author	Interpreted the data, revised the manuscript for intellectual content, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Nortina Shahrizaila, FRCP, PhD</b>	University of Malaya, Kuala Lumpur, Malaysia	Author	Interpreted the data, revised the manuscript for intellectual content, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Susumu Kusunoki, MD, PhD</b>	Kindai University Faculty of Medicine, Osaka, Japan	Author	Interpreted the data, revised the manuscript for intellectual content, member of the IGOS Steering Committee, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Helmar C. Lehmann, MD, PhD</b>	University Hospital of Cologne, Universitätsklinikum Köln, Germany	Author	Interpreted the data, revised the manuscript for intellectual content, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Thomas Harbo, MD, PhD</b>	Aarhus University Hospital, Denmark	Author	Interpreted the data, revised the manuscript for intellectual content, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>Soledad Monges, MD</b>	Hospital de Pediatría J.P. Garrahan, Buenos Aires, Argentina	Author	Interpreted the data, revised the manuscript for intellectual content, patient inclusion, acquisition of data
<b>Peter Van den Bergh, MD, PhD</b>	University Hospital St-Luc, University of Louvain, Brussels, Belgium	Author	Interpreted the data, revised the manuscript for intellectual content, IGOS Country Coordinator, patient inclusion, acquisition of data

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## Appendix 1 (continued)

Name	Location	Role	Contribution
<b>Hugh J. Willison, MD, PhD</b>	University of Glasgow, UK	Author	Interpreted the data, revised the manuscript for intellectual content, member of the IGOS Steering Committee, IGOS Country Coordinator, patient inclusion, acquisition of data
<b>David R. Cornblath, MD</b>	Johns Hopkins University School of Medicine, Baltimore, MD	Author	Interpreted the data, revised the manuscript for intellectual content, member of the IGOS Steering Committee, patient inclusion, acquisition of data
<b>Bart C. Jacobs, MD, PhD</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Author	Designed and conceptualized study, drafted the manuscript for intellectual content, member of the IGOS Steering Committee, member of the IGOS Coordinating Centre, IGOS Country Coordinator, patient inclusion, acquisition of data

## Appendix 2 Coinvestigators

Name	Location	Role	Contribution
<b>R.A.C. Hughes, MD</b>	MRC Centre for Neuro-muscular Diseases, National Hospital for Neurology and Neurosurgery, London, UK	Coinvestigator	Member of the IGOS Steering Committee
<b>K.C. Gorson, MD</b>	St. Elizabeth's Medical Centre, Tufts University School of Medicine, Boston, MA	Coinvestigator	Member of the IGOS Steering Committee, IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>H.P. Hartung, MD, PhD</b>	University of Düsseldorf, Germany	Coinvestigator	Member of the IGOS Steering Committee, IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>P.A. Van Doorn, MD, PhD</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Coinvestigator	Member of the IGOS Steering Committee, patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>B. Van den Berg, MD</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Coinvestigator	Member of the IGOS Coordinating Centre, foundation and maintenance of the study, coordination of communication among countries and sites, data processing and management, IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>J. Roodbol, MD</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Coinvestigator	Member of the IGOS Coordinating Centre, foundation and maintenance of the study, coordination of communication among countries and sites, data processing and management, patient inclusion, acquisition of data
<b>M. Van Woerkom, Research Coordinator IGOS</b>	Erasmus MC, University Medical Center Rotterdam, the Netherlands	Coinvestigator	Member of the IGOS Coordinating Centre, foundation and maintenance of the study, coordination of communication among countries and sites, data processing and management, patient inclusion, acquisition of data
<b>R.C. Reisin, MD</b>	Hospital Britanico, Buenos Aires, Argentina	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>S.W. Reddel, MD, PhD</b>	Concord Repatriation General Hospital, Sydney, Australia	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>Z. Islam, PhD</b>	International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>B. Islam, MD</b>	International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>Q.D. Mohammad, MD, PhD</b>	National Institute of Neurosciences and Hospital, Dhaka, Bangladesh	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>T.E. Feasby, MD</b>	University of Calgary, Canada	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>E. Dardiotis, MD</b>	University of Thessaly, Hospital of Larissa, Greece	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>E. Nobile-Orazio, MD, PhD</b>	Milan University, Humanitas Clinica and Research Institute Milan, Italy	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>K. Bateman, MD</b>	Groote Schuur Hospital, University of Cape Town, South Africa	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>I. Illa, MD, PhD</b>	Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>L. Querol, MD, PhD</b>	Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>S.T. Hsieh, MD, PhD</b>	National Taiwan University Hospital, Taipei	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data
<b>G. Chavada, MD</b>	University of Glasgow, UK	Coinvestigator	IGOS Country Coordinator, led and coordinated communication among sites, patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>J.M. Addington, MD</b>	University of Virginia, Charlottesville	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Ajroud-Driss, MD</b>	Northwestern University Feinberg, Chicago, IL	Coinvestigator	Patient inclusion, acquisition of data
<b>H. Andersen, MD, PhD</b>	Aarhus University Hospital, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>G. Antonini, MD</b>	Department of Neuroscience, Mental Health and Sensory Organs (NESMOS), Sapienza University, Sant'Andrea Hospital, Rome, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Ariatti, MD</b>	University Hospital of Modena, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Attarian, MD PhD</b>	CHU Timone, Marseille, France	Coinvestigator	Patient inclusion, acquisition of data
<b>U.A. Badrising, MD, PhD</b>	Leiden University Medical Centre, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>F.A. Barroso, MD</b>	Instituto de Investigaciones Neurológicas Raúl Carrea, FLENI, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>L. Benedetti, MD, PhD</b>	Ospedale Sant'Andrea La Spezia, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Beronio, MD</b>	Ospedale Sant'Andrea La Spezia, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Bianco, MD</b>	Milan University, Humanitas Clinica and Research Institute Milan, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>D. Binda, MD</b>	Valduce Hospital, Como; University of Milano-Bicocca, Monza, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Briani, MD</b>	University of Padova, Italy	Coinvestigator	Patient inclusion, acquisition of data

Continued

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>C. Bunschoten, MD</b>	Erasmus University Medical Centre, Rotterdam, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>J. Bürmann, MD</b>	Universitätsklinikum des Saarlandes, Homburg, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>I.R. Bella, MD</b>	University of Massachusetts Medical School, Worcester	Coinvestigator	Patient inclusion, acquisition of data
<b>T.E. Bertorini, MD</b>	The University of Tennessee Health Science Center (UTHSC), Memphis	Coinvestigator	Patient inclusion, acquisition of data
<b>R. Bhavaraju-Sanka, MD</b>	University Hospital/ University of Texas Health Science Center, San Antonio	Coinvestigator	Patient inclusion, acquisition of data
<b>T.H. Brannagan, MD</b>	Columbia University, New York, NY	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Busby, MD</b>	Leeds General Infirmary, Bradford, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Butterworth, MD</b>	Pinderfields Hospital, Wakefield, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Casasnovas, MD, PhD</b>	Bellvitge University Hospital Neurologic Diseases and Neurogenetics Group; Bellvitge Biomedical Research Institute (IDIBELL); Faculty of Medicine, University of Barcelona, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>G. Cavaletti, MD</b>	University Milano-Bicocca, Monza, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>C.C. Chao, MD, PhD</b>	National Taiwan University Hospital, Taipei	Coinvestigator	Patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>S. Chen, MD, PhD</b>	Rutgers, Robert Wood Johnson University Hospital, New Brunswick, NJ	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Chetty, MD</b>	Groote Schuur Hospital, University of Cape Town, South Africa	Coinvestigator	Patient inclusion, acquisition of data
<b>K.G. Claeys, MD, PhD</b>	University Hospitals Leuven; KU Leuven, Belgium	Coinvestigator	Patient inclusion, acquisition of data
<b>M.E. Conti, MD</b>	University Hospital Clinicas, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>J.S. Cosgrove, MD</b>	Leeds General Infirmary, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>M.C. Dalakas, MD</b>	Thomas Jefferson University, Philadelphia, PA; National and Kapodistrian University of Athens, Greece	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Demichelis, MD</b>	University of Genova, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>M.A. Derejko, MD, PhD</b>	Odense University Hospital, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>U. Dillmann, MD</b>	Universitätsklinikum des Saarlandes, Homburg, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>M.M. Dimachkie, MD</b>	University of Kansas Medical Center, Kansas City	Coinvestigator	Patient inclusion, acquisition of data
<b>K. Doppler, MD</b>	Universitätsklinikum Würzburg, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Dornonville de la Cour, MD</b>	National Hospital Copenhagen, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Echaniz-Laguna, MD</b>	Hopital de Haute-pierre, Strasbourg, France	Coinvestigator	Patient inclusion, acquisition of data

**Appendix 2** (continued)

Name	Location	Role	Contribution
<b>F. Eftimov, MD, PhD</b>	Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience Institute, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>C.G. Faber, MD, PhD</b>	Maastricht University Medical Centre, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>R. Fazio, MD</b>	Scientific Institute San Raffaele, Milan, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Fokke, MD</b>	Gelre Hospital, Zutphen and Apeldoorn, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>T. Fujioka, MD</b>	Toho University Medical Center, Japan	Coinvestigator	Patient inclusion, acquisition of data
<b>E.A. Fulgenzi, MD</b>	Hospital Cesar Milstein Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>T. Garcia-Sobrinho, MD</b>	Hospital Clínico de Santiago, Santiago de Compostela (A Coruña), Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>M.P.J. Garssen, MD, PhD</b>	Jeroen Bosch Hospital's Hertogenbosch, Zaltbommel and Drunen, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>H.M. Georgios, MD</b>	University of Thessaly, Hospital of Larissa, Greece; Medical School, University of Cyprus, Nicosia	Coinvestigator	Patient inclusion, acquisition of data
<b>C.J. Gijbsbers, MD</b>	Vlietland Hospital, Schiedam, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>J.M. Gilchrist, MD</b>	Southern Illinois University School of Medicine, Springfield	Coinvestigator	Patient inclusion, acquisition of data

**Appendix 2** (continued)

Name	Location	Role	Contribution
<b>J. Gilhuis, MD</b>	Reinier de Graaf Gasthuis, Delft, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>E. Giorli, MD</b>	Ospedale Sant'Andrea La Spezia, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>J.M. Goldstein, MD</b>	Neurology, Neuro-muscular Diseases, Electromyography, Hospital for Special Surgery, New York; Weill Medical College of Cornell University, New York, NY	Coinvestigator	Patient inclusion, acquisition of data
<b>N.A. Goyal, MD</b>	University of California, Irvine	Coinvestigator	Patient inclusion, acquisition of data
<b>V. Granit, MD</b>	Montefiore Medical Center, New York, NY	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Grapperon, MD</b>	CHU Timone, Marseille, France	Coinvestigator	Patient inclusion, acquisition of data
<b>G. Gutiérrez, MD</b>	Hospital Universitario Infanta Sofia, San Sebastian, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>R.D.M. Hadden, MD, PhD</b>	King's College Hospital, London, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>J.V. Holbech, PhD</b>	Odense University Hospital, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>J.K.L. Holt, PhD, FRCP</b>	The Walton Centre, Liverpool, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Homedes Pedret, MD</b>	Bellvitge University Hospital, Barcelona, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Htut, MD</b>	St. George's Hospital, London, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>K. Jellema, MD, PhD</b>	Haaglanden Medisch Centrum, The Hague, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data

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## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>I. Jericó Pascual, MD, PhD</b>	Complejo Hospitalario de Navarra, Pamplona, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>M.C. Jimeno-Montero, research nurse</b>	Hospital Universitario Infanta Sofia, San Sebastian, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>K. Kaida, MD, PhD</b>	National Defense Medical College, Saitama, Japan	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Karafiath, MD</b>	University of Utah School of Medicine, Salt Lake City	Coinvestigator	Patient inclusion, acquisition of data
<b>H.D. Katzberg, MD</b>	University of Toronto, Canada	Coinvestigator	Patient inclusion, acquisition of data
<b>L. Kiers, MD</b>	The Royal Melbourne Hospital, Parkville, Australia	Coinvestigator	Patient inclusion, acquisition of data
<b>B.C. Kieseier, MD</b>	Heinrich Heine University, Düsseldorf, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>K. Kimpinski, MD</b>	University Hospital, LHSC, London-Ontario, Canada	Coinvestigator	Patient inclusion, acquisition of data
<b>R.P. Kleyweg, MD, PhD</b>	Albert Schweitzer Hospital, Dordrecht, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>N. Kokubun, MD</b>	Dokkyo Medical University, Tochigi, Japan	Coinvestigator	Patient inclusion, acquisition of data
<b>N.A. Kolb, MD</b>	University of Vermont, Burlington	Coinvestigator	Patient inclusion, acquisition of data
<b>K. Kuitwaard, MD, PhD</b>	Albert Schweitzer Hospital, Dordrecht, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Kuwabara, MD, PhD</b>	Chiba University, Japan	Coinvestigator	Patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>J.Y. Kwan, MD</b>	University of Maryland School of Medicine, Baltimore	Coinvestigator	Patient inclusion, acquisition of data
<b>S.S. Ladha, MD</b>	Barrow Neurology Clinics, Phoenix, AZ	Coinvestigator	Patient inclusion, acquisition of data
<b>L. Landschoff Lassen, MD</b>	Glostrup Hospital, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>V. Lawson, MD</b>	Wexner Medical Center at The Ohio State University, Columbus	Coinvestigator	Patient inclusion, acquisition of data
<b>D. Ledingham, MD</b>	Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>S.T. Lucy, research project assistant</b>	University of Vermont Medical Center, Burlington	Coinvestigator	Patient inclusion, acquisition of data
<b>M.P.T. Lunn, MD, PhD</b>	National Hospital of Neurology and Neurosurgery, London, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Magot, MD</b>	Reference Centre for NMD, Nantes University Hospital, France	Coinvestigator	Patient inclusion, acquisition of data
<b>H. Manji, MD, FRCP</b>	Ipswich Hospital, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Marchesoni, MD</b>	Hospital Britanico, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
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<b>C. Márquez Infante, MD</b>	Hospital Universitario Virgen del Rocío, Seville, Spain	Coinvestigator	Patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>E. Martinez Hernandez, MD</b>	Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Barcelona, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>G. Mataluni, MD, PhD</b>	Dysimmune Neuropathies Unit, Neurological Clinic, Policlinico Tor Vergata, Rome, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Mattiazi, MD</b>	Hospital Militar Central, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>C.J. McDermott, MD</b>	Royal Hallamshire Hospital, NIHR Clinical Research Facility and Biomedical Research Centre, Sheffield, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>G.D. Meekins, MD</b>	University of Minnesota School of Medicine, Minneapolis	Coinvestigator	Patient inclusion, acquisition of data
<b>J.A.L. Miller, MD, PhD</b>	Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>G. Morís de la Tassa, MD</b>	Hospital Universitario Central de Asturias, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>J. Mozzoni, physio-therapist</b>	Hospital de Pediatría J.P. Garrahan, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Nascimbene, MD, PhD</b>	Luigi Sacco Hospital, Milan, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>R.J. Nowak, MD</b>	Yale University School of Medicine, New Haven, CT	Coinvestigator	Patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>P. Orizaloa Balaguer, MD</b>	Hospital Universitario-Marques de Valdecilla, Santander, Cantabria, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Osei-Bonsu, MD</b>	James Cook University Hospital, Middlesbrough, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>E.B. Lee Pan, MD</b>	Groote Schuur Hospital, University of Cape Town, South Africa	Coinvestigator	Patient inclusion, acquisition of data
<b>A.M. Pardal, MD</b>	Hospital Británico, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>J. Pardo, MD, PhD</b>	Hospital Clínico de Santiago, Santiago de Compostela (A Coruña), Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Pasnoor, MD</b>	University of Kansas Medical Center, Kansas City	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Pulley, MD</b>	University of Florida, Jacksonville	Coinvestigator	Patient inclusion, acquisition of data
<b>Y.A. Rajabally, MD, PhD</b>	Queen Elizabeth Hospital, Birmingham, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>S. Rinaldi, MBChB, PhD</b>	University of Oxford & Oxford University Hospitals NHS Foundation Trust, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Ritter, MD</b>	University Hospital of Cologne, Universitätsklinikum Köln, Cologne, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>R.C. Roberts, MD</b>	Addenbrooke's Hospital, Cambridge, Cambridge, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>I. Rojas-Marcos, MD</b>	Hospital Universitario Reina Sofia, Cordoba, Spain	Coinvestigator	Patient inclusion, acquisition of data

Continued

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>S.A. Rudnicki, MD</b>	University of Arkansas, Fayetteville	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Ruiz, MD</b>	University of Padova, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>G.M. Sachs, MD</b>	University of Rhode Island, Providence	Coinvestigator	Patient inclusion, acquisition of data
<b>J.P.A. Samijn, MD</b>	Maasstad Hospital, Rotterdam, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>L. Santoro, MD, PhD</b>	University Federico II, Naples, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Savransky, MD</b>	Hospital de Pediatría J.P. Garrahan, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Schenone, MD, PhD</b>	Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Infantile Sciences (DINOEMI), University of Genova; IRCCS Policlinico San Martino, Genova, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>L. Schwinding, MD</b>	Universitätsklinikum des Saarlandes, Homburg, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>M.J. Sedano Tous, MD</b>	Hospital Universitario-Marques de Valdecilla, Santander, Cantabria, Spain	Coinvestigator	Patient inclusion, acquisition of data
<b>Y. Sekiguchi, MD, PhD</b>	Chiba University, Japan	Coinvestigator	Patient inclusion, acquisition of data
<b>K.A. Sheikh, MD, PhD</b>	The University of Texas Health Science Center at Houston	Coinvestigator	Patient inclusion, acquisition of data
<b>N.J. Silvestri, MD</b>	Buffalo General Medical Center, NY	Coinvestigator	Patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>S.H. Sindrup, MD, PhD</b>	Odense University Hospital, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>C.L. Sommer, MD</b>	Universitätsklinikum Würzburg, Germany	Coinvestigator	Patient inclusion, acquisition of data
<b>B. Stein, MD</b>	St. Joseph's Regional Medical Center, Paterson, NJ	Coinvestigator	Patient inclusion, acquisition of data
<b>A.M. Stino, MD</b>	Wexner Medical Center at The Ohio State University, Columbus	Coinvestigator	Patient inclusion, acquisition of data
<b>A. Spyropoulos, MD</b>	Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK	Coinvestigator	Patient inclusion, acquisition of data
<b>J. Srinivasan, MD, PhD</b>	Lahey Hospital & Medical Center, Burlington, MA	Coinvestigator	Patient inclusion, acquisition of data
<b>R. Styliani, MD</b>	University of Thessaly, Hospital of Larissa, Greece	Coinvestigator	Patient inclusion, acquisition of data
<b>H. Suzuki, MD</b>	Kindai University Faculty of Medicine, Osaka, Japan	Coinvestigator	Patient inclusion, acquisition of data
<b>H. Tankisi, MD, PhD</b>	Aarhus University Hospital, Denmark	Coinvestigator	Patient inclusion, acquisition of data
<b>D. Tigner, research nurse</b>	University of Calgary, Canada	Coinvestigator	Patient inclusion, acquisition of data
<b>P. Twydell, DO, MS, FAAN</b>	Spectrum Health System, Grand Rapids, MI	Coinvestigator	Patient inclusion, acquisition of data
<b>P. Van Damme, MD, PhD</b>	University Hospital Leuven, Belgium	Coinvestigator	Patient inclusion, acquisition of data
<b>A.J. Van der Kooi, MD, PhD</b>	Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience Institute, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data



## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>G.W. Van Dijk, MD</b>	Canisius Wilhelmina Hospital, Nijmegen, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>T. Van der Ree, MD</b>	Westfries-gasthuis, Hoorn, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>R. Van Koningsveld, MD, PhD</b>	Elkerliek Hospital, Helmond and Deurne, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>F. Valzania, MD</b>	Arcispedale S. Maria Nuova, IRCCS Reggio Emilia, Italy	Coinvestigator	Patient inclusion, acquisition of data
<b>J.D. Varrato, MD</b>	Lehigh Valley Health Network, Allentown, PA	Coinvestigator	Patient inclusion, acquisition of data
<b>F.H. Vermeij, MD</b>	Sint Franciscus Gasthuis, Rotterdam, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>J. Verschuuren, MD, PhD</b>	Leiden University Medical Centre, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>L.H. Visser, MD, PhD</b>	Elisabeth-TweeSteden Hospital, Tilburg and Waalwijk, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data
<b>M.V. Vytopil, MD</b>	Lahey Hospital & Medical Center, Burlington, MA	Coinvestigator	Patient inclusion, acquisition of data
<b>M. Wilken, MD</b>	Instituto de Investigaciones Neurológicas Raúl Carrea, FLENI, Buenos Aires, Argentina	Coinvestigator	Patient inclusion, acquisition of data
<b>C. Wilkerson, Research Nurse</b>	The University of Texas Health Science Center at Houston	Coinvestigator	Patient inclusion, acquisition of data
<b>P.W. Wirtz, MD, PhD</b>	Haga-Ziekenhuis, The Hague, the Netherlands	Coinvestigator	Patient inclusion, acquisition of data

## Appendix 2 (continued)

Name	Location	Role	Contribution
<b>Y. Yamagishi, MD, PhD</b>	Kindai University Faculty of Medicine, Osaka, Japan	Coinvestigator	Patient inclusion, acquisition of data
<b>L. Zhou, MD, PhD</b>	Icahn School of Medicine at Mount Sinai, New York	Coinvestigator	Patient inclusion, acquisition of data
<b>S.A. Zivkovic, MD, PhD</b>	University of Pittsburgh Medical Center, PA	Coinvestigator	Patient inclusion, acquisition of data

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