



REVIEW

Outcome and its predictors in Guillain–Barré syndrome

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ABSTRACT

Despite the use of plasma exchanges and intravenous immunoglobulins, Guillain–Barré syndrome (GBS) still carries non-negligible morbidity and mortality. Furthermore, the psychosocial consequences of GBS may persist longer than expected. Various aetiological, clinical, electrophysiological and immunological factors may carry prognostic predictive value. The objective of this article was to perform a summary of the current knowledge-base on outcome and its determinants in adequately-treated adult-onset GBS. Relevant prospective literature was reviewed through a Medline search of English-language articles published between 1966 and March 2012. GBS causes severe persistent disability in 14% of patients at 1 year. Loss of full strength, persistent pain and need for professional change occurs in about 40%. Mortality is of about 4% within the first year. Analysis of prognostic predictors consistently demonstrates the negative impact of higher age, preceding diarrhoea, greater disability/weaker muscles at admission, short interval between symptom-onset and admission, mechanical ventilation and absent/low amplitude compound muscle action potentials. Further outcome studies will soon be underway and may in future contribute to adequately integrate all potential factors in more reliable predictive models.

INTRODUCTION

Guillain–Barré syndrome (GBS) is an acute, usually postinfectious neuropathy of common occurrence with a yearly incidence rate between 1.1 and 1.8 per 100 000.¹ More recent data from a meta-analysis of 13 epidemiological studies from Europe and North America refined the estimated yearly crude incidence as lying between 0.81 and 1.89 per 100 000.² GBS incidence increases exponentially with age, with age-specific rates increasing from 0.62 per 100 000 among 0–9-year-olds to 2.66 per 100 000 among 80–89-year-olds. Male subjects are more commonly affected with an RR of 1.78.² The most common preceding infection causing GBS has been shown to be *Campylobacter jejuni* enteritis. Other incriminated infectious agents include cytomegalovirus, Epstein–Barr virus, *Mycoplasma pneumoniae* and *Haemophilus influenzae*.³ In its typical form, GBS causes rapidly progressive diffuse proximal and distal weakness of the four limbs, sensory loss and symptoms and areflexia. By definition, the maximal weakness is reached within 4 weeks. However, in the majority of cases, nadir is attained within 2 weeks. Facial, bulbar and respiratory muscle weakness is frequent, and autonomic involvement well described. The diagnosis of GBS is clinical but

may be aided by electrophysiology which is also important to characterise the two main electrophysiological subtypes: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is sensory and motor and displays demyelinating changes on nerve conduction studies, and acute motor axonal neuropathy (AMAN), which is primarily axonal and thought to be purely motor. There are also axonal forms with sensory involvement described as acute motor and sensory axonal neuropathy (AMSAN). More recently, it has been shown that the pathophysiology of axonal subtypes is characterised besides axonal degeneration by reversible conduction failure and that AMAN and AMSAN which share a common immunological profile and electrophysiological features represent a continuum in the axonal GBS spectrum.^{4–5} Rise in cerebrospinal fluid (CSF) protein level with normal CSF cellularity, also known as ‘albumino-cytological dissociation’, is characteristic of GBS, and present in over 90% of patients 2 weeks postonset.² Imaging can also be contributory to the diagnosis of GBS, with MR of the lumbar spine demonstrating thickened and/or enhancing nerve roots.⁶

The prognosis of GBS is generally considered favourable. Despite the demonstrated efficacy of plasma exchange (PE) and intravenous immunoglobulins (IVIg), GBS however remains a disabling disease in a significant proportion of patients, and these treatments have not improved mortality. Long-term function is compromised in a significant proportion of subjects. Prognosis and potential determinants of clinical outcome in the disorder have been studied by several investigators in more recent years. Although several review articles have considered the various aspects of GBS, a synthesis of the important question of prognosis and its determinants has not, to date, to our knowledge, been performed. In this article, we review the literature on the specific issue of outcome and its predictors in adequately treated, adult-onset GBS.

METHODS

The literature between 1966 and March 2012, searched from Medline, on outcome and its predictors in PE or IVIg treated adult-onset GBS was reviewed. The search terms ‘Guillain–Barré syndrome’, ‘treatment’, ‘prognosis’, ‘predictors’ and ‘outcome’ were utilised. Only papers published in English were considered. From the papers found from an initial search, we exclusively reviewed and here report for the outcome study those relating to prospectively conducted studies on prognosis in

GBS patients of adult age, adequately treated by PE or IVIg, currently the only two evidence-based treatments for GBS, established at two (for mild cases) or four (for moderate or severe cases) sessions of PE, or alternatively, IVIg at the dose of 2 g/kg, over 2 or 5 days.^{7 8}

The outcome measures used varied in different studies and time to improve on the GBS disability scale was the main prognostic data available. However, as in clinical practice questions of importance relate to probabilities for a given patient to reach particular levels of function at specific times, we considered predetermined outcome measures rather than median times taken to reach one particular stage, especially given the wide standard deviations. The main outcome measures that we decided to derive from the literature were the probabilities, following adequate treatment, of:

1. Ability to walk with aid at 4 weeks
2. Ability to walk unaided at 4 weeks
3. Need for ventilatory support at 4 weeks
4. Ability to walk without aid at 6 months
5. Occurrence of a relapse within 1 year
6. Recovery of full motor strength recovery at 1 year
7. Ability to walk without aid at 1 year or later
8. Persistence of severe motor sequelae (defined by the loss of at least one of the following six functions: ability to walk, with or without aid, climb stairs, dress, cut meat, or write) at 1 year
9. Need to change professional activity due to GBS by 1 year
10. Death within the first year.

Finally, the literature referring to prospective studies about potential prognostic predictors in treated GBS was reviewed and analysed considering prospective studies where a majority, but not necessarily all patients, were adequately treated.

RESULTS

Outcome in appropriately treated GBS: analysis of prospective studies

Initial literature on GBS prognosis relates to retrospective studies done prior to use of PE and IVIg and states recovery rates of 50%–94%.^{9 10}

We initially considered a total of 29 papers relating to prospective literature on the topic. We excluded 19 studies where not all patients had been appropriately treated. In the following sections, we summarise the data on preselected outcome measures of the 10 included studies. As PE and IVIg are now considered equally effective treatments in GBS, outcome data were pooled.

The first placebo-controlled trial of PE for GBS was published in 1984.¹¹ Although the results were negative, the prognostic data for the treated group is here used for recovery of full strength at 1 year, mortality, severe motor sequelae at 1 year and relapses within the first year. A second study randomised 38 GBS patients to receive PE or supportive care alone.¹² Although also negative for its primary outcome measure, this trial provided data for most of our prognostic questions for treated patients. The North-American plasma exchange study provided data on several measures within the first year.^{13 14} The French Cooperative Group on Plasma Exchange published in 1987 and complemented in 1992 with 1-year data gave information for most selected prognostic questions.^{15 16} A further PE trial was published in 1987,¹⁷ and provided us with 1-year data on recovery of full motor strength, mortality, presence of severe motor sequelae and relapses. A randomised controlled trial of the Dutch Guillain-Barré Study Group comparing IVIg and PE followed in 1992.¹⁸ From Kaplan-Meier curves shown, only

10%–20% of patients from both groups recovered independent locomotion at 4 weeks. More precise data were not available. Mortality data at 1 year were used in our final analysis.

In 1997, the second French trial of PE was published.¹⁹ Patients were stratified into severity groups: ‘mild’ (who were able to walk with or without help but who could not run, or who could stand up unaided), ‘moderate’ (who could not stand up unaided) and ‘severely affected’ (requiring mechanical ventilation) and randomised to have different number of PE sessions or no treatment. Two sessions of PE for the mild group and four for the moderate and severe groups were shown to be effective. The results of the study provide data on 1-year functional outcome for the three groups. We used these data, considering, for each outcome measure, the patient groups receiving the number of PE sessions found effective versus supportive care only or versus another number of PEs.

A comparative trial of PE versus IVIg versus PE followed by IVIg was later published in 1997.²⁰ One of the secondary outcome measures was the ability or not to walk unaided at 48 weeks. Relapse and mortality data up to 48 weeks were also provided. We considered 48-week data not to be likely significantly different from 1 year and included them in our analysis. As the three treated groups (PE, IVIg and PE+IVIg) did not differ in outcome, we used mean proportions of the three groups.

In 2004, the Dutch study of methylprednisolone in addition to IVIg versus IVIg alone in GBS was reported.²¹ One secondary outcome measure of use in our analysis was the proportion of patients able to walk independently at 1 year. This, comparable in between treated groups, averaged 81.8%. Mortality data at 1 year were also included.

The first long-term study of residual health status was published in 1997 analysing a cohort of 123 GBS patients followed up 3–6 years after their illness.²² All had participated in the Dutch IVIg versus PE trial.¹⁸ The authors found residual altered psychosocial function in all GBS patient groups whether or not they had persistent residual symptoms. However, the ‘physical sickness impact profile’ score correlated with the GBS functional score. The same group later showed long-term reduction in health-related quality of life despite good physical recovery²³ and studied the effects on private life of GBS patients 3–6 years after the illness, describing severe residual symptoms in 11% of subjects, with 69% having no or minimal residual. Also, and importantly, employment change was needed in 38% of cases and leisure activities had altered in 52% after the illness. However, over 20% of patients still noticed improvement 2.5–6.5 years after onset. The same authors in 2005 also published findings relating to the same population, in terms of patients’ experience of their functioning after 1 year.²⁵ Only 33% felt subjectively completely cured at 1 year. As patients were also objectively assessed at 1 year, proportions of those with ability to walk at 1 year or with persistent significant disability were utilised.

Although pain was not one of our pre-established outcome measures analysed and despite not all patients being treated, we decided to also consider an additional prospective study of pain in GBS given this symptom’s potential significant impact on subsequent quality of life. In this study of 156 patients, the majority, but not all, treated with IVIg or IVIg and steroids, 66%, had pain in the acute phase and 38% had pain at 1 year.²⁶ Of note, these included patients with pure motor forms of GBS, where pain is unexpected. Interestingly, pain occurrence correlated with previous diarrhoeal illness and adjunction of steroids to IVIg did not help.

Results for each preselected outcome are summarised in table 1.

Table 1 Summary of preselected outcomes evaluated from data of prospective analyses of adequately treated Guillain–Barré syndrome (GBS) patients with plasma exchange (PE) or intravenous immunoglobulins (IVIg) and pooled results

Study	Design	Outcome 1 (ability to walk with aid at 4 weeks)	Outcome 2 (ability to walk unaided at 4 weeks)	Outcome 3 (need for ventilatory support at 4 weeks)	Outcome 4 (ability to walk unaided at 6 months)	Outcome 5 (relapse strength at 1 year)	Outcome 6 (recovery of full motor strength at 1 year)	Outcome 7 (ability to walk unaided at 1 year or later)	Outcome 8 (persistence of severe motor sequelae at 1 year or later)	Outcome 9 (need to change employment due to GBS)	Outcome 10 (death within 1 year of diagnosis)
Greenwood <i>et al</i> , 1984 ¹¹	Therapeutic (PE), controlled	NA	NA	2/14	NA	1/14	4/14	NA	1/14	NA	2/14
Osterman <i>et al</i> , 1984 ¹²	Therapeutic (PE), controlled	12/18	7/18	4/18	NA	1/18	16/18	NA	1/18	NA	1/18
The GBS Study Group, 1985 ¹⁴	Therapeutic (PE), controlled	NA	NA	26/122	100/122	2/122	NA	NA	22/122	NA	3/122
French Cooperative Group, 1987 ¹⁵	Therapeutic (PE), controlled	13/109	15/109	12/109	NA	6/109	70/109	NA	11/109	NA	7/109
Färkkilä <i>et al</i> , 1987 ¹⁷	Therapeutic (PE), controlled	NA	NA	NA	NA	NA	12/13	NA	0/13	NA	2/13
Van der Meché Schmitz, 1992 ¹⁸	Therapeutic (PE vs IVIg), controlled	NA	NA	NA	NA	NA	NA	NA	NA	NA	3/150
French Cooperative Group, 1997 ¹⁹	Therapeutic (PE), controlled and 'dose-ranging'	6/45‡	13/45‡	0/45**	NA	14/361¶	210/361¶	NA	41/361¶	NA	14/361¶
PE/Sandoglobulin Trial, 1997 ²⁰	Therapeutic PE versus IVIg versus PE + IVIg	NA	NA	NA	NA	NA	NA	NA	57/365* †	NA	19/379
van Koningsveld <i>et al</i> , 2004 ²¹	Therapeutic IVIg + PE versus IVIg + placebo	NA	NA	NA	NA	NA	NA	184/225§	41/225††	NA	10/225§
Bernsen <i>et al</i> , 2002 ²⁴	Therapeutic (PE vs IVIg), controlled	NA	NA	NA	NA	NA	NA	108/122	14/122	31/82	NA
Total		31/172 (18%)	35/172 (20.3%)	44/308 (14.3%)	100/122 (82%)	24/624 (3.8%)	312/515 (60.6%)	292/347 (84.1%)	188/1349 (13.9%)	31/82 (37.8%)	61/1391 (4.4%)

The values in bold correspond to the percentages for each outcome.
 *Excluding missing data in each treated group.
 †Considering 48-week instead of 52-week follow-up data.
 ‡Only data for these outcomes were available for patients in the 'mild' group (obtained from the Cochrane review).
 §Including both treated groups which were equivalent and averaging.
 ¶Including all patients in the effectively treated groups (ie, 46 in the two PE in the group for mild disease; the 155 treated by four PE in the moderate disease group; all 161 treated patients by four or six PE in the severe disease group).
 **Included mild group.
 ††Only including those unable to walk independently at 1 year.
 NA, not applicable.

Predictors of prognosis in GBS: descriptive review of the literature

We here used data from studies where a majority, but not necessarily all patients, had received adequate treatment to evaluate the currently proposed predictors of prognosis in GBS. We separated for ease of reference, clinical, electrophysiological and serological markers, although considerable overlap proved inevitable as several groups of investigators studied different predictors among the three categories. Clinical predictors were for convenience separated between those relating to mechanical ventilation and those relating to long-term disability.

Clinical predictors
Predictors of mechanical ventilation

Both French PE trials^{15 19} first gave rise to a large analysis of the clinical predictors of mechanical ventilation.²⁷ Multivariate analysis identified five predictors of mechanical ventilation within 30 days of admission which were: (1) a time from

symptom onset to admission of <7 days, (2) inability to cough, (3) inability to stand, (4) inability to lift the elbows and (5) inability to lift the head. Having several predictors increased any individual patient's risk of requiring mechanical ventilation.

Walgard *et al* more recently published a multivariate logistic regression model for early prediction of respiratory insufficiency in GBS.²⁸ Again, data prospectively collected from 397 patients from two previously discussed therapeutic trials and a pilot study.^{18 21 29} Results were validated in a separate cohort of 191 GBS patients followed up prospectively in the setting of a pilot study³⁰ and of an observational study. Multivariate logistic regression analysis showed that (1) Medical Research Council (MRC) Sum Score at admission, (2) number of days between onset of weakness and admission and (3) facial and/or bulbar weakness at admission were all strong predictors of mechanical ventilation in the first week of hospital stay. An 'Erasmus GBS Respiratory Insufficiency Score' or 'EGRIS' was derived on the regression coefficients of these three predictors in the combined

cohort of patients from the derivation and validation sets. The EGRIS provided an estimated risk of mechanical ventilation based on five categories for the MRC Sum Score (MRC Sum Score 60–51: 0; 50–41: 1; 40–31: 2; 30–21: 3; ≤ 20 : 4), three categories for days between onset of weakness and hospital admission (>7 days: 0; 4–7 days: 1; ≤ 3 days: 2), and two categories for facial/bulbar weakness at admission (absence: 0; presence: 1). Risk categories for respiratory insufficiency were identified, EGRIS of 0–2 corresponding to a ‘low risk’ (4%), EGRIS 3–4 corresponding to an ‘intermediate risk’ (24%) and EGRIS 5–7 labelled as ‘high risk’ (65%).

A prospective study of 76 GBS patients from Iran (80% treated with PE or IVIg) indicated a significant correlation between a history of diarrhoea and subsequent need for mechanical ventilation. Previous diarrhoea predicted worse outcome at 6 months.³¹

Predictors of long-term functional disability

Analysis of data from The Plasma Exchange/Sandoglobulin trial participants demonstrated that death or inability to walk at 48 weeks was associated with preceding diarrhoea, severe arm weakness and age >50 years.³²

Visser and coworkers, using data of 147 patients who had participated in the Dutch GBS trial comparing IVIg and PE,¹⁸ found by multivariate logistic regression analysis that a previous gastrointestinal illness, age >50 years and MRC Sum Score <40 pretreatment were predictors of a poor outcome.³³ Subsequently, using data from 388 patients previously included in trials,^{18 21 29} van Koningsveld *et al* derived a clinical prognostic scoring system for GBS outcome at 6 months.³⁴ The findings were then validated in 374 other patients who had participated in another international randomised trial.²⁰ All data had been prospectively collected. In the multivariate analysis, age, preceding diarrhoea and GBS disability score at 2 weeks after study entry emerged as the three main predictors of poor outcome at 6 months. An ‘Erasmus GBS Outcome Score’ (EGOS) was derived by the authors, where score ranged from 1 to 7, with three categories for age (>60 (1 point), 41–60 (0.5 point), <40 (0 point)), two categories for diarrhoea (presence (1 point) or absence (0 point)) and five categories for GBS disability score (grade 0 or 1 (1 point), 2 (2 points), 3 (3 points), 4 (4 points) or 5 (5 points)), at 2 weeks. As a result, the authors were able to provide stratification into four groups of roughly equal size using derivation and validation patient samples. An EGOS of 1–3 implied a mean risk of inability to walk independently at 6 months of 0.5%, an EGOS of 3.5–4.5 implied a mean risk of 7%, an EGOS of five implied a mean risk of 27% and an EGOS of 5.5–7 implied a mean risk of 52%.

More recently, Walgaard *et al* also published a clinical prediction model applicable early in the course of GBS predicting outcome at 6 months.³⁵ As in their study on respiratory insufficiency described above, the investigators used the same above-mentioned cohorts of patients for derivation and validation. Multiple logistic regression was used and (1) high age, (2) preceding diarrhoea and (3) low MRC Sum Score at admission and day 7 were independently associated with being unable to walk at 4 weeks, 3 months and 6 months. The authors as a result proposed a ‘modified EGOS’, which they claimed, in contrast to the EGOS, could be used at hospital admission and day 7, with a greater prognostic accuracy when used at day 7, when MRC Sum Score proves a more accurate predictor. The main difference with the EGOS was the use of the MRC Sum Score rather than the GBS disability score, as the model using the former performed better.

Electrophysiological predictors

The American Plasma Exchange trial data,^{14 36} in univariate analysis, showed as the most powerful predictor of poor outcome a mean distal compound muscle action potential (CMAP) amplitude $<20\%$ of lower limit of normal. In multivariate analysis, distal CMAP was, together with ventilatory status, the factor influencing the percentage of patients improved at 4 weeks. When time to improve by 1 grade on the GBS disability scale was the outcome measure evaluated, prior length of illness >7 days was also a significant predictor. When time to reach GBS disability grade 2 (independent walking) was the analysed outcome, age was additionally a significant predictor. In a further analysis of participants of the Plasma Exchange/Sandoglobulin trial,³⁷ neurophysiological findings were classified ad hoc as primary demyelinating, primary axonal, equivocal, inexcitable or normal. An association was found between inexcitable nerves and death or inability to walk unaided at 48 weeks. However, no difference of outcome was detected between axonal and demyelinating forms.

A French analysis studying prospectively 60 consecutive cases (52 treated with PE or IVIg and eight untreated) suggested that demyelinating electrophysiology may be a predictor of mechanical ventilation.³⁸ The same group later described, in an analysis of 70 subjects (62 treated with PE or IVIg, eight untreated), a prospective study of phrenic nerve electrophysiology and its relation with need for mechanical ventilation, which they failed to confirm. They concluded that prediction of respiratory failure should rely on clinical features and vital capacity measurements only.³⁹ These authors otherwise described in another prospective study of 154 GBS patients (137 treated by PE or IVIg) over an 8-year period (1998–2006) the clinical and electrophysiological predictors of respiratory failure.⁴⁰ Demyelinating electrophysiology was found more common in patients requiring ventilation. Quite puzzling, in our opinion, was that none of the patients who had to be ventilated had axonal electrophysiology whereas a substantial proportion of non-ventilated patients had equivocal electrophysiology. Conduction block affecting the common peroneal nerve was also shown to be a useful predictor of mechanical ventilation. Vital capacity was found useful as additional parameter. Conduction block $<44.4\%$ taken in combination with a vital capacity $>81\%$ than predicted indicated a $<2.5\%$ chance of requiring mechanical ventilation. On the other hand, a similar degree of conduction block, but a vital capacity of 17%–80%, implied a chance of mechanical ventilation of about 28%. Interestingly, they found that conduction block $>44.4\%$ independently suggested a risk of mechanical ventilation of about 40%. Otherwise poor recovery at 6 months, defined as a GBS grade >2 , was predicted independently by the aforementioned degree of conduction block of the common peroneal nerve and age >40 years. Importantly, low distal median CMAP amplitudes were not found to be predictive although summated CMAPs were not analysed or described.

In another recent prospective Iranian study, axonal electrophysiology predicted a worse outcome at 6 months.³¹

Finally, another recent prospective French study described a not better specified ‘sciatic nerve motor conduction block’ together with a clinical feature described as ‘lack of foot flexion ability’ at admission to intensive care, and at the end of immunotherapy, as significantly associated with prolonged mechanical ventilation beyond 15 days.⁴¹ Neither the electrophysiological nor the clinical parameter was further defined or explained by the authors and remained most unclear.

Biological predictors

Few studies, including limited numbers of patients, addressed the potential use of biological markers as prognostic predictors in GBS. In the Plasma Exchange/Sandoglobulin trial participants, anti-GM1 antibodies were present in a higher proportion of patients with axonal physiology or inexcitable nerves, and patients with pure motor GBS were more likely to have IgG anti-GM1 antibodies and to have had preceding diarrhoea but had a similar outcome to that of other GBS patients. From the same trial, further published results of prognostic factor analysis showed that death or inability to walk at 48 weeks was associated with raised soluble interleukin-2 receptor concentration and, unexpectedly, with absence of IgM anti-GM1 antibodies.⁵² These results contrasted with what had been described by several groups during the previous decade in that patients with GBS and *C jejuni* infection were more likely to have neurophysiological features of axonal neuropathy, anti-GM1 antibodies, pure motor GBS and a worse outcome than other GBS patients.^{42–44}

A study of 41 prospectively recruited GBS patients (32 treated with PE or IVIg) was described in relation to IgG anti-GM1 antibody status.⁴⁵ The anti-GM1 positive group showed two different patterns of recovery and included a significantly higher proportion of patients with poor recovery, but also a significantly higher proportion with markedly rapid recovery. Underlying correlation with *C jejuni* serology was not ascertained. A further study of the prognostic value of anti-GM1 antibodies evaluated a total of 134 consecutive GBS patients over 6 months.⁴⁶ It found positivity to anti-GM1 antibodies of the IgG1 subclass was the most frequent, was associated with preceding gastro-enteritis and positive *C jejuni* serology, as well as slow/incomplete recovery. On the other hand, the IgG3 subtype, less frequent, was associated with preceding respiratory illness and rapid recovery within a month. In this study, the outcome could be influenced by various treatments received. The authors, however, concluded that at least in the 21 PE treated patients, IgG subclass of anti-GM1 antibody was closely associated with outcome because the frequency of PE treatment did not differ between the patients with the IgG1 and IgG3 antibodies.⁴⁶ More recently, a prospective, Brazilian study of 41 IVIg treated GBS patients followed up for at least 4 months was unable to detect any impact on worse prognosis of anti-GM1 antibodies and positive *C jejuni* serology.⁴⁷

Visser *et al*⁵³ found in addition to the clinical predictors described earlier that a recent cytomegalovirus infection was an indicator of poor outcome. These findings were consistent with those of a previous study by the same group which had indicated high frequency of respiratory insufficiency, cranial neuropathy and severe sensory loss in cytomegalovirus-associated GBS.⁴⁸

Raised liver enzymes were found to represent a predictor of mechanical ventilation in the participants of the French PE studies,²⁷ although this finding has not been replicated since to our knowledge.

A first prospective analysis of 23 GBS patients was described as showing CSF neurofilament level as a biomarker for electrophysiological axonal damage, and of worse motor and functional outcome.⁴⁹ A further larger prospective multicentre controlled study demonstrated the utility of CSF neurofilament and τ , as useful prognostic markers. This study also showed that higher age and need for ventilatory support were associated with poorer prognosis.⁵⁰ In another study including 20 AIDP and 17 axonal GBS patients (28 treated by IVIg, five treated with PE and four untreated), serum levels of glial fibrillar acid protein were

increased in axonal subtypes compared with AIDP patients and controls and correlated with GBS functional grade at 6 months.⁵¹

A prospective French study of the relationship between plasma cortisol and respiratory failure in 93 GBS patients (82 treated by PE or IVIg)⁵² showed after adjustment for validated clinical and electrophysiological predictors increased baseline cortisol level as an independent predictor for respiratory failure at least 24 h later.

A recent analysis from India prospectively studied 50 GBS patients and described the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in 48% of cases at some stage of the illness.⁵³ MRC scores at admission and discharge were higher in patients with SIADH who on the other hand had a higher rate of bulbar weakness and greater need for ventilatory support. Age >50 years, ventilatory support, hyponatremia and bulbar weakness were significantly associated with mortality. In this observational study, 23/24 GBS patients with SIADH required PE compared with only 8/26 without SIADH.

We summarise in figure 1 the findings from the selected literature of predictors of mechanical ventilation and of later functional prognosis in GBS. Table 2 highlights what we believe represent, at this point in time, the main clinically useful prognostic predictors from each category.

DISCUSSION

We have here reviewed the prospective English-language literature in relation to outcome and its predictors in GBS as currently treated with PE or IVIg. Although clearly desirable, a meta-analysis providing risk ratios for each one of the predictors of poor prognosis was in our opinion unfortunately not feasible reliably or meaningfully due to the large heterogeneity of the various studies analysed in this review.

Even when appropriately treated GBS remains fatal in about 4% of cases, up to about 20% of patients are able to walk unaided at 4 weeks, and only 60% recover full motor strength at 1 year, at which stage about 14% are left with a severe disability. Importantly, > 80% are able to walk independently at 6 months. Modest further improvement is usually to be expected, with this figure only reaching 84% at 1 year. However, individual patients may experience further slow recovery up to 6 years after presentation. These findings highlight the current limitations of available therapies for GBS and the need to find newer, more effective treatment options. The issue of a second dose of IVIg, the usefulness of which was suggested by pharmacokinetic studies⁵⁴ and currently under investigation,⁵⁵ is raised. The relapse rate at 1 year was 3.8% in agreement with previously reported figures.^{56, 57} Neither PE nor IVIg has shown an impact on reducing deaths, and this highlights the importance of supportive care in the management of GBS.

In the longer-term, it appears clear that GBS impairs function as well as social life beyond 1 year, resulting in work changes in nearly 40% of patients and in persistent pain in about 40% of all cases, including in pure motor forms, at 1 year and likely beyond. These outcomes, although studied in fewer analyses and in smaller cohorts, are of major importance to patients, their carers and treating general practitioners and/or neurologists. GBS, although of acute onset, appears to subsequently become for many patients a chronic condition, severely impacting on lifestyle over years rather than months, sometimes irreversibly. Encouragingly, improvement appears sustained long after disease onset by mechanisms which are uncertain.

One limitation of our review is that all 10 studies selected were performed in Western countries where AIDP is reported as

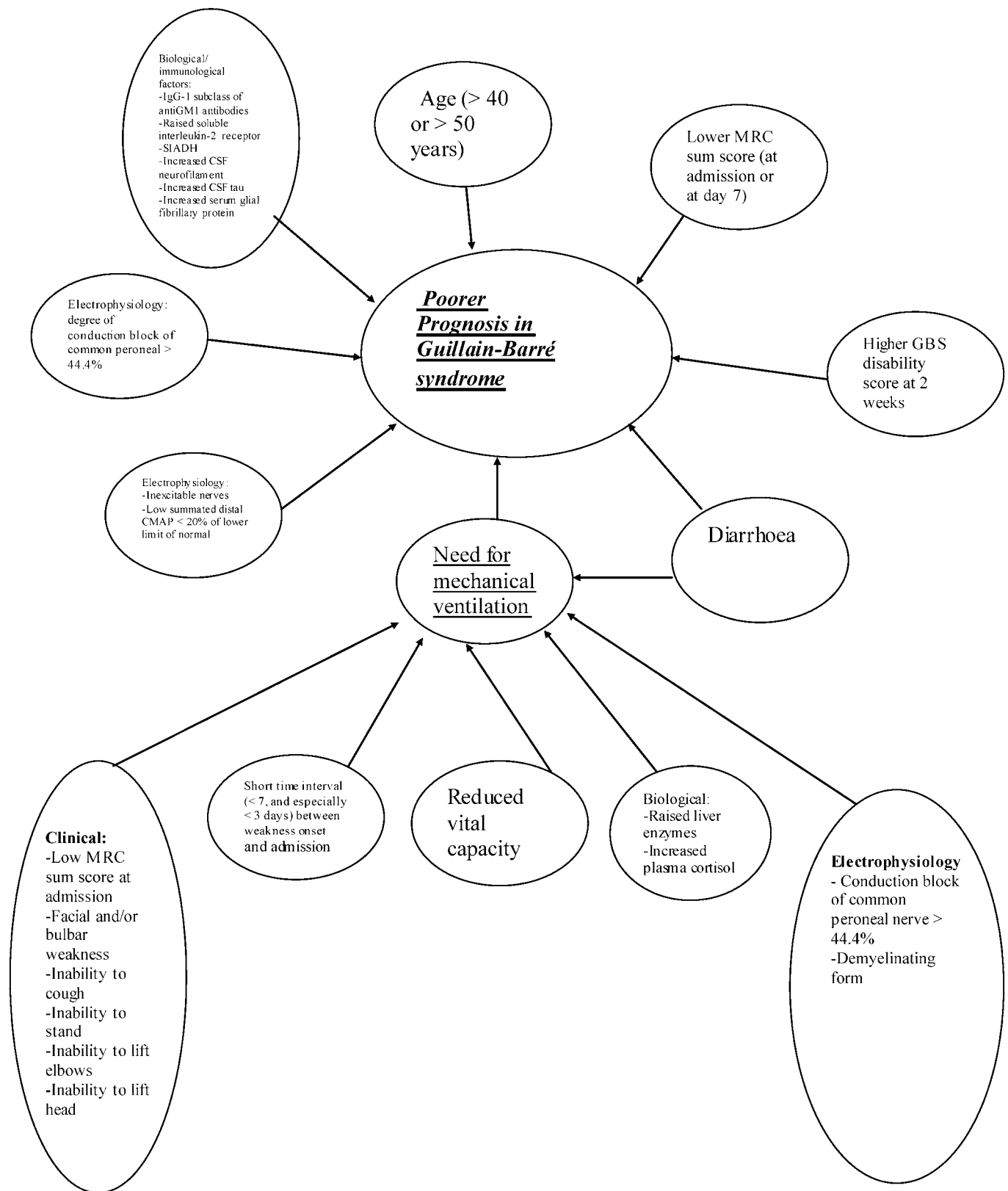


Figure 1 Summary of currently identified/suggested predictors of mechanical ventilation and of prognosis in Guillain-Barré syndrome (GBS). CSF, cerebrospinal fluid; IgG, immunoglobulin G; MRC, Medical Research Council; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

the most frequent subtype accounting for 90% of all GBS patients,²⁸ whereas the frequency of AMAN is higher in China, Japan and Bangladesh.^{31 58 59} It has been debated whether AMAN carries or not a worse prognosis. AMAN patients may

either rapidly and fully recover or improve very slowly and incompletely.⁶⁰ This apparent contradiction may be reconciled by the fact that besides axonal degeneration, some AMAN patients with antibodies to gangliosides show transient

Table 2 Main likely predictors of prognosis in Guillain–Barré syndrome: derived from findings of prospective literature of studies including a majority of treated patients

Category	Predictor
Clinical	Age >40 or 50 years
	Reduced vital capacity
	Need for mechanical ventilation
	Preceding diarrhoea
	Low MRC Sum Score at admission
	Low MRC Sum Score at day 7 postadmission
Electrophysiological	Short interval between weakness onset and admission
	Facial and/or bulbar weakness
	Inexcitable nerves
	Low summated distal compound muscle action potential <20% of lower limit of normal
Biological	None of definite value
	More confirmatory studies required

MRC, Medical Research Council.

conduction block/slowing in intermediate and distal nerve segments which rapidly recovers without the development of abnormal temporal dispersion, a phenomenon named reversible conduction failure.^{4 45} The relative amount of axonal degeneration and reversible conduction failure in an individual patient may well explain the dichotomous outcome pattern in AMAN prognosis. For this reason, the characterisation of primary axonal neuropathy is not necessarily a predictor of poorer outcome. Another drawback of our analysis relates to the fact that except for one study which compared the number of PE needed,¹⁹ all others studied patients who were unable to walk and therefore initially severely disabled. This undoubtedly impacted on our findings. Our aim was however to evaluate the issue of prognosis in treated adult-onset GBS and exclusion of cases of mild GBS is consequently a limitation that could not be avoided.

Regarding clinical prognostic predictors, most studies demonstrate higher age (>40 or >50 years) as an indicator of poor outcome. Similarly, preceding diarrhoea, more severe weakness with consequent low MRC score on admission and high early GBS disability grade all appear reliable predictors of outcome at 6 months, and probably later. Electrophysiologically, the most consistently described finding predictive of poor outcome has been low mean or summated CMAPs. In contrast are the reports of demyelinating electrophysiology and of common peroneal nerve conduction block >44.4% as predictors of respiratory failure.^{39 45} It is difficult, from a pathophysiological point of view, to understand why involvement of a leg nerve would be the best indicator of developing respiratory dysfunction. Additionally, electrophysiological assessment was made once only an average of 2 days after admission. A recent study however underlined that it may be difficult or even impossible to make a distinction between axonal and demyelinating features in early recordings.⁴ For these reasons, we believe that more than electrophysiology, clinical factors such as age, facial and bulbar weakness, inability to cough, MRC Sum Score, speed of weakness progression and vital capacity, all easily obtainable at bedside, should be used in priority to predict mechanical ventilation.

Positivity of antibodies to gangliosides can either suggest poor recovery or rapidly reversible weakness. Determination of IgG subclass, IgG1 or IgG3, may be helpful for prognostic purposes.³⁴ It is difficult to explain why, in the study by Hadden *et al*,³² the presence IgM anti-GM1 antibodies was found to be a good prognostic factor although this might be partly explained by confounding with other factors. CSF neurofilament and serum

glial fibrillar acid protein level appear promising potential prognostic markers but results should be confirmed in larger studies.

CONCLUSION

Knowledge of prognostic factors can substantially improve patient care and provides essential prognostic answers for patients and relatives at an early stage in the course of the illness. There are many persistent uncertainties in the optimal way in which clinical, electrophysiological and biological markers may be combined to establish prognosis at an early stage, and therefore allow, ideally, eventual tailoring of treatment to individual patients' needs. Further larger, prospective international studies of outcome in GBS looking at each one of the relevant measures and potential predictors will hopefully shed more light on these important questions in future. The 'IGOS 1000' (International Guillain–Barré syndrome Outcome Study),⁶¹ which is to start imminently, will hopefully achieve this important objective.

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Information for patients from JNNP

Who is most likely to improve after treatment for Guillain-Barré syndrome?

What do we know already?

Guillain-Barré syndrome is a rare but serious condition that affects the nervous system, which controls your senses and your movements. If you have Guillain-Barré syndrome, your immune system, your body's defence against infection and illness, attacks and damages your nerves. This leads to muscle weakness that can cause problems walking and moving your limbs, talking, breathing and controlling your stomach and bladder. Around 80 in 100 people with Guillain-Barré syndrome make a full recovery within a few weeks or months. But some people may take longer to recover, and doctors can't be sure what's likely to happen to people once they start treatment.

To find out more, researchers looked at 10 studies of more than 5,000 people with Guillain-Barré syndrome. In particular, they looked to see if there were certain things, called predictors, that meant people were more likely to do well and feel better if they had treatment for Guillain-Barré syndrome. They looked at what things predicted if, after treatment, people would:

- ⤴ Be able to walk with or without help
- ⤴ Be able to breathe without help from a machine
- ⤴ Have their symptoms come back again within a year of starting treatment
- ⤴ Be able to do everyday things like climb stairs, dress themselves, cut meat, or write a year after treatment
- ⤴ Need to change jobs because of their illness a year after treatment
- ⤴ Die within the first year after treatment.

What does the new study say?

Overall, after treatment for Guillain-Barré syndrome, around 4 in 100 people died. Around 20 in 100 people were able to walk without help after 4 weeks, and 80 in 100 people were able to walk without help after six months. Around 60 in 100 people got back their muscle strength after one year, while 14 in

100 people still had a disability after one year. Around 4 in 100 people who recovered had their symptoms come back in the first year.

The researchers found that people who were older (particular aged 50 and over), people who had weaker muscles, who were more disabled or who had diarrhoea were the most likely to do poorly, even after treatment for Guillain-Barré syndrome.

People who had diarrhoea and people with muscle weakness were also more likely to need help with breathing. People who had nerve damage that affected the face, or who were unable to cough, stand, lift their elbows or lift their head, were also more likely to need help with breathing.

In turn, people who needed help with breathing were also less likely to do well after treatment.

How reliable are the findings?

Reviews like these can be useful for looking at information from a lot of studies, and often the more studies that are included in a review, the more reliable the results tend to be. The researchers noted though that the majority of people who took part in the study were unable to walk and were already severely disabled at the beginning of the study. This could have influenced how well they did after taking treatment, and made the results less reliable.

What does this mean for me?

Guillain-Barré syndrome is a complex illness and it's not easy for doctors to know what is likely to happen to individuals. It could be useful, if you have Guillain-Barré syndrome, to have some insight into what is likely to happen, and if you have treatment how likely it is to help your symptoms. Studies like these look at evidence from large groups of people and make conclusions based on averages, but they can't tell what is likely to happen to you. This study has flagged up some potential things that might predict who is likely to do better or worse after treatment for Guillain-Barré syndrome. But the researchers themselves say we will need a lot more research, and further studies, before we can be sure if these things are definitely linked to improvements for people with Guillain-Barré syndrome.

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