The role of immunotherapy in Guillain-Barré syndrome: understanding the mechanism of action

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Introduction: Guillain-Barré syndrome (GBS) is the most frequent cause of acute flaccid paralysis and, despite treatment, there continues to be an associated mortality and severe disability ranging from 9 to 17%. This article reviews the rationale behind the existing immunotherapy in GBS and discusses the future direction that work in this area should follow.

Areas covered: The pathogenesis of GBS and the current evidence for the different forms of immunotherapy in GBS are reviewed. The proposed mechanism of action of each treatment — (steroids, plasma exchange and intravenous immunoglobulin (IVIG)) — in GBS are discussed.

Expert opinion: Both plasma exchange and IVIG are equally effective in GBS although the latter is preferred in view of its ease of access and lower rates of complications. Although not clinically established, there may be a role for the concomitant use of steroids with IVIG and, in patients with severe disease and poor prognostic scores, plasma exchange followed by IVIG or two successive IVIG may prove beneficial.

Keywords: acute autoimmune neuropathies, Guillain-Barré syndrome, immunotherapy, pathogenesis

1. Introduction

Guillain-Barré syndrome (GBS) is an acute form of immune-mediated polyneuropathy. Since the near-elimination of polio worldwide, GBS has become the most common cause of flaccid paralysis [1,2]. The disease typically follows a monophasic course and is also typically preceded by an infectious episode, such as a respiratory or gastrointestinal infection. The clinical presentation is characterized by an acute onset of flaccid paralysis associated with the loss of reflexes and cerebrospinal fluid analysis can show albuminocytological dissociation [3]. The reported incidence of GBS, in studies from Europe and the United States, ranges from 1 to 2 per 100,000 population [4-6]. There also appears to be a slight male preponderance and a linear rise of incidence with age [5,7]. GBS can be further classified into two major subtypes based on electrophysiological and pathological findings: acute inflammatory demyelinating neuropathy (AIDP) and acute motor axonal neuropathy (AMAN), involving the peripheral nerve myelin and axons respectively [8,9]. Based on the current electrophysiological criteria [10,11], AIDP appears to be the predominant subtype in the Western population, accounting for 95% of cases [11], whereas AMAN occurs more frequently in studies of GBS in China [12], Japan [13] and Central America [14], presenting in 30 – 47% of GBS cases. More recent studies in Asia based on electrophysiology continue to show variable presentations of the two subtypes of GBS, with AMAN presenting in 8% of 51 Indian patients [15], 22% of 41 patients in Israel [16], and 67% of 100 patients in Bangladesh [17].
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Article highlights.

- Guillain-Barré syndrome (GBS) is the most common cause of flaccid paralysis with a reported incidence of 1–2 per 100,000 population.
- GBS has two major subtypes; acute inflammatory demyelinating neuropathy (AIDP) and acute motor axonal neuropathy (AMAN), and forms a continuous spectrum with Fisher syndrome (FS) and Bickerstaff brainstem encephalitis (BBE).
- Molecular mimicry between pathogenic microbes and host antigens are likely triggers of the antibody-mediated process that underlies the pathogenesis of GBS and its related conditions. This has been proven in the AMAN subtype.
- Macrophages act as scavengers, removing injured nerve by-products, and their removal by steroids may delay the nerve recovery process in GBS, which may explain why steroids alone are ineffective in GBS.
- Plasma exchange (PE) and intravenous immunoglobulin (IVIG) are equally effective in hastening the recovery in GBS and improving outcome.
- Plasma exchange most likely works by eliminating the pathological autoantibodies that can induce nerve injury and inhibit the regeneration of injured nerves.
- The mechanism of action of IVIG includes provision of anti-idiotypic antibodies that can neutralize autoantibodies, inhibition of complement activation and membrane attack complex formation on Schwann cell surface lead to vesicular demyelination and axonal degeneration.
- FS patients recover spontaneously and do not warrant treatment; BBE patients are best treated with either PE or IVIG as mortality has been reported.
- Future research includes further clarification of the pathogenesis of GBS, investigating the mechanisms of action of the current immunotherapies and exploring the possible therapeutic effects of complement inhibitors in GBS.

In recent years, serial electrophysiological studies in GBS patients have suggested that the current electrophysiology criteria may be insensitive at detecting other possible GBS subtypes, such as AMAN with conduction block. In this group of patients, initial electrophysiology may mimic ‘demyelination’ but subsequent studies support an axonal pathology. Fisher syndrome (FS) is characterized by an acute onset of ataxia, areflexia and ophthalmoplegia; when there is axonal pathology.

Data on FS have been gleaned from the description of FS as a variant of GBS. The estimated annual incidence of FS is 0.9/100,000 [25]. It is also reported to have an incidence of approximately 1–5% of GBS from Western countries, although this is higher in Asian countries such as Taiwan (19%) [26] and Japan (25%) [27]. There are no incidence data on BBE but clinical experience suggests that it has a lower incidence than FS.

The current established treatments of GBS are plasma exchange (PE) and intravenous immunoglobulin (IVIG) [28]. Unfortunately, despite treatment, there continues to be an associated mortality and severe residual disability of 9 and 17%, respectively, in GBS patients. By contrast, both FS and BBE have a good prognosis and there is no good evidence to support the use of immunotherapy in either condition at present. This article discusses the current evidence on the pathogenesis of GBS and its related conditions, reviews the efficacy of the various therapies in GBS and discusses other possible treatments that could be developed and assessed for the treatment of GBS, FS and BBE.

2. Pathogenesis

2.1 Guillain-Barré syndrome

Antecedent infections appear to play an important role in the development of GBS. Prospective studies have demonstrated Campylobacter jejuni and cytomegalovirus infections to be significantly more frequent in patients with GBS than in controls [29,30]. The epidemiological association established between C. jejuni infection and GBS noted that patients with an antecedent C. jejuni infection had a more severe form of GBS with axonal degeneration [31]. The growing evidence suggests that microbial organisms are likely triggers of an autoimmune response leading to the peripheral nerve injury seen in GBS [32,33].

The pathological processes underlying AIDP and AMAN are different but the final pathway is common. In AIDP, complement activation and membrane attack complex formation on Schwann cell surface lead to vesicular demyelination [9]. In AMAN, antibodies against motor axons lead to complement-mediated membrane attack complex formation at the nodal axolemma and, in severe cases, axonal degeneration of the motor axons develop [8]. In other words, GBS is a complement-mediated autoimmune disorder.

Although the target antigen in AIDP has yet to be identified, research over the last 20 years has clarified some of the associated autoantigens in AMAN. Gangliosides make up the components of the plasma membrane and are found abundantly in the nervous system. The ceramide moiety is anchored in the external leaflet of the lipid bilayer whereas the sialylated oligosaccharides are exposed extracellularly. Many studies have reported the presence of various anti-ganglioside antibodies in patients with AMAN, namely IgG anti-GM1, -GM1b, -GD1a and -GalNAc-GD1a antibodies [34-37]. C. jejuni-related GBS is likely to be
associated with AMAN \[38\]. Molecular mimicry exists between gangliosides and the lipo-oligosaccharides of \textit{C. jejuni} isolated from an AMAN patient \[39,40\]. Rabbits sensitized with GM1 ganglioside developed IgG anti-GM1 antibodies followed by acute flaccid paralysis, and pathological studies confirmed the characteristic features of AMAN \[41,42\]. A replica of AMAN was also produced by sensitizing the rabbits with \textit{C. jejuni} lipo-oligosaccharides from an AMAN patient \[33\]. Along with the epidemiological association between GBS and \textit{C. jejuni} infection \[43\], this sequence of events established GBS as the first autoimmune disorder to be triggered by molecular mimicry in humans \[44\].

Immunohistochemical studies performed on the peripheral nerves of AMAN rabbit models have successfully demonstrated the underlying mechanism of peripheral nerve injury in AMAN as follows \[45\]. AMAN rabbits were studied at the acute progressive phase (a few days after onset), early recovery (2 weeks after onset) and late recovery (4 weeks or more after onset). In the acute phase, there was lengthening of the nodes of Ranvier and IgG was noted to be deposited at some nodes where GM1 was expressed, as shown in AMAN patients. This binding of autoantibodies triggered complement activation at the nodes and, eventually, the membrane attack complex formation at the nodal axolemma \[45\]. This is followed by disappearance of the sodium channel clusters due to the destruction of their stabilizing components, which include the axonal cytoskeleton at nodes, Schwann cell microvilli and paranodal axoglial junctions. This alteration would significantly lower the safety factor of impulse transmission, causing muscle weakness in the acute phase of clinical illness. As the clinical course progressed into the early recovery phase, complement levels decreased but macrophage invasion was noted to be more prominent. This suggests that complement activation is crucial in acute nerve injury and macrophages are the scavengers that remove the injured nerve by-products. The sequential finding of complement activation followed by macrophage recruitment is compatible with the autopsy findings in AMAN patients \[8\]. In severe cases, axonal degeneration can also occur.

### 2.2 Fisher syndrome and Bickerstaff brainstem encephalitis

Chiba and colleagues identified IgG autoantibodies against GQ1b in patients with FS and proposed that these autoantibodies were diagnostic markers of FS \[46\]. Anti-GQ1b antibodies occur in 83% \((n = 466)\) \[23\], 96% \((n = 24)\) \[47\] and 100% \((n = 9)\) \[48\] of FS patients. The association of IgG anti-GQ1b antibodies with BBE was first found in a patient with acute ophthalmoplegia, ataxia and areflexia, who was initially comatose but made a complete recovery 2 months after the onset of her illness \[49\]. BBE (the diagnosis in this patient) was at the time thought to be distinct from FS. However, the unexpected presence of anti-GQ1b antibody led the authors to confirm anti-GQ1b antibodies in two separate BBE patients, which decreased with their clinical improvement.

Patients with FS and BBE present with an antecedent episode prior to the onset of their neurological symptoms. Epidemiological association between \textit{C. jejuni} and \textit{Haemophilus influenzae} infections have been established in patients with FS \[50\] and a study looking at the serological evidence of infection in BBE and FS patients found \textit{C. jejuni} and \textit{H. influenzae} to be the two most common infecting agents in this group of patients \[25,51\]. Molecular mimicry whereby the lipo-oligosaccharides of \textit{C. jejuni} isolated from FS or BBE patients mimic the GQ1b has been demonstrated \[51,52\]. Other mimics include the GQ1b-like lipo-oligosaccharide of \textit{H. influenzae} isolated from an FS patient \[53\]. Therefore, it is likely that the infectious agents of patients with FS or BBE carrying various GQ1b mimics induce the production of IgG anti-GQ1b antibodies leading to the development of the disease.

Immunohistochemical studies show that GQ1b is highly expressed in the extramedullary regions of the human oculomotor, trochlear and abducens nerves \[54\]. Neuromuscular junctions may be particularly vulnerable to autoantibody attack as they are outside the blood–nerve barrier, and monoclonal anti-GQ1b antibody has been shown to bind to motor endplates of human oculomotor muscles \[55\]. Postural body sway analysis results suggest that FS patients also have a dysfunctional proprioceptive afferent system, and ataxia is caused by the selective involvement of muscle spindle afferents \[56\]. These muscle spindles contain specialized muscle fibres, which have motor innervations enriched with sensory endings. It is likely that the neural components and infratusal muscle fibres of these spindles are important targets in FS because they have also been labelled by monoclonal anti-GQ1b antibodies in humans \[55\]. The muscle spindles are the likely underlying cause of ataxia experienced by FS patients. This would also explain the good outcome seen in FS and BBE patients who typically show recovery with no sequelae \[23,27\].

In BBE, the characteristic distinguishing clinical feature is altered consciousness, which is central in origin. Although the evidence is lacking, it is postulated that the breakdown of the blood–brain barrier at vulnerable sites such as the area postrema or blood–nerve barrier at the roots of the oculomotor cranial nuclei allow access to anti-GQ1b antibodies. This is followed by autoantibody binding to its related sites within the brainstem reticular formation resulting in altered consciousness.

To summarize, the possible mechanism underlying the pathogenesis of FS and BBE is as follows: i) infection by a micro-organism expressing GQ1b epitope triggers the production of IgG anti-GQ1b antibodies; ii) these antibodies bind to GQ1b which are highly expressed on the oculomotor nerves and group 1a muscle spindles producing FS; iii) in some patients, these antibodies can also penetrate deficient sections of the blood–brain barrier, binding to GQ1b that may be expressed in the reticular formation, thus causing BBE \[57\].
3. Current immunotherapies in Guillain-Barré syndrome

Several randomized, controlled trials have looked at the various immunotherapies in the treatment of GBS. These trials have looked mainly at the efficacy of steroids, PE and IVIG in hastening the recovery in GBS.

3.1 Steroids

In view of the fact that GBS is an immune-mediated neuropathy, the use of steroids would be expected to help improve the course of the illness. However, several trials have shown that steroids alone do not confer any added benefit in the treatment of GBS as compared to placebo or supportive treatment. In fact, a meta-analysis of four trials using oral corticosteroids showed significantly less improvement in patients who were on treatment as compared to those who were not [58]. One trial looking at the effects of intravenous methylprednisolone also showed no significant improvement in patients who received treatment compared to placebo [59].

The reasons why steroids alone are ineffective in GBS remain unclear. If we were to look back at the pathogenesis of the AMAN rabbit, pathological studies suggest that macrophages are more prominent in the recovery phase than in the acute progressive phase, when they exert their effects as scavengers of the injured peripheral nerves (Figure 1) [45]. It is possible that by inhibiting this effect with steroids, the nerve repair process is also affected. The AMAN rabbit model may be helpful to confirm this hypothesis. In AIDP patients, complement-mediated myelin damage was seen before the invasion of macrophages into the myelin [9], suggesting that the macrophages are also scavengers of the injured nerve fibres in AIDP. Treatment with steroids may remove the scavengers, which may have a role in aiding the remyelination process in AIDP, hence delaying recovery in AIDP.

However, the role of steroids when used in combination with IVIG should not be completely disregarded. Although the initial results of a trial using this combination therapy showed no significant improvement, the authors noted a possible effect in favour of the combined steroids and IVIG therapy when adjusted for known prognostic factors such as age. The use of steroids in combination with IVIG was not harmful and could possibly further hasten the recovery in GBS [60,61]. The effectiveness and the action mechanism of methylprednisolone in combination with IVIG could be further investigated in the AMAN animal model.

3.2 Plasma exchange

The first suggestion that PE would be beneficial in an autoimmune disorder dates back to 1959 when a case of thrombotic thrombocytopenic purpura went into remission following fresh blood exchange [62]. In 1978, Brettle et al. first reported the use of PE in the treatment of a patient with acute polyneuropathy, noting this patient’s rapid recovery [63]. Several case reports and case series of the successful use of PE were later reported [64-66]. In 1985, PE was established as a treatment for GBS following a large trial that compared PE with conventional therapy in 245 patients with GBS [67]. The PE group showed improvement at 4 weeks, improvement of one clinical grade, improved time to independent walking and improved outcome at 6 months, all of which were statistically significant. PE was particularly effective in patients who received the treatment within 7 days of onset and in patients who had a more severe disease, requiring mechanical ventilation. The beneficial effects of PE were later confirmed by the French clinical trial of 220 patients with GBS [68]. Patients received four plasma exchanges, with either albumin or fresh frozen plasma as the replacement fluid. There was no difference in the efficacy between fresh frozen plasma and albumin as the replacement fluid. However, due to the potential risk of viral infections, fresh frozen plasma should never be chosen as a replacement fluid in PE.

The question as to the optimum number of exchanges in GBS was addressed in a trial that randomized 556 GBS patients according to their severity and specified them to receive different numbers of exchanges [69]. A 1.5 plasma volume per exchange regime was instituted. Patients who were considered mild received either no treatment or two PE. Those who were moderately affected (could not stand unaided) received either two PE or four PE and patients who were severe (ventilated patients) received either four or six PE. The trial results showed that in the mild and moderate groups, two and four exchanges, respectively, were more beneficial; no difference was seen when six exchanges were used instead of four in the severe group. Based on the hypothesis that PE removes pathogenic antibodies, the effect of the number of PEs on the reduction of immunoglobulin was investigated in 11 patients with GBS [70]. There was a significant decrease in immunoglobulin by 40 - 60% after the first two sessions but no further reduction was seen subsequently, implying that at least two PE are required in the treatment of GBS.

A mouse model of AMAN was produced by passive transfer of anti-GM1 and -GD1a antibodies using normal human sera as a complement source. This study indicates that the pathogenic autoantibodies are responsible in the development of AMAN [71,72]. Passive immunization with anti-GM1 and -GD1a antibodies directly inhibits axon regeneration in mice [73,74]. These findings support the hypothesis that PE works by eliminating the pathological autoantibodies, at least in AMAN.

3.3 Intravenous immunoglobulin

The rationale for using IVIG was based on its success in improving the clinical course of other autoimmune disorders such as idiopathic thrombocytopenic purpura [75]. In 1988, Kleyweg et al. reported the use of IVIG in eight patients with severe GBS where they observed a beneficial effect in some patients [76]. By this stage, the efficacy of PE had already
The possibility of IVIG having a comparable effect to PE was investigated in a randomized trial of 150 patients. The interim results suggested that IVIG was not only equally effective but was better tolerated, with fewer complications. This makes IVIG a more attractive therapeutic option. In particular, not all centres are able to offer PE and not all patients can tolerate it; for example, children and patients with haemodynamic instability. A further randomized controlled trial involving 383 patients investigated the efficacy of PE against IVIG as well as the benefits of treatment with PE followed by IVIG. This trial confirmed that IVIG and PE were comparable in reducing disability at 4 weeks, and there were also no significant differences between the two in the secondary outcome measures. The combination of PE followed by IVIG also showed no significant differences compared with either PE alone or IVIG alone. It is worth noting that the numbers of patients who received less than 75% of PE or IVIG were 18/121 and 3/130, respectively, suggesting that IVIG was better tolerated. In children, GBS is associated with a better prognosis, justifying trials of IVIG in comparison to supportive treatment only; all trials have shown that IVIG hastens the recovery of muscle strength by 4 weeks.

The current dosage of IVIG used in the treatment of GBS is 0.4 g/kg given over 5 days, or a total of 2 g/kg. This dose is based on its use in other autoimmune conditions. The optimum dosage of IVIG in GBS is not known but administering IVIG over 3 days compared to 6 days showed no significant difference in the outcome. The pharmacokinetics of IVIG also varies in GBS patients and some have a smaller rise in serum IgG following the administration of IVIG. These patients were also noted to have a significantly poorer outcome, with fewer able to walk unaided at 6 months, raising the possibility that this group of patients would benefit from either having a higher dose or a second course of IVIG. Studies have suggested IVIG may confer greater benefits compared to PE when there is a presence of C. jejuni infection and anti-GM1 antibodies in patients with GBS.

The mechanism by which IVIG exerts its effects is multifactorial. It includes: the suppression of antibody production and the provision of anti-idiotypic antibodies that can neutralize autoantibodies; inhibition of complement activation and membrane attack complex formation; modulation of the expression and function of Fc receptors on macrophages and other effector cells; and suppression of cytokine, chemokine and adhesion molecules.

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translated to the effects of IVIG in hastening the recovery of patients with AMAN. Further animal studies are required before we can conclude that IVIG prevents axonal degeneration in AMAN by inhibiting complement deposition and the subsequent membrane attack complex formation.

4. Immunotherapy in Fisher syndrome and Bickerstaff brainstem encephalitis

There have been no randomized clinical trials of treatment in FS or BBE [90]. Both IVIG and PE have been used in the treatment of both. In FS, although IVIG slightly hastens recovery, the final outcome remained unchanged [91]. BBE also generally has a good prognosis; however, reports of mortality would justify treatment with either IVIG or PE. In the FS or BBE cases presenting with a GBS overlap, treatment with either PE or IVIG is recommended as randomized controlled trials have established the efficacy of both treatments in GBS [28,92].

5. Future treatment and research

Despite the established treatments of IVIG and PE in GBS, there continues to be mortality of up to 9% and severe disability of 17% [28]. These statistics are derived from well-structured trials in referral centres. It is likely that the morbidity and mortality are higher in countries and centres that do not have similar resources made available to them. The cost of treatments also differs between countries and can have significant financial impact on existing health resources in many countries. Both treatments are associated with potential complications and trials have shown that not all patients are able to complete the full dose of treatment. Moreover, the trials have also shown that some patients develop treatment-related fluctuations as well as treatment failures [93]. For these reasons, better treatments need to be developed for these conditions.

Understanding the pathogenesis of GBS and its related conditions is crucial to the understanding and development of treatment options in GBS. Although there has been a better understanding of the pathogenesis of AMAN and FS [57,94], this has not been sufficient to result in a direct clinical benefit in terms of effective treatments. Molecular mimicry leading to autoantibody formation and complement activation appears to play a key role in the development of these conditions. Complement inhibitors such as nafamostat mesilate have long been in clinical use in Japan for the treatment of disseminated intravascular coagulation and acute pancreatitis without any serious adverse effects. Nafamostat mesilate has already been shown to be effective in the AMAN rabbits where treated rabbits showed less complement deposition and sodium channel cluster disappearance when compared to the non-treated rabbits [95]. The humanized monoclonal antibody, eculizumab was shown to protect against complement-mediated damage in the murine model of FS [96]. Both studies provide the rationale for undertaking clinical trials of complement inhibitors such as nafamostat mesilate and eculizumab in GBS and other antibody-mediated neuropathies where complement activation is believed to be involved.

Within the scope of the existing treatment, further studies to address the value of adding a second IVIG course or a higher dosage of IVIG for severe GBS patients are required. Recently, a clinical prognostic scoring system was developed based on age, preceding diarrhea and the GBS disability score [97]. There may be a role for this score (referred to as the Erasmus GBS outcome score) to be used in identifying patients with a worse prognosis who may benefit from treatment escalation. Severe GBS patients who show only a transient rise in their serum IgG following IVIG treatment are also likely to require a second course of IVIG. The same applies to those who show treatment-related fluctuations and relapses [93]. Special groups of patients in whom the benefits of treatment with PE or IVIG are less clear include FS and BBE patients, as well as those with mild forms of GBS and patients who present 2 weeks after the onset of illness. Further trials to look at this group of patients would also allow for a more comprehensive recommendation of treatment in GBS.

6. Conclusion

It is almost 20 years since PE and IVIG were established as effective treatments in GBS. In that time, there have been significant advances in the immunopathogenesis of GBS. Unfortunately, at present we are still some way from being able to translate this knowledge into developing new effective treatments in GBS. Complement inhibitors appear to be a promising therapeutic option and further work will need to be done to explore their use in GBS and its related conditions.

7. Expert opinion

GBS is a post-infectious, immune-mediated condition and there is good evidence to suggest that molecular mimicry between microbial components and self-antigens leads to autoantibody formation, resulting in complement-mediated nerve injury. Both PE and IVIG have been established as effective treatments in GBS but, despite this, there is still as much as 20% mortality and severe disability. The ultimate goal in the treatment of GBS is to develop cost-effective therapies that are easily available to all centres and that will allow patients to achieve complete remission of their monophasic disease without developing unwanted side effects.

Based on the current evidence from clinical trials, the recommendations are that patients who present within 2 weeks of the onset of illness and are not able to walk unaided should receive either PE or IVIG (given within this period), both of which will hasten their recovery and improve their outcome. IVIG is preferable as it can be administered immediately and has fewer complications and contraindications than PE. However, we know that the
clinical presentations in GBS can be heterogeneous and there may be situations when these recommendations could be modified to provide better treatment options. The use of steroids in combination with IVIG is not harmful and could possibly further hasten the recovery in GBS. We therefore suggest the combination therapy of IVIG and methylprednisolone in patients with GBS, even if the final clinical outcome is similar to that of IVIG alone. Severe GBS patients with a poor prognostic score and those who show only a transient rise in their serum IgG following IVIG treatment are likely to require a second course of IVIG. The same applies to those who show treatment-related fluctuations and relapses. Although not clinically proven, administering IVIG following PE is theoretically more effective than IVIG alone and this could also be considered in GBS patients with a worse prognosis. In cases of mild GBS and uncomplicated FS, treatment with either IVIG or PE is currently not warranted in view of the good prognosis but we would recommend treating patients with BBE and FS overlapped with GBS.

Despite treatment with PE and IVIG, there continues to be up to 20% who either die or are severely disabled. Moreover, both treatments have their drawbacks in terms of cost, availability (they are typically available only in specialist tertiary centres) and complications. Better treatment options are required and intensive research into this area is urgently needed. Many areas within this field remain unclear. For example, the mechanisms by which IVIG is effective in GBS have yet to be fully determined. We hypothesize that IVIG acts by neutralizing the pathogenic antibodies, inhibiting autoantibody-mediated complement activation and membrane attack complex formation, which would have resulted in nerve injury. We also hypothesize that steroids alone are ineffective because of their role in removing macrophages, which are in fact the scavengers that are necessary in the recovery process of nerve injury.

The last 20 years have certainly seen major advances in unravelling the pathogenesis of GBS and we believe that the translation of this work to therapeutic advances in GBS and its related conditions is only a matter of time.

**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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