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REVIEW

# Guillain-Barré Syndrome: Progress in Diagnosis, Biomarkers, Neuroimaging and Management

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**Abstract:** Guillain–Barré syndrome (GBS) is the leading cause of acute flaccid paralysis worldwide and represents a heterogenous spectrum of acute autoimmune polyradiculoneuropathies. Over the past decade, large international cohorts and advances in neuroimmunology have improved understanding of its clinical subtypes, infectious triggers, and pathophysiology. This review summarises recent progress across key aspects of diagnosis, prognostication, and treatment. We first describe updated perspectives of clinical heterogeneity including GBS variants and geographical variability, and the recognition of autoimmune nodopathies as an important differential diagnosis. We then discuss updated knowledge on antecedent infections including *Campylobacter jejuni* and anti-ganglioside antibodies, as well as the revised role of electrodiagnosis, as an exclusively diagnostic tool rather than allowing definite and meaningful subtype classification. Established prognostication models such as Erasmus GBS Outcome Score and Erasmus GBS Respiratory Insufficiency Score as well as emerging fluid biomarker candidates spanning biochemical, immunological, nerve-structural markers are reviewed. Advances in neuroimaging that aid in diagnosis and subtyping of GBS are also discussed. Finally, we highlight the evidence reaffirming intravenous immunoglobulin or plasma exchange as current standard-of-care and critically evaluate ongoing and recently completed trials including complement inhibitors.

**Keywords:** diagnosis, Guillain-Barré syndrome, pathophysiology, prognosis, treatment

## Introduction

GBS is the leading cause of acute flaccid paralysis worldwide and represents a heterogeneous group of disorders characterized by autoimmune injury to the peripheral nerves.[1] Over the past decade, substantial progress has been made across multiple aspects, including clinical and regional heterogeneity, significance of antecedent infections, prognostication models, electrodiagnosis, refinement of anti-ganglioside antibody (AGA) testing, the recognition of autoimmune nodopathies (AN) as differential diagnoses, and the emergence of novel imaging and fluid biomarkers. Large prospective international cohorts such as the International GBS Outcome Study (IGOS) have played a pivotal role in driving these developments.

Despite these advances, GBS still remains a clinical diagnosis due to limitations of currently available diagnostic investigations. Therapeutic strategies also continue to rely on regimens established decades ago, as recent clinical trials have not yet led to changes in standard care, underscoring the need for future research. In this review, we summarize the major progress in the diagnosis and treatment of GBS over the last decade. We also highlight key updates reflected in the 2023 revised EAN/PNS guidelines and discuss emerging candidates of targeted therapeutics.

## Clinical Characteristics

Clinical presentation of GBS varies widely across patients in terms of symptom pattern (motor vs sensory), distribution, and severity. Despite this heterogeneity, all cases share an acute onset followed by a gradual recovery phase lasting over

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several months. GBS is temporally defined when the nadir is reached within 4 weeks, although in most patients, the nadir reaches within two weeks.[2] The best-characterized subtype is classic sensorimotor GBS, which begins distally and ascends with progressive sensory disturbances and motor weakness, and loss or reduction of deep tendon reflexes. This subtype predominates in Europe (72%) and America (68%).[3,4] In contrast, pure motor GBS, which typically lacks sensory signs or symptoms and often demonstrates axonal features such as low CMAP amplitudes on electrophysiology, is more common in Asian countries (as reported in Bangladesh, 71%).[3] Cranial and autonomic nerve involvement are also observed commonly.[3–5]

A substantial proportion of patients present with variant forms. The most frequent being Miller Fisher syndrome (MFS), characterized by the triad of ataxia, ophthalmoplegia, and areflexia. Anti-GQ1b antibodies are highly specific and thus recommended in this form.[6] Incomplete forms or overlap with sensorimotor GBS are not uncommon. Bickerstaff brainstem encephalitis (BBE) comprises a rare variant among the MFS spectrum, presenting with ophthalmoplegia, ataxia, and impaired consciousness. Other regional forms of GBS include the pharyngeal-cervical-brachial variant (associated with anti-GT1a antibodies), which mainly affects facial, bulbar, and upper limb muscles; the paraparetic variant involves only the lower limbs; and purely sensory GBS (often linked to anti-GD1b antibodies). In such atypical presentations, meticulous evaluation for alternative diagnoses is essential.

Approximately 8~16% of patients may experience treatment-related fluctuations (TRFs) – initial stabilization or improvement after IVIg or plasma exchange followed by subsequent deterioration.[7,8] TRF reflects ongoing disease activity beyond the pharmacologic duration of IVIg, and re-treatment with IVIg or plasma exchange is recommended in these cases. When progression or relapse occurs more than twice and beyond 8 weeks from onset, acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered, and long-term immunotherapy may be required. AN can also present with acute onset and chronic course, but are typically poorly responsive to IVIg or corticosteroids.[6] Therefore, testing for nodo-paranodal antibodies and consideration of more effective treatments such as rituximab should be considered in those with acute-onset CIDP.

## Antecedent Events

GBS is understood as an autoimmune process against the peripheral nervous system that develops following an immune trigger such as an antecedent infection. GBS may also occur after certain vaccines for influenza, herpes zoster, and SARS-CoV-2 vaccines, but at a much smaller magnitude relative to their public health benefits. More than 70% of patients have a history of symptomatic infection within 6 weeks of onset, most commonly gastroenteritis or upper respiratory tract infection, which supports the diagnosis.[3] Nearly half of patients show serological evidence of a recent infection, including *Campylobacter jejuni, Mycoplasma pneumoniae*, hepatitis E virus (HEV), Cytomegalovirus (CMV), and Epstein-Barr virus (EBV) Multiple positive serologies can also be identified in approximately 6% of cases.[3]

Among all pathogens, *C. jejuni* is the most frequently identified trigger in GBS and has the most well-established causal relationship. Epidemiologic data indicate that for every 1,000 *C. jejuni* infections, approximately 0.3~1.2 cases of GBS occur, corresponding to a 77~100-fold higher risk compared with the general population.[9,10] The sialylated lipo-oligosaccharide (LOS) on the surface of *C. jejuni* share structural similarity with gangliosides such as GM1 or GQ1b, which are distributed at the nodes of Ranvier or the motor nerve terminals.[11] Consequently, *C. jejuni* infection may elicit cross-reactive immune responses through molecular mimicry, leading to peripheral nerve damage. Among the various LOS classes, class A is strongly associated with GM1 antibody and motor GBS, whereas class B shows a particular association with GQ1b antibody and MFS variant.[12] Capsular genotypes have also been recognized as an additional factor linked to GBS.[13]

Recent serological investigations have deepened our understanding of how antecedent infections relate to GBS subtypes and prognosis. In the IGOS cohort of 1,000 patients, 76% reported an antecedent event, and this was less frequent in sensorimotor GBS (59%) compared with other subtypes.[3] As expected, *C. jejuni* was the most common pathogen (30%) across all continents and was symptomatically associated with gastroenteritis. Patients with *C. jejuni* associated GBS showed more severe weakness at nadir and a poorer recovery. Their clinical presentations further varied by region; pure motor variants with axonal EDX subtypes were notably more common in Asian than in Western

populations, suggesting possible regional variation in bacterial strains and ganglioside distribution within peripheral nervous system.

Pathogens mainly linked to respiratory infections were CMV and *M. pneumoniae*.[3] CMV infection was associated with sensorimotor, demyelinating GBS, while *M. pneumoniae* infection was associated with a slower progression to nadir, younger onset age, and cranial nerve involvement. CMV-related GBS appears to be extremely rare in Asia or Africa. HEV, like *C. jejuni*, was associated with poor prognosis, whereas EBV and CMV related cases showed better outcomes. Symptomatic infection did not always correspond to serological findings; broad serological testing can be therefore helpful for subtyping and prognostication.

## Electrodiagnosis

Earlier Electrodiagnosis (EDX) criteria proposed by Ho et al (1995) and Hadden et al (1998).[14,15] They classify cases as AIDP when marked slowing of motor conduction velocity, prolonged distal motor or F-wave latencies, and temporal dispersion (Ho) or conduction block (Hadden) predominate; Acute motor axonal neuropathy (AMAN) is defined when such demyelinating features are absent and CMAP amplitudes are low. This framework was however challenged by reports that AMAN patients could also exhibit EDX features within the "AIDP" range.[16] In 2010, Uncini and colleagues proposed that serial recordings could improve recognition of AMAN by determining whether early conduction blocks represent an axonal pathology, by evolving into reversible conduction failure (RCF) or axonal degeneration.[17] However, this approach might be practically limited by its inability to provide early subtyping. In 2015, Rajabally and colleagues suggested that strengthening the cut-off values for conduction slowing for AIDP diagnosis may allow for reliable identification of axonal GBS with a single initial study.[18] Since, various studies have been conducted to attempt to delineate the best possible set of criteria, but have been hampered by methodological issues starting with gold-standard definition for any given subtype, as well as the important issues of technical performance and timing of EDX studies together with the dynamic nature of changes observed throughout the natural history of the disease as well as from therapeutic intervention.[19–23]

The 2023 EAN/PNS GBS guidelines (Table 1), through re-evaluation of the evidence as well as therapeutic relevance, shifted the value of EDX for GBS from electrodiagnostic subtype classification, towards an exclusively more diagnosis-focused approach.[6] The reason for this shift is largely practical; (1) currently there is no gold standard for a reliable subtyping, and (2) therapeutic strategies do not differ between subtypes. A two-tiered framework for interpreting electrophysiology was proposed; the first tier comprising high-sensitivity supportive features, including absent

**Table 1** Key Changes in GBS Management From Previous Guidelines to 2023 EAN/PNS Recommendations

| Management | Previous Guideline Position | 2023 EAN/PNS Guideline Position |
|---|---|---|
| **Mildly Affected, Ambulant Patients** | Immunotherapy recommended for any patient who had lost the ability to walk (or was rapidly deteriorating). | Formalizes "watchful waiting" as a valid option for mildly affected patients who remain able to walk independently. |
| **Poor Response to Initial IVIg** | A second course of IVIg could be considered | Strong recommendation AGAINST a second IVIg course |
| **Sequential or Combination Therapy (IVIg + PE)** | Some evidence of benefit was debated; sequential therapy was sometimes used in desperate cases. | Advises against both sequential and combination regimens. |
| **Corticosteroids** | Recommended against use. | Stronger recommendation against use, reinforced with updated evidence. |
| **Supportive Care** | Acknowledged as important, particularly respiratory monitoring. | Dramatically expanded and formalized as a pillar of treatment. Includes detailed, evidence-based guidance on pain management, dysautonomia, rehabilitation, and psychological support. |


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H-reflexes (95~100% sensitive), indirect discharges and abnormal facial nerve studies or blink responses, which help confirm clinical suspicion but lack specificity. The second tier consisted of high-specificity abnormalities notably the sural sparing pattern (91~98% specific), and distal CMAP duration prolongation (91~100% specific) that substantially increase diagnostic certainty. It is noteworthy that the evidence base for this approach remains limited and that further work is needed to fine-tune the use of EDX in GBS diagnosis, particularly in the differential diagnosis with clinical mimics, as illustrated through subsequent studies.[24] Although the guidelines emphasized that initial EDX may appear normal in early GBS and therefore does not exclude the diagnosis, the accuracy of this statement remains unproven if extensive testing is performed and all relevant parameters are analysed.

## Prognostication

Patients with GBS vary substantially in severity, rate of progression, and outcomes, making prognostication essential for patient counselling and for clinical trials. Despite treatment, disability is seen in 14% of patients at one year with 4% mortality within the first year. Furthermore, loss of full strength, persistent pain and need for professional change occurs in about 40%.[25] Modelswere developed and validated using several simple but clinically meaningful predictors –age of onset, preceding diarrhoea, and muscle weakness – to estimate short- and long-term outcomes. In 2007, the Erasmus GBS Outcome Score (EGOS) was introduced, assigning 1~7 points based on onset age, preceding diarrhoea, and the GBS disability score at 2 weeks, predicting the likelihood of independent ambulation at 6 months with good accuracy (AUC 0.85).[26] The model was later revised in 2011 so that it could be applied as early as hospital admission, replacing the 2-week GBSDS with the MRC sum scores at admission or at 1 week (modified EGOS; range 0~9 points at admission and 0~12 points at week 1).[27]

In 2010, the Erasmus GBS Respiratory Insufficiency Score (EGRIS) was developed to predict the risk of mechanical ventilation, using 3 parameters; interval from onset to hospital admission, presence of facial/bulbar weakness, and the MRC sum score at admission (progression rate), resulting in a 0~7 point scale.[28] All of these models have been successfully validated in independent cohort studies, supporting their utility in both clinical and research settings.[29–32] A modified EGRIS was recently proposed based on bulbar weakness, progression speed, and MRC grade of neck flexion and bilateral hip flexion, producing 0~32 point scales.[33] Future research may aim to achieve independent validation of the modified EGRIS and to further improve prognostic accuracy through eventual integration of fluid biomarkers.

## Autoantibody Testing

Since AGA were first identified in patients with GBS, their prevalence, clinical and electrophysiological correlates, prognostic value, and pathogenic mechanisms have been extensively investigated.[34–38]AGAs primarily bind to the nodes of Ranvier of motor/sensory myelinated fibres or to the motor nerve terminals of cranial or limbs nerves, leading to complement activation, immune cell infiltration, and subsequent irreversible axonal degeneration. Classically, GM1 and GD1a are associated with AMAN, GQ1b with the MFS spectrum, GT1a with PCB variants, and GD1b with acute sensory axonal variants, reflecting the antigenic distribution within PNS[34,37] *Mycoplasma pneumoniae* or CMV infection frequently associates with autoantibodies to GalC and GM2, respectively, although the causal relationships have not been fully established.[39] Emerging evidence suggests that AGAs may also serve as prognostic biomarkers in GBS. A Japanese study in 2020 showed that GD1a seropositivity was associated with poor outcomes along with the modified EGOS score.[40] High acute-phase GM1 antibody titres and their persistence during follow-up independently predicted worse prognosis.[41]

The 2023 EAN/PNS guidelines limit the use of AGA testing for routine diagnosis of GBS.[42] (1) AGA testing in the most common sensorimotor type of GBS is of very low sensitivity, and is therefore not recommended. (2) Classifying GBS subtypes using AGA profiles is also discouraged, since it rarely affects therapeutic decisions. However, GQ1b antibody testing can be diagnostically valuable in patients within the MFS spectrum, in whom electrodiagnosis and CSF analysis are often non-contributory; in these cases, GQ1b antibodies have been reported to exhibit near 100% specificity.[5]

Recent combinatorial glycoarray studies have highlighted new opportunities to enhance the diagnostic value of AGA testing in GBS. In the work by Halstead et al, IgG AGAs against 12 individual antigens and 66 combinations were analysed in serum samples from 266 GBS patients and 579 controls.[43] This approach improved sensitivity from 49.2% to

58.3%, while maintaining specificity above 80%. More recently, a comprehensive profiling study within the IGOS cohort examined IgG, IgM, and IgA reactivity against 136 targets in 1,413 GBS patients and 1,061 controls. 92.6% of patients demonstrated reactivity to at least 1 target.[39] Notably, several heteromeric complex antibodies showed superior diagnostic performance and better prediction of GBS subtypes and/or prognosis.

One of the pragmatic barriers to the broad routine use of AGA testing in clinical practice lies in the assay reliability. A recent Spanish inter-laboratory pilot study evaluated the performance of commonly used commercial antibody detection kits.[44] The sensitivity of three immunoblot-based assays for anti-ganglioside IgG antibodies was worryingly low at 25.7%, indicating a clear need for improvement, and this is also consistent with the authors' own experience. Cost-effective selection of target antigen/complexes as well as the maintenance of high assay quality would be mandatory for future AGA testing.

## Autoantibody Beyond Gangliosides

Although their pathogenic significance was initially characterized in CIDP, many patients with autoimmune nodopathy (AN) presents as acute-onset CIDP and initially fulfil diagnostic criteria for GBS.[8,45] Because AN is generally poorly responsive to IVIg and may instead benefit from B-cell depleting therapies, timely recognition is clinically important. Among these antibodies, anti-neurofascin-155 (NF155) is the most frequently detected in AN. However, the clinical phenotype usually differs from classic GBS, demonstrating a subacute or chronic onset, in usually young adults, and characteristic phenotype such as coarse, postural and intention tremor and sensory ataxia.[46,47] GBS patients harbouring anti-NF155 antibodies may demonstrate a severe clinical-electrophysiological profiles characterized by significantly greater disability at nadir, a higher prevalence of axonal injury patterns evidenced by reduced CMAP amplitudes, and more frequent F-wave latency abnormalities.[48] Patients with anti-NF186 or anti-pan-NF antibodies may present with an acute, aggressive, and often life-threatening motor weakness, making them an important differential diagnosis in GBS.[49–51] Antibodies to contactin-1 (CNTN1) or contactin-associated protein 1 (CASPR1) have also been associated with severe and aggressive courses, sometimes with motor-predominant involvement (CNTN1) or prominent neuropathic pain (CASPR1).[52,53]

Serological profiling demonstrated an association between CMV infection and anti-moesin autoimmunity in GBS, in one study. In this cohort of 40 GBS patients, anti-moesin IgG antibodies were identified in 83% of individuals (5 of 6 patients) with recent CMV seroconversion.[54] This serological correlation suggests that CMV infection may trigger anti-moesin antibody production through mechanisms of molecular mimicry or epitope spreading, thereby contributing to the breakdown of peripheral nerve integrity and initiating the autoimmune cascade characteristic of GBS. Autoantibodies identified in GBS and its mimics are summarized with their clinical relevance, in Table 2.

**Table 2** Autoantibodies Associated with GBS

| Antibody | Association |
|---|---|
| **Anti-GQ1b** | >90% of MFS<br>Bickerstaff brainstem encephalitis |
| **Anti-GT1a** | Pharyngeal-cervical-brachial variant and MFS overlaps. |
| **Anti- GT1b**[49] | AIDP |
| **Anti-GM1** | Axonal GBS, especially AMAN. ~25-30% |
| **Anti-GM1b**[50] | Associated with pure motor GBS |
| **Anti-GD1a** | AMAN, often co-occurs with anti-GM1. |
| **Anti-GD1b** | Acute sensory ataxic neuropathy and MFS. |
| **Anti-GalNAc-GD1a** | AMAN and pure motor Fisher |

(*Continued*)


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**Table 2** (Continued).

| Antibody | Association |
|---|---|
| **Anti-GD3**[51] | MFS with pyramidal tract symptoms |
| **Anti-LM1**[52] | AIDP |
| **Anti-NF155** | Subacute/chronic onset, tremor, sensory ataxia, young men |
| **Anti-NF186**<br>**Anti-panNF** | Acute, aggressive weakness |
| **Anti-CNTN1**<br>**Anti-CASPR1** | Rare; severe sensorimotor neuropathy, tremor, ataxia. Rapid progression. 60% nephropathy (CNTN1), neuropathic pain (CASPR1) |
| **Anti-Moesin** | Uncommon, but highly specific in context. Typically follows CMV infection. Generalized, severe GBS. |

**Abbreviations**: MFS, Miller Fischer syndrome; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, axonal motor axonal neuropathy; CMV, cytomegalovirus.

## Fluid Biomarkers Beyond Autoantibodies

Various biochemical, immunologic, and nerve structural biomarkers in blood and/or CSF have been investigated for diagnostic, prognostic, or monitoring value in GBS. An elevated CSF protein level with normal cellularity, referred to as albumino-cytological dissociation, is one of the most commonly used fluid biomarkers in GBS, reflecting blood-nerve-barrier disruption and present in more than 70% of patients. However, it is neither specific to GBS, and CSF protein levels may remain normal in the early stages (normal in 43% by ≤ 4 days).[5,55] CSF white blood cell counts are typically ≤5/μL but may increase to 5–50/μL; counts exceeding 50/μL should prompt consideration of alternative diagnoses.[6]

Pharmacokinetic biomarkers related to IVIg therapy have also been explored. In 2009, the Erasmus group demonstrated that a higher increase in serum IgG levels following IVIg treatment was associated with more favourable clinical outcomes.[56] However, and importantly, subsequent research 10 years later failed to demonstrate the value of repeat immunoglobulin dosing in severe GBS, contradicting the conclusions of an association between the increase in IgG level post -IVIg and outcome.[57] Albumin is an easily obtainable marker in practice, and binds to neonatal Fc receptor (FcRn) to play a role in the recycling and maintenance of IgG levels. Lower post-treatment albumin levels are significantly associated with mechanical ventilation and greater short- and long-term motor weakness and functional disability.[58] In contrast, pre-treatment albumin levels may have some value in predicting acute-phase outcomes such as the length of hospital stay, but seem to have limited utility in long-term prognostication.[29] Evidence also suggests a role for complement markers, which serve as a main effector mechanism in GBS.

Inflammatory cytokines or complements which are central to GBS pathophysiology have also been proposed as potential biomarkers. Higher serum C3 levels have been found to predict worse outcomes at 1 and 3 months, independent of established clinical prognosticators, and parallel disease activity longitudinally.[59] Validation of this finding, anddetermination of its potential diagnostic utility, needs to be conducted in larger studies, ideally incorporating a broader panel of complement biomarkers such as activated fragments. Interleukin-8 (IL-8) is a proinflammatory cytokine released predominantly by monocytes and macrophages. Recent findings suggest that CSF IL-8 levels are higher in GBS, particularly in AIDP, than in CIDP and other disease controls.[60] These observations were replicated by an independent group using an unbiased Olink proteomic approach, which demonstrated that CSF IL-8 levels in GBS exceed those in CIDP or healthy controls, and that they correlate with both short-term and long-term outcomes.[61]

Sphingomyelin in CSF has also been proposed as a potential biomarker, showing associations with demyelinating GBS and with functional disability at the time of sampling.[62] The clinical utility of these reported CSF biomarker remains constrained by limited availability of CSF specimens, therefore limiting a wide use. Highly sensitive analytical platforms such as single molecule array (SIMOA) enabled detection of nerve-derived molecules in blood, expanding the landscape of candidate biomarkers in GBS. In 2020, a pilot Austrian study reported that serum neurofilament light chain (NFL) levels were elevated in GBS patients compared with mixed controls which correlated with short-term outcomes.[63]

That same year, a Spanish group reported similar findings in a cohort of 100 GBS patients and 50 healthy controls.[64] This study further suggested that serum NFL levels were particularly high in axonal variants, and predictive of outcomes at 1 year. Subsequent studies have indicated that serum NFL may provide an additional prognostic value beyond existing clinical prognostic model, and may correlate with disease activity over time.[65,66] The recent discovery of peripherin and periaxin as novel PNS-specific fluid biomarkers has equally been promising. Using in vitro myelinating co-culture models, these markers were shown to selectively reflect axonal and myelin injury, respectively. In blood samples from GBS patients, levels of both markers were significantly elevated, while they remained largely unchanged in those with CNS disorders. When combined, these two markers showed promise for GBS subtype classification and for monitoring disease activity, providing a new direction for biomarker-driven precision care.[67,68]

However, despite the growing body of research in recent years, most biomarkers have not been implemented into clinical decision-making and remain largely at the research stage for several reasons. Many biomarkers are based on small regional cohorts or lack external validation. Nerve-derived blood biomarkers, particularly serum NFL,[6] require highly sensitive analytical platforms and thus remain inaccessible in routine practice despite their potential utility. Even well-validated biomarkers must address practical issues such as cost, turnaround time, and assay standardization before they can be adopted in clinical use.

### Neuroimaging

Magnetic resonance imaging (MRI) and nerve ultrasound (NUS) are not used as routine tests for the diagnosis of GBS. Multiple reports have indicated the value of imaging in GBS,[69,70] and few have attempted to demonstrate its value in separating GBS from acute-onset CIDP. Although on occasion helpful for GBS diagnosis itself, particularly in presence of near-normal EDX or CSF, the value in separating clinically distinct entities such as GBS and acute-onset CIDP is unconvincing.

## Treatment: Current and Future Targets

### Current Therapies

Conventional first-line treatments for GBS in non-ambulant patients consists of either intravenous immunoglobulin (IVIg) at a standard dose of 0.4 g/kg/day for 5 days or plasma exchange, with the choice often guided by practical considerations such as availability and patient co-morbidity.[6] The 2023 EAN/PNS guidelines for GBS introduced several critical refinements that differ from previous recommendations, reflecting an evolution towards a more evidence-based and patient-stratified approach. A key departure is the firm stance against a second intravenous IVIg course for patients with a poor initial response, a practice previously permitted despite limited evidence but now contraindicated due to established lack of efficacy.[57,71–73] The guidelines also maintained the strong recommendation against corticosteroids and the equivalency of IVIg and plasma exchange as first-line therapies. Furthermore, a watchful waiting strategy for mildly affected, ambulant patients was formally endorsed. The role of supportive care was also substantially elevated with expanded, specific recommendations for pain management, rehabilitation, and dysautonomia.

Sequential and combination use of IVIg and PE in GBS has been a subject of extensive clinical investigation. While the sequential strategy of administering IVIg immediately following a course of PE is biologically plausible, aiming to first remove antibodies and then modulate the immune system, large clinical trials have consistently demonstrated that it offers no significant improvement in long-term functional outcomes compared to either treatment alone.[74–76] Similarly, combination therapy, where both treatments are administered concurrently, has also failed to show a superior benefit, despite the theoretical advantage of attacking the disease process through two distinct mechanisms.[74,76] The prevailing expert opinion strongly advises against both sequential and combination regimens due to this established lack of enhanced efficacy, which is coupled with increased risks, higher costs, and greater resource utilization.[6]

### Potential Future Targeted Therapies

Novel potential more targeted therapies for GBS are currently under review, however none are yet available or used in clinical practice (Figure 1).

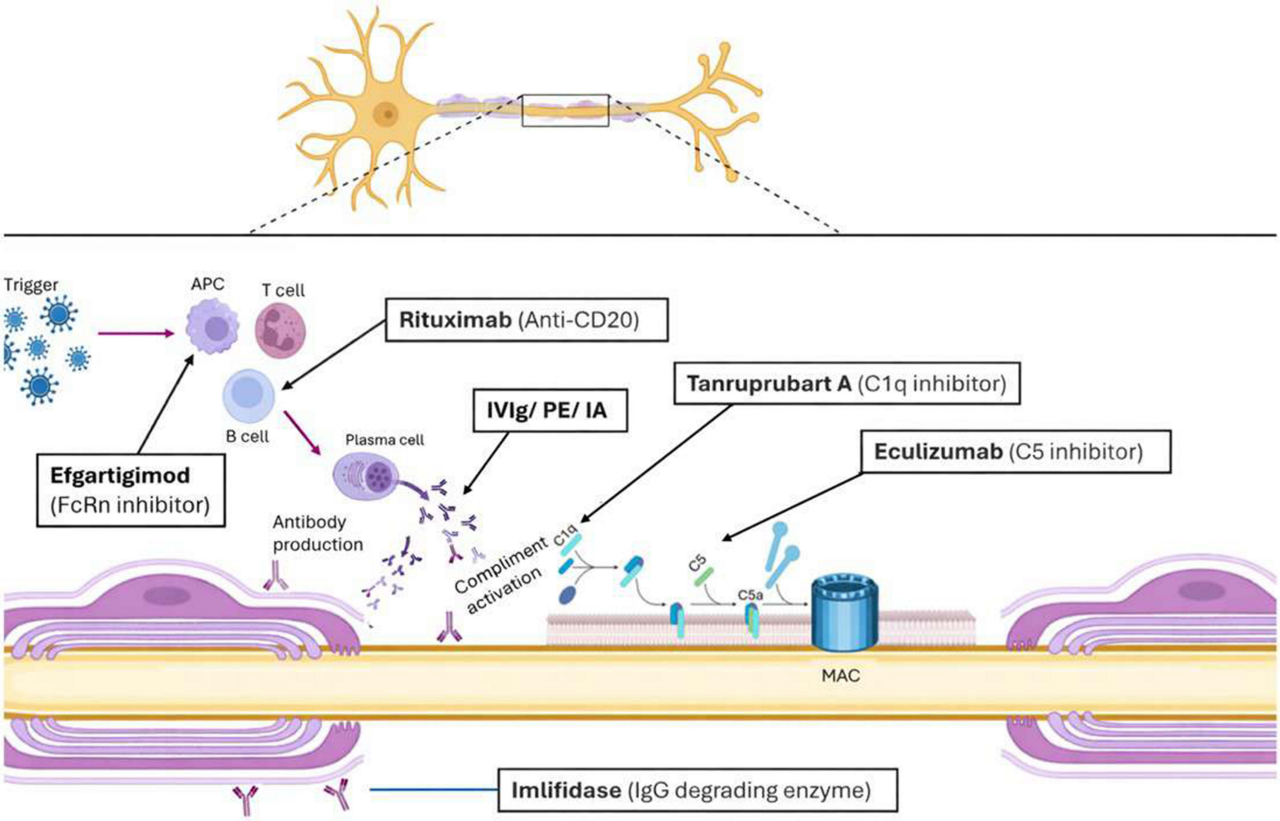


**Figure 1** GBS therapy targets.
**Abbreviations**: APC, antigen presenting cells; IVIg, immunoglobulins; PE, plasma exchange; IA, immunoadsorption; MAC, membrane attack complex; C1q, complement component 1q; C5, complement component 5; FcRn, neonatal Fc receptor.

## Complement-Targeted Therapies

The complement system is a pivotal driver of pathogenesis in GBS, especially within antibody-mediated subtypes such as acute motor axonal neuropathy. AGAs binding to nerve gangliosides trigger the cascade, culminating in membrane attack complexes (MAC; C5b-9) that cause axonal degeneration and recruit macrophages via C5a chemotaxis. Although no specific autoantibodies have been identified in AIDP, complement deposits are also found in myelin sheaths in these patients, offering complements as a promising therapeutic target for GBS regardless of subtypes.

The efficacy and safety of eculizumab, an anti-C5 monoclonal antibody that inhibits formation of the MAC in the terminal complement cascade, have been evaluated in a Phase 2 (NCT02493726, published in 2018) and a Phase 3 trial (NCT04752566, published in 2024).[77,78] Eculizumab given with standard IVIg demonstrated favourable safety profiles, but failed to meet the primary efficacy endpoints in both studies when compared with IVIg monotherapy.

Tanruprubart (ANX005) is a humanized IgG4 monoclonal antibody targeting C1q, inhibiting the classical complement pathway, which is triggered by pathogenic autoantibodies, at upstream. In a Phase 1 study, ANX005 demonstrated the intended pharmacological effects, along with promising efficacy and safety outcomes. Unpublished reports from a subsequent phase 3 trial (NCT04701164) also suggested favourable outcomes.[79] The trial was conducted in a setting where access to IVIg was extremely limited (in Bangladesh and the Philippines), and the control arm did not receive standard-of-care therapy. This limits external validity and prevents meaningful head-to-head comparison with IVIg.

## Neonatal Fc Receptor-Targeted Therapies

Neonatal Fc receptors represent another key player in GBS immunopathology. FcRn is responsible for recycling IgG molecules, thereby preventing their lysosomal degradation and prolonging the half-life of pathogenic autoantibodies. Efgartigimod, a therapeutic FcRn blockade has recently shown success in CIDP.[80] The potential benefit of efgartigimod has also been explored in GBS in case reports or small case series.[81–83] The absence of randomized controlled trials

precludes definitive conclusions regarding efficacy, optimal dosing, timing of administration, and safety in GBS. Moreover, extrapolation from its demonstrated benefit in Chronic Inflammatory Demyelinating Polyneuropathy may not be fully appropriate given the distinct pathophysiological dynamics and typically monophasic course of GBS. Collectively, these limitations underscore the need for adequately powered, controlled clinical trials before FcRn inhibition can be considered a validated therapeutic strategy in GBS.[81–84]

### B Cell and Antibody-Targeted Therapies

GBS pathogenesis is driven by a humoral immune response, where B-cells produce antibodies that mistakenly attack peripheral nerves due to molecular mimicry from prior infections like *C. jejuni*. These pathogenic antibodies cause damage by activating complement, recruiting macrophages, or directly interfering with nerve signalling. Targeting this axis involves depleting B-cells with through anti-CD20 monoclonal antibodies such as rituximab (currently in a Phase III trial performed by All India Institute of Medical Sciences New Delhi). An alternative strategic approach focuses on direct mitigation of circulating pathogenic antibodies through extracorporeal elimination techniques. While plasma exchange is non-specific, immunoadsorption (IA) offers a more selective removal method and has been shown to be as effective as plasma exchange with a potentially better safety profile, though it may carry a higher relapse risk.[85] Across the studies included in the metanalysis,[85] several methodological limitations should be acknowledged. Most trials were conducted in relatively small cohorts, substantially limiting statistical power and the robustness of efficacy and safety conclusions. Considerable heterogeneity was present in disease severity and duration, treatment protocols, including differences in processed plasma volumes, number and timing of sessions, and overall treatment intensity, which complicates cross-study comparisons. In several studies, details regarding randomization procedures, blinding, and comparator arms were either limited or not clearly reported, raising concerns about potential selection and observer bias. Collectively, these limitations underscore the need for adequately powered, methodologically rigorous, and standardized randomized controlled trials to more definitively establish IA's efficacy and optimize treatment protocols.

### IgG Degradation

Imlifidase is an IgG-degrading enzyme derived from Streptococcus pyogenes which can cleave and inactivate all four subclasses of human IgG. Data from the Phase II, 15-HMedIdeS-09 (NCT03943589) study demonstrated that severe GBS patients treated with a single dose of imlifidase, plus IVIg had rapid overall improvement in functional status including expedited recovery of muscle strength, fast return to independently walking, and a median time to independently walk by 16 days. The full results of this study have not yet been published. It remains difficult to fully comment on the study's limitations based on the preliminary information available; however, the small sample size and the absence of a direct comparison between IVIg alone and IVIg combined with imlifidase may represent important limitations.

## Failed or Withdrawn Therapies

Several investigational GBS therapies have failed in development. Recombinant Interferon-beta showed no benefit over standard care in a randomized trial, and cerebrospinal fluid filtration was abandoned due to inefficacy.[86] Among newer biologics, the complement inhibitor crovalimab (NCT05494619) was withdrawn from a clinical trial by the sponsor, and a T-regulatory cell therapy (CK0801) (NCT03773328) was also discontinued for undisclosed reasons.

# Conclusion

The landscape of GBS has evolved from a clinically defined acute neuropathy to a molecularly characterized spectrum of acute autoimmune neuropathies. This paradigm shift has been driven by recent advances in multiple aspects, including its clinical heterogeneity, deeper understanding of antecedent infections and their relevance, a reconsideration about the role of EDX, validated prognostic models, and expanding role of autoantibodies and other fluid biomarkers. Nonetheless, current therapeutic strategies remain largely rooted in treatment regimens established decades ago, and recent therapeutic

trials have yet to change therapeutic landscape. Future studies should further refine the role of EDX and fluid biomarkers and test novel targeted therapeutics through rigorously designed randomised studies.

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