Journal of Neurology (2021) 268:2402–2419
https://doi.org/10.1007/s00415-020-09742-2

REVIEW

Axonal variants of Guillain–Barré syndrome: an update

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Received: 16 January 2020 / Revised: 30 January 2020 / Accepted: 31 January 2020 / Published online: 5 March 2020

Abstract

Axonal variants of Guillain–Barré syndrome (GBS) mainly include acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, and pharyngeal-cervical-brachial weakness. Molecular mimicry of human gangliosides by a pathogen's lipooligosaccharides is a well-established mechanism for *Campylobacter jejuni*-associated GBS. New triggers of the axonal variants of GBS (axonal GBS), such as Zika virus, hepatitis viruses, intravenous administration of ganglioside, vaccination, and surgery, are being identified. However, the pathogenetic mechanisms of axonal GBS related to antecedent bacterial or viral infections other than *Campylobacter jejuni* remain unknown. Currently, autoantibody classification and serial electrophysiology are cardinal approaches to differentiate axonal GBS from the prototype of GBS, acute inflammatory demyelinating polyneuropathy. Newly developed technologies, including metabolite analysis, peripheral nerve ultrasound, and feature selection via artificial intelligence are facilitating more accurate diagnosis of axonal GBS. Nevertheless, some key issues, such as genetic susceptibilities, remain unanswered and moreover, current therapies bear limitations. Although several therapies have shown considerable benefits to experimental animals, randomized controlled trials are still needed to validate their efficacy.

Keywords Axonal GBS · Acute motor axonal neuropathy · Acute motor and sensory axonal neuropathy · Guillain–Barré syndrome

A generic view of GBS

First reported in 1916 by Guillain et al. [1], Guillain–Barré syndrome (GBS) is a autoimmune disease of the peripheral nervous system (PNS) that is clinically characterized by acute flaccid paralysis and/or sensory/autonomous nerve dysfunction. The annual incidence of GBS is 0.81–1.89 per 100,000 persons worldwide, and appears to be increasing exponentially, along with increasing age, in Western countries [2, 3]. The relative risk of GBS for males is 1.78-fold higher than that for females [2]. A majority of patients with GBS exhibit tetraplegia with sensory disturbance and loss of deep tendon reflexes. About 10% of patients with atypical GBS share normal or even hyperexcitable tendon reflexes during the early phase, especially those with pure motor signs or those diagnosed with an acute motor axonal neuropathy (AMAN), based on electrophysiology [4, 5]. Patients with classical sensorimotor GBS usually present with rapidly progressive symmetric weakness with sensory loss [5, 6]. The initiation of GBS is suggested to be caused by a complicated hyperreactive autoimmune response targeting the PNS [7].

Albuminocytologic dissociation is a hallmark of GBS and can be detected in almost 90% of GBS cases [8]. Usually, albumin in the cerebrospinal fluid (CSF) increases from the 2nd week after onset; albuminocytologic dissociation is notable in 70% of patients at the end of this week, and peaks during the 3rd week [8]. Accompanied by obvious inflammatory infiltration and demyelination of the peripheral nerves, GBS was initially defined as an acute inflammatory demyelinating polyneuropathy (AIDP). Currently, AIDP is the most prevalent subtype of GBS worldwide, yet the

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incidence of axonal GBS has increased in Asia and Europe during the past decade [3, 9]. Recent work focusing on the axonal variants of GBS (axonal GBS) has mainly concentrated on optimizing diagnosis and treatments. Computer-assisted feature analysis has resulted in greater diagnostic accuracy and plasma metabolite measurement has provided novel biomarkers [10, 11]. Based on precision medicine, identification of individual gene polymorphisms may predict the risk of axonal GBS; immune therapies (e.g., anti-B cell therapy, anticomplement therapy, and anticytokine therapy, among others) appear to be promising for the treatment of axonal GBS [12–14].

From "Chinese paralysis" to axonal GBS

More than half a century had passed before axonal variants were recognized in the 100-year history of GBS (Fig. 1) [15, 16]. The earliest probable cases of axonal GBS were recorded in Jordan in 1978; 16 GBS patients developed a rapidly progressive paralysis after a polluted water-associated diarrhea epidemic, and electrophysiology revealed polyphasic and M-shaped motor units [17]. In 1986, axonal involvement, i.e., axonal degeneration in nerve roots and distal nerves, was pathologically confirmed in an autopsy study of GBS [18]. Nonetheless, it was not until 1993 that "Chinese paralysis", a term previously used to describe annual epidemics of acute-onset flaccid paralysis among children and young adults in northern China during the summer months, was redefined as a new subtype of GBS, namely AMAN, characterized by axonal degeneration [19, 20]. Electrophysiological studies of such patients revealed a reduction in the compound muscle action potentials (CMAPs) [21]. Anti-GM1 antibody is commonly associated with AMAN, acting to block presynaptic transmitter release from motor nerves in a complement-dependent way [22]. High rates of *Campylobacter jejuni* (*C. jejuni*) infection and serum anti-GM1 IgG positivity have also been observed in AMAN [21]. In 2001, Yuki et al. for the first time established an AMAN animal model by inoculating rabbits with bovine brain gangliosides and described a Wallerian-like degeneration at the PNS caused by anti-GM1 antibodies [23].

The International Guillain–Barré Syndrome Outcome Study (IGOS) has reported a higher incidence and morbidity of axonal GBS in Bangladesh than in other Asian and European countries [24]. Younger age, fewer sensory deficits, and a trend of poorer recovery were cardinal features in Bangladeshi GBS cases [24]. A retrospective study reported that AMAN is the most common subtype, accounting for 55.8% of GBS cases in northern China [25]. Classification of GBS subtypes can be made according to multiple factors, including antecedent infection, autoantibody classification, electrophysiological patterns, geographical differences, and genetic susceptibility [26].

Clinical features of axonal GBS

Axonal GBS includes systematic subtypes, i.e., AMAN and acute motor sensory axonal neuropathy (AMSAN), and several regional variants, e.g., pharyngeal-cervical-brachial weakness (PCB) [27]. Precedent infection with *C. jejuni* is most commonly seen in patients with axonal GBS. Besides *C. jejuni*, viruses including Zika virus (ZIKV), cytomegalovirus (CMV), hepatitis viruses (types A, B, C, and E), human immunodeficiency virus (HIV), Epstein–Barr virus (EBV), shigella, clostridium, *Haemophilus influenzae* and *Mycoplasma pneumoniae*, have all been associated with the disease onset of GBS [28, 29]. Patients with either AMAN or AMSAN display motor nerve involvements [30]. Electrophysiological studies on patients with AMAN during the early phase may reveal reversible conduction blocks (CBs), reversible conduction failures (RCFs), or decreased CMAP amplitudes [27]. Electrophysiological diagnosis 3–6 weeks after GBS onset, however, is more reliable than that within 1–2 weeks [27]. Antibody detection is mainly used for the classification of axonal GBS. Anti-ganglioside IgG and IgM antibodies were first detected in patients with GBS in 1988 [31]. Antibodies to GM1 and GD1a are frequently elevated in patients with AMAN/AMSAN [32]. For PCB, anti-GQ1b and anti-GT1a antibodies are identifiable in patients [33, 34]. Given the fact that commercialized antibody detection kits have barely exhibited satisfactory sensitivity and specificity, antibody diagnostics may be optimized using synthetic ganglioside mimics to provide more convincing diagnostic values [35].

Despite the fact that Miller Fisher syndrome (MFS) was occasionally classified as an axonal subtype, more researchers would rather consider MFS as an independent variant of GBS [33]. GQ1b is mainly localized in the paranodal myelin of cranial nerves innervating ocular muscles; MFS and Bickerstaff brainstem encephalitis (BBE) are associated with elevated levels of anti-GQ1b antibody [36, 37]. In this regard, both MFS and BBE have been categorized into anti-GQ1b antibody syndrome [38]. Autopsy studies on patients with MFS revealed segmental demyelination in the PNS and the spinal cord [39]. The high recurrence rates of MFS and BBE also support that anti-GQ1b antibody syndrome mainly involve myelin pathologically [40, 41]. PCB accounts for 3% of GBS cases and shares clinical features with axonal GBS, including facial palsy, dysarthria, muscle weakness, and areflexia in upper extremities [34]. Half of the patients with MFS developed PCB, BBE, and conventional GBS in the first 7 days after onset, while the proportion of autoantibodies did not change significantly during this shift [42],

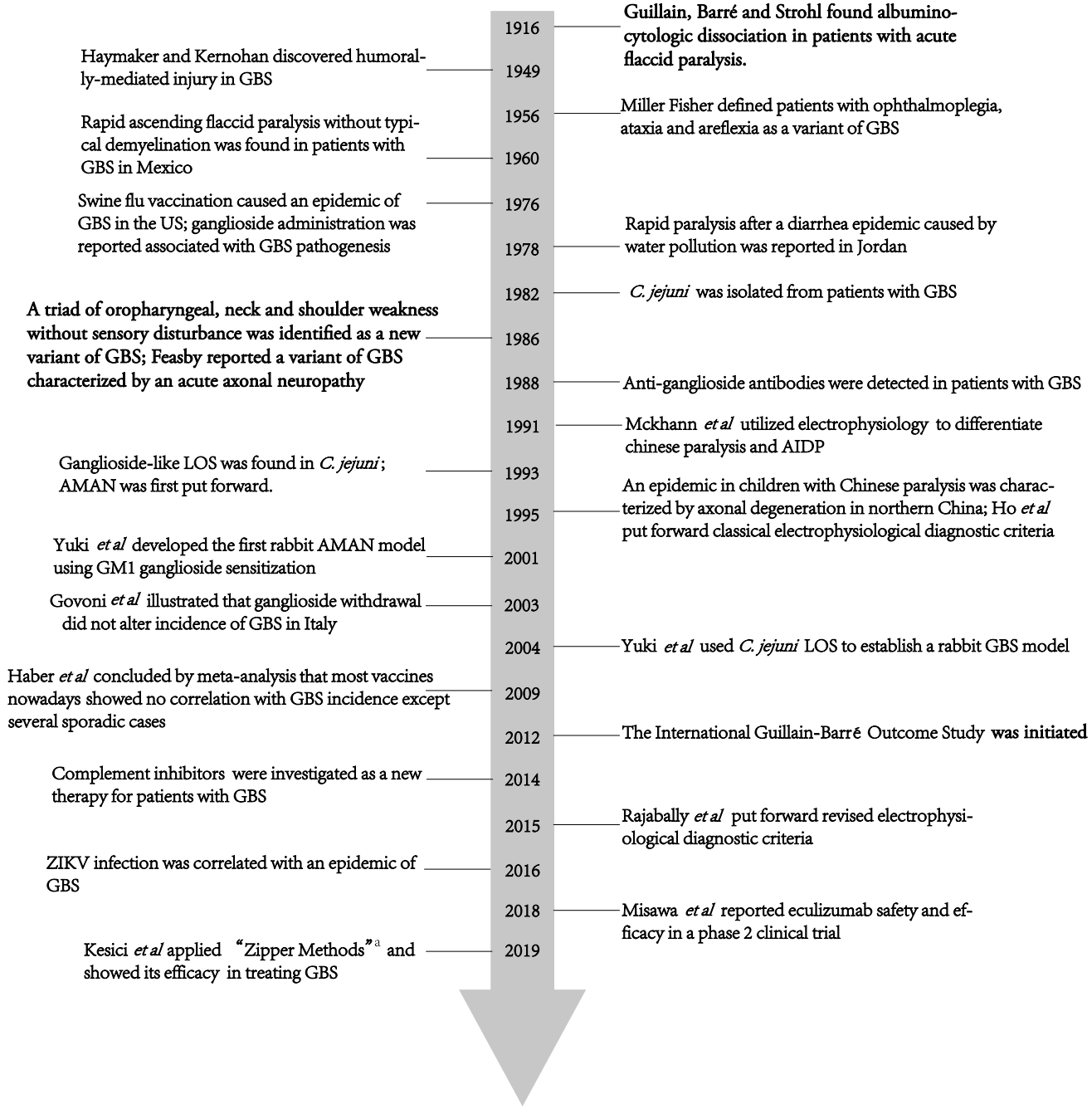


Fig. 1 Chronicle of the investigation of axonal GBS. [a]Zipper methods (1 course): PE was conducted with 1.5 volume of patients' plasma (5% albumin replacement) in the first session followed by a standard IVIg infusion (0.4 g/kg body weight). The second PE session was applied with one volume change after 24 hours from the end of the IVIg infusion. Each PE session was followed by IVIG infusions. This PE-IVIg cycle was repeated for 5 times. *AMAN* acute motor axonal neuropathy, *AMSAN* acute motor sensory axonal neuropathy, *C. jejuni Campylobacter jejuni, GBS* Guillain–Barré syndrome, *IVIg* intravenous immunoglobulin, *LOS* lipooligosaccharide, *MFS* Miller Fisher syndrome, *PCB* pharyngeal-cervical-brachial weakness, *PE* plasma exchange, *ZIKV* Zika virus

indicating that a portion of patients with PCB and conventional GBS also belong to anti-GQ1b antibody syndrome.

Presenting as unilateral or bilateral facial paralysis (BFP), Bell's palsy was occasionally regarded as a regional subtype of GBS [43]. BFP is the most common cranial nerve feature of GBS and 23% of BFPs are Bell's palsy [44]. In Colombia, 30% of GBS patients had accompanying facial palsy [45]. BFP with paresthesia is a GBS variant, and BFP itself is also highly indicative of GBS [5]. Nevertheless, typical anti-ganglioside antibodies were undetectable in patients with

BFP with paresthesia [32]. Importantly, in a HSV-associated facial paralysis model, facial nerve demyelination was observed in the descending root [46]. More pathological evidence may be required to include or exclude Bell's palsy as a subtype of axonal GBS.

To interpret the pathogenesis of axonal GBS through AMAN

C. jejuni infection and molecular mimicry

The preceding infections in patients with AMAN involve a variety of bacteria and viruses; in fact, 40–70% of GBS cases are preceded by a prodromal acute infection [47]. In southern China, antecedent gastrointestinal infection was closely associated with development of AMAN [48]. Similarly, 53% of *C. jejuni*-associated GBS cases in the Netherlands were diagnosed as axonal GBS [49]. In line with these findings, *C. jejuni* was demonstrated as a major GBS-associated pathogen in the greater Paris area between 1996 and 2007 [50]. Notwithstanding, more than half of the patients with anti-ganglioside antibodies did not have an antecedent *C. jejuni* infection in Japan [51]. A possible explanation for the inconsistency is that the virulence or antigen composition may differ between different strains of *C. jejuni*. An alternative explanation is that infections with other pathogens may account for the production of anti-ganglioside antibodies. Besides *C. jejuni*, *Haemophilus influenzae*-associated respiratory tract infections have been proposed to precede GBS; non-encapsulated *Haemophilus influenzae* has a GM1-like structure and may trigger axonal GBS [52]. The associations between anti-ganglioside antibodies and various pathogens merit further investigation. For example, the cathelicidin release, inflammasome responses, cell receptor and signaling pathways in intestinal epithelial cells and their roles in immune network in *C. jejuni*-associated gastrointestinal infection are still unknown [53].

Molecular mimicry is a widely accepted hypothesis to explain hyperreactive autoimmunity in *C. jejuni*-associated axonal GBS (Fig. 2) [54]. The presence of GM1-like epitopes on the lipopolysaccharide (LPS) of *C. jejuni* was first illustrated by Yuki et al. [55]. After recognizing that *C. jejuni* LPS carried GQ1b and GD1a-like epitopes [56], researchers hypothesized that a similarity in human gangliosides and lipooligosaccharide (LOS) of *C. jejuni* may

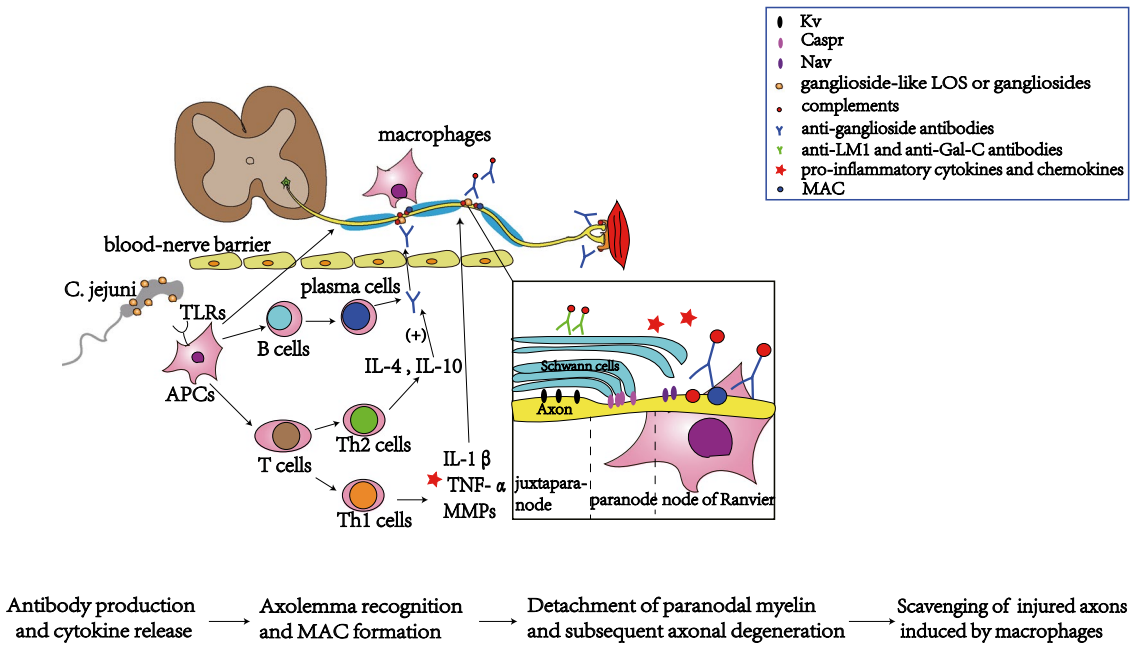


Fig. 2 Cellular mechanism in AMAN pathogenesis. Ganglioside-like LOS loaded on *C. jejuni* is recognized by TLRs expressed on APCs. APCs activate B cell and T helper cell proliferation. B cells develop into plasma cells and produce anti-ganglioside antibodies. Activated T helper cells secrete pro-inflammatory cytokines and chemokines and facilitate the penetration of macrophages across the blood–nerve barrier. Anti-ganglioside antibodies attack the nodes of Ranvier and activate complements to form MAC. MACs target axolemma and injure paranodal myelin and Nav channels. Anti-Gal-C and anti-LM1 antibodies also damage Schwann cells and myelin sheaths. IL-1β, TNF-α and MMPs aggravate the autoimmunity and macrophages phagocytose injured axons. (*AMAN* acute motor axonal neuropathy, *Caspr* contactin-associated protein, *IL* interleukin, *C. jejuni Campylobacter jejuni, Gal-C* galactocerebroside, *Kv* voltage-gated potassium channels, *GBS* Guillain–Barré syndrome, *LOS* lipooligosaccharide, *MAC* membrane attack complex, *MMPs* matrix metalloproteinases, *Nav* voltage-gated sodium channels, *Th1 and Th2 cell* T helper cell 1 and 2, *TLR* Toll-like receptor, *TNF-α* tumor necrosis factor-α)

trigger molecular mimicry [54]. Consistently, GT1a-like LOS expressed on *C. jejuni* promoted the production of anti-GT1a antibody in almost 53% of patients with GBS [57]. Interestingly, GM1-like and GD1a-like LOS may constitute a complex mimicking GM1b and trigger anti-GM1b IgG antibody release [58]. In this regard, LOS subtyping may benefit axonal GBS classification: *C. jejuni* isolated from patients with AMAN frequently had GM1-like and GD1a-like LOS [7]. After comparing the proteins extracted from the peripheral nerves of GBS patients and *C. jejuni*, researchers found that heat shock protein (HSP) chaperones of both also shared a high primary sequence homology and conservation of epitopes, implying a possible HSP mimicry [59]. In summary, molecular mimicry is a widely accepted hypothesis to explain the pathogenesis of axonal GBS. Nevertheless, only a few pathogens (i.e., *C. jejuni* and *Mycoplasma pneumoniae,* among others) have been corroborated to trigger GBS by molecular mimicry [54, 60]. Further investigations are required to identify unknown antibodies and explore other pathogens that may cause mimicry.

Unknown pathogenesis with other antecedent bacterial or viral infections

A case report proposed that a potential neurotropism of ZIKV may be associated with GBS onset [61]. Anti-ZIKV IgM was detected in most AMAN cases in Colombia [27, 62]. During the outbreak of ZIKV in Colombia, 20 of 42 patients with GBS had an antecedent ZIKV infection [63]. Interestingly, when a ZIKV outbreak occurred during 2013–2014 in French Polynesia, most patients with GBS were compatible with the electrophysiological diagnostic criteria of AMAN [64]. The positive rate of typical anti-ganglioside antibody emerging in ZIKV-associated AMAN was 31% at onset and was increased to 48% after 3 months [64]. Notably, during this epidemic anti-GA1 antibody was the most common anti-ganglioside antibody in ZIKV-associated GBS patients' sera [64]. In an outbreak of ZIKV in Bangladesh, cranial, autonomic, and sensory nerves were involved in ZIKV-associated GBS patients, yet electrophysiological studies confirmed most patients as AIDP [65]. In Brazil, ZIKV accounted for almost the same incidence of AMAN and AIDP [66]. ZIKV-associated GBS bears a higher morbidity during the acute phase and more frequent cranial nerve deficits alongside acute neuropathy and 6 months afterwards [67]. Interestingly, ZIKV infection has been shown to damage the Golgi apparatus in neurons, implying a possible intracellular mechanism by a disruption of posttranslational modification [68]. ZIKV-infected mice mainly develop seizures, neurodegeneration, and behavioral changes without typical GBS features [69]. The mechanisms underlying ZIKV-triggered GBS are unknown and need to be deciphered, e.g. through antibody and cytokine detection via high-throughput ELISA or flow cytometry.

Besides ZIKV, other viruses have been associated with axonal GBS. For instance, AMAN has been attributed to the initiation of hepatitis E infection [70]. Influenza A H1N1 infection may trigger AMAN as well [71]. CMV infection has been associated with 15% of GBS cases, mainly causing severe sensory symptoms [72]. Interestingly, electrophysiological results in virus-associated GBS exhibited higher motor and lower sensory action potentials compared to *C. jejuni*-associated GBS, providing a new strategy to differentiate between the two [49]. Although infections caused by *C. jejuni* and *Mycoplasma pneumoniae* have been demonstrated to trigger GBS by molecular mimicry [51, 59], whether other pathogens induce GBS in a similar manner or by sharing unknown pathways remains unclear.

Does ganglioside administration trigger AMAN?

The first AMAN model was established in rabbits by inoculation with a bovine brain ganglioside mixture [23]. Ganglioside as a nutritional drug has hitherto been widely used in China for nerve regeneration, although ganglioside-associated GBS cases have scarcely been documented [73]. GBS may occur following intravenous administration of exogenous ganglioside [74], and high titers of anti-GM1 antibodies were identified in these patients [75]. In fact, ganglioside-associated GBS had been reported in Europe several decades before, leading to the withdrawal of ganglioside from the European market [76]. In spite of this, no significant relationship between ganglioside use and incidence of GBS was found in a consistent study from 1981 to 2001 in Italy [77, 78].

Anti-GM1 antibodies have been detected in patients receiving ganglioside therapy [75]. More severe functional deficits at nadir and poorer recovery in ganglioside-associated GBS have been reported in northeast China [79]. Ganglioside-associated GBS bears more severe clinical features with poorer short-term prognosis than non-ganglioside-associated GBS [79]. Up to 91.67% of patients with ganglioside-associated GBS were diagnosed with AMAN according to the Rajabally's criteria [74]. However, most patients who received ganglioside did not develop either AIDP or AMAN [80]. We speculate that ganglioside might be contaminated with endotoxin during the production process, which could cause GBS by serving as immunogen and adjuvant. More evidence is needed to reach a con or pro consensus on the clinical use of ganglioside.

Does vaccination trigger AMAN or AIDP?

Vaccination has frequently been monitored as a trigger for GBS, and the guidelines for disease presentation, data collection, and analysis of vaccination-associated GBS have been documented elsewhere [81]. Vaccines, including the influenza, rabies, oral polio, diphtheria and tetanus toxoid, meningococcal, measles and mumps, hepatitis, and smallpox vaccines have all been associated with sporadic GBS [82]. Indeed, swine flu vaccine-induced GBS during the 1976–1977 outbreak is considered to be the earliest and most severe vaccination-associated GBS [83].

In addition to introducing pandemic flu outbreaks, the influenza virus can trigger antecedent upper respiratory tract and gastrointestinal infections, which are also closely associated with the development of GBS [84]. The influenza vaccine prevents influenza infections as well as lowering the risk of influenza-associated GBS [85]. According to a meta-analysis, influenza A (H1N1) 2009 monovalent inactivated vaccines resulted in approximately 1.6 excess cases of GBS per million people vaccinated; nonetheless, the overall effects were beneficial [86, 87]. Several subsequent studies supported the safety of vaccinations [88–92]. Nevertheless, a study in Québec argued that H1N1 vaccine led to a small but significant risk (2 per million), especially in people older than 50 [93]. Ganglioside contamination in nerve tissue-derived vaccines may account for GBS triggered by the rabies vaccination [94]. Quality control during production is therefore of utmost importance for ganglioside or LPS to be used as an exogenous supplement or contamination.

Generally, specific biological markers that represent a cause-and-effect association with the disorder have been proved to exclude causality in vaccine-associated GBS; however, GBS cases are only temporally associated with numerous vaccines [81]. The interval between vaccination and onset of GBS must be defined to better evaluate the association. Unfortunately, GBS surveillance after vaccination in recent years has provided few valuable results [84, 92]. Instead, sporadic cases were continuously reported, alerting the public to vaccination-associated GBS. Vaccination itself can introduce symptoms similar to mild GBS, including, fatigue and limb weakness. Likewise, mild GBS cases may be less frequently referred to neurologists, leading to a possible underestimation of vaccination-associated GBS [95]. Nonetheless, vaccinations largely may indirectly reduce GBS incidence by controlling ZIKV or hepatitis viruses; whereas the influenza vaccine may introduce a small increase of GBS risk, the benefits from inactivated vaccines remarkably outweigh the risks [84].

Differentiation between axonal GBS and AIDP

Antibody classification of axonal GBS

The differences between axonal and AIDP mainly refer to their associated antecedent infections, neurological features, electrophysiological results, and serum antibodies (Table 1) [73]. Antibodies to gangliosides are instrumental to differentiate GBS subtypes (Table 2). Antibody-dependent membrane attack complex (MAC) formation, C3b receptor-dependent phagocytosis, and cytokines released by infiltrated CD4 + T helper (Th) cells are all involved in GBS pathogenesis (Fig. 2) [14, 96]. Clinical and electrophysiological features appeared to be determined by anti-ganglioside antibodies, and the antibodies were associated with motor axonal GBS in both Japan and Italy [27]. Motor and sensory nerves express similar quantities of GM1 and GD1a, although their expression in other tissues may differ

Table 1 Differentiation between AMAN and AIDP

GBS subtypes	AMAN	AIDP
Antecedent infection	Gastrointestinal infection (mainly *C. jejuni*)	Respiratory infection
Trigger factors	Ganglioside administration; vaccination; monoclonal antibody treatment	Vaccination; monoclonal antibody treatment
Clinical features	Mainly motor deficits; rarely involves cranial nerves (< 20%); without pain or sensory loss; with absent tendon reflex (normal or even exaggerated reflexes may exist in the early phase or atypical GBS); with rapid or slow recovery	Progressive para-/tetra-paresis; sensory deficits; hypo- or areflexia; cranial nerve palsies; progressive course; over-month recovery
Electrophysiological results	Usually no evidence of AIDP (may show segmental CBs in an early phase); show RCFs or decreased CMAP amplitudes	Slower sensorimotor nerve conductions or CBs; excessive temporal dispersions of CMAPs; a prolonged DML or F-wave latency
Antibody classification	Mainly anti-GM1 and anti-GD1a antibodies	Not routinely detectable
Involved nerves	Motor nerves	Sensorimotor, cranial, and autonomic nerves

AIDP acute inflammatory demyelinating polyneuropathy, *AMAN* acute motor axonal neuropathy, *CB* conduction block, *CMAP* compound muscle action potential, *DML* distal motor latency, *RCF* reversible conduction failures

Table 2 Antibody classification in GBS subtypes [32]

GBS subtypes	Antibodies
AMAN	Anti-GM1, anti-GM2, anti-GD1b, anti-GT1b, anti-GM3, anti-GD1a, anti-GalNac-GD1a
AIDP	Anti-LM1, anti-Gal-C
AMSAN	Anti-GM1, anti-GM1b, anti-GD1a
MFS	Anti-GQ1b, anti-GM1b, anti-GT1a, anti-GD3, anti-GD1c
BBE	Anti-GQ1b
PCB	Anti-GT1a, anti-GQ1b, anti-GD1b

AIDP acute inflammatory demyelinating polyneuropathy, *AMAN* acute motor axonal neuropathy, *AMSAN* acute motor sensory axonal neuropathy, *BBE* Bickerstaff brainstem encephalitis, *MFS* Miller Fisher syndrome, *PCB* pharyngeal-cervical-brachial weakness

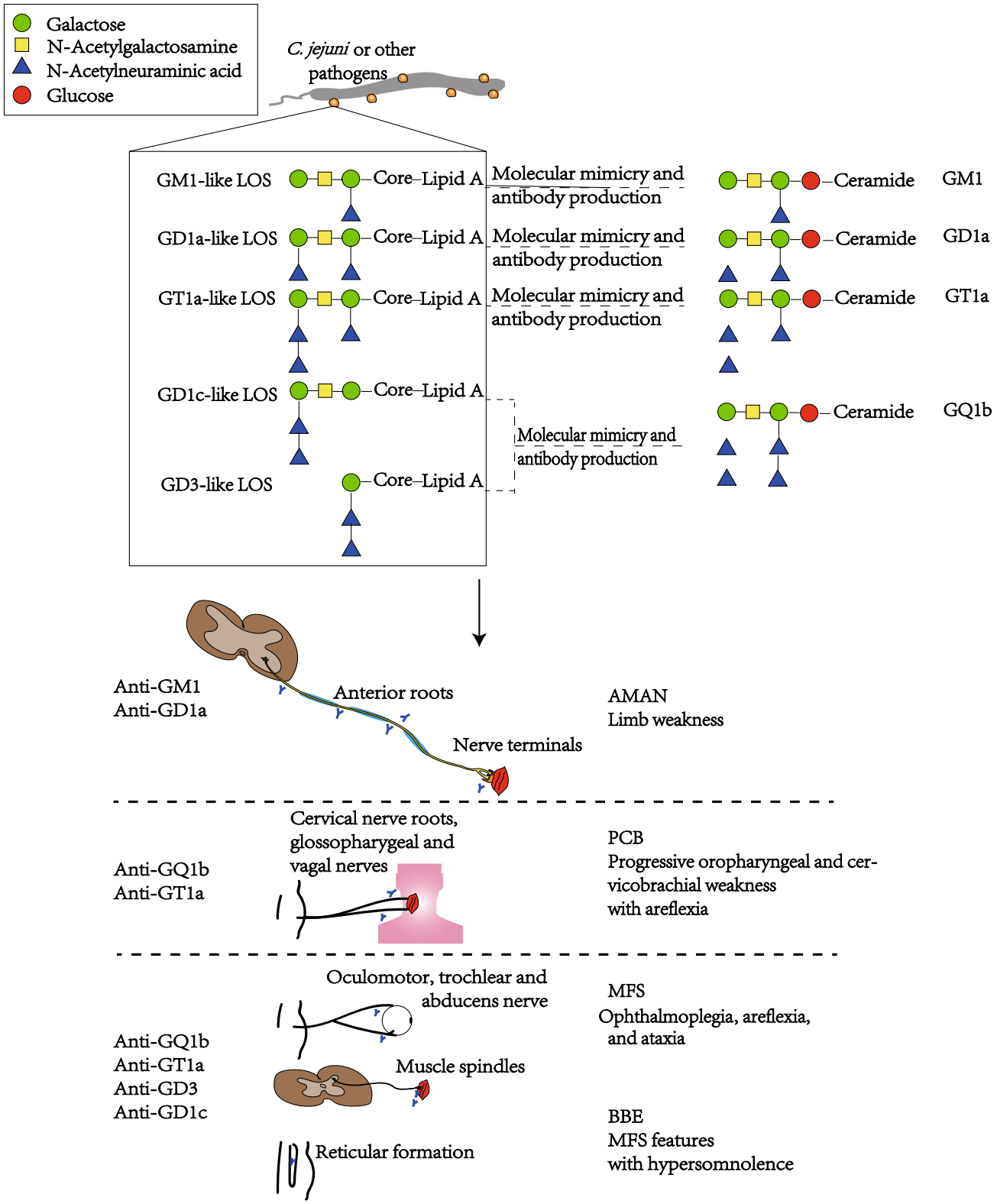
[32]. Anti-GM1 and anti-GT1a antibodies were predominantly of the IgG1 and IgG3 subclasses [97]. IgG1 and IgG3, as complement-fixing IgGs, promote MAC generation and alter Na^+ channel function in axonal injury, leading to a transient conduction block and accounting for rapid recovery of AMAN after treatment [98]. Higher titers of antibodies against neurofascin and persistent IgG4 responses to neurofascin-155 have also been detected in autoimmune neuropathies [99]. Of note is that the presence of IgM antibody does not always support a diagnosis of GBS in that this antibody can be detected in patients with *C. jejuni* enteritis but without GBS [100]. Although predominant antibody-mediated immunity was hypothesized in AMAN, the usefulness of rituximab and corticosteroids in GBS, even if in the early phase, is still controversial [101, 102]. Putatively, autoantibody classification instead of early electrophysiology better predicts the final diagnosis and electrophysiological profiles of GBS [27]. In a European study, serum IgG antibodies were detected in over 80% of the patients with AMAN [103]. Fc gamma receptors of gangliosides can be targeted by autoantibodies, initiating MAC formation and axonal degeneration [104]. In murine experimental autoimmune neuritis (EAN), axonal degeneration was observed at onset (day 10 post-immunization), became severe at peak (day 16 post-immunization), and persisted during recovery (days 22–25 post-immunization) [105]. Autoantibodies induce both axon and myelin deficits through autoimmune reactivity simultaneously, but the potency of autoimmunity may differ [106]. PCB was identified accompanied with anti-GQ1b and anti-GT1a antibody in case studies [8, 34]. Interestingly, GT1a was found in the neuropil of the spinal cord dorsal horn and spinal trigeminal nucleus; GQ1b was mainly expressed in the paranodal myelin of oculomotor nerves, muscle spindle afferents, peripheral nerves, and reticular formation [107] (Fig. 3).

However, the detection of autoantibodies has limitations. Although GQ1b antibody in serum has a relatively high specificity for MFS and BBE [108], most other anti-ganglioside antibodies have been proposed by only a few groups, with unknown reproducibility. Moreover, the antibody diagnosis for GBS is currently time-consuming and assay-dependent; hence, Leonhard et al. suggest not waiting for antibody test results before starting treatment [5]. A retrospective study in Islamabad reported negative anti-ganglioside antibodies in 15 patients with GBS, including 9 patients with axonal profiles in NCS [109]. Moreover, the antibody titer and affinity are not correlated to disease severity, although high titers of specific anti-GM1 antibody targeting cellular GM1 were more frequently detected in patients with severe GBS [110]. Collectively, limited specificity and sensitivity of anti-ganglioside antibodies, unknown pathogenetic role of diverse antibodies, and lack of reliable commercialized assay kits are the major concerns for utilizing antibodies as a diagnostic tool. Their utilization should be further optimized by using antibody-triggered GBS animal models or established models (e.g. the EAN model). Drugs that specifically target an antibody can be developed for precision medicine only when specific antibodies are confirmed to play a pivotal role in the etiology of axonal GBS.

Electrophysiological manifestations of axonal GBS

The classical electrophysiological criteria to differentiate GBS subtypes were put forward by Ho et al. [21] in 1995 and Hadden et al. [111] in 1998. Notably, electrophysiological studies in the early phase of GBS have occasionally yielded equivocal results [112]. Early-reversible changes on the axolemma may probably explain the rapid resolution of conduction slowing/block upon electrophysiological studies [51]. Thus electrophysiological studies 3–6 weeks after GBS onset may efficiently differentiate AMAN from AIDP [27]. In other words, the reduction patterns in serial recordings of RCFs at the axolemma of the node of Ranvier and the length-dependent CMAP caused by axonal degeneration can be later disclosed in AMAN [112]. By using sensitive and specific cut-off values for demyelination, Rajabally et al. proposed new criteria for electrodiagnosis in 2015 [113] (Table 3). If the criteria of neither AIDP nor axonal variants are met, a serial recording of distal motor latency (DML) and CMAP amplitudes is conducive to the differential diagnosis of GBS; patients without GBS have been characterized with prolonged DMLs and rapidly increasing CMAP amplitudes [114].

For the electrophysiological profiles of PCB, NCS showed prolongation of DMLs and F-wave latencies in median and ulnar nerves 4 days after PCB onset [115]. CBs at the cubital tunnel and decreased CMAP amplitudes between the Erb's point and axilla were confirmed in these



cases [115]. Collectively, NCS of PCB exhibits an axonal loss and polyradicular nerve involvement pattern, similar to the electrodiagnostic features of AMAN [116] (Table 4).

Genetic polymorphisms in axonal GBS

While GBS is not considered a genetic disease, host factors do play a role in the pathogenesis of GBS following

◂**Fig. 3** Molecular mimicry in GBS variants. *C. jejuni* or other pathogens synthesize GM1-, GD1a-, GT1a-, GD1c-, and GD3-like LOS and trigger anti-ganglioside antibody production. In AMAN, anti-GM1, and anti-GD1a antibodies target axolemmas located at anterior roots and nerve terminals, and cause limb weakness. In PCB, antibodies specifically against GT1a expressed at glossopharyngeal and vagal nerves lead to oropharyngeal and cervicobrachial weakness with areflexia. In MFS, anti-GQ1b and anti-GT1a antibodies bind to oculomotor, trochlear and abducens nerves and muscle spindles as well as Purkinje neurons in the cerebellum, causing ophthalmoplegia, areflexia and cerebellar ataxia. Anti-GQ1b and anti-GT1a antibodies also react with the reticular formation and introduce BBE. *AMAN* acute motor axonal neuropathy, *BBE* Bickerstaff brainstem encephalitis, *C. jejuni Campylobacter jejuni, GBS* Guillain–Barré syndrome, *LOS* lipooligosaccharide, *MFS* Miller Fisher syndrome, *PCB* pharyngeal-cervical-brachial weakness

C. jejuni infection [22]. The different morbidities of axonal GBS in Western and Asian countries could reflect genetic polymorphisms and may dictate individual sensitivity to diverse GBS variants [22, 25]. Patients with AMAN have been shown more likely to have the *TNFA-863AA* allele of a tumor necrosis factor (TNF)-α encoding gene than healthy controls [117], while patients with the *TNFA-238A* allele were more likely to develop anti-GM1 autoantibody [117]. Fas receptor-Fas ligand (Fas-FasL) is a classical apoptotic pathway involved in eliminating autoreactive B and T cells involved in molecular mimicry. Single nucleotide polymorphisms (SNPs) of Fas, including *FAS-670G* and *FAS-1377G/-670G,* were associated with elevated anti-GM1 antibody titers [118]. A meta-analysis illustrated that differentiating polymorphisms of *HLA-DQB1* may facilitate GBS diagnosis: the *HLA-DQB1*030*× polymorphism and *HLA-DQB1*060*× polymorphism were significantly associated with Asian patients and all patients, respectively, when compared to healthy controls [119]. *HLA-DQB1*0501-*0602* and *DQB1*0201* alleles exhibited a difference between patients with *C. jejuni*-associated axonal GBS and AIDP, but this difference was not significant after Bonferroni corrections [120].

The genetic polymorphisms of *C. jejuni* may account for the severity and diversity of GBS. Eleven classes of new LOS loci were identified after sequencing LOS biosynthesis loci and LOS biosynthesis regions were found to be highly variable zones in *C. jejuni* strains [121]. A single-base deletion in a glycosyltransferase gene, *cgtA*, involved in LOS biosynthesis led to failed GT1a mimicry in the host [57]. Furthermore, the *cst-II* gene in *C. jejuni* has been shown to determine the terminal sugar regions of LOS to mimic different sugar residues of gangliosides; patients with *cst-II* (Thr51)-type *C. jejuni* antecedent infection were found more likely to have elevated anti-GM1 and anti-GD1a antibodies and to develop AMAN [122]. *Orf10/orf11* genes regulate sialic acid biosynthesis and transfer during LOS biosynthesis, and their deficiency has been reported to attenuate the immune reactivity of plasma cells in GBS patients' sera and prevent axonal degeneration in an AMAN mouse model [123]. H and P classes *C. jejuni* with nonsialylated LOS were detected in patients with GBS, which have different *Orf*28 and *Orf*39 deletion and insertion conditions, both contributing to truncated LOS [124]. *NeuA1* also contributes to the biosynthesis of LOS; GBS cases triggered by *C. jejuni* with *neuA1* deficiency showed ameliorated immune reactivity in sera [4]. Despite these genes being associated with *C. jejuni* virulence, whether *C. jejuni*-associated axonal GBS correlates with virulence is unclear. *C. jejuni*-associated infection was common, but few cases developed GBS. The risk of GBS in *C. jejuni*-infected cohorts may depend on the genetic backgrounds of individuals, variation in the virulence of *C. jejuni*, and the severity of infections. A genome-wide association study (GWAS) on a GBS cohort reported no significant associations in individual SNPs and imputed HLA types between patients with GBS and healthy controls [125]. To further understand these blind spots, larger GWAS studies for GBS cases and *C. jejuni* strains should be conducted to reveal the underlying interrelationship between genetic background, GBS epidemiology, and clinical characteristics.

Emerging diagnostic technologies

Electrophysiological studies and antibody classification have been used as basic diagnostic techniques [30]. Intriguingly, several newly developed technologies and biomarkers could assist the differentiation of GBS subtypes. For instance, soluble receptor for advanced glycation end products (sRAGE) can prevent degenerative or inflammatory neurological diseases by blocking expression of RAGE, an initiator of inflammation and oxidative stress [126]. sRAGE was decreased in the serum of patients with early phase AMAN, suggesting its potential as a sensitive biomarker [126]. In addition, levels of 55 plasma lipid metabolites showed significant differences between GBS and healthy controls after metabolomic analysis; patients with GBS were characterized with lower levels of creatinine, serotonin, and higher levels of isoleucine [11]. An integrative metabolomic approach was used to analyze CSF samples of 86 patients with GBS in Korea [127]. Significant elevations of lysophosphatidylcholines and sphingomyelins seemed unique for AIDP and AMAN; these lipids exhibited a potential association with the Hughes functional scale scores, according to a metabolome-wide multivariate correlation analysis [127]. Feature selection from datasets using a cluster algorithm provided a high purity of GBS characterization through artificial intelligence, implying a possibility for computer-assisted GBS diagnosis [10]. Imaging technologies like MRI may help exclude CNS disorders like stroke [5]. Peripheral nerve ultrasound, developed in recent years, can differentiate AIDP

Table 3 Electrophysiological criteria of AMAN and AIDP

	Ho et al. [21]	Hadden et al. [111]	Rajabally et al. [113]
AIDP	Must have two or more nerves with at least one of the following features: 1. motor nerve conduction velocity < 90% in LLN [< 85% if d-CMAP < 50% in LLN] 2. distal motor latency > 110% in ULN [> 120% if d-CMAP < 100% LLN] 3. unequivocal temporal dispersion 4. F-wave latency > 120% ULN	Must have two or more nerves with at least one of the following features: 1. motor nerve conduction velocity < 90% in LLN [< 85% if d-CMAP < 50% in LLN] 2. distal motor latency > 110% in ULN [> 120% if d-CMAP < 100% LLN]; 3. p-CMAP/ d-CMAP ratio < 0.5 and d-CMAP > 20% LLN; 4. F-wave latency > 120% ULN	Must have two or more nerves with at least one of the following features: 1. motor nerve conduction velocity < 70% LLN 2. distal motor latency > 150% ULN 3. F-response latency > 120% ULN, or > 150% ULN if d-CMAP < 50% LLN; OR p-CMAP/ d-CMAP ratio < 0.7 (excluding tibial nerve) in two nerves with an additional parameter in one other nerve; OR F-wave absence in two nerves with d-CMAP > 20% LLN with an additional parameter in one other nerve
AMAN	Not including features in AIDP with d-CMAP < 80% in at least two nerves	1. not including features in AIDP (except in one nerve if d-CMAP < 10% LLN) 2. d-CMAP < 80% in at least two nerves	not including features in AIDP (except in one nerve if d-CMAP < 10% LLN) and at least one of following features: 1. d-CMAP < 80% LLN in two nerves 2. F-wave absence in two nerves with d-CMAP > 20% LLN, in absence of any demyelinating feature in any nerve 3. proximal CMAP/d-CMAP ratio < 0.7 in two nerves (excluding tibial nerve) 4. F-wave absence in one nerve with CMAP > 20% LLN OR proximal CMAP/d-CMAP ratio < 0.7 (excluding tibial nerve) in one nerve with d-CMAP < 80% LLN in one other nerve

AIDP acute inflammatory demyelinating polyneuropathy, *AMAN* acute motor axonal neuropathy, *d-CMAP* distal compound muscle action potentials, *LLN* lower limit of normal, *p-CMAP* proximal compound muscle action potentials, *ULN* upper limit of normal

Table 4 Clinical features and NCS of axonal GBS

Axonal subtypes of GBS	Clinical features	NCS results
AMAN	Mainly motor deficiency; rarely involves cranial nerves (< 20%); without pain or sensory loss; usually with absent tendon reflex; with rapid or slow recovery	Axonal polyneuropathy features without sensory action potential alternation; no demyelinating features; transient motor nerve conduction block
AMSAN	Motor deficiency as AMAN; with sensory loss	Axonal polyneuropathy features with sensory attenuated or absent action potential
PCB	Rapidly progressive oropharyngeal, neck, and shoulder weakness; without sensory abnormality; usually without involving lower limbs	A few patients showed motor and sensory action potential changes in arms; sometimes with prolongation in F-wave latencies
Bell's palsy	Usually with unilateral facial paralysis; sometimes with bilateral facial paralysis; a few with ear pain, hyperacusis, and taste loss	Facial nerve degeneration-like features

AMAN acute motor axonal neuropathy, *AMSAN* acute motor sensory axonal neuropathy, *BBE* Bickerstaff brainstem encephalitis, *NCS* nerve conduction studies, *PCB* pharyngeal-cervical-brachial weakness

with a sensitivity > 85% [128]. Additionally, ultrasound indicators, including three sub-scores and ultrasound pattern sum scores, were significantly increased in chronic inflammatory demyelinating polyradiculoneuropathy but without evident changes in axonal GBS [129]. Nerve ultrasound may reveal segmental enlargement of spinal and proximal nerve roots in patients with GBS and MRI may show the thickening part of spinal nerve roots and cauda equina [130].

Cytokines and T-cell ratios can predict AMAN with considerable accuracy. For instance, elevated IL-23 and IL-27 levels have been identified in patients with AMAN [131]. The ratio of circulating memory T follicular helper (Tfh) subsets, Tfh2 and Tfh17 appears promising for identifying

GBS subtypes: the ratio of (Tfh2 + Tfh17)/Tfh1 was significantly higher in AMAN than in AIDP [132]. Moreover, (Tfh2 + Tfh17)/Tfh1 ratio is a promising biomarker for predicting the severity and progression of AMAN [132].

The diagnostic accuracy of axonal GBS could be improved. Particularly, whether autoimmune antibodies can be used as clinical biomarkers of axonal GBS merits further investigation. Electrophysiological studies have not been able to define a part of GBS; serial electrophysiological recordings and new criteria are in urgent need for the undefined GBS subtypes. Different criteria of electrophysiology should be compared for a better definition of electrophysiological profiles for axonal GBS. Likewise, the diagnostic value of imaging methods, including MRI and nerve ultrasound, awaits corroboration for accurate diagnosis. Taken together, electrophysiology remains a mainstay in the diagnosis of axonal GBS, although the electrophysiological criteria of regional GBS have yet to reach consensus.

Canonical and advanced treatments for AMAN

Despite persistent efforts in laboratory and preclinical studies, treatments for patients with AMAN still rely on IVIg and plasma exchange (PE) [133–135]. Corticosteroids have been proven useless and even detrimental in patients on mechanical ventilation (MV) or after the acute phase [136]. IVIg mainly functions by inhibiting macrophage activation and preventing the binding of antibodies and complements [133]. IVIg may dimerize anti-ganglioside IgG antibodies and remonomerize IgG dimers to disable autoantibodies whereby mitigating immunoreactivity in patients' sera [137]. IVIg efficacy has been shown to differ between AMAN and AIDP: a higher Hughes functional grading scale (HFGS) score was observed in patients with AMAN after IVIg treatment compared to those with AIDP; however, only 24% of AMAN patients experienced rapid recovery after IVIg treatment [138]. Regarding pediatric cases, children with AMAN respond better to IVIg [139]. AMAN patients with CBs displayed a higher reduction of HFGS after IVIg treatment compared to those without CBs and patients with AIDP [140]. In contrast, investigation of the long-term prognosis of GBS patients revealed that IVIg treatment did not improve the long-term outcomes of patients [141]. In current practice, patients with treatment-related fluctuations and treatment failures are frequently retreated with a second course of IVIg or PE [142], despite inconsistent conclusions from clinical observations [143, 144].

PE is usually conducted as five sessions with 40–50 mL plasma/kg per session within 7–14 days, which remarkably hastens recovery compared to supportive care alone [145]. IVIg started at the 2nd week after onset achieved comparable benefits without an increase of adverse events [133]. A recent pilot study reported that combined use of IVIg and PE reduced mortality, facilitated earlier weaning from MV, and shortened hospital stay, with an excellent outcome in AMAN patients who required intensive care [146]. In fact, PE scavenges pathogenetic antibodies and IVIg neutralizes or blocks pathogenetic antibodies [143, 147], implying that either PE or IVIg is more effective in patients with ganglioside autoantibody-associated axonal GBS than those with lymphocyte infiltration-dominated AIDP. Theoretically, the use of PE followed by IVIg can be a more effective and safer treatment for patients with GBS. Notwithstanding, a previous study illustrated that IVIg after PE did not provide any extra benefit [133]. To optimize treatment of axonal GBS, whether the combination of PE and IVIg facilitates prognosis of axonal GBS remains to be explored. Clinical trials testing PE or IVIg efficacy can put more emphasis on treating axonal GBS because of its pathogenic humoral immune response.

Newly developed drugs, including rEV576 [148], erythropoietin [149], cysteine protease [150], and nafamostat mesilate (NM) [151], targeting the hyperreactive immune responses in AMAN exhibited promising therapeutic potentials in GBS animal models. Monoclonal antibodies against eculizumab [152], anti-C1q [153], anti-GD3, anti-idiotype [154], anti-IL-17 [14], anti-CD2, and anti-selectin [101] inhibit the initiation of complement deposition, and MAC, immune cell recruitment, and axonal injury are attenuated in GBS animal models. Evidence suggests that complement inhibition combined with IVIg might improve outcome in GBS [155]. In line with these findings, eculizumab was tested in a multicenter, double-blind, randomized phase 2 clinical trial, and 61% of patients with GBS in the eculizumab-treated group were able to walk independently after 4 weeks compared to 45% in the placebo control group [13]. Rituximab, an anti-CD20 monoclonal antibody, was demonstrated to facilitate EBV resolution and muscle strength recovery in an allogeneic hematopoietic stem cell transplantation-triggered AMAN case [12]. IFN-β can decrease adhesion and transmigration capacities of lymphocytes extracted from GBS patients' blood [156]. In spite of this, a randomized controlled clinical trial involving 13 patients treated with IFN-β and IVIg showed insignificant difference in any efficacy measure compared to six patients treated with placebo and IVIg [157]. Further, no benefits were verified in improving progressive limb weakness or motor deficits of patients after applying OKT3, an anti-T-cell monoclonal antibody [158]. Thus far, no biological drugs have been approved by the FDA; more preclinical investigations to identify their efficacy and side effects are under way [101].

Vitamin deficiency can induce peripheral neuropathy [159], and serum folate was found to correlate with GBS severity and progression duration [160]. Likewise,

Table 5 Emerging diagnostic and therapeutic strategies in GBS management

Diagnostic technology	Benefits in GBS diagnosis	References
Promising diagnostic technologies		
Peripheral nerve ultrasound	Segmental nerve edema of spinal and proximal nerve roots detected	Telleman et al. [130]
sRAGE	Decreased in serum of patients with AMAN	Zhang et al. [126]
Lipid metabolomics	55 lipid metabolites significantly decreased in the serum of patients with GBS	Tang et al. [11]
Integrative metabolomics	Significant elevations of lysophosphatidylcholines and sphingomyelins detected in CSF of GBS patients	Park et al. [127]
Correlation-based feature selection	Feature selection used for better identification of subtypes	Hernández-Torruco et al. [10]

Drugs	Mechanisms	Subjects	Efficiency	References
Newly developed therapeutic strategies				
Anti-T cell monoclonal antibody	Rapidly depletes circulating T cells	3 GBS cases	2 patients showed continued progressive clinical deficits 8 and 14 days after treatment	Feasby [158]
IFN-β	Inhibits lymphocyte adhesion and prevent hyperreactive immune responses	26 GBS cases and 6 healthy controls	IFN-β induces a dose-dependent efficacy in decreasing adhesion of lymphocytes and endothelial cells in patients with GBS	Créange et al. [156]
IFN-β + IVIg	Inhibits pro-inflammatory cytokine release	13 GBS cases and 6 GBS controls	All 19 patients showed clinical features similar to baseline	Pritchard et al. [157]
Eculizumab	Inhibits complement protein C5 and MAC formation	23 GBS cases and 11 GBS controls	61% patients in eculizumab-treated group were able to walk at week 4 compared to 45% in controls	Misawa et al. [13]
Vitamin B6 supplementation and weight gain therapy	Diminishes nutrition deficiency induced by alcoholism, bariatric surgery, or anorexia	13 patients with acute axonal neuropathy	Rescues vitamin B6 and thiamine deficiency in alcohol- or diet deficiency-related axonal polyneuropathy	Hamel et al. [161]
Anti-c1q monoclonal antibody	Attenuates MAC, immune cell recruitment, and axonal injury through inhibiting antibody production	mice	Attenuates axonal damage and improved respiratory function	McGonigal et al. [153]
Eculizumab	Inhibits complement protein C5 and MAC formation	Mice	Prevents GQ1b injection-triggered respiratory deficits and motor neuropathies	Halstead et al. [152]
rEV576	Inhibits complements and attenuates Schwann cell and axonal injury	Mice	Diminishes deposition of C3c and MAC at neuromuscular junctions; attenuates conduction blocks in electrophysiological study	Halstead et al. [148]
Anti-GD3 anti-idiotype monoclonal antibody	Counteracts the effects induced by pathogenic antibodies	Rats	Reduces anti-GD3 antibody titers and improves motor nerve functions	Usuki et al. [154]
Erythropoietin	Modulates the immune system towards anti-inflammatory responses	Rats	Decreases inflammation at peripheral nerves and increases macrophages at the later stage of GBS	Mausberg et al. [149]
Nafamostat mesilate	Inhibits serine protease and complement cascade including C1s, C1r, C3a, C3b, C5a, C5b, and C5b-9	Rabbits	C3 deposition is significantly inhibited; Nav channel clusters disruption is ameliorated	Phongsisay et al. [151]
Cysteine protease	Cleaves IgG antibodies and Fc fragments	Rabbits	Lowers frequencies of axonal degeneration in anterior spinal roots and promotes clinical recovery	Wang et al. [150]

AMAN acute motor axonal neuropathy, *C5* complement5, *CSF* cerebrospinal fluid, *GBS* Guillain–Barré syndrome, *IFN-β* interferon β, *IgG* immunoglobulin G, *IVIg* intravenous immunoglobulin, *MAC* membrane attack complex, *sRAGE* soluble receptor for advanced glycation end products

nutritional loss caused by bariatric surgery or alcoholism may lead to poor nutritional status and worsen the prognosis in patients with axonal neuropathy [161]. Hence, neurotrophic therapies, including vitamin supplementation, might benefit the outcome of GBS. To normalize the inconsistent therapies, Leonhard et al. summarized ten steps in GBS diagnosis and management from early GBS suspicion to final rehabilitation, providing an acceptable standard for effective GBS treatment [5]. Even with those traditional or advanced therapies, sequelae are frequent, highlighting the importance of rehabilitation after discharge.

Whether the combination of PE and IVIg facilitates the prognosis of axonal GBS remains to be explored. Potential therapies using monoclonal antibodies to target proinflammatory cytokines or complements should be further investigated and translated into clinical practice (Table 5). Importantly, strategies to impede relapses and reduce complications (i.e., pressure ulcers, infection, deep vein thrombosis, and hospital-associated psychiatric disorders, among others) should be integrated to achieve a better prognosis. More importantly, it remains an unmet need to identify self-limited cases in the outpatient settings so as to avoid unnecessary treatment and to alleviate iatrogenic injury.

Conclusions

Axonal GBS is unique as to its pathogenesis being autoantibody-mediated immune responses to incompletely characterized antigens that exist in the axolemma or the node of Ranvier with subsequent axonal degeneration. *C. jejuni* and ganglioside administration-triggered molecular mimicry are specific pathogenic factors when comparing axonal GBS with other subtypes. Decreased CMAP amplitudes and RCFs are typical electrophysiological features of axonal GBS. Serial electrophysiological recordings may identify reversible nerve conduction block and help differentiate axonal GBS from AIDP. Potential biomarkers, like autoantibody classification, can assist in differentiating between axonal subtypes, including AMAN/AMSAN and PCB, and other biomarkers (i.e., lipid metabolites, sRAGE, lysophosphatidylcholines, and sphingomyelins, among others) are still under investigation. Until now, IVIg and PE have still been the mainstay for the treatment of either AIDP or axonal GBS. Monoclonal antibodies, including eculizumab, rituximab, and alemtuzumab, have shown preliminary potentials; however, more clinical trials are needed to validate their efficacy and identify possible side effects. To further investigate novel therapeutic targets of axonal GBS, the animal model for AMAN should be optimized. Large GWAS studies on patients with axonal GBS may identify the correlation between genetic background and disease onset of axonal GBS. More sensitive biomarkers should be investigated to differentiate between moderate GBS and self-limiting courses. Moreover, infection-associated and vaccination-associated GBS surveillance networks should be consolidated.

Acknowledgements The work was supported by grants from the National Key R&D Program of China (No. 2017YFC0110304 to JF), and the National Natural Science Foundation of China to (No. 31600820 to MZ and No. 81771257 to JF).

Author contributions HLZ conceived the topic and designed the outline of this review; PS drafted the manuscript; MZ and YW contributed to the literature review and manuscript writing; XZ and XW contributed to the figure preparation; JZ, HLZ and JF critically revised the manuscript.

Funding The work was supported by grants from the National Key R&D Program of China (No. 2017YFC0110304 to JF), and the National Natural Science Foundation of China to (No. 31600820 to MZ and No. 81771257 to JF).

Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

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