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REVIEW

Autoimmunity and cytokines in Guillain-Barré syndrome revisited: review of pathomechanisms with an eye on therapeutic options

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ABSTRACT. Guillain-Barré syndrome (GBS) is the most common cause of acute paralysis in the United States. *Campylobacter jejuni* is a common trigger for GBS, igniting autoimmunity as a result of molecular mimicry between *C. jejuni* lipooligosaccharide (LOS) and host gangliosides. Evidence also suggests an active role for cell-mediated and innate immunity in pathogenesis of GBS. Infection alone is not enough for GBS to develop, infection with the same strain might yield different outcomes in different patients. *C. jejuni* strains with low to absent molecular mimicry to self-antigens can cause full-blown GBS with positive autoantibodies. A role for T helper 17 and IL-17 in acute phase of GBS is also identified. Currently, no biological treatment is validated for severe, ventilation-dependent patients with GBS, who might not benefit from either IVIG or plasma exchange therapy. Use of biologic agents in treatment-resistant GBS, especially anti-IL-17 agents, such as secukinumab, ixekizumab, and brodalumab, is to be hoped. This review covers up-to-date knowledge on autoimmune mechanisms responsible in different subtypes of GBS: acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy; as well as the experimental autoimmune neuritis (EAN), a commonly used animal model of GBS.

Key words: Guillain-Barré syndrome, *Campylobacter jejuni*, experimental autoimmune neuritis, acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute inflammatory radicular polyneuropathy and is clinically characterized by spreading of muscle weakness from proximal to distal muscles and diminished deep tendon reflex. GBS is the most common cause of acute paralysis in the United States and its prevalence appears to be relatively constant among different geographical regions [1, 2]. The incidence of GBS is estimated between 0.84/100,000 per year and 1.91/100,000Guillain-Barré syndromeyear in North America and Europe [2-5]. These estimates are similar to reports in Japan and Australia, whereas the incidence is reported to be lower in East Asia and Middle East [3, 6, 7].

GBS is considered an infection-triggered autoimmune disease, as about two-thirds of patients report a history of a recent viral or bacterial infections, before the onset of neurological symptoms [8-12]. Respiratory and gastrointestinal infections are the most common preceding types of infections in GBS. *Campylobacter jejuni* is the most common pathogen detected, detected in about one-third of positive stool cultures [13], and 44-88% of positive direct stool samples [14-18], from patients with GBS. Fortunately, somewhere between 1 in 3,000 to 5,000 of symptomatic patients infected with *C. jejuni* develop GBS [19, 20], indicating that host factors are important in the predisposition to the development of GBS [21-23]. A commonly believed autoimmune hypothesis regarding GBS pathology suggests that antigen/molecular mimicry and anti-ganglioside autoantibodies are two main pathogenic factors in GBS. Meanwhile, molecular mimickery and humoral autoimmune responses cannot fully explain the pathology and nature of GBS. Here, we provide an update for the current status of GBS. *Figure 1* summarizes main autoimmune pathomechanisms involved in GBS.

DATA SELECTION

References for this article were extracted through a comprehensive search in Scopus, PubMed, and Embase databases, updated through the date of submission. The MESH search term ("Guillain-Barré Syndrome" OR "GBS" OR "Neuritis, Autoimmune, Experimental" OR "EAN" AND "autoimmunity" OR "autoimmune" OR "auto-immune") was adapted to search all databases. A total number of 1,754 references were extracted and selected by title and

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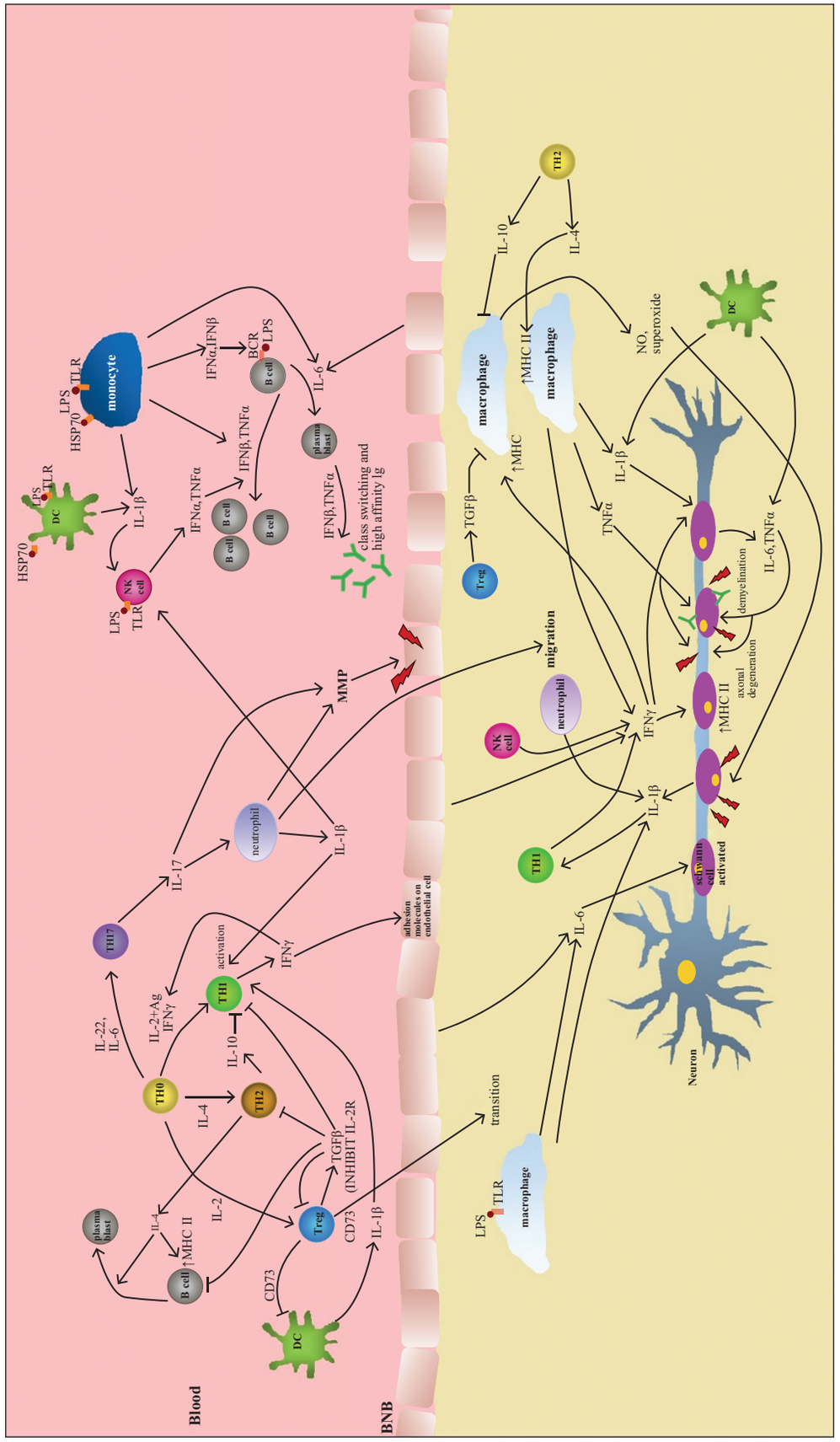

Figure 1

Autoimmune mechanisms involved in Guillain-Barré syndrome. Bacterial and viral antigens such as lipopolysaccharides (LPS) activate immune cells by Toll-like receptors and some other patterns recognize receptors. In response to these exogenous antigens which have mimicry to host ganglioside or myelin proteins, B cells produce antibodies. Cytosine secretions help to class switching and enhancement of immunoglobulin (Ig) affinities. On the other hand, T helper 1 (Th1) and T helper 17 (Th17) migrate through blood nerve barrier (BNB) and initiate inflammation by producing cytokines and stimulating macrophages, dendritic cells (DC), Schwann cells, and epithelial cells. Importantly, Th17 cell disrupts the intact BNB by stimulating neutrophils to secret matrix metalloproteinase (MMP). T helper 2 (Th2) seems to have a role in recovery phase by secreting anti-inflammatory cytokines. Also regulatory T cell (Treg), which is the suppressor of inflammation, decreases in both quantity and function to prevent autoimmune response. IL-1β: interleukin 1β; IL-6: interleukin 6; IL-2: interleukin 2; IL-10: interleukin 10; IL-17: interleukin 17; IL-4: interleukin 4; IL-22: interleukin 22; TNFα: tumor necrosis factor α; IFNα: interferon α; IFNβ: interferon β; IFNγ: interferon γ; TGFβ: transforming growth factor β; MHC: major histocompatibility complex; CD73: cluster of differentiation 73; TH0: naïve T cell; NK cell: natural killer cell; NO: nitric oxide.

abstract by two independent authors to include a primary number of 200 references. Included references were then evaluated through full-text review and full texts were accessed through the Digital Library of Tehran University of Medical Sciences portal site. The reference lists of the included articles were also skimmed to look for potentially missed/gray literature.

CLINICAL SUBTYPES OF GUILLAIN-BARRÉ SYNDROME

Based on electrophysiological characteristics and patterns of nerve root and axonal involvement, GBS can be divided into several subtypes [24]. While all subtypes have the same clinical presentation, two most common patterns can be distinguished.

Acute inflammatory demyelinating polyneuropathy (AIDP)

This is the most common clinical picture by which GBS presents in adults of western countries, comprising about 85% of patients [16]. AIDP is clinically characterized by progressive muscle weakness and neuromuscular paralysis, like other subtypes of GBS. Segmental demyelination and lymphocyte infiltration with secondary axonal damage are key pathological features of this subtype, respectively, seen in peripheral nerves and nerve root biopsies [23, 25, 26].

AIDP is a prototypic example of an autoimmune reaction mediated by molecular mimicry. Bacterial and viral epitopes are presented to T cells by activated neurotropic macrophages in the peripheral nervous system. Cross reactivity of pathogen epitope-specific T-cells, the resulting cytokine production, and the release of free radicals, disrupts blood nerve barriers (BNB) and destructs the myelin sheet culminating in acute demyelinating syndrome. The BNB has an almost similar structure to the blood brain barriers (BBB) but instead of astrocyte podocyte playing the main barrier role in BBB, the endothelial basement membrane helps with the barrier function of BNB [27]. The BNB also has a specific immunologic role in T-cell migration [27]. Experimental autoimmune neuritis (EAN) is an animal model close to AIDP, using the myelin sheet epitopes, P0 and P2, as two major cross-antigens to induce T-cell-mediated neuritis. In this model, activated T-cells are also responsible for production of anti-Schwann cells autoantibodies that directly target the mature, myelin-producing Schwann cells [23]. EAN is therefore a model for mixed humoral and cellular immunity response against myelin sheath epitopes.

Acute motor axonal neuropathy (AMAN)

Being the second most common pathological subtype, AMAN is most common among patients with East Asian origin [28]. As its name indicates, axonal degeneration is the primary feature of this subtype [29] with mild lymphocyte infiltration and minor inflammation [9, 26, 30]. Again, molecular mimicry has a strong pathogenic role in this phenotype, considering high degree of analogy between *C. jejuni* antigens and host gangliosides such as ganglioside M1 (GM1), ganglioside M1b (GM1b), ganglioside D1a (GD1a), and N-acetylgalactosaminyl GD1a (GalNAc-GD1a), primarily expressed on the surface of the motor axolemma. B cells play an important role with the production of autoantibodies that cross react with axon ganglioside and perpetuate axonal degeneration by activating macrophages and the complement system [23, 31].

IMMUNOPATHOLOGY OF AUTOIMMUNITY IN GUILLAIN-BARRÉ SYNDROME

Cell-mediated immunity

Humoral immune responses either derived by anti-ganglioside autoantibodies, or by molecular mimicry to myelin proteins, are dependent on a functional cell-mediated immunity to maintain antibody production against neoantigens that further fuel autoimmunity. T cells infiltrate myelin sheath during acute phase of GBS and peripheral blood mononuclear cells of patients with GBS are shown to be responsive to GM1 and GM3 [32]. T-cell reactivity and proliferation in response to gangliosides and myelin-derived proteins have been addressed by several other studies, summarized below.

Regulatory T cells

Regulatory T (Treg) cells are crucial for the maintenance of peripheral tolerance, as they prevent maturation and downregulate cytokine production and activation of autoreactive T cells, particularly the $CD4^+$ helper T-cell subtype. A decrease in numbers or loss of function of Treg cells can result in aberrant activation of autoreactive T cells [27].

Quantitatively, Treg cells are reduced in number, at least in acute/attack phase of GBS, when demyelination progressively involves an increasing number of peripheral nerve sheaths [28-31]. Patients with an AIDP subtype show a decrease in the number of circulating mature $FOXP3^+$ T cells, and activated HLA-DR-positive Treg cells, in the early phases of disease [32]. This acute reduction in the number of mature $CD4^+$ $CD25^+$ Treg cells is reversible in that treatment with intravenous immunoglobulin (IVIg) restores peripheral Treg cell populations [29], a result replicated by other studies reporting a significant improvement in the number and function of $FOXP3^+$ Treg cells after IVIg treatment, in both AIDP and AMAN patients [29-31]. Whether the reduction in Treg cells is a primary pathogenic event or a secondary phenomenon in response to an increase in other T-cell subpopulations remains to be elucidated. Anti-ganglioside antibodies are also more prevalent in patients with lower $CD4^+CD25^+$ T cells as compared to those with a normal mature Treg cell population [28]. Nonetheless, the reduction of Treg cells does not associate with severity or clinical subtype of GBS [28]. Finally, GBS has been reported in patients with advanced stage of acquired immune deficiency syndrome (AIDS) with $CD4^+$ count fewer than 50 cells/mm^3 but relatively spared Treg cell population, suggesting that $CD4^+$ helper T cells are dispensable for the induction of GBS pathology [33, 34].

The functional status of Treg cells has been addressed by a number of other studies. It was initially demonstrated that the function of Treg cells, in terms of preserved immunosuppressive traits, FOXP3 expression, and cytotoxic T lymphocyte antigen-4 (CTLA-4) and CD45RO levels, is intact in both AIDP and AMAN subtypes of GBS [29]. Although quantitatively sufficient, $FOXP3^+$ mature Treg cells appear to be functionally insufficient in the suppression of Th1 and Th17 cytokine production and proliferation *in vitro* [32]. Further evidence in line with functional defects of Treg cells in GBS comes from studies investigating surface expression of suppressor molecules on these cells. Treg cells deficient in CTLA-4 have been shown to induce an autoimmune phenotype in mice, including EAN [35, 36]. CTLA-4 effectively blocks activation of antigen-presenting cells (APC) by binding to costimulatory molecules B7-1 (CD80) and B7-2 (CD86) in dendritic cells and conveying an inhibitory signal. CTLA-4 further suppresses effector T cells by attenuating signal transduction *via* the T-cell receptor for antigen in these cells [37-39]. Mice deficient in the expression of the *B7* gene also develop autoimmune peripheral neuropathy, regardless of the presence of Treg and Breg cell populations in the spleen. These mice have lower counts of regulatory T and B cells, which could effectively prevent antigen presentation and cytokine production by Th1 cells upon adoptive transfer [40].

CD73 is another membrane bound surface molecule expressed by Treg cells and together with CD39, acts as an ecto-5'-nucleotidase, converting extracellular adenosine-5-monophosphate to adenosine. CD73 can thereby promote immunosuppression through adenosine: adenosine receptor (A2A) interaction in dendritic cells [35, 41, 42], induce anergy within effector T cells and promote Treg cell maturation [43]. CD73 has also been shown to facilitate lymphocyte infiltration and chemotaxis into peripheral nerves, in experimental autoimmune encephalomyelitis (EAE) [44-46] and has shown a similar role in promoting lymphocyte infiltration into nerve sheaths of patients diagnosed with GBS/AIDP [47].

T helper 1 (Th1) and T helper 2 (Th2)

Serum expression of Th1 and its associated cytokines, such as interferon-γ (IFN-γ), interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6, increase in early phases of GBS and decrease during the recovery phase [48]. Similarly, an increase in the IFNγ/IL-4 ratio is observed in sera of GBS patients during the acute phase, stimulating further maturation of naive T cells into Th1 cells, whereas the Th2 subtype is the predominant T-cell population during the recovery phase [48]. A similar reaction happens in sciatic nerves and lymph nodes of EAN mice, where Th1 cytokines are upregulated during the acute phase and Th2 cytokines are augmented in the recovery stage [49]. Administration of intravenous immunoglobulins effectively reduces Th1 numbers and levels of proinflammatory cytokines [32]. It is also supposed that the clomipramine and imipramine-induced reduction in suppression of myelin auto-reactive T and B cells is a result of a reduced number of Th1 cytokines in the peripheral nerves of EAN rats [50].

Interestingly, despite a growing population of IFN-γ-secreting Th1 cells during acute phase of GBS, no specific reactivity to myelin proteins P0, P2, or PMP22 is seen, showing an independent role for Th1 cytokines in induction of peripheral neuro-inflammation [51]. Meanwhile, GM1-specific helper T cells expand and respond to GM-1 with IFN-γ production in peripheral blood of patients with GBS [52].

There are nonetheless conflicting studies reporting that both Th1 and Th2 cell populations are expanded in GBS patients with an unchanged Th1/Th2 balance and $IL\text{-}4^+/IFN\gamma^+$ ratio during the active phase of GBS [53] and an absence of a sequential increase in Th1 and Th2 populations, as well as a concomitant increase in proinflammatory cytokines in some patients with GBS [54].

T helper 17 (Th17) cells

Plasma levels of interleukin 17 (IL-17) and interleukin 22 (IL-22), which are the main Th17 cytokines, are increased during acute stage of GBS, concurrent with increased levels in the CSF [49, 54]. This is accompanied by an upregulation of expression of transcripts for retinoic acid receptor-related orphan receptor gamma (RORγ) and signal transducer and activator of transcription 3 (STAT3) which are critical Th17 transcription factors [49, 55]. Peripheral production by T lymphocytes comprises the main source of IL-17 and IL-22 in GBS, a process that is reversed after IVIg therapy [56].

Th17 and IL-17A levels are also increased in sciatic nerve specimen of mice with EAN [57], and associated with the severity of neuritits in these animals [58]. Blocking phosphorylation of STAT3 in EAN animal models alleviates inflammation along with a decrease in the Th17 cell population, as well as RORγ and IL-17 expression in peripheral neurons [59]. Similarly, blocking Th17 cell infiltration could effectively downregulate IL-17A production, ameliorate neuroinflammation, and improve the clinical picture in EAN mouse models, albeit not in the AMAN subtype [60-62].

Follicular T helper (Tfh) cells represent a distinct subpopulation of memory T cells with characteristics of a germinal center follicular cell. Tfh cells are necessary for B-cell maturation and antibody isotype switching [63]. The Tfh2 and Tfh17 subtypes are endowed with an ability to induce B-cell maturation *via* the production of IL-21 [64], and have been shown to expand in GBS [64, 65]. This increase is confined to patients with AMAN phenotype, as the Tfh2 and Tfh17 cell counts are unchanged in AIDP patients [64]. Also, inhibition of glycolysis in T cells of EAN mice is reportedly associated with a downregulation of the Th17, Th1, and Tfh subtypes, and increased Treg cell development and a prevention of disease progression in mice with EAN [66].

Gamma delta T cells (γδ T cells) and natural killer cells

The γδ T cells are a small subgroup of T cells, endowed by surface expression of both T cell and NK-cell receptors. The rich surface repertoire enables a variety of activating as well as inhibitory signals to be transduced by this T-cell subgroup. Because of their

ability to recognize non-protein bacterial antigens, the γδ TCR can respond to a variety of bacterial and non-bacterial stimuli. Expansion of the γδ T cell subset is observed in active lesions and CSF of multiple sclerosis patients [67]. The γδ T cell subset is also known to be the predominant source of IFNγ and proinflammatory cytokine production and to mediate oligodendrocyte cytotoxicity in chronic lesions of multiple sclerosis [68, 69].

It has been shown that γδ T cells derived from peripheral blood of GBS patients can promote expansion and upregulation of NK-cell receptors *in vitro* and produce excessive amounts of IL-4 in response to non-protein antigens [70]. Peripheral blood γδ T cells could be expanded after exposure to different non-protein antigens of *C. jejuni in vitro* [71]. γδ T cells can infiltrate peripheral nerve sheaths and mediate immune response and antibody production against ganglioside-like epitopes on peripheral nerves [72, 73]. In contrast, presence of the IFN-γ-producing γδ T cell subset is decreased in the acute phase of GBS [74], suggesting a preponderance and IL-4 and antibody production, over the production of IFN-γ in this subtype. In line with these results, patients with increased anti-GM1 antibody titers or anti-*C. jejuni* antigens show an expansion of the population of $CD8^+$ γδ T cells [75].

A study published two decades ago reported no differences in the frequency of NK cell populations in patients with GBS [76], nor did it show any change in severity of cellular infiltration, demyelination, and antibody response to myelin proteins, after blocking NK cells surface receptors in EAN rats [77]. Studying the role of killer-cell immunoglobulin-like receptor polymorphisms in predisposition to GBS has yielded inconclusive results [78].

Humoral immunity

Glial cells and anti-glial antibodies

Presence of neuropsychiatric symptoms such as depression in about 67%, anxiety in 82%, hallucination in 60%, delusion in 70%, and REM sleep abnormalities in GBS patients [79, 80] points to the involvement of the central nerve system in GBS. The inflammatory neuropathy and circulating mediators of inflammation induce immunophenotypic changes in Schwann cells, with increased expression of HLA class I and class II expression [81]. The latter cells also express costimulatory molecules similar to those on T cells, such as B7-1 (CD80), B7-2 (CD86), as well as intercellular adhesion molecules and cell surface adhesion markers [82]. Immunoactive phenotypes are also seen in endothelial linings of the blood-brain barrier as well as the blood-nerve barrier. Immunoactivated endothelial cells facilitate leukocyte margination and migration, induce maturation in naive lymphocyte, and mediate interactions between T cells and APC [83].

IgG autoantibody against non-myelinating Schwann cells has been found in 24% of GBS patients and 26% of CIDP patients [84], whereas anti-astrocyte autoantibodies are present in the sera of 60% of GBS patients [85]. Interestingly, sera of patients with GBS react with monoaminergic neurons of the ventral tegmental area, cholinergic nuclei of the forebrain, as well as nor-adrenergic neurons in the brain stem. This observation provides justification for the variety of neuropsychiatric abnormalities seen in GBS [86]. Less than 10% of patients with CNS involvement have positive serum anti-GM1 antibody in their serum, suggesting that CNS involvement in GBS is independent of anti-axonal or anti-myelin circulating autoantibodies.

B cells and anti-ganglioside antibody

Gangliosides are naturally processed glycolipids that are ubiquitously present on the extracellular surface and cell membranes of the nervous system. Gangliosides are composed of oligosaccharide in the form of sialic acid residues extending across the cell membrane, composing the main antigenic part of the molecule [87]. Anti-ganglioside antibodies are the most frequent autoantibodies found in GBS and are present in sera of up to 80% of patients with axonal subtype (AMAN), and 62% of patients with demyelinating subtypes (AIDP) [88]. These antibodies are more frequent in patients who have been infected by *C. jejuni* strains in which surface lipooligosaccharides (LOS) or lipopolysaccharides (LPS) mimic host oligosaccharide strains in gangliosides. Together, these considerations support a role of antigen and molecular mimicry as a principal mechanism for autoantibody production in GBS [89]. Both T-cell-dependent and T-cell-independent pathways of B-cell activation appear to be functional in the pathology of GBS [90, 91]. Bacterial LPS is a T-cell-independent antigen that primarily triggers production of low-affinity anti-ganglioside IgM antibodies [92]. Short-lived plasma blasts that are produced as a result undergo affinity maturation and IgG class-switching under persistent exposure to culprit antigen, as is seen during prolonged *C. jejuni* infection [93]. Antigen sialylation, which occurs in LPS of most *C. jejuni* strains, increases the likelihood of high affinity autoantibody production. Affinity maturation of autoantibodies is crucial to produce the characteristic neuro-inflammatory phenotype since low affinity IgM or IgG autoantibodies fail to reproduce GBS in animal models sensitized with GM1 [94]. Importantly, high titers of IgM anti-GM1 antibodies are produced by peripheral blood mononuclear cells (PBMC) derived from patients with GBS and multifocal motor neuropathy, whereas IgG and IgA anti-GM1 autoantibodies are confined to GBS, supporting involvement of a T-cell-dependent antibody response [91]. Furthermore, IgM anti-GM1 antibodies of GBS patients are polyclonal in nature, in contrast to oligoclonal antibodies in patients with multifocal motor neutropathy [95], in line with T-cell-dependent antibody production against axonal components in GBS. Importantly, GM1 is found in higher concentration in ventral root neurons compared with dorsal roots [96], justifying higher prevalence of motor neuropathy in patients with anti-GM1 [97]. Backing up the above evidence, immunization of mice, that lack the ability to produce complex gangliosides and express GM3 and GD3 instead, with ganglioside-mimicking LPS was found to result in a strong, T-cell-

dependent, antibody production with predominance of IgG autoantibodies. This was attributed to lack of tolerance formation to self-complex gangliosides, resulting in a predominant T-cell-dependent response [98].

Antigen mimicry by itself is not sufficient to induce peripheral neuritis. Patients infected with *C. jejuni* strains with molecular mimicry to ganglioside T1 (GT1) did not develop GBS, whereas others with no proven mimicry to GT1 or other gangliosides showed signs of peripheral neuritis. Mutation in glycosyltransferase after autoantibody induction may help *C. jejuni* to escape from the host immune system at the expense of losing molecular mimicry or switching to LPS/LOS subtypes that are less antigenic [93].

Anti-myelin protein antibodies

Several studies have investigated the role of antibody production against myelin proteins and their roles in pathogenesis of the disease [99-102]. Myelin protein zero (P0) is the major part of structural glycoproteins in membrane of PNS myelin sheets, and myelin P2 protein is another membrane protein in PNS and a lesser amount in CNS, both used to induce EAN in animal models. Molecular mimicry between some viral epitopes and P0 can initiate cross-reactivity and autoimmune response [103], hence the production of auto-antibodies against myelin proteins, in particular P0, in patients with GBS and CIPD patients [104]. Circulating T cells from GBS patients show increased IL-4 and IL-10 secretion after stimulation with P0 and P2 and PMP22 during the recovery phase [105, 106], whereas P2 IgG reactivity is increased during the peak of disease in GBS patients [107]. Finally, induction of tolerance to P0 by nasal administration of the antigen prevents development of EAN and downregulates the Th1 response [108, 109].

Significance of other autoantibodies in GBS is yet to be demonstrated. Serum autoantibody secretion against gliomedin and neurofascin, which are adhesion molecules in the Ranvier nodes, is shown to disrupt their aggregation role in the clustering of voltage-gated sodium channel in EAN rats [110, 111]. IgG fixation against neurofascin, gliomedin, and neuronal cell adhesion molecule has been detected in sera of GBS patients in about 43% of cases [112]. In contrast, autoantibodies against PMP22, another Schwann cell surface protein, are rare in GBS patients [51].

Innate immunity

Innate immune receptors

Toll-like receptors (TLRs) are crucial parts of the innate immunity and are endowed by a unique property that enables recognition of a myriad of pathogen-associated molecules. Among the best studied are TLR4 that forms a complex with LPS of gram-negative bacteria such as *C. jejuni* andTLR9 that recognizes unmethylated CpG islands in DNA viruses [113]. TLRs are strategically expressed on the surface of APC, from dendritic cells to T and B cells, and their activation is paramount to the induction of innate and adaptive immune response to pathogens. The TLR-4 signaling-mediated pathway starts by the triggering of the CD14 and LPS-binding protein (LBP) complex on the surface of the APC, resulting in the formation of the TLR4 homodimer. This is followed by intracellular TLR4 signaling through either the Myeloid differentiation primary response gene 88 (MyD88)-dependent or the MyD88-independent pathways. Both pathways culminate in activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [114], which in turn activates several cytokine and chemokine genes to form an inflammatory cellular phenotype. On the other hand, TLR9, an intracellular receptor that recognizes viral CpG DNA motifs ferried into endosomal compartments as part of the intracellular life cycle of DNA viruses [113], activates MyD88 through a set of similar intracellular signaling components. *Figure 2* summarizes the main pathways involved in TLR signaling in patients with GBS.

Critically, it has been shown that mice lacking the MyD88 gene show complete resistance to the induction of autoimmune encephalopathy, whereas in wild-type mice TLR expression and MyD88 activation is enhanced during the active phase of the disease [115]. Expression levels of TLR4 and TLR9, as well as activated forms of MyD88, show upregulation during induction of EAN in an experimental rat model [116]. Upregulation of TLR9 expression is observed in PBMC and splenocytes, in addition to the sciatic nerve, and is maintained during the entire course of disease [116, 117]. Moreover, TLR9 expression is enhanced during the entire course of EAN in PBMC of GBS patients and is shown to correlate with their disease severity and disability [118-120]. TLR9 suppression in mice was shown to induce tolerance in plasma DCs, downregulate costimulatory molecules and Th1 cytokine secretion, altogether accelerating EAN recovery [121]. TLR9 blocking also ameliorated clinical scores in these animals [122].

In another study, although TLR2, TLR4, MyD88, and NF-κB activation were upregulated in PBMCs of patients with GBS, and correlated with disease severity and the ability of dendritic cells to produce TNF-α and IL-1β and type 1 IFN [123, 124]. Both TLR2 and CD14, which also act as co-receptor for TLR2 to bind to the heat shock protein 70 (HSP70), are upregulated along with CD14 and HSP70 in the sciatic nerve of rats with experimentally induced EAN. These results are however controversial as elevated TLR2 levels were shown to be directly correlated with disease severity in EAN [120], in contrast with those of a previous study showing TLR2 and TLR6 mRNA levels to have a negative correlation with clinical severity [117]. Polymorphism in the TLR4 gene could even predict risk for GBS in the Indian population and some polymorphisms are more common in the AMAN subtype [19].

Importantly, sialylation of *C. jejuni* LPS amplifies the TLR-MD2 interaction with the LPS:LBP:CD14 complex, which potentiates dendritic cell activation and IFN-β and TNF-α secretion. This results in a stronger costimulation for the T-cell-dependent response to LPS, increased B-cell proliferation, and as mentioned above, high affinity autoantibody production. Sialylated LOS also induces CD40-independent

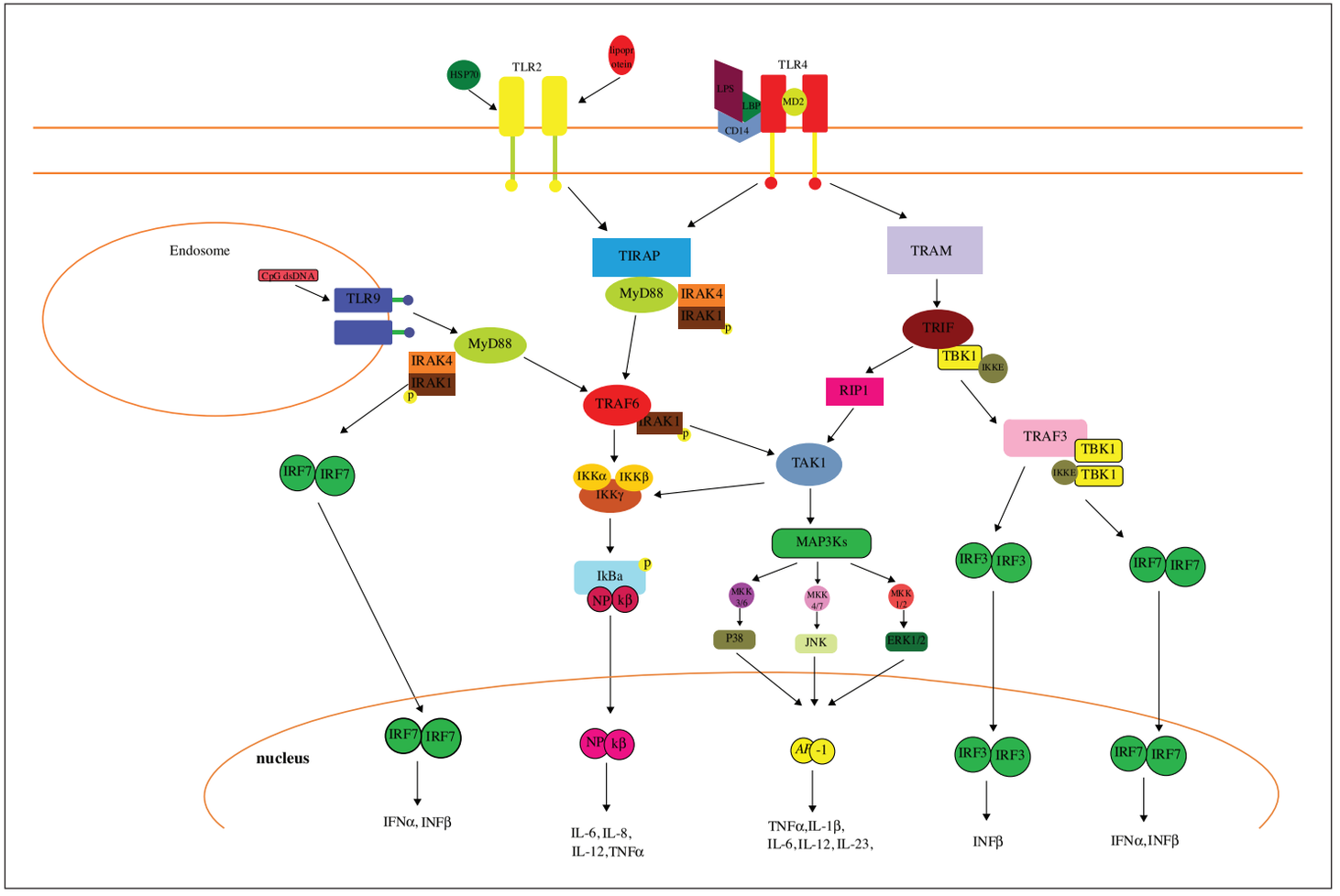

Figure 2

Toll-like receptors and their intracellular signaling in a view. Toll-like receptor 4 (TLR4) presents on cell membranes of neutrophils, dendritic cells (DCs), B cells, macrophages and epithelial cells, and recognize lipopolysaccharide (LPS) by making homodimer and TLR4:CD14:LBP (lipopolysaccharide binding protein) complex. TLR4 signals through two pathways 1. The MyD88 (myeloid differentiation primary response gene 88)-dependent pathway and 2. TRIF (myeloid differentiation primary response gene 88)-dependent pathway or MyD88-independent pathway. Toll-like receptor 2 and Toll-like receptor 6 heterodimer activates MyD88-dependent pathway in DCs, macrophages and neutrophils, after stimulation with heat shock protein 70 (HSP70) or lipoprotein. Toll-like receptor 9 (TLR9) despite pervious TLRs presents in endosome and is activated by unmethylated CpG sequences in DNA molecules, and similarly signals through MyD88-dependent pathway. MyD88-dependent and TRIF-dependent pathway signaling activate transcription factors including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interferon regulatory factor-7 (IRF7), interferon regulatory factor-3 (IRF3) and activator protein 1 (AP-1) which regulate cytokine secretion e.g. interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 12 (IL-12), interleukin 1β (IL-1β), interleukin 23 (IL-23), tumor necrosis factor α (TNFα), interferon α (IFNα) and interferon β (IFNβ). TIRAP: Toll-interleukin 1 receptor (TIR) domain containing adaptor protein; MAP3K: mitogen-activated protein kinase 3; TRAM: TRIF-related adaptor molecule; IRAK1: interleukin 1 receptor-associated kinase 1; IRAK4: interleukin 1 receptor-associated kinase 4; TRAF6: tumor necrosis factor receptor associated factor 6; TRAF3: tumor necrosis factor receptor associated factor 3; IKK: inhibitor of nuclear factor kappa-B kinase; IkBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; TAK1: transforming growth factor beta-activated kinase 1; RIP1: receptor-interacting serine/threonine-protein kinase 1; TBK1: Tank-binding kinase 1; MEK1/2: MAPK/ERK kinase 1 and 2; MKK3/6: MAPK kinase 3/6; MKK4/7: MAPK kinase 4/7; JNK: c-Jun N-terminal kinases; P38: mitogen-activated protein kinases; ERK1/2: extracellular signal-regulated kinases 1/2; P: phosphorylation (arrows show activation).

immunoglobulin class switching, which further increases antibody affinity to self-ganglioside [125]. High titers of anti-GM antibody, as previously mentioned, correlate with disease severity in GBS [123].

Other innate immune receptors, including the killer-immunoglobulin-like receptors (KIRs), are also implicated in GBS. Unlike TLR, KIR expression is principally confined to the plasma membrane of NK. KIRs interact with their respective HLA I ligands to initiate and/or regulate NK cells cytotoxic function [126]. Results from various studies have shown no difference between frequencies of KIR gene among GBS, CIDP, and healthy controls, whereas HLA-B Bw4-T and the inhibitory pair KIR-3DL1/HLA-B Bw4-T are more frequent in both GBS and CIDP patients compared to controls REF. The HLA-C2 and the inhibitory pair KIR-2DL2/HLA-C2 frequencies have also been shown to predict higher GBS risk [78, 127].

Finally, we need to mention the nucleotide oligomerization domain (NOD)-like receptors, which are intracellular pattern recognition receptors expressed in a variety of cell types. Specific homozygote genotypes of NOD1 have been shown to be associated with higher GBS risk, especially the AMAN and AIDP subtypes [128]. The exact role of NOD-like receptors and their therapeutic potential in GBS remains elusive.

Cytokines

Cytokines are the key chemical modulators in the immune system and play an important role in the pathogenesis of GBS [129]. Cytokines such as IL-1, IFN-γ, TNF-α, IL-6, IL-17, and IL-22 are proinflammatory modulators, whereas some other such as IL-10 and transforming growth factor-β (TGF-β) are known to have profibrotic and anti-inflammatory effects. Overall, it appears that a shifting balance toward inflammatory cytokines is responsible for GBS pathology [18, 129], but the bigger picture is more complicated. IL-17 [129], IL-23 [130], IL-16 [131], IL-27 [132], and IL-8 [133] are other proinflammatory cytokines found to be upregulated in serum or nerve sheaths in EAN or GBS.

Proinflammatory cytokines. As the prototype proinflammatory cytokine, IL-1β, is abundantly produced by macrophages, monocytes, dendritic cells, and Schwann cells during the acute phase of GBS [129]. Increased IL-1β is also detected in sciatic nerve and lymph nodes of EAN models [49]. IL-1β is upregulated in infiltrating PBMC of the sciatic nerve in EAN rats, even before clinical signs of neuritis appear, and therefore may act as a crucial factor to initiate the pathogenesis [129, 134, 135]. Together with IL-6 and TNF-α, IL-1β induces Th1 and Th17 maturation and further activation of monocyte/macrophages to produce IFN-γ, which further fuels T helper cell differentiation into the Th1 phenotype. Excessive amounts of IFN-γ have been shown to induce IL-6 and TNF-α production in Schwann cells, in mouse models of neuritis [136, 137]. Similarly, IL-1β, IFNγ, IL-6, and TNF-α expression in sciatic nerves peaks during acute GBS and returns to normal levels during the recovery phase [138]. There are inconsistent results regarding role of IFN-γ in acute phase of GBS, as production of this cytokine has been shown to be dispensable from the described model of blood-nerve barrier disruption in early GBS [139-141]. IL-1β and IL-6 production is also enhanced in the CSF of patients with GBS [142], in line with the concomitant central neuroinflammation. Circulating IL-6 is also shown to be able to cross blood-brain barrier [143], and might, at least partly, contribute to acute neuropsychological changes observed in acute GBS.

Circulating proinflammatory cytokines are shown to disrupt the blood-nerve barrier, alter its immune active phenotypes, increase its permeability, and promote T-cell infiltration. The proinflammatory milieu prepare the ground for circulating anti-myelin autoantibodies to enter the neural sheet, leading to focal demyelination, as seen in the AIDP subtype of GBS [144, 145]. TNF-α has also been shown to reproduce a demyelination phenotype in CNS in experimental models of autoimmune encephalitis [146]. Macrophage infiltration and proinflammatory cytokine production directly induce demyelination, nerve lesions, and axonal degeneration [147] and appear to be the principal mechanisms of axonal degeneration in the AMAN subtype.

Similar to other proinflammatory cytokines, Th17 cell and RORγ expression increase in peripheral blood and CSF of GBS patients during the acute stage of the disease [148] and CSF levels of IL-17 and IL-22 directly correlate with GBS disability scale scores [149]. Similar to other proinflammatory cytokines, IL-17 and IL-22 disrupt blood brain barrier and blood-nerve barrier, facilitating neutrophil activation and their infiltration into the nerve sheaths [150]. Neutrophils are able to release active forms of matrix metalloproteinases (MMPs), and IL-17 itself activates certain MMPs, further breaching the blood-nerve barrier [151-153].

IFN-γ and IL-2. IFN-γ is a major Th1 cytokine with a positive feedback on Th1 cell maturation. IFN-γ is produced by many cell types other than Th1 cells, including endothelial cells, cytotoxic T cells, NK cells, as well as macrophages [154]. IFN-γ in turn can induce immunophenotypic changes in Schwann cells and enhance antigen-presenting properties of APC and expression of adhesion molecules on endothelial cells [155]. IFN-γ can further perpetuate and extend the initial immune response by facilitating leukocyte infiltration and antigen presentation in later stages of GBS [156]. Administration of monoclonal antibody against IFN-γ alleviates disease symptoms in Lewis rats, whereas recombinant IFN-γ exacerbates disease severity in actively induced EAN or adaptive transfer-induced EAN [157]. Linomide, a synthetic immunomodulatory compound, can suppress IFN-γ production in macrophages, which results in induced IL-1β and TNF-α mRNA expression, hence mitigating neuroinflammation in EAN rats, and prevents the development of clinical signs of EAN [158]. Interestingly, mice deficient in IFN-γ showed a compensatory higher percentage of Th17 cells and elevated IL-17A serum levels [159], suggesting a redundancy in the proinflammatory effect of these cytokines.

IL-2 promotes Treg cell differentiation [160] and suppresses Th17 cell maturation [161] and is essential for maturation of almost all types of T lymphocytes. Levels of soluble IL-2Rα, which essentially antagonizes IL-2 function, are elevated in acute GBS and are restored to baseline levels during recovery [162]. This happens parallel to a downregulation of IL-2 in early phase GBS and upregulation during the recovery phase [163]. Interestingly, non-sialylated serotypes of *C. jejuni* fail to stimulate expression of CD25, i.e., the α subunit of the IL-2R, in PBMC of healthy individuals [139].

Anti-inflammatory cytokines. As mentioned above, several reports in the literature show that serum levels of both TGF-β and IL-10 increase during acute GBS and correlate with clinical severity [140, 164], whereas there are studies that report otherwise [48, 138, 165]. Similarly, increased IL-10 and IL-10 mRNA expression in sciatic nerves and lymph nodes has been found during recovery stage of EAN [134, 135, 138], whereas others have detected no significant changes in IL-10 expression either in CSF or in serum of GBS patients [142]. Importantly, both IL-6 and IL-10-producing PBMC expand during early phase of GBS, suggesting a potential natural balance between pro- and anti-inflammatory cytokines, which may justify the self-limiting nature of the disease [165].

IL-10 inhibits almost all aspects of Th1 cell-related pathogenesis, from downregulation of IFN-γ expression [166], to LPS-dependent IL-1β and TNF-α stimulation [167] and induction of nitrous oxide or reactive oxygen secretion [168]. Although specific IL-10 gene (*IL10*) polymorphisms are shown to predict GBS risk in some populations, no correlation between *IL10* polymorphisms and the clinical course of the disease has been found [169]. IL-4 increases in the recovery phase and helps limit the disease [106, 129, 138]. Few reports, however, have found no significant difference in the number of IL-4-producing PBMC between healthy control and GBS patients [53] and no detectable IL-4 in CSF and blood of GBS patients [170]. Together, these facts implicate that GBS cannot be explained merely by an imbalance in the production of Th1/Th2 or pro- and anti-inflammatory cytokines and points out to the function involvement of Th17 cells.

CONCLUSION AND FUTURE DIRECTIONS

A large body of literature providing both *in vitro* and *in vivo* evidence on the etiopathogenesis of GBS notwithstanding and despite experimental animal models for GBS being available for years, the pathogenesis of GBS remains uncertain. GBS is conventionally known as a post-infectious disease and *C. jejuni* has been identified as a major trigger factor in susceptible patients. Nevertheless, infection alone is not enough for GBS to develop and infection with the same strain might yield different outcomes in different patients, whereas even infection with *C. jejuni* strains with low to absent molecular mimicry to self-antigens might result in GBS [3, 4]. GBS is a multifactorial autoimmune disorder, presenting features from acute onset polyneuropathy to chronic peripheral neuritis and from a self-limiting process to a corticosteroid-resistant, life-threatening condition [8].

Cell-mediated immunity seems to play a crucial role in immunopathology of all types of GBS, especially the AIDP subtype, based on extensive T-cell infiltration in myelin sheets and PNS. Although initial reports were in favor of a Th1/Th2 ratio imbalance and shift toward a Th1 cytokine profile during acute phase GBS and a Th2 cell prominence in the recovery phase [18, 48, 51]. Emerging evidence supports the role of Th17 and IL-17 in acute phase of GBS, where disruption of BNB and neutrophil activation and infiltration, initiate demyelination and facilitate production of autoantibodies [56, 151, 153]. Impaired Treg cell function or reduction in number of Tregs induced by IL-17 perpetuates the Th17-driven inflammatory milieu in acute GBS [27, 29, 31, 32]. γδ T cells can recognize non-protein antigens and precipitate antibody secretion in GBS patients in response to ganglioside-like epitopes [72, 74].

Humoral immunity is recognized as the major culprit in the AMAN subtype. *C. jejuni* LOS/LPS shares molecular epitopes with host gangliosides enriched in cell membrane of neurons [88, 89], thereby triggering the generation of autoantibodies that target axonal gangliosides and, less commonly, myelin proteins as hallmark features in pathogenesis in this subtype. Finally, the high probability of GBS after infection with specific *C. jejuni* strains can be attributed to the degree of mimicry between LOS and ganglioside, *C. jejuni* LOS sialylation status and hosts polymorphisms in pattern recognition receptors such as TLR, NOD, and KIR [78, 89, 125, 127, 128].

IVIg treatment remains to be the first-line treatment for GBS. Suggested mechanisms include:

– neutralization of anti-ganglioside autoantibodies by the anti-idiotype antibody pool;
– reduction in the production of IL-2 and IFN-γ which are major pathogenic cytokines in the AMAN subtype;
– mitigating complement activation and formation of a membrane attack complex;
– inhibition of macrophage activation by Fc receptor blockade;
– reduction in proinflammatory cytokine production;
– stimulation of remyelination, especially in the AIDP subtype [171].

Evidence supporting the efficacy of IVIg in acute GBS is multiple and a second course of IVIG is warranted in patients with severe GBS, unresponsive to the first course of IVIG or in those with deterioration despite the first course. Patients with rapidly progressive weakness and grave initial presentation are often put on plasma exchange, for which data on efficacy, or superiority over IVIg, are limited [172]. Currently, no biological treatment is validated for severe, ventilation-dependent patients with GBS, which can be attributed to additional risk posed by infectious and non-infectious side-effects of these agents. It is to be hoped that anti-IL-17 agents, including the fully humanized IgG1 and IgG4 monoclonal antibodies, secukinumab and ixekizumab, respectively, specific for IL-17A, or brodalumab a humanized anti-IL-17 receptor monoclonal antibody are put into trial for

treatment of GBS in persistent, IVIG-resistant or acute, rapidly progressive, patients.

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