

# Guillain-Barré syndrome induced by *Campylobacter jejuni*

## Abstract

**Purpose of review:** Guillain-Barré syndrome (GBS) is a neurologic disease that produces ascending paralysis that affects people all over the world. Several infectious agents have been associated with GBS and many reports suggest that infection with *Campylobacter jejuni* (*C. jejuni*), a common enteric pathogen, may cause GBS by triggering demyelination of peripheral nerves. This review provides an update on the *C. jejuni* infections engaged in the developing of GBS.

## Summary and results:

Guillain-Barré syndrome is the most common cause of acute neuromuscular paralysis, yet its cause and pathogenesis are unknown. In approximately two thirds of patients, neuropathic symptoms follow an infection — often a mild, undiagnosed respiratory or gastrointestinal illness. The organism that has most frequently been described in association with GBS is *C. jejuni*, a gram-negative rod that is now the most common cause of bacterial gastroenteritis in developed countries. Although there has been a plethora of case reports and studies documenting the association, the specific clinical and epidemiologic features are not well known. In addition, there is controversy about whether those with preceding *C. jejuni* infection have a more severe form of the GBS. *C. jejuni* is thought to cause this autoimmune disease through a mechanism called molecular mimicry, whereby *C. jejuni* contains ganglioside-like epitopes in the lipopolysaccharide (LPS) moiety that elicit autoantibodies reacting with peripheral nerve targets. It seems that heterogeneity in the LPS structure determines the specificity of the antiglycolipid response and thereby the clinical features in patients with a post-campylobacter infection neuropathy.

**Keywords:** *Campylobacter jejuni*, Guillain-Barré syndrome, autoantibody, autoimmunity

## 1. Introduction:

In developed countries, *C. jejuni* is a leading cause of acute gastroenteritis. In 1982, Rhodes and Tattersfield [1] reported the first case of a patient who developed GBS after *C. jejuni* enteritis. Actually *C. jejuni* infection frequently precedes GBS, but it is far more common than GBS, the risk of developing GBS after *C. jejuni* infection actually is considerable. In the USA, it is estimated that about one in every 1000 *C. jejuni* infection is followed by GBS [2]. In Ireland, three populations in which outbreaks of *C. jejuni* infection had occurred were investigated, involving an estimated 8000 cases [3]. No cases of GBS were detected in the 6 months following the outbreaks in those local populations. The point estimate for the risk of GBS following *C. jejuni* infection was 0 in 8000. GBS-related *C. jejuni* is reported to be associated with the specific Penner serotypes O:19 in Japan and O:41 in South Africa, but the association is not as strong in other countries. There are some reports of the association of GBS after *C. jejuni* infection with certain Human Leukocyte Antigen (HLA) types, but no specific immune response genes have been reported.

## 2. Bacteriology

Campylobacter species are gram-negative bacilli that have a curved or spiral shape. The complete genome sequence of *C. jejuni* was characterized. Of note was the finding of hypervariable regions that might be important in the survival of the organism [4]. *Campylobacter* species are motile by means of unipolar or bipolar flagella. The organisms grow quite slowly; 72–96 h is required for primary isolation from stool samples, and isolation from blood can take even longer. They grow best at 42°C in selective media with microaerophilic condition. Because most *Campylobacter* species are resistant to cephalothin (an agent to which most other stool flora are susceptible), the usual method for isolation from stool samples is use of a medium that contains cephalothin [5].

Outbreaks have been associated with drinking raw milk or contaminated water and eating poultry. There are several other sources including pets and other animals, and sewage contamination. Chicken is a natural reservoir of the *C. jejuni* where it colonizes in the mucosal layer of the gastrointestinal tract and can transfer between chickens through the faecal-oral route. Actually *C. jejuni* infection is one of the most commonly identified bacterial causes of acute gastroenteritis worldwide. In developing countries, *Campylobacter* species are an important cause of childhood morbidity caused by diarrheal illness. They are among the most common causes of diarrhea in travelers from developed nations. In many studies in the United States and other industrialized countries, *Campylobacter* infections were found to cause diarrheal disease >2–7 times more frequently than infections with *Salmonella* species, *Shigella* species, or *Escherichia coli* O157:H7 [6, 7]. Although 14 species of *Campylobacter* have been identified, in the United States >99% of reported infections with *Campylobacter* are with *C. jejuni* [8].

The epidemiology of *Campylobacter* infections is quite different in developing countries than in the industrialized world. In tropical developing countries, *Campylobacter* infections are hyperendemic among young children, especially those aged <2 years. Asymptomatic infections occur commonly in both children and adults, whereas, in developed countries, asymptomatic *Campylobacter* infections are unusual. In addition, in developing countries, outbreaks of infection are uncommon and the illness lacks the marked seasonal nature observed in industrialized nations. Nevertheless, in both developed and developing countries, *Campylobacter* remains one of the most common bacterial causes of diarrhea [9,10].

Some type of *C. jejuni* strains (Eg: serotype O:19, O:41) more frequently has been associated with GBS. More studies are necessary in characterize the strains.

### 3. Guillain-Barré syndrome

Peripheral nerve diseases are among the most prevalent disorders of the nervous system. Because of the accessibility of the peripheral nervous system to direct physiological and pathological study, neuropathies have traditionally played a unique role in developing our understanding of basic mechanism of nervous system injury and repair. At present they are providing new insight into the mechanisms of immune injury to the nervous system. A rapidly growing evidences of peripheral nervous system disorders are now suspected to be immune-mediated, and in the best understood of these disorders, the molecular and cellular targets of immune attack are known, and the pathophysiology follows directly from the specific immune injury.

GBS is an autoimmune disorder in which peripheral nerves are damaged and cannot transmit signals efficiently. The immunological attack consists of deposits of immunoglobulins and complement on the axon and Schwann cell surface accompanied by macrophage and T-cell infiltration of the nerve [11]. The disease typically progresses from the legs up the body to the trunk and may even affect the respiratory system, causing almost complete paralysis. In GBS, the myelin sheath protecting the nerves is mainly damaged and because nerves cannot transmit signals to muscles, muscles will not function properly, thus causing paralysis. No one knows exactly what causes GBS or why some people get it and other do not. Most people who get GBS do so after having a bacterial or viral infection. In some cases, it has been connected to certain immunizations, such as the flu vaccine [11].

Because GBS is a syndrome and not a disease, it might be difficult to diagnose. The symptoms are not always the same in every person, but typically reflexes will be lost and the process is typically symmetric.

Other important features are elevated CSF protein without significant inflammatory cells. The nadir of clinical worsening should occur within one month of onset.

Patients recover spontaneously and their recovery is accelerated by immunomodulating therapies, such as plasma exchange and intravenous immunoglobulins [12]. Even when patients are treated in well-equipped intensive care units, mortality rates still range from 3–7% [13].

Acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) are main clinical features of GBS and AIDP is the most common subtype of GBS.

#### 4. Epidemiology of Guillain-Barré syndrome

Since the eradication of polio in most parts of the world, GBS has become the most common cause of acute flaccid paralysis with an annual incidence of 0.6–4 cases per 100,000 populations. Actually GBS has now become the most common cause of acute flaccid paralysis worldwide [14, 15].

Males are more frequently affected than females (1.25 : 1). It occurs in all age groups but the incidence appears to increase with age. In developed countries, AIDP appears to affect an older population, while in northern China AMAN affects primarily children and young adults [16]. No consistent geographical variations have been reported and most studies have failed to identify the seasonal variation in GBS.

#### 5. Pathogenesis of Guillain-Barré syndrome

GBS is self-limiting, muscle weakness with partial or complete recovery occurring over weeks to months. The rate of recovery is facilitated by plasma exchange, and its therapeutic effect presumably is related to the removal of circulating factors. GBS is caused by the body's immune system attacking the peripheral nerves. The fact that the syndrome usually comes on after an infection (or extremely rarely, after an immunization) has led us to suspect that at a molecular level, some infectious agents look like parts of the nervous system. This causes the immune system to mistake the identity of peripheral nerves, thinking that parts of the nerve are an infectious agent. As a result, the immune system releases antibodies that attack the peripheral nerves.

How GBS affects an individual person depends on where the antibodies attack the nerve. For this reason, GBS is perhaps best thought of as a family of disorders, which can cause different kinds of problems.

In AIDP, antibodies don't attack the nerve cells directly, but instead damage the glial support cells that surround the axon of the nerve. Typically, this leads to sensory changes and weakness that starts in the toes and fingertips and spreads upwards, worsening over a matter of days to weeks. People with GBS may also suffer from a deep aching pain in their weakened areas and back. Like most forms of GBS, both sides of the body tend to be equally affected in AIDP.

Immunopathological studies suggest that the target of immune attack differs with the GBS subtype. As it is noted, In AIDP, the attack appears to be directed against a component of Schwann cells. In AMAN, attack appears to be against the axolemma and nodes of Ranvier [17]. These findings indicate that the presence of IgG, which binds effectively with complements and macrophages, is the most important factor in the development of GBS

Rees et al. showed that anti-GM1-positive patients were more likely to have axonal degeneration and less sensory disturbance than were anti-GM1 antibody-negative patients [18]. Walsh et al. reported that 14 of 95 (15%) patients with GBS had anti-GM1 antibodies and that the predominant immunoglobulin class was IgG not IgM [19]. Kusunoki et al. found antibody to the minor monosialosylganglioside GM1b to be a useful diagnostic marker of GBS [20].

Patients with the anti-GM1b-positive was distinguished by more rapidly progressive, more severe, and predominantly distal weakness. Cranial nerve involvement and sensory deficits are less common in the patients with anti-GM1b antibodies. The presence of these antibodies was associated with slower

recovery. Clinical manifestations predominantly were associated with anti-GM1b antibodies of the IgG isotype [21].

Gangliosides are sialic acid-containing glycolipids, expressed abundantly in the nervous system. They are composed of a ceramide tail inserted in the lipid bilayer and a highly variable oligosaccharide moiety protruding externally. More than 100 different types of gangliosides have been identified. Gangliosides are implicated in cell growth and differentiation but they also serve as receptors for bacterial toxins and have a function in signal transduction.

## 6. Mechanism of the syndrom

It is believed that a susceptible human host generates autoantibodies that target both the bacterial ganglioside-like lipooligosaccharide (LOS) structures and human peripheral nerve gangliosides, which triggers axonal degeneration and demyelination of the peripheral nerves. The paralysis or muscle weakness may occur because the immune system breaks the protective Schwann cells surrounding the nerves, allowing enzymes to begin breaking down the myelin “insulation” of nerve axons that help ensure reception and speed of nerve impulses [22].

Contrary to what is expected from an antibody response against carbohydrate antigens, the isotype of the ganglioside antibodies in GBS patients is not only IgM but also IgA and IgG [10]. Furthermore, the IgG antibodies have a high titer and are of the IgG1 and IgG3 subclass [10], pointing to an isotype switch involving T-cell help. Interestingly, activated T cells have been identified in the affected nerves and acute phase blood samples from GBS patients. These activated cells are CD4<sup>+</sup> and CD8<sup>+</sup> and express αβ or γδ TCRs [23]). Until now, there have been no reports describing glycolipid reactive T cells in GBS patients, although γδ T cells reacting with non-peptidic *Campylobacter* antigens have been recovered from nerves and peripheral blood of GBS patients [24].

Frequently, an impaired γδ T-cell response towards non-peptidic antigens has been described in GBS patients with an antecedent *Campylobacter jejuni* infection, perhaps underlying the deviant antibody response [25].

The wide range of gangliosides to which antibodies have been reported in GBS patients include GM1, AsialoGM1, GM1b, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, LM1, GalC, and sulfated glucuronyl paragloboside (SGPG).

Gas-liquid chromatography-mass spectrometric analysis showed that the purified LPS has galactose (Gal), *N*-acetylgalactosamine (GalNAc), and *N*-acetylneuraminic acid (NeuAc) ie, the sugar components of the GM1 ganglioside [26].

A single strain of *C jejuni* has several ganglioside-like LPSs. A patient with *C jejuni*-associated GBS could have several types of antiganglioside IgG antibodies. Infection by such a *C jejuni* strain may induce a single anti-ganglioside IgG in some patients and a combination of antibodies in others [26]. In Chinese patients with GBS, 24% of those with AMAN, but none of those with AIDP, had anti-GD1a IgG antibody, indicating that this antibody is closely associated with AMAN but not AIDP [27].

The presence of antibodies to the main epitops of LPS (figure 1) was shown to be related to antecedent *C. jejuni* infection. GBS patients with them had a more rapidly progressive, more severe and predominantly distal weakness, but less sensory loss, paraesthesia, and cranial nerve involvement [21].

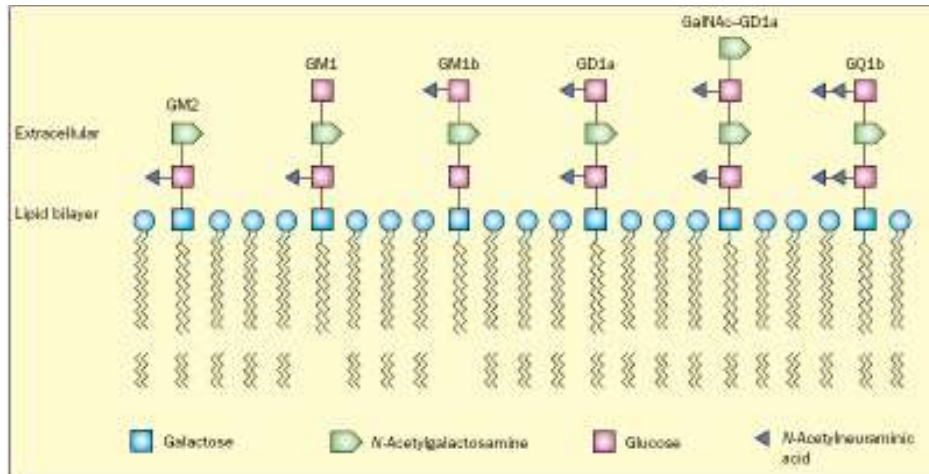


Figure 1. Gangliosides implicated as antigens in GBS. GM1, GM1b, GD1a, and GalNAc-GD1a may be target molecules for IgG antibodies in AMAN and GM2 is a possible target for IgM antibody in AIDP subsequent to cytomegalovirus infection. GQ1b may be a target molecule for IgG antibody in Miller Fisher Syndrom. (reprinted from Yuki N. in Lancet Infect Dis. 2001 Aug;1(1):29-37.

The GD1a epitope is present in *C. jejuni* LPSs isolated from patients with GBS [28]. The GM1b and GalNAc-GD1a epitopes also are expressed in *C. jejuni* LPSs isolated from patients with AMAN who had anti- GM1b and anti-GalNAc-GD1a IgG antibodies [21].

Actually antibodies to >20 different glycolipids have now been associated with a wide range of clinically identifiable acute and chronic neuropathy syndromes. Particular progress has been achieved in understanding the link between acute motor axonal neuropathy and antibodies to GM1, GD1a, GM1b and GalNAc-GD1a, and between the cranial, bulbar and sensory variants of GBS and antibodies to the gangliosides GQ1b, GT1a, GD1b and GD3. In addition to clinical and serological studies, the origins and measurement of antiglycolipid antibodies and their relationships to similar carbohydrate structures on infectious organisms, particularly *C. jejuni*, are discussed in the context of a molecular mimicry hypothesis.

Major advances have been made in animal modelling of antiglycolipid antibody-associated diseases, both in vitro and in vivo. This has advanced our understanding of the role of anti-GQ1b antibodies in Miller Fisher syndrome with particular respect to the motor nerve terminal as a potential site of injury, and led to the creation of rabbit models of anti-GD1b and anti-GM1 antibody-mediated sensory and motor neuropathy, respectively. With such information in place, it will now be possible to determine the precise mechanisms by which antibodies injure the different compartments of peripheral nerve and establish how a range of immunomodulating therapies, including current treatments, exert their therapeutic effects. Despite these very significant advances, considerable gaps in our knowledge persist, and it is likely that other pathogenic pathways operate in inflammatory neuropathy that are unrelated to glycolipid antibodies[21].

## 7. Serological and Culture studies

In 1982, Rhodes and Tattersfield were the first to report on a patient who developed GBS 10 days after *C. jejuni* infection [28]. Then Various electrodiagnostic and pathologic studies have shown that *C. jejuni* infection is significantly associated with primary axonal dysfunction [29, 30] and several reports are also available suggesting role of *C. jejuni* infection in the demyelinating process [31, 32].

GBS is now recognized as a post-infectious complication of *C. jejuni* infection, but its incidence is <1 per 1000 infections [9]. The first line of evidence supporting Campylobacter infection as a trigger of GBS

is narrative reports. The second line of evidence is serologic surveys, which have demonstrated that sera from GBS patients contain anti-*C. jejuni* antibodies, consistent with recent infection. And also a culture study showed that a high proportion of GBS patients have *C. jejuni* in their stools at the time of onset of neurologic symptoms [33].

Actually there are numerous reports described patients who developed GBS following *C. jejuni* infections [35–38]. It is also believed that GBS following *C. jejuni* infection may be more severe, for instance, having fulminating disease with quadriplegia and requiring ventilator support within 24–48 h of onset [38–39]. Neurologic symptoms typically occur 10 days to 3 weeks after onset of diarrhea. The longest reported interval between onset of *C. jejuni* enteritis and onset of GBS symptoms is 23 days [11]. Actually the median interval from the onset of diarrhea to the onset of neuropathic symptoms for most *C. jejuni*-positive patients is 10 days, evidence that GBS is a consequence of an immune response to *C. jejuni* rather than the direct effect of the organism or one of its toxins [39].

Although *C. jejuni* infections are a common trigger of GBS, the risk of developing GBS after *C. jejuni* infection is actually quite small [40]. The risk of developing GBS is increased after infection with certain *Campylobacter* serotypes. In the United States, Penner type O:19 is most commonly associated with GBS [42]; in South Africa, Penner type O:41 is the serotype most frequently associated with GBS

Almost 25%–40% of GBS patients worldwide suffer from *C. jejuni* infection 1–3 weeks prior to the illness [43]. The short interval between the acute infection and the development of symptoms enables identification of the triggering infectious agents and even their culture *in vitro* for further microbial investigations. Culture [41] and serological [42, 43] studies have proved that *C. jejuni* cause infections in GBS patients. The isolation rate of *C. jejuni* from stool culture of GBS patients' ranges from 8% to 50% [41] and seropositivity ranges from 24% to 76% [42, 43, 44].

*Campylobacter* is not a part of normal, stool flora, and detection of the organism would not be expected in the absence of recent infection. However, obtaining culture confirmation of an association with GBS and preceding *C. jejuni* infection is difficult because most patients with *Campylobacter* infection would have already cleared the bacteria when their GBS symptoms began. Nevertheless several investigators have succeeded in isolating *C. jejuni* from the stools of patients with GBS at the onset of their neurologic symptoms. Kuroki et al. [45] isolated *C. jejuni* from 30% of GBS patients, whereas Rees et al. had a isolation rate of 8% [46]. In a similar study, *Campylobacter* was recovered from 4 (44.9%) of 9 GBS patients with diarrhea [47]. In a prospective study, *C. jejuni* and *C. upsaliensis* were detected in patients having AIDP and AMAN type, respectively [48]. Other researchers identified *C. jejuni* infections in GBS cases with culture (2.5%) and with PCR (22.5%), respectively [49].

In a large study conducted in North America and Europe involving 229 GBS patients, 52 (22.7%) patients had positive serology for *C. jejuni*, and 56% of them showed demyelinating neurophysiology [50]. A study in Japan investigating 86 GBS patients showed that of the 20 (23.3%) *C. jejuni*-positive patients, 70% had AMAN and 15% had AIDP [30]. These results raise the possibility that *C. jejuni* infection can elicit both axonal and demyelinating subtypes of the disease.

A high prevalence of antibodies to *C. jejuni* in the serum of patients with GBS have documented in other studies too [43, 50–54].

In a large, blinded, case-control study of 118 GBS patients and 113 controls in the United States, GBS patients were more than five times as likely to have serologic evidence of a recent *Campylobacter* infection [56]. The association was detected using all three immunoglobulin classes, and it was observed in all age groups and in all seasons. However, it was most pronounced in those > 60 years old and during summer months. In this study, male patients also were more likely than female GBS patients to have evidence of preceding *C. jejuni* infection.

In a retrospective serologic study, Kaldor and Speed found that 38% of patients with GBS had a recent *C. jejuni* infection [48]. Saida et al. showed among 205 Japanese GBS patients in their study, 44% had serologic evidence of recent *C. jejuni* infection, compared with 1% in healthy controls [56]. Rees et al. subsequently made a prospective case-control study of 96 patients with GBS and systematically examined all the patients and controls for evidence of *C. jejuni* infection. There was evidence of recent *C. jejuni* infection in 26% of the patients with GBS, compared with 2% of the household controls (a member

of the patient's household) and 1% of the age-matched hospital controls [46]. In a British prospective study, 14 of 99 (14%) patients with GBS had serological evidence of *C. jejuni* infection, compared with only 2% of the controls [52] and finally Anti-GM1b antibody was present in 22 of 104 cases investigated by Yuki et al [57]. Of 132 patients with GBS, 25 (19%) had anti-GM1b antibodies. IgM antibodies were present in 14, IgG antibodies in 15, and both in four patients. The 25 patients with anti-GM1b antibodies had a clinical pattern distinct from that of the other 107 GBS patients, more frequently showing serological evidence of recent infection by *C. jejuni* [57].

## 8. Other experiments

There are numerous reports of patients who developed GBS after receiving bovine brain ganglioside indicative that an antecedent infectious agent with a ganglioside-like structure causes this syndrome. A lipopolysaccharide was extracted from the *C. jejuni* isolated from a patient with GBS who had anti-GM1 IgG antibody [9]. It reacted with cholera toxin (a specific ligand for the GM1-oligosaccharide) and could be purified by column chromatography [58]. Nuclear magnetic resonance showed that the oligosaccharide structure (Gal<sub>1-3</sub> GalNAc<sub>1-4</sub> [NeuAc<sub>2-3</sub> Gal<sub>1</sub>]) protrudes from the LPS core. This terminal structure is identical to that of the terminal tetrasaccharide of the GM1 ganglioside. This was the first report of molecular mimicry between human nerve tissue and an infectious agent isolated from a patient with GBS [21].

The oligosaccharide structures of GM1-like and GD1a-like LPSs were clarified in a *C. jejuni* strain from an enteritis patient [59, 60]. The *C. jejuni* LPS induced anti-GM1 IgM antibody in rats, but they did not show muscle weakness [61]. Ang et al. immunized rabbits with *C. jejuni* LPS from GBS-associated strains bearing a GM1 epitope [63]. All the animals produced high anti-GM1 IgG antibody titres, but none developed overt signs of muscle weakness.

Clinical symptoms in animals are induced by immunization with gangliosides or with purified *Campylobacter* lipo-oligosaccharides. The experiment providing ultimate proof for the molecular mimicry hypothesis in GBS would consist of the induction of cross-reactive antibodies and clinical symptoms following experimental oral infection with a *Campylobacter* strain bearing a ganglioside mimic, whereas infection with a mutant strain lacking only the ganglioside mimic leaves the animals unaffected.

Other animal studies have also shown that immunization and infection with *C. jejuni* or purified LOS result in a cross-reactive anti-ganglioside and LOS response [63, 64]. As expected, the specificity of the anti-ganglioside antibodies in the animals was similar to the specificity in GBS patients from whom these *Campylobacter* strains were derived [63]. This forms strong evidence that the ganglioside autoantibodies in humans can be induced by molecular mimicry between *Campylobacter* LOS and gangliosides. The immunized and infected animals did not develop neuropathy but the anti-ganglioside antibodies generated in animals share pathogenic properties with human GBS sera [64]. Rabbits sensitized with a bovine brain ganglioside mixture containing GM1, GD1a, GD1b, and GT1b, developed high anti-GM1 IgG antibody titres and flaccid limb weakness of acute onset; moreover, they had a monophasic illness course [65,66].

In an animal experiment, the production of paralytic neuropathy in chickens experimentally fed *C. jejuni* isolated from one of a patient is reported. An average of 33% of the chickens became paralyzed. The median time after inoculation to paralysis was 12 days [67]. So experimental inoculation with *C. jejuni* may provide a new model for understanding some forms of GBS.

## 9. Role of *C.jejuni* infection In GBS

Gangliosides are highly expressed in nervous tissues and are considered as cell surface molecules implicated in various biologic cellular functions. There have been several reports of motor neuron disease and multifocal motor neuropathy associated with IgM antibody to GM1 ganglioside [68, 69]. The molecular mimicry between infectious agents and gangliosides may function in the production of anti-ganglioside antibodies. This sugar mimicry is one possible cause of the GBS and MFS; however, unidentified host factors may contribute to the development of these syndromes [70]. GBS is suggested

to be provoked by molecular mimicry between sialylated lipooligosaccharide (LOS) structures on the cell envelope of these bacteria and ganglioside epitopes on the human peripheral nerves, resulting in autoimmune-driven nerve destruction [70]. Earlier, the *C. jejuni* sialyltransferase (Cst-II) was found to be linked to GBS and demonstrated to be involved in the biosynthesis of the ganglioside-like LOS structures. Apart from a role in pathogenicity, It seems that *Cst-II*-generated ganglioside-like LOS structures confer efficient bacteriophage resistance in *C. jejuni* [71].

Terminal structure of *C.jejuni* LPS is identical to the terminal tetrasaccharide of the GM1 ganglioside. The study was the first to demonstrate the existence of molecular mimicry between nerve tissue and the infectious agent isolated from a GBS patient [59]. Aspinall et al. [72] reported that a hyaluronic acid-like repeat unit of LPS is an antigenic determinant of PEN 19. Glycosaminoglycans, including hyaluronic acid, may play an important role in the development of autoimmune diseases [73].

MFS, a variant form of GBS, is characterized by ophthalmoplegia, ataxia, and areflexia. Sera from patients with MFS have IgG anti-GQ1b antibody during the acute phase of the illness [74–76]. The existence of molecular mimicry between GM1 and lipopolysaccharide of *C. jejuni* isolated from a GBS patient and that between GQ1b and *C. jejuni* lipopolysaccharides from patients with MFS are shown by Yuki [77]. Ang et al. also showed that *C.jejuni* Isolated from GBS patients more frequently had a GM1-like epitope than isolates from MFS patients. GQ1b-like epitopes were present in all MFS-associated isolates and was associated with anti-GQ1b antibody reactivity and the presence of oculomotor symptoms. These results demonstrate that the expression of ganglioside mimics is a risk factor for the development of post-*Campylobacter* neuropathy [78].

It seems that antibody reactivity against GM1, GM1b, and GalNAc-GD1a is associated with pure motor GBS [80, 81], and as it is noted anti-GQ1b antibody reactivity showed a strong association with oculomotor symptoms and ataxia [81].

Polymerase chain reaction-based restriction fragment length polymorphism analysis of an *flaA* gene showed that all HS-19 isolates, regardless of a GBS association, had an identical and distinguishable pattern, Cj-1, suggesting that HS-19:Cj-1 isolates are distinctive among *C. jejuni* isolates. Lectin typing showed that all GBS-associated HS-19 isolates contained terminal b-N-acetylglucosamine residues on their cell surface, but HS-19 isolates from patients with enteritis did not [56].

Kuroki et al. reported a possible association between GBS and Penner's heat-stable diagnostic (HS) O serotype HS-19, a rare serogroup in diarrheic patients without neurologic disease [45, 82]. In Beijing, 62% of 46 GBS patients had serologic evidence of *C. jejuni* infection, compared with 9% of healthy controls [83], and in Shijiazhuang, Hebei Province, 66% of 38 GBS patients had serologic evidence of *C. jejuni* infection, compared with 16% of village controls. Studies from Australia [43] and the United States [84] also found high frequencies (38% and 36%, respectively) of *C. jejuni* infection in patients with GBS.

A model of AMAN associated with anti-GM1 IgG antibody has been established. Inoculation with GM1 may induce high anti-GM1 IgG antibody titres, the autoantibody thereafter binding to the GM1 expressed on rabbit peripheral nerve axons, thereby producing dysfunction of the motor nerves followed by Wallerian-like degeneration [85]. A similar mechanism may function in the development of AMAN subsequent to *C. jejuni* enteritis, but animal models showing limb weakness produced by sensitization with the GM1-like LPS are required to validate the molecular mimicry theory[21].

Serologic evidence of *C. jejuni* infection in 55 Chinese patients with clinically defined GBS was correlated with anti-GM1b and anti-GalNAc-GD1a IgG antibodies [86]. Ogawara et al. showed that *C. jejuni* infection is frequently associated with AMAN or anti-ganglioside IgG antibodies. These findings suggest that three phenomena—axonal dysfunction, IgG antibodies against GM1, GD1a, or GalNAc-GD1a, and *C. jejuni* infection—are closely associated [32].

GM(1)- and GD(1a)-like ganglioside mimicry in *Campylobacter jejuni* lipooligosaccharide (LOS) is considered to be involved in the pathogenesis of *Campylobacter*-induced GBS. Compared with gastroenteritis-related isolates, GBS-related *C. jejuni* isolates were strongly associated with the expression of GD(1a)-like mimicry. The presence of a few genes involved in LOS ganglioside mimicry, *cst-II*, *cgtA*, and *cgtB*, was also associated with GBS-related strains. GD(1a)-like epitope expression may be an important virulence phenotype associated with the risk of developing GBS following campylobacter infection.

To better understand the immune events leading to GBS, it is essential to know how sialylated LOS are recognized by the immune system. Heikema et al. showed that GBS-associated *C. jejuni* strains bind to human sialoadhesin (hSn), a conserved, mainly macrophage-restricted I-type lectin. Using hSn-transduced THP-1 cells, they observed that *C. jejuni* strains with  $\alpha(2,3)$ -sialylated LOS, including strains expressing GM1a- and GD1a-like epitopes, bind to hSn. This observation is of importance, as these epitopes are frequently the targets of the cross-reactive antibodies detected in GBS patients. Interestingly, the Sn binding domains were not constitutively exposed on the surface of *C. jejuni*. Heat inactivation and the environmental conditions which food-borne *C. jejuni* encounter during its passage through the intestinal tract, such as low pH and contact with bile constituents, exposed LOS and facilitated Sn binding. Sn binding enhanced bacterial uptake and increased the production of interleukin-6 (IL-6) by primary human Sn-expressing monocyte-derived macrophages compared to control conditions, where Sn was blocked using neutralizing antibodies or when nonsialylated *C. jejuni* was used. Sn-mediated uptake has been reported to enhance humoral immune responses. As *C. jejuni* strains expressing ganglioside mimics GD1a and GM1a are closely associated with GBS, Sn binding may be a determining event in the production of cross-reactive antibodies and the development of GBS [86].

Using a unique, well-characterized strain collection, Heikema et al demonstrated that GBS-associated *C. jejuni* strains bind preferentially to sialoadhesin (Sn, Siglec-1, or CD169), a sialic acid receptor found on a subset of macrophages. In addition, using a whole-cell enzyme-linked immunosorbent assay (ELISA), *C. jejuni* strains with sialylated LOS bound exclusively to soluble Sn. Mass spectrometry revealed that binding was sialic acid-linkage specific with a preference for  $\alpha(2,3)$ -linked sialic acid attached to the terminal galactose of the LOS chain as seen in the gangliosides GD1a, GM1b, and GM3. This molecular interaction was also related to functional consequences as a GBS-associated *C. jejuni* strain that bound Sn in a whole-cell ELISA adhered to surface-expressed Sn of Sn-transfected CHO cells but was unable to adhere to wild-type CHO cells. Moreover, a sialic acid-negative mutant of the same *C. jejuni* strain was unable to bind Sn-transfected CHO cells. This is the first report of the preferential binding of GBS-associated *C. jejuni* strains to the Sn immune receptor ( $P = 0.014$ ). Moreover, because this binding is dependent on sialylated LOS, the main pathogenic factor in GBS progression, the present findings bring us closer to unraveling the mechanisms that lead to formation of cross-reactive antibodies in GBS disease [87].

Carbohydrate mimicry [Galbeta1-3GalNAcbeta1-4(NeuAalpha2-3)Galbeta1-] was seen between the lipo-oligosaccharide of *C. jejuni* isolated from an AMAN patient and human GM1 ganglioside. Sensitization with the lipo-oligosaccharide of *C. jejuni* induces AMAN in rabbits as does sensitization with GM1 ganglioside. Paralyzed rabbits have pathological changes in their peripheral nerves identical to changes seen in human GBS. *C. jejuni* infection may induce anti-ganglioside antibodies by molecular mimicry, eliciting AMAN [88,89].

**10. Conclusion:** The first causal relationship for *C. jejuni* and GBS was hypothesized in 1982 based on a case report and similar reports continued after this. Isolation and growth of *Campylobacter* from the stool of GBS patients also supported such a relationship, but was assumed to underestimate bacterial presence, as time from initial infection to culture and culture methodology could strongly influence recovery of the bacterium. Lab techniques to detect antibodies to *C. jejuni* have also been used to demonstrate presence of the organism in GBS patients, although this technique is subject to cross-reaction with closely related bacteria. Animal models have strengthened support for the association, as rabbits and mice have been injected with molecules similarly shaped to those of *C. jejuni* and have developed high titers of antibodies that also react against nerve cells. Now there are strong supports for the hypothesis that molecular mimicry between *C. jejuni* LPS and gangliosides plays a key role in the induction of antiganglioside antibodies and neurological symptoms in patients with GBS. The timing of GBS following *C. jejuni* infection suggests a humoral, immunopathogenic mechanism.

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