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Guillain-Barré Syndrome
Epidemiology, Pathophysiology and Management

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Contents

Abstract

Guillain-Barré syndrome (GBS) is clinically defined as an acute peripheral neuropathy causing limb weakness that progresses over a time period of days or, at the most, up to 4 weeks. GBS occurs throughout the world with a median annual incidence of 1.3 cases per population of 100 000, with men being more frequently affected than women. GBS is considered to be an autoimmune disease triggered by a preceding bacterial or viral infection. *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus and *Mycoplasma pneumoniae* are commonly identified antecedent pathogens.

In the acute motor axonal neuropathy (AMAN) form of GBS, the infecting organisms probably share homologous epitopes to a component of the peripheral nerves (molecular mimicry) and, therefore, the immune responses cross-react with the nerves causing axonal degeneration; the target molecules in AMAN are likely to be gangliosides GM1, GM1b, GD1a and GalNAc-GD1a expressed on the motor axolemma. In the acute inflammatory demyelinating polyneuropathy (AIDP) form, immune system reactions against target epitopes in Schwann cells or myelin result in demyelination; however, the exact target molecules in the case of AIDP have not yet been identified. AIDP is by far the most common form of GBS in Europe and North America, whereas AMAN occurs more frequently in east Asia (China and Japan).

The prognosis of GBS is generally favourable, but it is a serious disease with a mortality of approximately 10% and approximately 20% of patients are left with severe disability. Treatment of GBS is subdivided into: (i) the management of severely paralysed patients with intensive care and ventilatory support; and (ii) specific immunomodulating treatments that shorten the progressive course of GBS, presumably by limiting nerve damage. High-dose intravenous immunoglobulin (IVIg) therapy and plasma exchange aid more rapid resolution of the disease. The predominant mechanisms by which IVIg therapy exerts its action appear to be a combined effect of complement inactivation, neutralisation of idiotypic antibodies, cytokine inhibition and saturation of Fc receptors on macrophages. Corticosteroids alone do not alter the outcome of GBS.

Guillain-Barré syndrome (GBS) is the most common cause of acute, flaccid paralytic disease in developed countries now that poliomyelitis has been virtually eliminated.[1,2] The term GBS defines a clinical entity that is characterised by rapidly progressing limb weakness and the loss of tendon reflexes.[3] The disorder affects children and adults of all ages, and both sexes, although men are more frequently affected than women.

In the majority of patients (60–70%), the neuropathy is preceded by a bacterial or viral illness, usually an upper respiratory tract infection or gastroenteritis.[2,4] Paralysis of muscles develops acutely (over a period of days or, at the most, 4 weeks) and reaches a plateau. After a brief plateau phase, in most patients improvement begins with a gradual resolution of the paralysis that lasts from weeks to months. Although substantial recovery is common, GBS is a serious disease with a mortality rate of 5–10% and a requirement for mechanical ventilation in 25% of patients.

Intravenous immunoglobulin (IVIg) therapy and plasma exchange hasten early recovery, but even in cases when these treatments are used approximately 20% of the patients are left with a severe disability, such as requiring a support to walk.[5] Therefore, more intensive or effective treatments are necessary to improve the prognosis of GBS.

This article reviews the epidemiology, pathophysiology and management of GBS.

1. Epidemiology

1.1 Annual Incidence

There have been more than 30 population-based surveys of GBS from defined geographical areas of Europe, Australia, and North and Latin America.[2,6] Most studies have reported similar figures for the annual incidence of GBS. The annual incidence has ranged from 0.4 to 4.0 (median 1.3) cases per population of 100 000. A recent survey involving 1752 Japanese patients with GBS showed an annual incidence of 1.15 cases per population of 100 000

(unpublished data, Japanese Research Group of Neuroimmunological Disease). These observations indicate that GBS occurs throughout the world without geographical clustering.

1.2 Age and Sex

GBS is known to occur at all ages. Many epidemiological studies reveal a slight peak in late adolescence and young adulthood, which may be due to an increased risk of infections by cytomegalovirus (CMV) and *Campylobacter jejuni*, and in the elderly, who are possibly susceptible to autoimmune disorders because of decreased immune suppressor mechanisms.[6]

In almost all series, men are more frequently affected than women (1.25 : 1).[6] In general, autoimmune disorders appear to be more prevalent among women; this preponderance of GBS among men is therefore unusual. However, a similar preponderance among men is found with other immune-mediated peripheral neuropathies such as chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and Miller Fisher Syndrome (see also section 2.4).[7]

1.3 Host Susceptibility

As detailed in section 3.1, *C. jejuni* is the most common pathogen that elicits GBS. Enteric infection with *C. jejuni* occurs in association with an estimated 2 million cases of diarrhoea per year in the US,[8] but only a very small proportion of these are followed by development of GBS. *C. jejuni* isolated from patients with GBS and from patients with enteritis but no GBS have ganglioside-like structures on the lipopolysaccharide (LPS) of the outer membrane, but only patients who develop GBS have been shown to have elevated serum antiganglioside antibodies; those with uncomplicated diarrhoea do not.[9] These findings indicate that patients who develop GBS respond differently to *C. jejuni* infection and that there is a host susceptibility which is a determinant for the occurrence of GBS.[10]

However, there is little evidence to suggest the existence of a susceptible immunogenetic background for developing GBS. Most studies have attempted to identify an association between the occurrence of GBS and a particular HLA type, but no firm conclusion has yet been established. A study from Japan reported that all six Japanese patients with *C. jejuni*-related GBS had HLA B35.[11] A study in England investigating HLA type class II alleles showed that in *C. jejuni*-related GBS, HLA DQB 1*03 was present in 83% of the 30 patients, compared with 49% of the 67 patients with GBS who had negative serology for *C. jejuni*.[12] However, a later series comparing 81 Japanese patients with GBS and 87 healthy control individuals showed no significant difference in HLA type.[13] Therefore, HLA type-data in relation to the occurrence of GBS are conflicting at present.

Further studies will be required to clarify the host factors of susceptibility.

2. Pathogenesis and Diagnosis of Clinical Subtypes

GBS is a clinical syndrome that includes a number of pathological and electrophysiological subtypes (table I).[14-16] Each subtype of GBS presumably has an independent immunopathogenesis, and constitutes subgroups with similar but somewhat different clinical features (table II). Electrodiagnostic criteria can be used to differentiate between the GBS subtypes. Although the precise incidence of each subtype of GBS has not been elucidated, the major forms are acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN), with a third type – acute motor and sensory axonal neuropathy (AMSAN) – being much less common.

2.1 Acute Inflammatory Demyelinating Polyneuropathy

AIDP is the most common form of GBS in Western countries and accounts for 85–90% of the pa-

Table I. Clinical subtypes of Guillain-Barré syndrome

Acute inflammatory demyelinating polyneuropathy
Acute motor axonal neuropathy
Acute motor and sensory axonal neuropathy
Miller Fisher syndrome

Table II. Clinical features of the two major subtypes of Guillain-Barré syndrome (GBS)

Feature	Acute inflammatory demyelinating polyneuropathy	Acute motor axonal neuropathy
Preceding infection	Cytomegalovirus	*Campylobacter jejuni*
	Epstein-Barr virus	*?Haemophilus influenzae*
	Mycoplasma pneumoniae	
Frequency (% of GBS)	Europe and North America: 90%	Europe and North America: <10%
	China: 20%	China: 60–80%
	Japan: 40%	Japan: 40%
Epidemics	None	Children
Cranial nerve involvement	Frequent	Rare
Sensory nerve involvement	Frequent	None
Autonomic nerve involvement	Frequent	Rare
Tendon reflexes	Absent	Usually absent
		Occasionally exaggerated
Recovery	Generally good	Two patterns (rapid or slow)
Electrophysiology	Demyelination	Axonal degeneration
		Reversible conduction block
Target molecules	Unknown (Schwann cells or myelin)	GM1, GM1b, GD1a, GalNAc-GD1a (at the nodes of Ranvier)

tients with GBS.[13] The eponym GBS has been used interchangeably with AIDP. However, recent neurophysiological and pathological observations have led to a reclassification of GBS (table I).

AIDP is considered to be an autoimmune disorder triggered by an antecedent infection (see section 3). Electrodiagnostical and pathological studies show typical demyelination suggesting that the immune target in this form of GBS is within the Schwann cell surface membrane or the myelin. There is prominent lymphocytic infiltration of the peripheral nerves and macrophage invasion of the myelin sheath and Schwann cells,[17,18] but the precise target molecules of the immune reaction in patients with AIDP are not yet known, in contrast to the axonal form of GBS (see sections 2.2 and 3).

AIDP is diagnosed when electrodiagnostic testing of a patient with GBS shows slowing of nerve conduction suggestive of demyelination in two or more motor nerves.[13,19]

2.2 Acute Motor Axonal Neuropathy

In China[19-21] and Japan,[22,23] a considerable number of patients with GBS have a type of axonal neuropathy that is referred to as acute motor axonal neuropathy (AMAN). The term AMAN was originally introduced for cases of acute ascending paralysis observed among rural children in northern China, occurring annually as a summer epidemic.[19,21] Later studies have shown that AMAN can occur in adults, irrespective of the season.[22,23]

Electrophysiological and pathological studies confirmed that AMAN is a disorder of pure motor axonal degeneration. Autopsy studies of Chinese patients with AMAN revealed axonal degeneration of motor fibres without demyelination, suggesting an immune response directed primarily against the axonal membrane.[24] Axonal dysfunction in AMAN is not only caused by simple degeneration but also quickly reversible conduction block at the nodes of Ranvier,[22] which is probably responsible for rapid clinical recovery in the subgroup of AMAN patients (see section 4.2). AMAN is often triggered by enteric infection by *C. jejuni* (see section 3.1) and is frequently associated with antiganglioside antibodies (GM1, GM1b, GD1a or GalNAc-GD1a).[23]

AMAN is diagnosed when electrodiagnostic testing of a patient with GBS shows there is a reduction of compound muscle action potential without significant conduction slowing.[13,19]

2.3 Acute Motor and Sensory Axonal Neuropathy

A further axonal subtype of GBS is AMSAN, in which neurophysiological and pathological findings indicate axonal degeneration of both motor and sensory nerves.[24] The incidence of AMSAN is suggested to be very low, being <10% of that of AMAN.[23]

2.4 Miller Fisher Syndrome

A related condition, usually regarded as a variant of GBS, is Miller Fisher syndrome (MFS), which is characterised by a unique clinical triad, namely, ophthalmoplegia, ataxia and areflexia.[25] This disorder is closely associated with antibodies against ganglioside GQ1b. The antibody recognises epitopes expressed in the nodal regions of the ocular motor nerve.[26]

2.5 Incidence of Clinical Subtypes

The frequency of the subtypes of GBS is expected to vary considerably among countries. The annual incidence of GBS in Western countries described in section 1.1 probably represents that of AIDP, because in Europe and North America, 90% of GBS is caused by AIDP.[2,14] In contrast, 60–80% of reported patients with GBS in northern China were classified with disease of the AMAN type;[19] however, the annual incidence of GBS in China has not been reported. Additionally, in a series involving 86 Japanese patients with GBS, electrodiagnostic analysis showed similar frequencies of AIDP (40%) and AMAN (40%).[23] In our experience between 1990–2002, 163 patients with GBS were referred to Chiba University Hospital (Chiba, Japan) or its affiliated hospitals. Of these patients, 51 (31%) were diagnosed as having AIDP, 64 (39%) as having AMAN, and two (1%) as having AMSAN (unpublished data). The remaining 46 patients were not classified by electrodiagnostic criteria. During the same period, 52 patients with MFS were referred to our facilities.

3. Antecedent Infections and Immunopathogenesis

Two-thirds of patients with GBS have an antecedent acute infectious illness, most commonly an upper respiratory tract infection or gastroenteritis that has resolved by the time of the onset of neurological symptoms. The interval between the preceding infection and the onset of GBS ranges from 1 to 3 weeks (mean 11 days).[27]

In many patients, the pathogen responsible for the prodromal illness is unidentified, but a number of studies have shown that there is frequently serological evidence for the presence of a pathogen that could potentially be responsible for eliciting the onset of GBS. Figure 1 shows the frequencies of positive serology in patients with GBS in studies conducted in The Netherlands[28] and Japan.[23] *C. jejuni*, CMV, Epstein-Barr virus (EBV) and

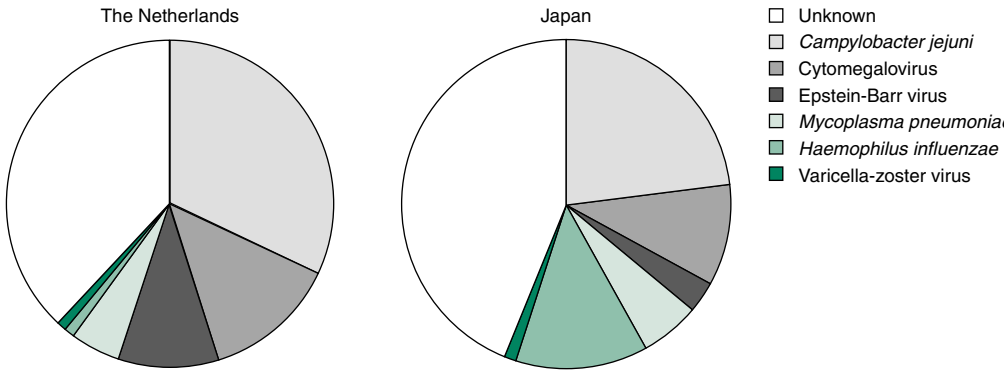

Fig. 1. Incidence of positive infection serology in patients with Guillain-Barré syndrome from studies conducted in The Netherlands[28] (n = 154) and Japan[23] (n = 86).

Mycoplasma pneumoniae are commonly identified pathogens preceding GBS in both The Netherlands and Japan. *Haemophilus influenzae* infections were frequently found only in the Japanese series. The frequencies appear to depend on the sensitivity and specificity of serological assays, and such results cannot be directly compared. Nonetheless, figure 1 shows that *C. jejuni* is likely to be the most common antecedent pathogen and CMV the second most common antecedent pathogen associated with GBS development in both Europe and Japan.

Many other identified pathogens have been reported as triggers for GBS in anecdotal reports or in small series but there is a lack of statistically valid evidence. The association of GBS with HIV has been reported on a number of occasions but the association is so infrequent that it has not been detected in follow-up studies of HIV-infected cohorts.[6]

Detailed studies of the molecular structure of antecedent pathogens, particularly *C. jejuni*, are now providing new insights into putative immunological mechanisms of nerve damage in patients with GBS, as described in the following sections.

3.1 *Campylobacter jejuni*

C. jejuni is a major cause of bacterial gastroenteritis throughout the world and has been recognised as the most frequent antecedent pathogen for GBS. Serological or culture evidence of a recent *C. jejuni* infection ranged from 23% to 45% in a series of patients with GBS in the UK, The Netherlands, US and Japan.[6] This bacteria is strongly associated with the AMAN form of GBS observed in summer epidemics among children in rural areas of northern China;[19] serological evidence of *C. jejuni* infection was found in 66% of Chinese patients with GBS.

Immune responses against *C. jejuni* have been postulated to be involved in the pathogenesis of GBS, especially of the AMAN type, by the induction of antibodies that cross-react with structures, most likely gangliosides, expressed on the peripheral axons. Serum samples from numerous patients who have AMAN subsequent to *C. jejuni* infection contain high titres of antibodies against the following gangliosides: GM1, GM1b, GD1a or GalNAc-GD1a.[23] The LPS from *C. jejuni* contains a terminal tetrasaccharide identical to that of GM1.[26] These observations have led to the concept of 'molecular mimicry', which implies the sharing of homologous epitopes between bacterial LPS and ganglioside surface components of peripheral nerves, especially on the axolemma. It is postulated that because of these molecular similarities, antibody responses mounted against the bacteria could also attack neuronal axons in some individuals, leading to GBS (figure 2).

Moreover, immune responses against *C. jejuni* have been postulated to be involved in the pathogenesis of MFS by the induction of antibodies to ganglioside GQ1b. This antibody is found in approximately 90% of patients with MFS and therefore is diagnostic of MFS.[29] The antibody binds to the GQ1b epitope within the LPS of isolates from patients with MFS.[30] GQ1b is distributed in human ocular motor nerves, which suggests a close association between anti-GQ1b antibodies and ophthalmoplegia in MFS.[29] These findings also support molecular mimicry as an explanation for the pathophysiology of MFS.

C. jejuni may be cultured from the stool for several weeks after the end of a diarrhoeal illness caused by this pathogen. In Japan, the majority of *C. jejuni* isolated from patients with GBS were of the Penner 19 serotype; this serotype was infrequent in patients with enteritis who did not develop GBS.[31] However, this association has not been observed in England.[32]

C. jejuni infection appears to be closely associated with the axonal form of GBS (AMAN) based on the results of studies conducted in China,[19] Japan[23] and Western countries.[33] However, this association is not consistent with the frequency of *C. jejuni* infection and AMAN in Western countries, where the incidence of antecedent *C. jejuni* infection has been reported to be 21–32% in patients with GBS but the percentage of patients with GBS with the AMAN form is <10%. The reason for this discrepancy is unknown. In the case of *C. jejuni*-associated GBS, antiganglioside antibodies or in-

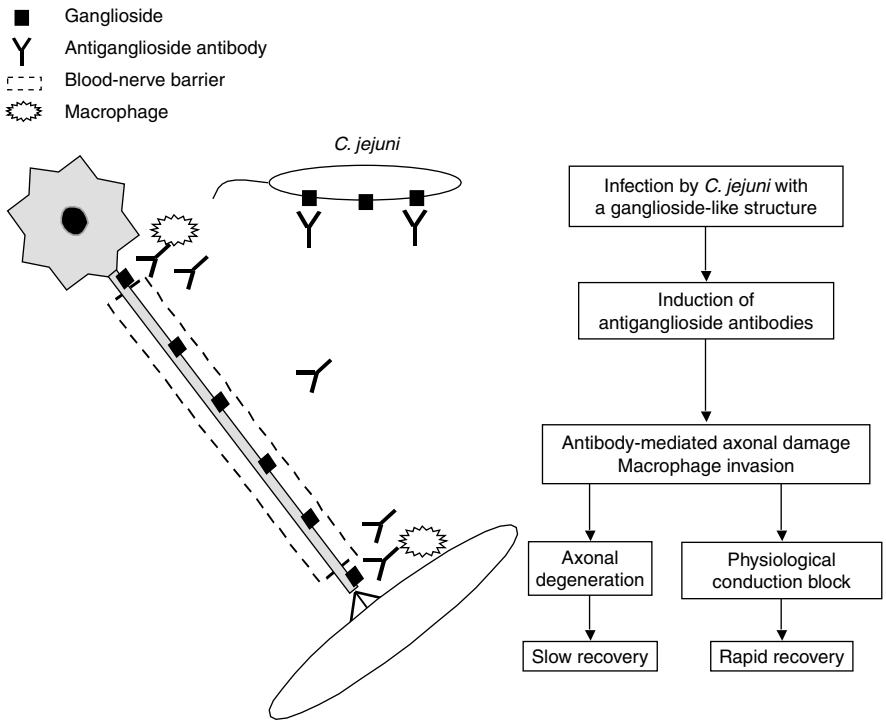

Fig. 2. A 'molecular mimicry hypothesis' for the axonal form of Guillain-Barré syndrome. Infection by *Campylobacter jejuni* with a ganglioside GM1-like structure in the lipopolysaccharide of the outer membrane results in the induction of antiganglioside antibodies. The antibodies cross-react with the gangliosides expressed on the axonal membrane. The blood-nerve barrier is anatomically deficient in the distal nerve terminals and nerve roots, and these regions are preferentially affected by an immune attack. The resolution of physiological nerve conduction failure at the nodes of Ranvier results in a rapid recovery in some patients, but axonal degeneration is associated with slow and incomplete recovery in other patients.

flammatory substances such as cytokines and nitric oxide possibly cause physiological nerve conduction failure at the nodes of Ranvier where ion channels are clustered, and therefore the electrodiagnostic findings may mimic those of AIDP.[22] However, the possibility that *C. jejuni* infection elicits either AMAN or AIDP cannot be excluded.

3.2 Cytomegalovirus

CMV causes respiratory tract infection, mononucleosis-like syndrome or a nonspecific flu-like illness. This virus is the most common viral trigger of GBS, with a prevalence ranging from 10 to 22% in several studies of GBS.[27] This virus is especially common in young female patients and causes typical AIDP with electrophysiological evidence of demyelination,[23,27] in contrast with *C. jejuni*-related axonal GBS.

CMV-related GBS is characterised by a prominent involvement of the cranial and sensory nerves. Some patients with CMV-related GBS have serum antibodies against ganglioside GM2,[34] but the specificity of the antibodies and their significance for the pathogenesis of GBS is unknown.

3.3 *Haemophilus influenzae*

A study in Japan showed serological evidence of *H. influenzae* infection in 13% of 41 consecutive patients with GBS.[35] Most of the GBS patients with *H. influenzae* infection had antiganglioside antibodies and an electrodiagnosis of AMAN: the features were similar to those of patients with GBS associated with *C. jejuni* infection. Cytochemical

staining with cholera toxin suggested the presence of a ganglioside GM1-like structure on the surface of *H. influenzae* isolated from patients with GBS.[36] A particular strain of *H. influenzae* may have a GM1-like structure that can elicit axonal GBS.

3.4 Guillain-Barré Syndrome and Vaccination

A small number of case series and case reports[6] have suggested a possible link between GBS and vaccination, but no causal relationship has been established; coincidental infections were not ruled out in many cases.

However, rabies vaccines prepared from infected animal brain tissues appears to carry an increased risk of GBS, presumably because of contamination with myelin antigens.[37] Moreover, swine-flu influenza vaccine, administered to 45 million Americans during 1976–7, resulted in a small excess risk of developing GBS that persisted for up to 6 weeks after immunisation.[38] A survey of mass influenza vaccination programmes of the US army did not show any increased incidence of GBS.[39]

There have been a number of surveys of oral poliovirus vaccines and GBS, and this vaccination has not result in any increased risk of GBS.[40] Other studies investigating measles, influenza, typhoid, cholera and diphtheria-tetanus-pertussis vaccines have not demonstrated any significant association between the occurrence of GBS and a previous immunisation.[6]

Vaccination of persons with a history of GBS is controversial. Although the risk of any vaccination should be weighed against the risk of exposure, risk of GBS recurrence after immunisation is, in general, very low.[41,42]

4. Clinical Features

A patient with typical GBS can be readily identified. Paresthesias and numbness are frequent and early symptoms; however, such symptoms are occasionally absent throughout most of the illness. The major clinical manifestation is muscle weakness, which evolves more or less symmetrically over a period of several days or a week or two, and, rarely, over a somewhat longer period. Although most patients eventually recover, with or without residual disability, the weakness can progress to total motor paralysis and death from respiratory failure. Clinical features differ somewhat between the subtypes of the disease.

4.1 Acute Inflammatory Demyelinating Polyneuropathy

In AIDP, proximal as well as distal muscles of the limbs are involved, usually the lower extremities before the upper (ascending paralysis); the trunk, intercostal, neck and cranial nerves may be affected later. In addition to the paralysis of the four limbs, patients with AIDP more frequently have involvement of sensory nerves than patients with AMAN. Sensory loss occurs to a variable degree and, when present, deep sensation tends to be more affected than superficial. Tendon reflexes are usually absent. More than half of patients complain of pain and an aching discomfort in the muscles, mainly those of the hips, thighs and back.[4]

Moreover, AIDP is often associated with a variety of autonomic involvement. Some AIDP patients show a fluctuating heart rate (sinus tachycardia and bradycardia) and blood pressure (hypertension and hypotension). Consequently, the management of cardiovascular dysfunction is particularly important in the treatment of patients with AIDP because the dysfunction may cause sudden death. Urinary retention occurs in approximately 15% of patients soon after the onset of weakness but catheterization is seldom required for more than a few days.[4]

The speed of recovery from AIDP varies but its pace is steady. Often it occurs within a few weeks or months; however, if axons have degenerated, their regeneration may require more than 6 months. Little improvement can be expected in disabilities that last beyond 2 or 3 years.

4.2 Acute Motor Axonal Neuropathy/Acute Motor and Sensory Axonal Neuropathy

AMAN is entirely a motor form of neuropathy. In contrast with AIDP, in which tendon reflexes are invariably absent, some patients with AMAN de-

velop hyperreflexia during the early recovery phase or even at the peak of illness.[43,44] Autonomic dysfunction is rarely observed and is mild if present.

The pattern of recovery in AMAN is somewhat different from that in AIDP. In general, recovery from axonal degeneration takes a much longer time than does recovery from demyelination. However, the mean recovery times of AMAN and AIDP are similar.[45] In contrast to the relatively uniform speed of recovery among patients with AIDP, two patterns of recovery are found for patients with AMAN: some patients recover quickly within days, and others experience slow and poor recovery.[46] The slow recovery pattern is due to extensive axonal degeneration, whereas the rapid recovery may be caused by the resolution of functional nerve conduction failure at the nodes of Ranvier.[45,46]

AMSAN is an axonal disorder similar to AMAN, but the sensory nerves are also involved. This subtype is very rare, but tends to be associated with severe illness and slow recovery.

4.3 Miller Fisher Syndrome

MFS has distinct immunological and pathological features. Clinically, the triad of ophthalmoplegia, ataxia and areflexia is characteristic. If the diagnosing physician is aware of this unique combination of clinical manifestations, then a diagnosis is easily made.

The natural prognosis of MFS is generally good and specific immune treatment appears not to be indicated, unless the patient has concomitant GBS.[7]

5. Treatment

The pathogenesis of GBS is still not sufficiently understood, especially in the case of AIDP. It is likely that an antibody-mediated mechanism is largely responsible for AMAN, whereas in AIDP cellular mechanisms may be more important; however, antibodies are probably involved in the mechanism of demyelination.

Treatment of GBS is subdivided into techniques for managing severely paralysed patients requiring intensive care and ventilatory support, and specific therapy to lessen the nerve damage. Immunomodulating treatments such as plasma exchange and IVIg are indicated for patients who are unable to walk independently.

The Hughes functional grading scale[47] (table III) is widely used to evaluate clinical disability and the functional endpoint.

5.1 Supportive Treatment

The advent of respiratory assistance with improved care has significantly improved the outcome of patients with GBS. Care for severely affected patients is best provided in tertiary centres with intensive care facilities and a team of medical professionals familiar with the special needs of patients with GBS. Intubation and mechanical ventilation are required for 25–33% of these patients, and therefore respiratory support is the most important form of supportive treatment.[4]

Measurement of maximal expiratory vital capacity suffices for bedside guidance as to the adequacy of diaphragmatic strength and the likelihood of respiratory failure. If the vital capacity falls to 15 mL/kg, endotracheal intubation and mechanical ventilation should be considered. Patients with bulbar palsy may require intubation even earlier to prevent aspiration, but mechanical ventilation is not always required at the same time.[4]

Continuous monitoring of blood pressure and heart rate is useful to prevent death from arrhythmia and haemodynamic instability related to autonomic involvement. Hypotension secondary to dysautonomia, which occurs in approximately 10% of severely affected patients, is treated by intravenous volume infusion and the use of vasopressor agents for brief periods. Prominent hypertension is managed by

Table III. Hughes functional grading scale for Guillain-Barré syndrome

Score	Description
0	Healthy
1	Minor symptoms or signs, able to run
2	Able to walk 5m independently
3	Able to walk 5m with a walker or support
4	Bed- or chair-bound
5	Requiring assisted ventilation
6	Death

short-acting antihypertensive medication. The choice of short-acting agent is important because a drop in blood pressure may rapidly succeed hypertension.[4]

Prevention of thromboembolic complications such as deep vein thrombosis and pulmonary embolism with heparin has become routine for high-risk patients with GBS. Respiratory infections can be reduced by minimal sedation in the intensive care unit. Pain can be properly controlled with analgesics and ameliorated by early initiation of rehabilitation techniques such as frequent passive limb movement.[4] Passive movement is useful to prevent contractures.

5.2 Immunomodulating Treatment

As outlined in further detail in the following sections, plasma exchange is more effective than supportive treatment alone. IVIg therapy appears to be as effective as plasma exchange. However, corticosteroids alone do not alter the outcome of GBS.

5.2.1 Plasma Exchange

The value of plasma exchange has been addressed in a number of randomised, controlled studies in which the procedure was performed within 2 weeks after the onset of neurological symptoms.[48,49] Because of ethical constraints, such trials have not been placebo controlled with sham plasma exchange in severely paralysed patients, but randomisation and blinding of assessors have improved the validity of this evidence.

In a North American trial of 245 patients with severe GBS (unable to walk independently, Hughes grade ≥3),[48] 122 patients were randomly assigned to receive plasma exchange (50 mL/kg bodyweight for five sessions, given over 7–14 days), and 123 patients did not receive this treatment. Patients treated with plasma exchange improved more rapidly, that is they could be weaned from assisted ventilation more quickly (24 versus 48 days) and they were able to walk unaided within a shorter period of time (53 versus 85 days). French studies[50,51] supported these results and demonstrated that plasma exchange improves long-term outcome: at 1 year, 71% of those patients treated by plasma exchange recovered full motor strength compared with 52% of the control patients.

Two trials have compared the numbers of plasma exchanges required for a beneficial effect in patients with GBS.[4,5] In one trial, 304 patients with GBS who were unable to stand unaided were randomised to receive either four or two plasma exchanges. The median time to recover to the point of walking with an aid was significantly shortened in the group receiving four exchanges than in the group receiving two exchanges (24 versus 20 days). This benefit of four rather than two exchanges was associated with a slight increase in the incidence of unstable blood pressure and haematomas, but these risks were not considered sufficiently severe to outweigh the advantage of four exchanges. The same group of researchers examined six versus four exchanges in severely affected GBS patients requiring mechanical ventilation upon entering the study. No difference in the speed of recovery was observed between the two groups but adverse effects were more frequent in the six exchange group (46 versus 26%). From these data, the appropriate number of plasma exchanges for GBS patients presenting with moderate or severe disability was determined to be four. For mild GBS, two sessions of plasma exchange are significantly superior to none.[52]

Within 1–2 weeks of initial improvement after plasma exchange, a secondary worsening may be seen in approximately 10% of the patients.[53] This rebound relapse may be due to persistent activity of the disorder; additional treatment by plasma exchange has been shown to lead to renewed improvement.[54] Plasma exchange has an acceptable safety profile when the patient's condition is carefully monitored but is nonetheless not entirely free of risk, especially in haemodynamically unstable patients and in those with infectious complication. Such risks, as well as the high cost and the limited number of plasma exchange facilities, all point to the need to discover alternative treatments.

5.2.2 High-Dose Immunoglobulin

IVIg was first introduced for the treatment of idiopathic thrombocytopenic purpura in 1981[55] and it is now a promising therapy in patients with vari-

ous autoimmune diseases. This therapy was introduced for the treatment of GBS as an alternative to plasma exchange because it had the advantages of lower risk[56] and ease of application.

IVIg and plasma exchange were compared as regards their effectiveness in a multicentre study involving 150 patients with GBS in The Netherlands.[56] IVIg was given at a dosage of 400 mg/kg for 5 days consecutively, and the authors concluded that IVIg and plasma exchange were equally effective. However, the two patient groups were not equally matched and the assessors were not blinded. Thus, these two treatments were compared again in a large multicentre, randomised trial.[57] Plasma exchange (five times over 10–14 days) was compared with IVIg 400mg/kg/day for 5 consecutive days' treatment, and with a combined treatment of plasma exchange followed by IVIg in 379 patients with severe GBS. At 4 weeks after randomisation, an observer unaware of the treatment allocation assessed the Hughes functional grading score. The three groups did not differ significantly with regard to outcome measures (i.e. time to recover to unaided walking; time to discontinuation of mechanical ventilation; and recovery from disability within 48 weeks). The results of this trial confirmed that plasma exchange and IVIg have equivalent efficacy, and that a combination of the two treatments was not of significant advantage.

Because of its ease of application compared with plasma exchange, IVIg is now a preferred treatment for patients with GBS. The mechanisms of action of IVIg have not been fully elucidated, but it is known that IVIg has multiple functions, including the modulation of complement activation products, neutralisation of idiotypic antibodies, saturation of Fc receptors on macrophages and suppression of various inflammatory mediators such as cytokines, chemokines and matrix metalloproteinases; any or all of these could be the predominant mechanisms of IVIg in the treatment of GBS.[58]

Because previously large studies showing the efficacy of plasma exchange and IVIg in patients with GBS were conducted in Europe and North America, the majority of patients with GBS presumably had AIDP. Therefore, it has not been established whether plasma exchange and/or IVIg is effective for the axonal subtype of GBS (AMAN). Two preliminary reports have suggested that for patients with axonal GBS, IVIg is more efficacious than plasma exchange.[59,60] Because AIDP and AMAN presumably have independent immunopathogeneses, in the future it may be found that each subtype requires selective treatments.

5.2.3 Corticosteroids

Corticosteroids are widely used to treat many autoimmune disorders. As opposed to what might be expected in this context, corticosteroids have not been shown to be of benefit in patients with GBS.

In a large, controlled study involving 124 patients with GBS treated with a high-dose corticosteroid (intravenous methylprednisolone 500mg for 5 days) and 118 patients treated with placebo, no significant difference was observed in any of the following: mean disability at 4 weeks, proportion of patients who had improved one clinical grade, or clinical grade at 12 months.[47] The Cochrane evidence-based review of 2003, which included six eligible trials, concluded that corticosteroids alone should not be used in the treatment of GBS.[61]

Corticosteroids reduce the severity of experimental allergic neuritis,[62] an animal model of GBS; the lack of response to corticosteroids is, therefore, difficult to explain. It is possible that any beneficial effect of corticosteroids on the inflammatory reaction is counterbalanced by an adverse effect of corticosteroids on denervated muscle.[63] A recent, randomised study examining the combination of IVIg and high-dose intravenous methylprednisolone treatment and IVIg therapy alone failed to find any significant advantage to the combined treatment at the primary endpoint;[64] however, final data have not yet been published.

5.2.4 Potentially Interesting Future Treatments

Cerebrospinal fluid (CSF) filtration is a new, potentially effective treatment for patients with GBS. In a recent study conducted in 37 patients with GBS who were unable to walk unassisted, functional improvement was assessed at 28 days after randomisation to CSF infiltration or plasma ex-

change. It was concluded that CSF filtration and standard plasma exchange are equally efficacious.[65] This treatment needs further confirmation.

A therapeutic benefit from interferon-β has been suggested because interferon-β inhibits *in vitro* lymphocyte adhesion to recombinant vascular adhesion molecule-1.[66]

In experimental allergic neuritis (a model of GBS), two new cyclo-oxygenase-2 inhibitors were found to inhibit clinical and histological features of the disease, suggesting that these are useful as additional therapeutic agents in GBS.[67]

6. Conclusion

Through advances in epidemiology, immunology and microbiology, our understanding of the pathophysiology of the clinical syndrome of GBS is rapidly growing. Detailed studies of the molecular structure of *C. jejuni* are providing insights into putative immunopathogenesis of nerve damage in the axonal subtype of GBS. This bacteria is not the only aetiological factor, and other viruses or bacteria that elicit GBS could also share homologous epitopes to a component of the peripheral nerves (molecular mimicry).

Intensive supportive care for severely paralysed GBS patients has improved their prognosis, and IVIg and plasma exchange have been proven to shorten the progressive course of GBS, presumably by limiting nerve damage. However, these treatments may not be the final answer to GBS because a significant proportion of patients remain disabled. More intensive or effective treatments are required to improve the prognosis of such patients.

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