Guillain-Barré Syndrome

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REVIEW ARTICLE

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ABSTRACT

OBJECTIVE: **This article summarizes the clinical features, diagnostic criteria, differential diagnosis, pathogenesis, and prognosis of Guillain-Barré syndrome (GBS), with insights into the current and future diagnostic and therapeutic interventions for this neuromuscular syndrome.**

LATEST DEVELOPMENTS: **GBS is an acute, inflammatory, immune-mediated polyradiculoneuropathy that encompasses many clinical variants and divergent pathogenic mechanisms that lead to axonal, demyelinating, or mixed findings on electrodiagnostic studies. The type of antecedent infection, the development of pathogenic cross-reactive antibodies via molecular mimicry, and the location of the target gangliosides affect the subtype and severity of the illness. The data from the International GBS Outcome Study have highlighted regional variances, provided new and internationally validated prognosis tools that are beneficial for counseling, and introduced a platform for discussion of GBS-related open questions. New research has been undertaken, including research on novel diagnostic and therapeutic biomarkers, which may lead to new therapies.**

ESSENTIAL POINTS: **GBS is among the most frequent life-threatening neuromuscular emergencies in the world. At least 20% of patients with GBS have a poor prognosis and significant residual deficits despite receiving available treatments. Research is ongoing to further understand the pathogenesis of the disorder, find new biomarkers, and develop more effective and specific treatments.**

INTRODUCTION

Acute immune-mediated polyneuropathies are grouped under the umbrella term *Guillain-Barré syndrome* (GBS), which is one of the most common neuromuscular emergencies. GBS is a heterogeneous disorder that comprises several phenotypes, electrophysiologic features, and outcomes. This article discusses the clinical presentation, assessment, pathogenesis, and management of GBS.

EPIDEMIOLOGY

GBS is a rare, global disease with an incidence of 0.81 to 1.91 cases per 100,000 person-years in Europe and North America. Regional differences occur in the distribution of disease subtypes; demyelinating forms with a respiratory prodrome dominate in Europe and North America, whereas axonal subtypes with a preceding diarrheal illness are more common in Asia, particularly in Bangladesh and northern China.[1,2] Unlike other autoimmune diseases, GBS more

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RELATIONSHIP DISCLOSURE:
Dr Habib has received personal compensation in the range of $500 to $4999 for serving on scientific advisory or data safety monitoring boards for the National Institutes of Health/National Institute of Neurological Disorders and Stroke and UCB S.A., and as a consultant for Pfizer Inc and in the range of $5000 to $9999 for serving as a consultant for Alexion Pharmaceuticals, Inc, argenx, Genentech, Inc, Immunovant, Inc, and UCB S.A., and for serving on speakers bureaus for Alexion Pharmaceuticals, Inc, and argenx. The institution of Dr Habib has received research support from Alexion Pharmaceuticals, Inc, argenx, Cabaletta Bio, Inc, Genentech, Inc, Immunovant, Inc, Regeneron Pharmaceuticals Inc, and UCB S.A. Dr Waheed has received personal compensation in the range of $500 to $4999 for serving on a scientific advisory or data safety monitoring board for UCB S.A.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Habib and Waheed discuss the unlabeled/investigational use of IV immunoglobulin for the treatment of Guillain-Barré syndrome.

commonly affects men than women, and the incidence is higher in older age groups.[1,2]

Although several noninfectious factors including trauma, surgery, medications (including immune checkpoint inhibitors), and other systemic disorders have been reported as preceding the condition or as risk factors for the condition, infections are the most common antecedent event before the clinical development of GBS.[1] In case-control studies, *Campylobacter jejuni*, hepatitis E virus, cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae* have most consistently been associated with GBS.[3] Regional outbreaks of Zika virus–associated GBS in the mid-2010s occurred in French Polynesia, Latin America, and Caribbean countries.[4] In a study from south India, *C. jejuni*, dengue virus, and chikungunya virus were associated with GBS; however, the number of patients with GBS who were seropositive for chikungunya virus was much higher than those who were seropositive for *C. jejuni* (66.7% versus 32%), highlighting the difference in antecedent infection in tropical countries.[5]

A study that analyzed the first 1000 patients included in the International GBS Outcome Study for a recent infection with *C. jejuni*, hepatitis E virus, cytomegalovirus, Epstein-Barr virus, and *M. pneumoniae* led to some important observations.[6] *M. pneumoniae* was the most common preceding infection in children, and a higher percentage of demyelinating electrophysiologic features occurred with cytomegalovirus infection. Patients who tested positive for infection with *C. jejuni*, the most common infectious etiology (30% of all cases), had the most severe GBS presentations in all geographic areas. Although the distribution of infection was similar across geographic areas, the association between infection and clinical phenotype was different; the pure motor variant and axonal electrophysiologic subtype were more frequent in Asian compared with American or European cohorts. This finding suggests that the development of GBS may be influenced by immunogenetic variables in the host, such as variations in ganglioside distribution in nerve membranes or antibody binding ability. Microbial factors also play a role, such as differences in *C. jejuni* strains (Japan [strain O-19] and South Africa [strain O-41]),[7,8] and genetic polymorphisms in lipopolysaccharide biosynthesis genes in *C. jejuni* that modify ganglioside expression. Furthermore, this study also found subclinical infections in 28% of patients with GBS and a high frequency of coinfections (6%).[6] The latter point could point to true coinfections, which, if confirmed, would call for broad serologic testing, but it could also represent cross-reactive antibodies, particularly for flaviviruses, resulting from earlier flavivirus infection or vaccination. This is further demonstrated by the finding that all patients who were positive for dengue virus–specific IgM were also positive for other agents.[9]

Several cases resembling classic GBS, including typical therapeutic responsiveness, have been reported in close temporal association with COVID-19. However, a 2021 prospective cohort study and a 2022 retrospective epidemiologic study did not support any significant causal link between COVID-19 and GBS.[10,11] For more information, refer to the article "Infectious Neuropathies" by Aimee K. Boegle, MD, PhD, and Pushpa Narayanaswami, MD, FAAN,[12] in this issue of *Continuum*.

The more controversial issue has been the relationship between GBS and vaccinations. This association first came to light during the H1N1 epidemic of 1976 and again in 2009, creating widespread fears of vaccine-induced GBS.

Using surveillance data from the Centers for Disease Control and Prevention's Emerging Infections Program for the 2009 H1N1 pandemic, one study demonstrated a significantly lower cumulative risk of GBS in the vaccinated population compared with the unvaccinated population, indicating the benefit of vaccination.[13] Following the publication of several post–COVID-19 vaccine–associated GBS cases,[14] similar concerns exacerbated the public's existing reservations about different COVID-19 vaccines. A 2022 cohort study's interim analyses using surveillance data from the Vaccine Safety Datalink at eight participating integrated health care systems in the United States showed that the incidence of GBS in the 21 days after Ad.26.COV2.S was 32.4 per 100,000 person-years, which was substantially greater than the expected background rate of 1 to 2 per 100,000 person-years. GBS incidence in the 21 days after mRNA vaccination was 1.3 per 100,000 person-years, similar to the overall expected background rate. These results provided evidence that mRNA vaccines do not appear to be associated with GBS.[15] There are some conflicting data on the association of ChAdOx1 vaccine with GBS.[16-18]

Another study analyzed data from the US Vaccine Adverse Event Reporting System and found no increase in reporting rate following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination compared with the general population between December 2020 and October 2021, although the reporting rate was increased when comparing SAR-CoV-2 vaccination with other vaccinations.[19] These data alone should not be used to determine comparative safety among vaccine types, and it is important to consider other serious adverse events (eg, myocarditis and thrombosis with thrombocytopenia syndrome) that have also been associated with SARS-CoV-2 vaccines.[20]

In summary, research suggests that a causal relationship between COVID-19 vaccination and GBS has not been established for these vaccines, which supports the continuation of vaccination programs until there is clear, properly quantified evidence of increased GBS risk at a magnitude that outweighs the vaccination benefits.[21]

TERMINOLOGY BASED ON CLINICAL COURSE

A distinctive clinical course consisting of four phases is the key clinical hallmark of all GBS subtypes (FIGURE 2-1).[22,23] A prodromal phase is characterized by an antecedent event, which could be infectious or noninfectious, triggering a breakdown in immune tolerance and subsequent initiation of an immune-mediated process. This is followed by a progressive phase with the development of neuropathy symptoms, which by definition should not progress beyond 4 weeks. Symptoms typically reach a clinical nadir by 2 weeks; however, weakness can occasionally become established with an alarming speed, leading to respiratory failure requiring intubation within 12 to 24 hours of symptom onset. Patients then enter the plateau phase, which lasts for 1 to 4 weeks (median of 1 week), and subsequently enter the recovery phase, which can last several months.

More than 95% of patients with GBS experience a monophasic course, and less than 5% of cases have a documented recurrence.[24] Treatment-related fluctuations, defined as up to two relapses with worsening of at least one grade on the GBS disability scale or a decrease in the Medical Research Council (MRC) sum score, within 8 weeks of treatment initiation can occur in up to 10% of cases. Such treatment-related fluctuations often respond to re-treatment with the

KEY POINTS

- Demyelinating forms of Guillain-Barré syndrome (GBS) with a respiratory prodrome dominate in Europe and North America whereas axonal subtypes following a diarrheal illness are more common in Asia, particularly in Bangladesh and northern China.
- A small increased risk of GBS occurs after the Ad.26.COV2.S COVID-19 vaccine but not the mRNA vaccines.
- The GBS prodrome is followed by a progressive phase with the development of neuropathy symptoms, which by definition should not progress beyond 4 weeks.
- Treatment-related fluctuations can occur in up to 10% of patients with GBS and often respond to retreatment with the previously administered immunomodulatory therapy.

KEY POINT

- If a patient with an acute neuropathy has three or more relapses or progression beyond 8 weeks, then the diagnosis of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy should be considered.

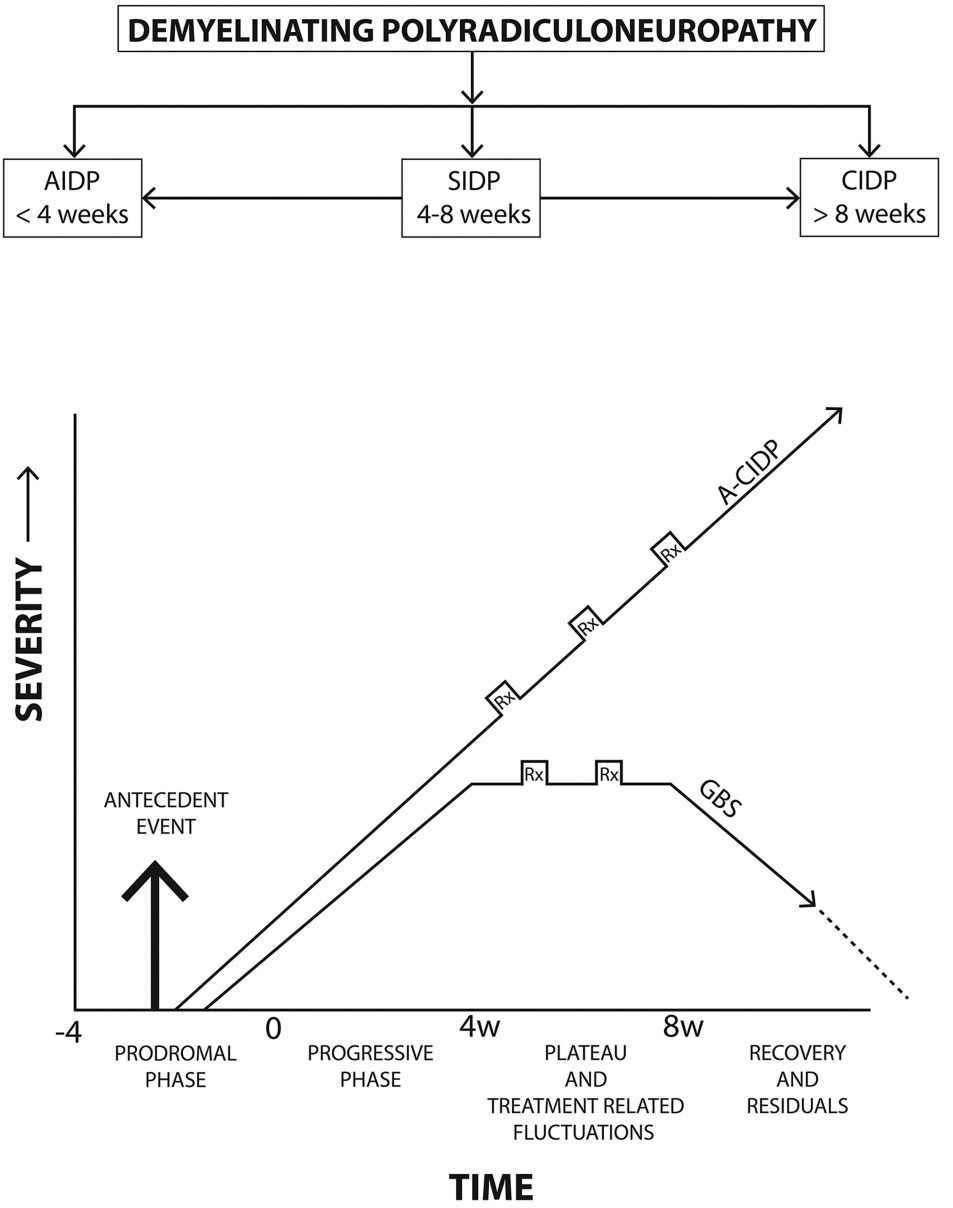

FIGURE 2-1

Clinical course of Guillain-Barré syndrome (GBS). The different subtypes of GBS fall on a continuum. In acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the progression is less than 4 weeks. Patients whose condition continues to worsen despite treatment may have acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP). In subacute inflammatory demyelinating polyradiculoneuropathy (SIDP), the progression is from 4 to 8 weeks. In typical CIDP, the progression is more than 8 weeks or with three or more fluctuations. Treatment-related fluctuations can occur in up to 10% of GBS cases.

Rx = treatment.

previously administered immunomodulatory therapy. Rapid pharmacokinetic clearance of intravenous immunoglobulin (IVIg) treatment leading to a shortened half-life is the potential explanation for IVIg-related treatment-related fluctuation.[25] However, in patients who have three or more relapses or progression beyond 8 weeks, the diagnosis of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) should be considered.[26] See the following section on treatment of patients whose condition worsens after initial improvement for details.

An intermediate subtype between GBS and CIDP, termed *subacute inflammatory demyelinating polyradiculoneuropathy*, has been described that reaches its nadir between 4 and 8 weeks. This represents a mixed group and requires careful follow-up as these patients are at risk of future relapses and evolution into CIDP and may require long-term immunosuppressive treatment.[27]

CLINICAL FEATURES

GBS can be classified based on neurophysiologic characteristics (axonal versus demyelinating forms) or clinical criteria because nerve conduction studies and CSF studies may be normal in the first week of symptom onset (FIGURE 2-2).

GBS has a wide range of clinical findings, indicating different degrees of involvement of motor, sensory, and autonomic nerve fibers along the spinal roots and cranial and peripheral nerves. TABLE 2-1 lists the core diagnostic criteria[28] of

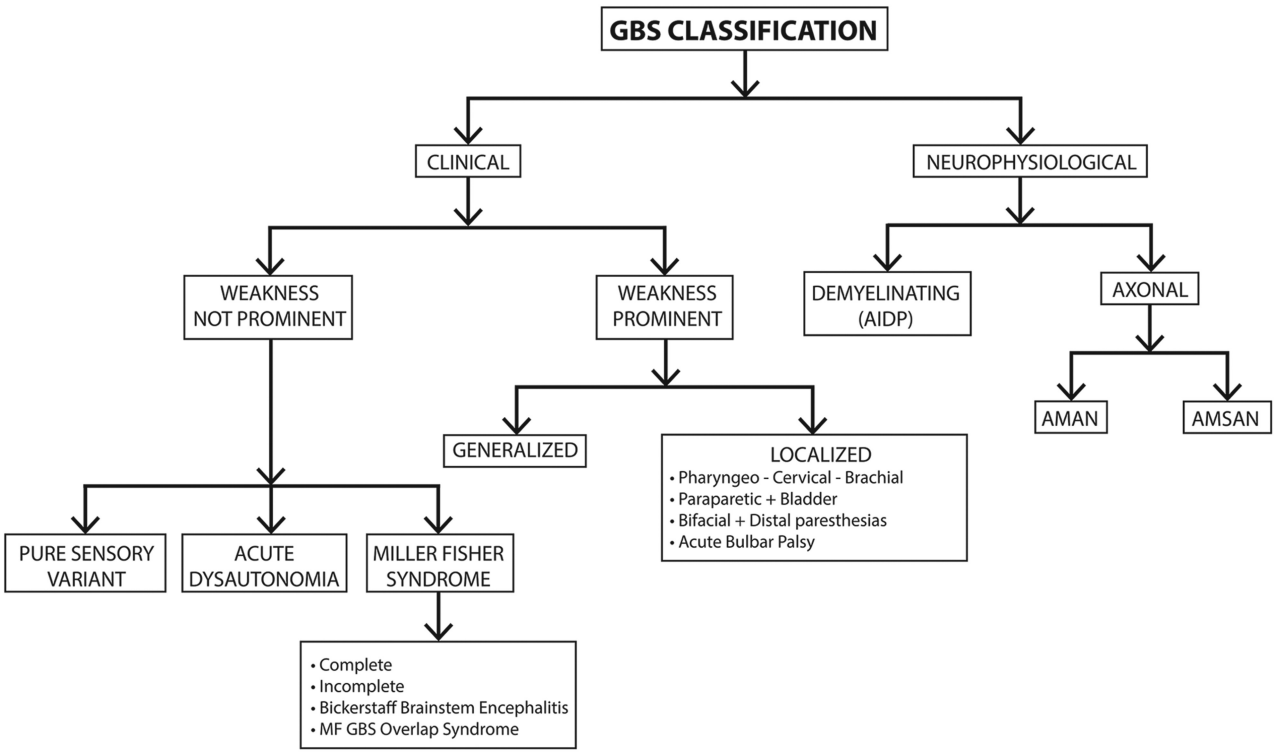

FIGURE 2-2

Clinical classification of Guillain-Barré syndrome (GBS). GBS classification is based on clinical and neurophysiologic features.

AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; AMSAN = acute motor-sensory axonal neuropathy; MF = Miller Fisher syndrome.

classic sensorimotor GBS, or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), representing the most common subtype in the United States and Europe (approximately 85% to 90% of cases).

Following an antecedent event, after a median interval of approximately 10 days, the earliest symptoms are distal paresthesia (acroparesthesia) and low back pain (due to nerve root inflammation), which are reported by approximately two-thirds of patients.[29] The presence of sensory symptoms helps exclude pure motor disorders such as motor neuron disease, myopathy, or myasthenia gravis; however, objective sensory loss is mild and delayed.

Since GBS is primarily a motor more than a sensory neuropathy, the main characteristic of classic GBS is the presence of symmetric weakness involving proximal and distal muscles. This is explained by the involvement of both proximal nerve roots and distal nerves (hence the term polyradiculoneuropathy), where the blood-nerve barrier is weak. An ascending pattern of weakness (legs earlier and weaker than arms) is more common than a descending presentation (onset in face and arms earlier than legs).

Weakness is accompanied by hyporeflexia or areflexia in approximately 90% of patients; however, this could be delayed by a week, while some patients with acute motor axonal neuropathy (AMAN) or Bickerstaff variants might have preserved reflexes or even hyperreflexia.[30]

Aside from limb weakness, involvement of cranial nerve-innervated muscles, particularly facial (50%), oropharyngeal (40%), and extraocular (ophthalmoplegia or ptosis in 5% to 15%) muscles, can occur; severe weakness of respiratory muscles, particularly the diaphragm, necessitates ventilatory support in 10% to 30% of patients with GBS.[31]

About two-thirds of patients have one or more autonomic abnormalities of variable severity. Although there are many variations since the sympathetic nerves are less myelinated, dysautonomia due to sympathetic hyperactivity

TABLE 2-1 **Diagnostic Criteria for Guillain-Barré Syndrome**[a]

Features required for diagnosis

- Progressive weakness of more than one limb
- Areflexia or hyporeflexia

Features that strongly support Guillain-Barré syndrome diagnosis

- Progression of symptoms over days to 4 weeks
- Relative symmetry of symptoms
- Mild sensory symptoms or signs
- Cranial nerve involvement, especially bilateral weakness of facial muscles
- Autonomic dysfunction
- Pain
- Elevated CSF protein
- Characteristic electrodiagnostic features

CSF = cerebrospinal fluid.
[a] Data from Asbury AK and Cornblath DR, Ann Neurol.[28]

typically predominates in the acute phase, and parasympathetic failure is more prominent in the recovery phase.[24,25] These autonomic manifestations include cardiac arrhythmias (sustained sinus tachycardia is the most common abnormality); labile blood pressure (can rarely result in posterior reversible encephalopathy syndrome [PRES] or takotsubo cardiomyopathy from an excess of catecholamines); orthostatic hypotension from a lack of compensatory postural increase in sympathetic activity and vascular resistance in the splanchnic circulation, and disruption of baroreceptor reflexes; abnormal sweating; pupillary abnormalities; and gastrointestinal dysmotility and genitourinary dysfunction typically manifesting as paralytic ileus or urinary retention, which can mimic a spinal cord lesion by causing double incontinence and a pseudosensory level in 5% of cases.[24,25] Since dysautonomia can mimic other systemic problems such as early sepsis and may be accompanied by denervation hypersensitivity, it poses diagnostic and therapeutic challenges. Antihypertensive and antiarrhythmic medications should therefore be prescribed very cautiously, especially in older adults, since they have the potential to cause severe hypotension or aggravate arrhythmias.[32,33]

Uncommon clinical features in GBS include papilledema (associated with severely elevated CSF protein), facial myokymia, hearing loss, meningeal signs, and vocal cord paralysis.[34]

GUILLAIN-BARRÉ SYNDROME VARIANTS

Once thought to be a singular condition, based on clinical, pathophysiologic, and pathologic traits, GBS is currently acknowledged to be a diverse syndrome with several different variants: axonal variants, Miller Fisher syndrome, and localized variants.

Axonal Variants

Based on electrophysiologic data, axonal variants include AMAN (CASE 2-1) and acute motor-sensory axonal neuropathy (AMSAN). Apart from the involvement of the sensory nerves in patients with AMSAN, the two forms of the disease differ significantly. Both forms can be caused by a preceding *C. jejuni* infection. AMAN is more prevalent in Asia, is typically preceded by diarrhea, is more common in the summertime, and affects children more frequently.

In contrast, AMSAN has less of a geographic or seasonal pattern, is characteristically preceded by respiratory illness, and is more common in adults. Clinically, AMSAN is often more severe, with frequent autonomic and cranial nerve dysfunction. Muscle stretch reflexes in AMAN might be normal (probably because of sparing of the Ia afferents) or even exaggerated (because of dysfunction of spinal inhibitory interneurons).[30]

Based on pathophysiology, AMAN has two patterns of recovery: quick recovery within days of treatment may occur due to the resolution of conduction block (reversible conduction failure), or recovery may be slow and poor when associated with extensive axonal degeneration.[35,36] Once patients with AMAN are reevaluated and other causes excluded, instead of trying to combine immunotherapies or repeat IVIg, early supportive interventions and multidisciplinary rehabilitation are recommended. In contrast, AMSAN usually has an early nadir and protracted clinical course and is associated with severe residual disability.

KEY POINTS

- Sensory symptoms help exclude pure motor disorders such as motor neuron disease, myopathy, or myasthenia gravis in patients with possible GBS; however, objective sensory loss is mild and delayed.
- Weakness is accompanied by hyporeflexia or areflexia in approximately 90% of patients with GBS; however, this finding may be delayed by up to a week, and some patients with acute motor axonal neuropathy might have normal or even exaggerated reflexes.
- Severe weakness of respiratory muscles, particularly the diaphragm, necessitates ventilatory support in 10% to 30% of patients with GBS.
- Acute motor-sensory axonal neuropathy is often clinically more severe than other variants of GBS, with frequent autonomic and cranial nerve dysfunction.
- Acute motor axonal neuropathy has two patterns of recovery: quick recovery within days because of the resolution of conduction block, or slow and poor recovery because of extensive axonal degeneration.
- Miller Fisher syndrome includes a spectrum of disorders with reactivity against specific antiganglioside GQ1b antibodies in approximately 85% to 90% of patients.

Miller Fisher Syndrome

Miller Fisher syndrome includes a spectrum of disorders with serum antiganglioside GQ1b antibodies in approximately 85% to 90% of patients. The complete form of Miller Fisher syndrome is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia and is more common in East Asia, particularly in Japan.[1] Ataxia in patients with Miller Fisher syndrome arises either from cerebellar pathology (central) or from selective involvement of Ia afferent neurons along their path from muscle spindles to the spinal cord (peripheral).[37] Incomplete forms include acute ophthalmoplegia, acute ataxic neuropathy, acute ptosis, mydriasis, and acute vestibular syndromes.[38-40] Bickerstaff brainstem encephalitis is a Miller Fisher syndrome–related disorder in which patients develop impaired consciousness and paradoxical hyperreflexia in addition to ataxia and ophthalmoparesis due to the respective involvement of the reticular formation and pyramidal tracts. In Bickerstaff brainstem encephalitis, brain MRI abnormalities are present in only 30% of cases.[41]

Patients with features of Miller Fisher syndrome who develop limb weakness and respiratory insufficiency are characterized as having the Miller Fisher syndrome–GBS overlap syndrome.

CASE 2-1

A 32-year-old man with no significant past medical history presented to the emergency department for evaluation of diffuse limb weakness. Without any preceding illness, he had woken 2 days before with neck pain and a feeling of weakness in his upper and lower extremities. He had been unable to complete his routine workout but could still ambulate independently. On the day of presentation his weakness progressed to the point that he was unable to get out of a chair, necessitating an emergency evaluation.

Initial evaluation revealed no numbness, tingling, bowel or bladder incontinence, dysarthria, dysphagia, or exertional dyspnea; his mental status and cranial nerve examinations were normal. Neck flexion and extension strength were Medical Research Council (MRC) grade 4/5. Severe, symmetric upper and lower extremity weakness (MRC grade 3/5 proximally and 2/5 distally) and global areflexia were noted. Light touch, temperature, and vibration sensations were normal. Within a few hours, his weakness progressed to quadriplegia. CSF revealed 74 red blood cells/mm^3, 2 white blood cells/mm^3 (51% macrophages, 31% lymphocytes), normal glucose (66 mg/dL), and normal protein (28 mg/dL). He was diagnosed with acute motor axonal neuropathy (AMAN), and IVIg therapy was initiated. He developed progressive respiratory distress requiring intubation and mechanical ventilation on the second day of admission. Electrodiagnostic testing performed on day 14 from symptom onset confirmed a diagnosis of AMAN with absent compound muscle action potentials (CMAPs) in the right median, ulnar, peroneal, and tibial nerves, and normal sensory nerve action potentials. Needle EMG showed some increased insertional activity in the right

Localized Variants

These variants are characterized by the involvement of certain muscle groups or nerves and may not progress to a typical generalized phenotype. The variants include weakness limited to the cranial nerves (bilateral facial palsy with paresthesia or acute bulbar palsy); oropharynx, neck and shoulder muscles, sparing the lower limbs and thus mimicking botulism (pharyngeal-cervical-brachial variant); lower limbs, thus mimicking an acute spinal cord lesion (paraparetic variant); sensory nerves (pure sensory ataxic variant); and autonomic nerves (acute pandysautonomia). However, as these variants do not meet the diagnostic criteria for GBS, controversy exists over their inclusion as clinical GBS variants.[42]

PATHOGENESIS AND PATHOLOGY

The following factors are important in the immunopathogenesis of GBS.

Molecular Mimicry

Because of the similarities between the antigenic structures of pathogens and humans (molecular mimicry), humoral and T-cell–mediated immune responses are generated following an infection such as with *C. jejuni*, contributing to nerve

biceps and deltoid muscles; no volitional motor unit potentials were recorded in any upper or lower extremity muscles examined, and the right trapezius was normal. Repeat lumbar puncture on day 15 showed an increase in CSF protein to 63 mg/dL with normal glucose and cell count. Serum *Campylobacter jejuni* IgG antibody titer was elevated (1:1280; normal, <1:320). A serum antiganglioside antibody test was negative, and extensive workup for other causes was also negative. Because of a lack of significant improvement, tracheostomy and percutaneous endoscopic gastrostomy were performed on day 14, and he was transferred to a long-term acute care facility, where he showed a very gradual recovery.

COMMENT

This case highlights some important aspects of Guillain-Barré syndrome (GBS). While typically GBS symptoms reach a clinical nadir by 2 weeks, occasionally weakness can progress at an alarming speed requiring intubation and mechanical ventilation within a few days of onset. Once extensive axonal degeneration was documented and evaluation for other causes was unrevealing the diagnosis of AMAN was established. In this setting, early supportive interventions and multidisciplinary rehabilitation are recommended rather than combining or repeating immunotherapies.

This case also highlights the presence of subclinical infection in GBS, which in a recent study was found to be present in 28% of patients. Although antecedent infection testing does not alter care, it may offer valuable prognostic information.

KEY POINTS

- The complete form of Miller Fisher syndrome, characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia, is more common in East Asia, particularly in Japan.
- Bickerstaff brainstem encephalitis is a Miller Fisher syndrome–related disorder, where, in addition to ataxia and ophthalmoparesis, patients develop impaired consciousness and paradoxical hyperreflexia because of involvement of reticular formation and pyramidal tracts.
- The localization of the target ganglioside antigens, as well as the binding specificity of the antiglycolipid antibodies, are associated with distinctive clinical subtypes of GBS.

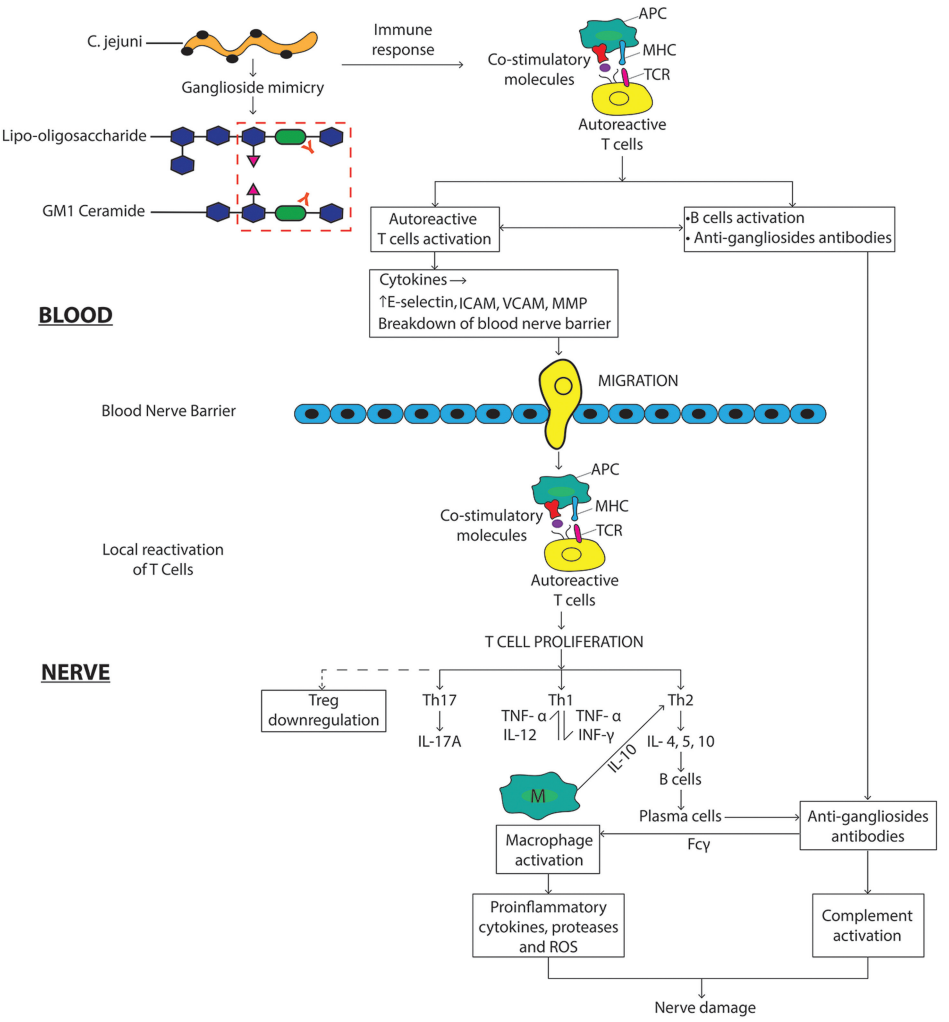

FIGURE 2-3

Different steps involved in Guillain-Barré syndrome (GBS) pathogenesis. (1) Antecedent infection leads to a cellular and humoral immune response generation against autologous targets via molecular mimicry. (2) Breakdown of the blood-nerve barrier. (3) Autoreactive T-cell proliferation, cytokine release, and antiganglioside antibodies production. (4) Recognition of antigenic targets and membrane attack complex formation. (5) Demyelination and axonal loss. (6) Macrophage invasion to remove debris.

APC = antigen-presenting cell; C. jejuni = *Campylobacter jejuni*; Fcγ = Fc gamma; ICAM = intercellular adhesion molecule; IFN-γ = interferon gamma; IL = interleukin; M = macrophage; MHC = major histocompatibility complex; MMP = matrix metalloproteinase; ROS = reactive oxygen species; TCR = T-cell receptor; Th1 = T helper 1; Th2 = T helper 2; Th17 = T helper 17; TNF-α = tumor necrosis factor α; Treg = regulatory T cells; VCAM = vascular cell adhesion molecule 1.

damage and GBS symptoms (FIGURE 2-3). These immune responses can be influenced by a combination of host and microbial factors; however, a potential role of genetic polymorphism, which confers susceptibility to GBS after an infection, requires further investigation.[43-45]

Neural Targets

The neural targets, especially in the axonal variants of GBS, are likely to be gangliosides that participate in receptor modulation, growth regulation, and

cell-cell interactions, particularly those between axons and glia. Their expression on the cell surface makes them potential antigenic targets for circulating components of the immune system.[46,47] The localization of these target ganglioside antigens as well as the binding specificity of the antiglycolipid antibodies have been associated with distinctive clinical subtypes of GBS (TABLE 2-2).[48,49]

Antiganglioside antibodies are not reliably present in all subtypes or patients with GBS. GM1 antibodies are common in axonal variants of GBS, particularly in those preceded by *C. jejuni* infection. The lipooligosaccharide molecules produced by *C. jejuni* strains linked to GBS frequently mimic the saccharide moieties of other gangliosides, including GM1a and GD1a.[47] Anti-GM1 and anti-GalNAc-GD1a antibodies are associated with motor abnormalities because GM1 and GalNAc-GD1a are mostly expressed on the axolemma of motor neurons, especially at the node of Ranvier of intramuscular motor nerve axons. GQ1b is strongly expressed in the extraocular muscles, muscle spindles, and reticular formation accounting for ophthalmoplegia, ataxia, and alteration of consciousness. The GQ1b antibody is thought to have a direct effect on the neuromuscular junctions between cranial nerves and ocular muscles. Dysphagia is explained by GT1a expression in the glossopharyngeal and vagal nerves.[50,51] IgG antibodies to moesin, which is located on Schwann cell microvilli at nodes and is associated with the rearrangement of plasma membrane flexibility, have been identified as a potential autoantigen in cytomegalovirus infection–related AIDP. Other studies have suggested the presence of IgG antibodies to myelin glycolipids such as galactocerebroside or LM1. In addition, IgG antibodies to neurofascin 155 or contactin-associated protein 1 have been detected in GBS sera associated with severe neuropathic pain, suggesting additional research into nodal and paranodal proteins as target antigens in GBS.[49]

Ganglioside Targets in Guillain-Barré Syndrome[a]

TABLE 2-2

Guillain-Barré syndrome subtype	Target antigen
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	LM1, Gal-C
Acute motor axonal neuropathy (AMAN)	GM1, GM2, GD1b, GT1b, GM3, GD1a, GalNac-GD1a
Acute motor-sensory axonal neuropathy (AMSAN)	GM1, GM1b, GD1a
Bickerstaff brainstem encephalitis	GQ1b
Miller Fisher syndrome	GQ1b, GM1b, GT1a, GD3, GD1c
Pharyngeal-cervical-brachial variant	GT1a, GQ1b, GD1b
Sensory ataxic variant	GD1b

[a] Gangliosides nomenclature: Gangliosides are composed of a glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids (eg, *N*-acetylneuraminic acid) linked on the sugar chain. In their nomenclature, G stands for ganglioside, the second letter represents the number of sialic acid residues (M = 1, D = 2, T = 3, Q = 4), the numeral represents the number of neutral carbohydrates, and the lowercase letter (a/b) represents the isomeric position of sialic acid residue.

KEY POINTS

- In acute inflammatory demyelinating polyradiculoneuropathy, demyelination and multifocal perivascular and endoneurial T-cell infiltration ensue along the length of the nerve, particularly early in the proximal nerve roots and distal nerve segments where the blood-nerve barrier is weak.
- Acute motor axonal neuropathy is characterized by the presence of IgG anti-GM1 or anti-GD1a autoantibodies, which bind to the nodal axolemma, leading to complement activation and membrane attack complex formation.

Immunopathogenesis

The immune attack begins when tolerance is broken in the setting of infections such as *C. jejuni* (FIGURE 2-3). Gangliosidelike lipooligosaccharides expressed on *C. jejuni* are identified by antigen-presenting cells and induce proliferation of autoreactive T cells and the production of antimyelin glycolipid antibodies by B cells. Autoreactive T cells not only promote the production of autoantibodies by plasma cells but also secrete various cytokines that, via upregulation of adhesion molecules (eg, E-selectin, intercellular adhesion molecule, vascular cell adhesion molecule 1, and matrix metalloproteinase-9) on endothelial cells, facilitate the breakdown of the blood-nerve barrier to activated T cells, macrophages, and antimyelin antibodies. Local reactivation and clonal proliferation into T helper 1, T helper 2, or T helper 17 cells occur in the peripheral nervous system if these T cells encounter an endoneurial macrophage exhibiting autoantigenic epitopes and the necessary recognition molecules. By producing tumor necrosis factor-α and interferon gamma, T helper 1 cells help macrophages recognize Schwann cells whereas T helper 2 cells promote proliferation and differentiation of B cells. Inflammatory mediators, such as proinflammatory cytokines, reactive oxygen species, and proteases released by activated macrophages propagate the inflammatory response and directly damage the Schwann cells and axons leading to demyelination and secondary axonal degeneration (contact-dependent injury). In addition, downregulation of regulatory T cells, which maintain tolerance and suppress other immune cells such as B, T, and dendritic cells, also contributes to the immunopathogenesis of GBS.[52]

Antimyelin antibodies that cross the damaged blood-nerve barrier, or are produced locally by B cells that have been stimulated by T cells, also contribute to nerve damage by either complement-dependent (C3b receptor-dependent phagocytosis and membrane attack complex [MAC] formation) or complement-independent pathways by binding to the Fc gamma receptors on macrophages. Macrophage activation leads to the further release of toxic mediators and phagocytoses of myelin and myelin debris.[53]

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. Although autoantigens for the pathogenesis of AIDP have yet to be unequivocally identified, autoantibodies may bind to myelin antigens, activate complement to form MAC on the outer surface of Schwann cells, and initiate vesicular degeneration of myelin (FIGURE 2-4). Demyelination and multifocal perivascular and endoneurial T-cell infiltration ensue along the length of the nerve, particularly early in the proximal nerve roots and distal nerve segments where the blood-nerve barrier is weak. Demyelination blocks saltatory conduction along the nerves, accounting for sensorimotor deficits. Macrophages subsequently invade myelin and act as scavengers to remove myelin debris. After myelin has been cleared, Schwann cells depart the basal lamina of nerve fibers to produce offspring Schwann cells around demyelinated fibers to regenerate myelin. By encasing short portions of the fiber, these offspring Schwann cells produce short internodes within the current internode, which are distinct markers indicating earlier demyelination with subsequent remyelination. The short internodes are responsible for persistent conduction abnormalities seen in electrodiagnostic studies, even after good clinical recovery (see Electrodiagnostic Studies for additional details).[54]

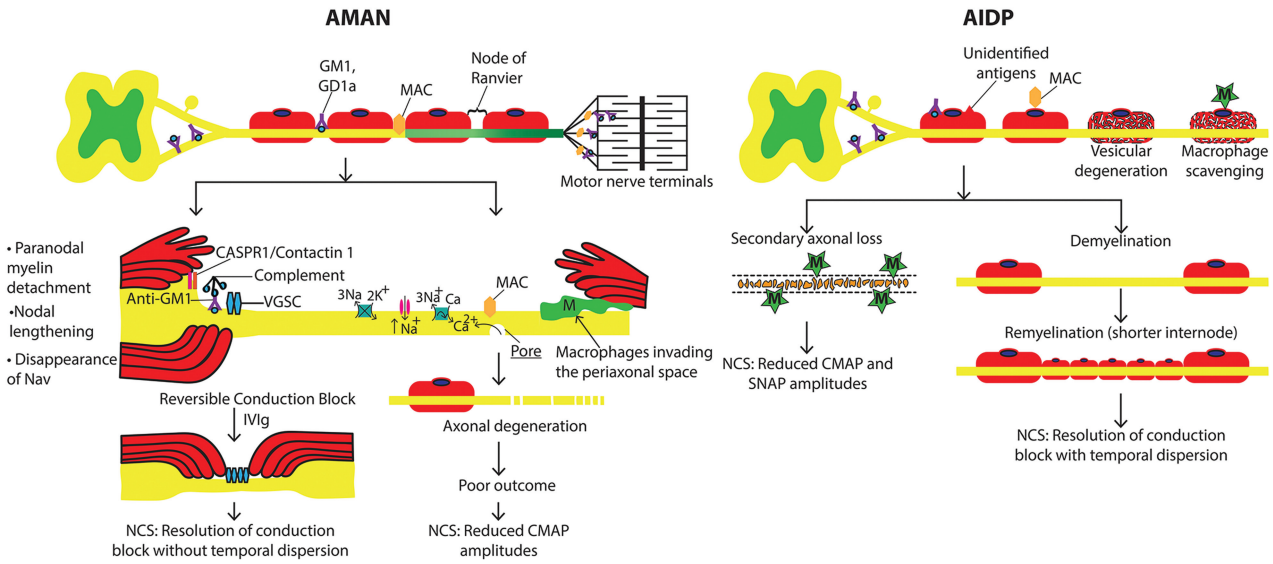

FIGURE 2-4

Pathologic and neurophysiologic correlation of Guillain-Barré syndrome (GBS). In acute motor axonal neuropathy (AMAN), specific gangliosides (GM1, GD1a) are targeted, which are located at nodal structures, ventral roots, and nerve terminals. Complement-mediated axonal conduction block from the loss of voltage-gated sodium channels and paranodal detachment could be reversible with treatment resulting in a prompt clinical recovery. However, intra-axonal calcium accumulation leading to axonal degeneration results in a poor outcome. In acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the antigenic targets are presumably located at the myelin sheath. A membrane attack complex (MAC) is formed as a result of complement activation leading to myelin destruction. Macrophages (M) then clear the debris. Intense inflammation leads to secondary axonal loss.

Ca = calcium; CASPR1 = contactin-associated protein-1; CMAP = compound muscle action potential; IVIG = intravenous immunoglobulin; K = potassium; Na = sodium; Nav = voltage-gated sodium channel; NCS = nerve conduction studies; SNAP = sensory nerve action potential.

Aside from the maintenance of rapid impulse propagation, several other crucial functions of myelinating Schwann cells maintain axonal integrity. These functions include mitigating energy consumption by creating the nodal architecture, regulating axon caliber by organizing axonal cytoskeleton networks, influencing mitochondrial distribution, providing trophic and possibly metabolic support, possibly supplying genetic translational materials, and safeguarding axons from toxic insults. The absence of these functions, particularly cytoskeletal organization in severe cases of AIDP, may trigger secondary axonal degeneration.[55]

ACUTE MOTOR AXONAL NEUROPATHY AND NODOPATHY. The antigenic targets in AMAN are located at nodal structures, ventral roots, and motor nerve terminals (FIGURE 2-4). The term *nodopathy* refers to the principal target areas in AMAN, the nodes of Ranvier, which are required to regenerate and propagate the action potential. At the nodes of Ranvier, where the voltage-gated sodium channels are located, gangliosides GM1 and GD1a are highly expressed.

AMAN is characterized by the presence of IgG anti-GM1 or anti-GD1a autoantibodies, which bind to the nodal axolemma, leading to complement activation and MAC formation. This leads to the disappearance of nodal sodium

channels and nodal lengthening. The extension of an autoimmune attack on the paranodal region destroys adhesion molecules (such as contactin and contactin-associated protein), leading to disruption of the axoglial junctions and detachment of the paranodal myelin terminal loop. Such a constellation of abnormalities results in inexcitable axolemma and nerve conduction block, causing muscle weakness. These changes can be reversible with treatment, resulting in the resolution of the conduction block (reversible conduction failure) and rapid reversal of weakness. However, in cases of intense immunologic activation, axonal degeneration may ensue, which explains the delayed recovery and poor outcomes seen occasionally in patients with AMAN. The axonal degeneration correlates with the intra-axonal accumulation of calcium from two potential mechanisms.[56] First, sodium/potassium pump inhibition caused by energy failure due to depletion of ATP results in an increase in axoplasmic sodium ions and axolemmal depolarization. Further sodium influx and buildup take place as a result of persistent sodium channel activation. Then, the function of the calcium/sodium exchanger is reversed, causing calcium ions to build up in the axoplasm. Second, MAC perforates the axolemma, resulting in pore formation via which calcium ions enter and accumulate in the axoplasm. The damaged axons are subsequently scavenged by macrophages that invade from the nodes into the periaxonal space (see the Electrodiagnostic Studies section for additional details).

AMSAN shares many similarities with AMAN, including paucity of inflammatory infiltration, although the attack in AMSAN is more severe and lasts longer, leading to more intense and ultimately widespread wallerianlike degeneration of both sensory and motor axons.

DIFFERENTIAL DIAGNOSIS

Diagnosis is relatively straightforward when a patient exhibits typical GBS symptoms, but the diagnosis can be challenging in patients with atypical presentations. Red flags suggesting a diagnosis other than GBS include the following[2,50]:

- **Severe respiratory dysfunction with limited limb weakness at onset**
- **Slow progression over 4 weeks without cranial nerve, autonomic, or respiratory involvement**
- **Severe sensory signs with limited weakness at onset**
- **Bladder or bowel dysfunction at onset**
- **Sharp sensory level on torso**
- **Marked persistent asymmetric weakness**
- **Fever at onset**
- **CSF pleocytosis (greater than 50 × 10/L), particularly if polymorphonuclear cells are prominent**

The differential diagnosis of GBS is large and depends on the clinical presentation, age, and geographic location of patients (**TABLE 2-3**).[51,57]

INVESTIGATIONS

The diagnosis of GBS rests on clinical characteristics, laboratory testing including CSF analysis, electrophysiologic studies, and occasionally radiologic investigations.

Laboratory Studies

All patients should undergo initial screening laboratory testing to rule out other potential reasons for sudden weakness, such as infections and metabolic or electrolyte disturbances. This includes a complete blood cell count, comprehensive metabolic profile, glycosylated hemoglobin, and thyroid function testing. Additional tests, such as vasculitic markers or toxicologic testing, may be required to investigate alternative reasons for abrupt-onset weakness, depending on the individual clinical presentation.

Testing for prior infections (eg, *C. jejuni*) might offer valuable epidemiologic data and may be a clue to prognosis, although such testing does not help with the diagnosis or change management of GBS.[58] A 2021 study has revealed a correlation between antibodies against combinations of gangliosides and various GBS variants, as discussed in the Pathogenesis section.[59] With a notable exception of the anti-GQ1b antibody, which is found in up to 90% of patients with Miller Fisher syndrome, the diagnostic value of other antiganglioside antibodies is limited, and assay dependent, and as such they are not recommended for routine testing. A negative test result does not rule out GBS, but a positive test result can be helpful, especially when the diagnosis is unclear, such as with an atypical presentation or in those cases with equivocal results on CSF analysis.[60,61]

CSF Analysis

The CSF examination is used not only to support the diagnosis of GBS but also to exclude other etiologies. Elevated total protein but normal cell count (albuminocytologic dissociation) is the most typical CSF abnormality in patients with GBS. This finding is explained by increased blood-nerve barrier permeability at the level of the proximal nerve roots. Protein levels might vary greatly, as they may be normal during the first week (up to 50% of patients) of the illness but increased in more than 90% of patients by the end of the second week.[1] According to a 2021 study, a high CSF protein level was linked with a demyelinating subtype and a severe disease course in the short term as measured by an inability to walk or run at week 2, but it did not add to the already established predictors for long-term outcomes.[62]

Mild CSF pleocytosis of 10 to 20 cells/mm^3 is seen in up to 5% of cases; however, the presence of marked pleocytosis of more than 50 cells/mm^3 should prompt evaluation for alternative causes. Given that IVIg therapy can raise CSF protein and white blood cell counts, CSF analysis following the start of IVIg therapy can be difficult to interpret.

Electrodiagnostic Studies

Electrodiagnostic studies (consisting of nerve conduction studies and needle EMG) based on the available electrophysiologic criteria[63-67] are performed to confirm the diagnosis, exclude mimics, offer prognostic data by differentiating between the axonal and demyelinating subtypes, and estimate the extent and location of axonal loss.

For the accurate electrodiagnosis of GBS subtypes, patients may require two studies between 1 and 3 weeks apart. The initial study assists in validating the diagnosis of acute neuropathy and is occasionally nonspecific or normal when performed very early in the course of the illness, when patients have initial proximal weakness only, or if the disease is very mild. The second study refines

KEY POINTS

- **Mild CSF pleocytosis of 10 to 20 cells/mm^3 is seen in up to 5% of patients with GBS. The presence of marked pleocytosis of more than 50 cells/mm^3 should prompt the evaluation for alternative causes.**
- **Given that intravenous immunoglobulin (IVIg) therapy can raise CSF protein and white blood cell counts, CSF analysis following the start of IVIg therapy can be difficult to interpret.**
- **Electrodiagnostic studies performed early in the course of GBS may be normal or show subtle or nonspecific abnormalities. Often, a repeat study performed several weeks later is required for definitive characterization of the disease subtype.**

the subtype classification and approximates the extent of any axonal loss, which helps with the prognosis.

Findings in demyelinating variants of GBS (FIGURE 2-4 and FIGURE 2-5A[68]) include early prolonged-latency or absent F waves and absent H reflexes, reflecting involvement of proximal nerve trunks or roots; increased distal latency and conduction block with temporal dispersion in motor nerves (prolonged distal compound muscle action potential [CMAP] duration of more than 8.5 ms seen in 65% with 98% specificity)[69]; reduced motor conduction velocities that are not seen until the third or fourth week of illness (an indication of conduction slowing as a sign of remyelination producing short internodes); and reduced recruitment (early) or fibrillation potentials (after several weeks) on

TABLE 2-3 Differential Diagnoses in Guillain-Barré Syndrome

Presentation	Differential diagnosis
Pure motor presentation Guillain-Barré syndrome (GBS) is predominantly a motor more than sensory neuropathy; however, in the absence of sensory symptoms such as in acute motor axonal neuropathy (AMAN), pure motor disorders need to be considered and excluded by appropriate testing	Infectious motor neuronopathies (West Nile virus, enteroviruses particularly in children, rabies and polio in pertinent geographic areas), myopathies, neuromuscular junction disorders (autoimmune, botulism, or from consumption of various plants such as hemlock or exposure to snake bites [eg, cobra or krait]), acute hypokalemic and thyrotoxic periodic paralysis, hypermagnesemia, acute predominantly motor neuropathies such as porphyria (upper limb predominance; abdominal, psychiatric, and autonomic symptoms) and lead toxicity (radial neuropathy with involvement of wrist and finger extensors), toxicity with organophosphates (eg, exposure to pesticides or plastics and petroleum manufacturing)
Paraparesis, spinal sensory level, or bowel and bladder dysfunction at onset Differential diagnosis in patients with the paraparetic variant of GBS should be considered	Spinal cord or cauda equina compression or spinal cord infarction, transverse myelitis
Asymmetric weakness Patients with GBS typically have symmetric sensorimotor deficits; in the setting of asymmetric weakness, the differential diagnoses need to be expanded accordingly	Vasculitic neuropathy (painful sensorimotor deficits in the distribution of individual peripheral nerves, involvement of other organs), multiple mononeuropathies, infections (eg, Lyme disease, [history of exposure and characteristic rash, ie, erythema migrans, in Lyme disease] diphtheria [following laryngeal infection] or poliomyelitis), leptomeningeal malignancy (eg, carcinomatosis or lymphomatosis [known cancer; headaches, encephalopathy, and multiple cranial neuropathies in leptomeningeal lymphoma])
Cranial neuropathies including ophthalmoplegia and bulbar dysfunction The differential diagnosis of anti-GQ1b antibody–associated GBS variants (Miller Fisher syndrome, Bickerstaff brainstem encephalitis, bulbar palsy) and pharyngeal-cervical-brachial subtype can mimic various conditions	Brainstem stroke (hyperacute onset), myasthenia gravis (fatigable weakness), botulism (pupillary abnormalities, dysautonomia, and descending paralysis), Wernicke encephalopathy (predisposing factors including alcoholism, prior gastric bypass surgery, hyperemesis gravidarum, and malnutrition), other etiologies for rhombencephalitis (infective, inflammatory, or infiltrative), and rarely, Lambert-Eaton syndrome (proximal weakness, areflexia, and dysautonomia)

CONTINUED ON PAGE 1343

needle EMG of weak muscles, especially when associated with secondary axonal loss.

A sparing pattern with preserved sural sensory nerve action potential (ie, "sural sparing" when the upper limb sensory responses are either absent or reduced [seen in 16% with 98% specificity])[70] suggests non–length-dependent neuropathies and also strengthens the suspicion for GBS. Additional studies, such as prolongation of blink reflex latencies, may be helpful with the bulbar-predominant presentation of GBS or when limb responses are absent.[71]

In AMAN, two patterns of conduction abnormalities are seen in serial studies. First, stable or worsening distal CMAP amplitudes with relatively preserved sensory amplitudes, distal motor latencies, and conduction velocities suggesting

CONTINUED FROM PAGE 1342

Presentation	Differential diagnosis
Severe diaphragmatic weakness with limited limb weakness at the onset When the severity of respiratory muscle weakness is disproportionate to limb weakness, the differential diagnosis should expand accordingly	Myasthenia gravis, high cervical cord intramedullary lesions (eg, tumor, abscess, inflammatory disease), Pompe disease, botulism, hypermagnesemia, or hypophosphatemia
CSF pleocytosis (>50 × 10/L) In patients with an elevated CSF cell count, the differential diagnosis should be considered and excluded by appropriate testing	Infections, particularly due to cytomegalovirus, human immunodeficiency virus (HIV), Lyme disease, polio virus; inflammatory disorders (eg, transverse myelitis); infiltrative disorders (eg, leptomeningeal carcinomatosis or lymphomatosis)
Other acute polyneuropathies Many polyneuropathies might resemble GBS by exhibiting sudden onset of symptoms	Critical illness polyneuropathy; toxic neuropathies such as those due to arsenic (environmental exposure, abdominal pain, Mee lines); thallium (alopecia), tetrodotoxin (from consuming incorrectly prepared raw puffer fish [fugu], a Japanese delicacy); plants (eg, buckthorn); n-hexane (eg, glue sniffing or occupational exposure); tick paralysis (asymmetric limb or bulbar weakness in children with normal CSF and quick recovery following removal of embedded tick); paraneoplastic polyneuropathies (often with a known systemic cancer and additional neurologic manifestations such as encephalopathy)
Sensory ataxia Differential diagnosis of the rare sensory ataxic variant of GBS differs from the typical motor-predominant subtype	Paraneoplastic ganglionopathy, Sjögren syndrome, pyridoxine toxicity, chemotherapy-induced polyneuropathy (eg, vincristine, cisplatin, carboplatin, taxanes)
Bifacial weakness The differential diagnosis in the bifacial variant of GBS is distinct from other subtypes	Infections (eg, Lyme disease, HIV infection); inflammatory (eg, sarcoidosis, meningitis [neoplastic or infectious], bilateral Bell's palsy, Melkersson-Rosenthal syndrome [facial palsy, granulomatous cheilitis, and fissured tongue])

CSF = cerebrospinal fluid.

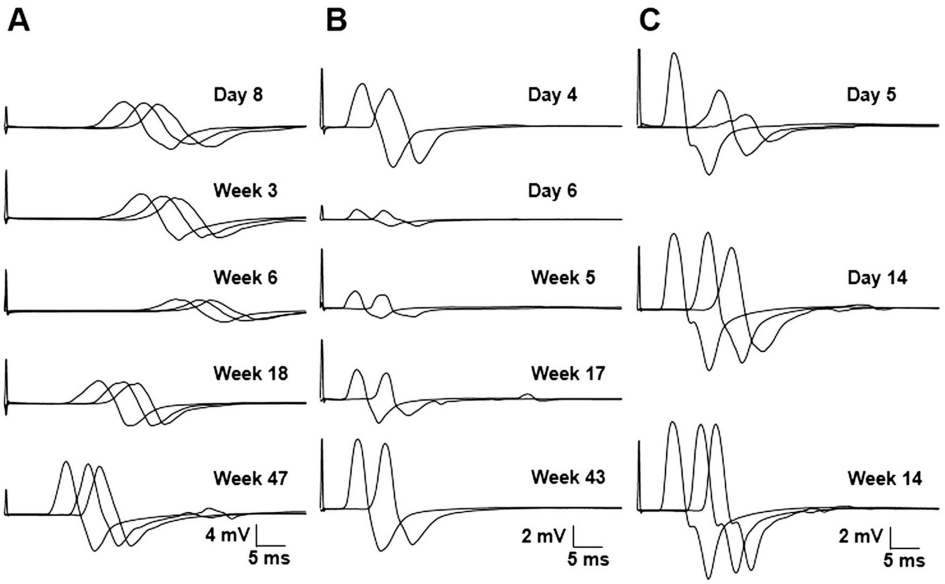

FIGURE 2-5

Electrodiagnostic findings in Guillain-Barré syndrome (GBS). Superimposed compound motor action potential (CMAP) recordings over the abductor pollicis brevis muscle, following stimulation of the median nerve at the wrist and elbow. *A*, Acute inflammatory demyelinating polyradiculoneuropathy demonstrating prolongation of distal latencies, CMAP temporal dispersion, and loss of CMAP amplitude culminating at week 6 with subsequent recovery. *B*, Acute motor axonal neuropathy (AMAN) demonstrating severe loss of CMAP amplitude culminating at day 6 with subsequent recovery and relative sparing of distal latencies and conduction velocities and no temporal dispersion. *C*, Acute motor-conduction-block with conduction blocks noted in the median nerve between wrist, forearm, and upper arm segments seen on day 5 with subsequent improvement in conduction blocks.

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axonal degeneration, lack of temporal dispersion, and F-waves that may be absent but are not significantly prolonged in latency (FIGURE 2-4 and FIGURE 2-5B[68]). Second, low-amplitude distal CMAPs or abnormally reduced CMAP amplitude between two sites of stimulation that rapidly resolves on serial conduction studies, without excessive temporal dispersion or conduction slowing, indicates reversible conduction block and is associated with prompt clinical recovery (FIGURE 2-4 and FIGURE 2-5C[68]). If distal reversible conduction failure is not recognized as the cause of decreased distal CMAP amplitudes in a single test, an incorrect diagnosis of axonal degeneration may be made, with an incorrect conclusion of poor prognosis.[72]

Both CMAP and sensory nerve action potential (SNAP) amplitudes are reduced in the AMSAN variant of GBS. Interestingly, reversible conduction failure restricted to sensory nerves (in the sensory ataxic variant and Miller Fisher syndrome) and to both motor and sensory nerves (in AMSAN and pharyngeal-cervical brachial variant of GBS) has also been identified.[73]

Neuroimaging

MRI of the neuraxis with contrast enhancement is an emerging tool but is not a part of the routine diagnostic evaluation of GBS. MRI can be helpful in

diagnosing GBS in the presence of red flags, identifying certain GBS variants such as the Miller Fisher syndrome and the pharyngeal-cervical-brachial and paraparetic variants, and excluding mimics including brainstem infection, stroke, myelopathy, or cauda equina syndrome. Spinal MRI scans can reveal thickening or enhancement of the intrathecal spinal nerve roots and cauda equina with a sensitivity of 83%, supporting a diagnosis of GBS, especially in young children in whom clinical and electrophysiologic examinations can be difficult.[29,74] Similarly, enhancement of cranial nerves or posterior columns has been described in cases of Miller Fisher syndrome.[75,76]

Peripheral nerve ultrasound may show enlarged cervical nerve roots early in the disease course, with progressive improvement of their cross-sectional area on serial studies performed during the recovery phase. Moreover, additional features such as sparing of sensory nerves and transient enlargement of nerve roots or the vagus nerve may help differentiate GBS from acute CIDP, with a positive predictive value of more than 85%.[77] Normalization of nerves on ultrasound studies, assessed 6 months from onset, may provide additional support for the diagnosis of GBS.[78]

EMERGING INVESTIGATIONS

Several recently developed technologies and biomarkers can help differentiate between the GBS subtypes. Some of these markers available on a research basis include levels of soluble receptor for advanced glycation end products, an integrative metabolomic approach using CSF samples as well as plasma lipid metabolites and cytokines and T-cell ratios.[79-83]

TREATMENT

Treatment of GBS includes both supportive and disease-specific interventions.

Supportive care

Supportive care is the cornerstone of GBS management. A summary of pertinent clinical interventions, their evaluation, and the pathophysiology of neuromuscular respiratory failure in GBS is summarized in FIGURE 2-6.[84,85]

PATIENT TRIAGE AND ASSESSMENT OF VENTILATION STATUS. The presence of one or more of the following factors[84-86] should prompt consideration of admission to the intensive care unit (ICU): dysautonomia, bulbar dysfunction, severe or rapidly worsening weakness (based upon the time between the onset of weakness and presentation, particularly affecting neck and hip flexors),[87] and evolving respiratory distress. Respiratory status is assessed by clinical bedside evaluation (FIGURE 2-6) such as respiratory rate; recruitment of accessory respiratory muscles; counting during the expiration phase after a single full-capacity inspiratory breath (the inability to count to 15 or more during a single breath predicts a subsequent need for mechanical ventilation); and diminished strength of cough. In addition, the "20/30/40 rule" can be applied to bedside pulmonary function tests: the patient is deemed at risk for respiratory failure if the vital capacity is <20 mL/kg, the maximum inspiratory pressure is <30 cm H_2O, or the maximum expiratory pressure is <40 cm H_2O. These parameters should be monitored every 2 to 4 hours in all patients with GBS in the acute setting; a rapid decline in respiratory function (>30% in 24 hours) should also prompt admission to the ICU. For patients with mild weakness who

KEY POINTS

- Spinal MRI can demonstrate thickening and enhancement of intrathecal spinal nerve roots, supporting a diagnosis of GBS with a sensitivity of 83%, especially in young children in whom clinical and electrophysiologic examinations can be difficult.
- The following factors may prompt admission of patients with GBS to the intensive care unit: dysautonomia, bulbar dysfunction, severe or rapidly worsening weakness, and evolving respiratory distress.
- A score of more than 4 on the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score suggests a high (≥65%) risk of respiratory failure, which warrants monitoring in an intensive care setting.

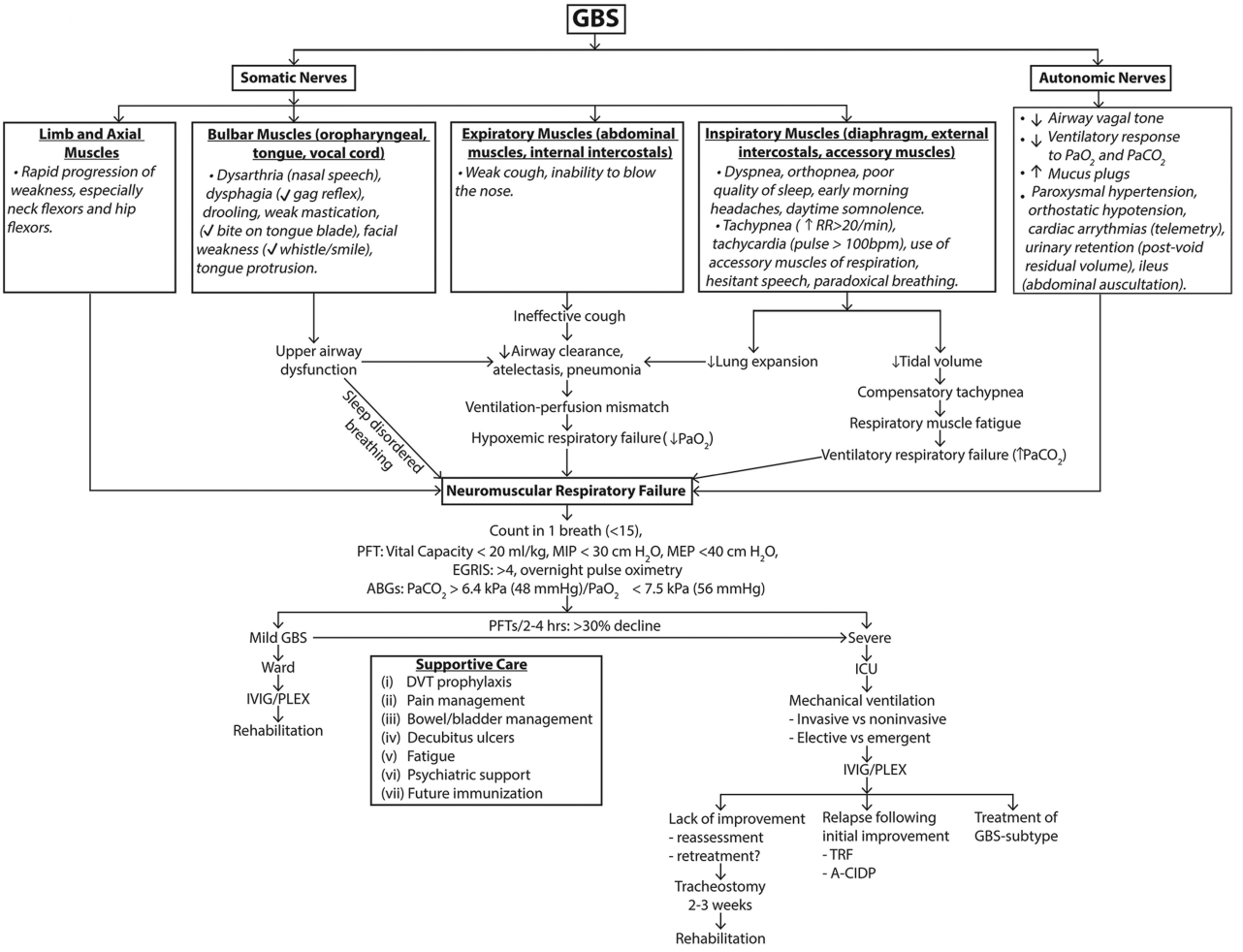

FIGURE 2-6

Neuromuscular respiratory failure in Guillain-Barré syndrome (GBS).

A-CIPD = acute-onset chronic inflammatory demyelinating polyradiculoneuropathy; ABG = arterial blood gas; DVT = deep vein thrombosis; EGRIS = Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score; ICU = intensive care unit; IVIG = intravenous immunoglobulin; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; PFT = pulmonary function testing; PLEX = plasma exchange; RR = respiratory rate; TRF = treatment-related fluctuation.

maintain clinical stability for at least 2 to 3 days, the frequency of monitoring can be decreased to every 6 to 8 hours.

The Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score (EGRIS) at the time of admission can also be used to predict the risk of respiratory failure within the first week of hospitalization; a score of more than 4 suggests a high (≥65%) risk of respiratory failure, thus prompting admission to the ICU (see the Prognosis section for details).[88]

Findings from a 2023 study concluded that the inclusion of MRC scores for selected proximal muscles, including neck and hip flexors, provided equal discriminative ability as the MRC sum score and might serve as a simplified tool for assessing respiratory insufficiency.[89]

Not all patients with GBS warrant admission to the ICU; those who have reached a clinical nadir or have experienced a modest decline over days with continued ambulation may be treated on the general ward with continuous monitoring.

MECHANICAL VENTILATION. Mechanical ventilation is required for 10% to 30% of all patients with GBS and is indicated in the presence of signs of impending respiratory failure. These include the presence of at least one major criterion (hypercarbia indicated by the partial pressure of arterial carbon dioxide >6.4 kPa [48 mm Hg], hypoxemia indicated by a partial pressure of arterial oxygen while the patient is breathing ambient air of <7.5 kPa [56 mm Hg], and a vital capacity <15 mL/kg of body weight) or two minor criteria (weak cough, impaired swallowing, and atelectasis). Ultimately, intubation is a clinical decision made at the patient's bedside. Intubation should ideally be elective, as emergency intubation can provoke dramatic blood pressure shifts and profound bradycardia by the introduction of an endotracheal tube in patients with dysautonomia. Additional safety precautions during intubation include the use of topical anesthesia, fiber optic laryngoscopy to assist intubation, short-acting benzodiazepines for sedation, and the avoidance of the use of depolarizing neuromuscular blockers (such as succinylcholine), which can provoke potentially fatal hyperkalemia owing to heightened chemosensitivity of denervated muscles.[90,91]

As patients with GBS would have already entered the progressive phase of the illness by the time respiratory muscle weakness ensues and is unlikely to reverse quickly, temporary intervention with noninvasive ventilation, especially in the presence of bulbar dysfunction, is not recommended. Moreover, noninvasive ventilation use might increase the likelihood of emergency intubation and aggravation of dysautonomia.[90,91]

OTHER SUPPORTIVE MEASURES. Patients with GBS need multidisciplinary supportive care to receive symptomatic treatment and prevent systemic complications (FIGURE 2-6). Physical therapy, occupational therapy, speech therapy, nutritional support, social services, and occasionally psychiatric support should be involved early.

Routine vaccinations after GBS are advised due to the low risk of GBS triggered by vaccine administration (one to two additional cases of GBS per million people vaccinated), which is significantly lower than the overall health risk posed by an infection-related illness. Additionally, vaccination may reduce the risk of GBS that may be triggered by infection (see the Epidemiology section for details). However, routine immunization is avoided in the acute phase and may be postponed for a few months due to the possibility that immunotherapies for GBS may impair the immunologic response to vaccination. Future avoidance may be considered when GBS manifests within 6 weeks after receiving a particular vaccination. For patients with a history of GBS, mRNA COVID-19 vaccines can be considered because of the potential increased risk of GBS linked with the Ad26.COV2.S COVID-19 vaccine.[50]

Immunotherapy

IVIg and plasma exchange have proven to be effective in multiple trials for the treatment of GBS.

KEY POINTS

- Patients with GBS who have reached a clinical nadir or have experienced a modest decline over days with continued ability to ambulate may be treated in the general ward with continuous monitoring.
- Intubation of patients with GBS and respiratory decline should be performed electively when possible, as emergency intubation can provoke dramatic blood pressure shifts and profound bradycardia by the introduction of an endotracheal tube in patients with dysautonomia.
- Noninvasive ventilation is usually insufficient for patients with GBS and respiratory decline and raises the risk of emergency intubation and aggravation of dysautonomia.
- Clinical trials have shown that IVIg and plasma exchange are effective in reducing the time to recovery in patients with GBS who are unable to walk a distance of 10 meters independently.

INDICATIONS AND TIMING TO INITIATE IMMUNOTHERAPY. Clinical trials have shown that IVIg and plasma exchange, when started within 2 and 4 weeks, respectively, of the onset of weakness are effective in reducing the time it takes for 40% to 50% recovery to begin in patients with GBS who are unable to walk a distance of 10 meters independently. Furthermore, a Cochrane analysis of plasma exchange for the treatment of GBS revealed that plasma exchange shortened the time on a ventilator, and the proportion of ventilator-dependent participants was significantly decreased.[92] Neither IVIg nor plasma exchange stops the progression of the disease or changes the degree of nerve damage. Given that the therapeutic advantages of plasma exchange were greatest in patients 1 week after the initiation of treatment, an early course of treatment with immunotherapy is preferred to minimize endoneurial inflammation and nerve injury.[92,93]

Although evidence from controlled trials is lacking, treatment should be considered for "mildly affected" ambulatory patients especially if they display rapidly progressive weakness or autonomic, bulbar, or respiratory involvement.[94]

SELECTION OF IVIG VERSUS PLASMA EXCHANGE. While both therapies are equally effective, the choice between plasma exchange and IVIg is dependent on local availability, patient preference, cost, risk factors, and contraindications. In general, IVIg is preferred due to its better tolerability and ease of administration.

IVIg is administered at a dose of 0.4 g/kg daily for 5 consecutive days, or 1 g/kg daily for 2 days; one study showed that children receiving therapy for 2 days as opposed to 5 days more commonly had treatment-related fluctuations.[95] Adverse effects include transfusion reactions, headache with or without aseptic meningitis, rash, acute hyperosmolar kidney injury (from sucrose-containing IVIg products), thromboembolism from hyperviscosity, and rarely IgA deficiency–related anaphylaxis.

Plasma exchange (200-250 mL plasma/kg body weight) is typically administered during five sessions over 10 days. One study found that two plasma exchange sessions were beneficial for patients who could walk with or without assistance but could not run; at least four exchanges were necessary for individuals who were more severely affected.[96] Complications of plasma exchange include hypotension, sepsis, transfusion reactions, thrombocytopenia, impaired clotting parameters, hypocalcemia, and issues with IV access. Early studies revealed that plasma exchange had a higher discontinuation rate than IVIg.[92]

TREATMENT OF PATIENTS WITH NO RESPONSE TO INITIAL IMMUNOTHERAPY. A therapeutic challenge arises in up to 40% of patients[93] who report no clinical improvement after reaching a plateau (at about 4 weeks) following initiation of immunotherapy, even when alternative etiologies have been reassessed and excluded. Two approaches have been studied: (1) combination therapy (plasma exchange followed by IVIg[97] or IVIg followed by plasma exchange, although the latter approach could be counterproductive by removing the previously administered immunoglobulins); or (2) retrial with a second course of IVIg.[98] These interventions either provide no additional benefit or are fraught with more adverse effects. The pathobiology in these patients

might represent a severe or prolonged immune attack leading to severe axonal degeneration. Further, lack of early improvement may not necessarily indicate that the treatment is ineffective, as progression could have been worse without therapy. Early supportive interventions are recommended in these patients, including percutaneous endoscopic gastrostomy if needed, tracheostomy (performed after at least 2 weeks of artificial ventilation if pulmonary function testing does not demonstrate sufficient improvement), and ultimate discharge to a rehabilitation facility.

TREATMENT OF PATIENTS WHOSE CONDITION WORSENS AFTER INITIAL IMPROVEMENT WITH IMMUNOTHERAPY. This group may represent patients with treatment-related fluctuations or acute-onset CIDP and frequently responds either to retreatment with the previously administered immunomodulatory therapy (treatment-related fluctuations) or long-term immunosuppressive medications (acute-onset CIDP). While the electrophysiologic findings are similar in these groups, patients with acute-onset CIDP are less likely to have autonomic nervous system involvement, facial weakness, a preceding infectious illness, or need for mechanical ventilation. Prominent sensory signs (rather than symptoms, which are common in AIDP) including impaired vibration and proprioception sensations leading to sensory ataxia, favor a diagnosis of acute-onset CIDP.[26]

TREATMENT IN GUILLAIN-BARRÉ SYNDROME SUBTYPES. Data from controlled trials are lacking on the best management of the different subtypes of GBS. Results from a small trial, albeit with methodologic limitations, suggested that the AMAN subgroup had better outcomes with plasma exchange than IVIg and that plasma exchange represented the most cost-effective option for this GBS subtype.[99] A 2022 retrospective study compared the outcomes of patients with GBS treated with IVIg to the disease's natural course, and discovered that IVIg was beneficial for AIDP but not for AMAN subtypes.[100] Prospective controlled trials are required to confirm these observations.

Most patients with pure Miller Fisher syndrome experience a mild course that resolves completely in 6 months without treatment. In these cases, withholding treatment seems reasonable, but close monitoring and immunotherapy may be warranted for patients who experience progressive spread to limb, cranial, or respiratory muscles.[94]

Since the effectiveness of immunotherapy in treating less common variants of GBS is not yet proven, decisions about acute treatment are made based on the severity of the symptoms and the overall clinical context.[101]

Corticosteroids

Although it is expected that corticosteroids should help reduce inflammation, and consequently disease progression in GBS, eight randomized controlled trials on the efficacy of corticosteroids in GBS have revealed no significant benefit, and treatment with oral corticosteroids has a detrimental impact on clinical outcomes.[102]

PROGNOSIS

Following GBS, functional recovery takes several weeks, and the degree of improvement varies based on individual risk factors.

KEY POINTS

- Repeating IVIg or plasma exchange for absence of clinical response after initial treatment for GBS provides no additional benefit.
- While the electrophysiologic findings are similar between acute inflammatory demyelinating polyradiculoneuropathy and acute-onset chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), patients with acute-onset CIDP are more likely to have sensory deficits or ataxia and less likely to have had a preceding infectious illness, autonomic nervous system involvement, facial weakness, or need for mechanical ventilation.
- Two validated prognostic models, the Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score and modified Erasmus GBS Outcome Score, are available in a user-friendly online version to guide the need for mechanical ventilation within a week of admission and the functional outcome of patients with GBS at 6 months, respectively.

Predictors of Need for Mechanical Ventilation and Long-term Functional Outcome

Two validated prognostic models, EGRIS and modified Erasmus GBS Outcome Score systems, are available in a user-friendly online version (gbstools.erasmusmc.nl) to predict the need for mechanical ventilation within a week of admission, and the functional outcome at 6 months, in patients with GBS.[84,103] EGRIS incorporates the time from onset of weakness to hospitalization, presence or absence of facial or bulbar weakness at admission, and MRC scores at admission to predict the risk of respiratory failure within the first week of hospitalization. The scale is scored from 0 to 7; higher scores indicate higher risk. The modified Erasmus GBS Outcome Score uses data at the time of hospital admission, or 1 week after admission, to predict the probability of being able to walk independently at 1, 3, and 6 months. It incorporates the patient's age, presence or absence of preceding diarrhea, and the MRC sum score to create scores from 0 to 12; higher scores indicate higher risk.

Overall, the long-term outcome of GBS is favorable; approximately 80% of patients can walk independently, and more than half recover fully after 1 year.[104] However, persistently low-amplitude CMAPs suggestive of axonal loss on electrodiagnostic studies are considered a poor prognostic factor, where recovery may continue well beyond the 1-year mark and could be incomplete.[105]

Residual Deficits

Despite immunomodulatory treatment, residual features such as weakness, paresthesia, fatigue, and pain can persist after 1 year, impacting the patient's daily activities and quality of life. Importantly, in one study 32% of patients had to change their work because of GBS.[106,107]

Predictors of Mortality

In GBS, the mortality rate varies from 3% to 7% overall and is around 20% in patients who become ventilator dependent. Regional variation does, however, exist as evidenced by the high mortality rate of 41% among ventilated patients in low-resource settings which, in addition to being caused by a lack of adequate intensive care facilities or subspecialty care, may also be linked to the absence of immunomodulatory treatments and the presence of the unfavorable risk factor of prior gastroenteritis for a poor prognosis.[108] Despite the fact that GBS is more common in men than in women, sex is not a reliable indicator of prognosis.[109] Data on disparities in GBS outcomes based on sex, race, or ethnicity are lacking.

Advanced age, severe disease, associated comorbidities, pulmonary and cardiac complications, use of mechanical ventilation, and presence of systemic infection are all indicators of a higher chance of death.[110] Acute respiratory distress syndrome, infections, pulmonary emboli, and sudden cardiac arrest are the most prevalent causes of death. These events can happen during the acute and recovery periods, indicating the need for continued supportive care.[111]

Prognosis in Special Situations

While studies have found no appreciable variations in the clinical manifestations of GBS linked with COVID-19,[112] Zika-associated GBS can be associated with

higher rates of bulbar or facial weakness, dyspnea, need for mechanical ventilation, and residual facial and bulbar deficits at 6 months.[113,114]

New Prognostic Markers

A 2020 study determined cutoff levels for serum neurofilament light chain at the time of acute illness that correlated with the probability of being able to walk and run independently 1 year from disease onset. Additionally, neurofilament light chain levels were higher in those with the pure motor variant, Miller Fisher syndrome, and preceding diarrheal illness than in individuals with a respiratory prodrome and sensorimotor GBS.[115]

KEY POINT

- **The overall mortality rate of patients with GBS varies from 3% to 7% overall and is around 20% in patients who become ventilator dependent.**

TRENDS AND FUTURE STUDIES

Despite the advances in our understanding of GBS, many uncertainties remain, and the only available immunotherapies are IVIg and plasma exchange. Future trends include understanding the role of host genetic factors, new diagnostic tools and biomarkers, vaccine safety studies, cost-effective strategies such as small-volume plasma exchange, development of prognostic models, therapeutic interventions targeting the hyperactive immune system, and promoting regeneration (different strategies are summarized in the literature[2,56]).

CONCLUSION

GBS is an immune-mediated disorder characterized by the presence of inflammation and complement activation, which targets either myelin or axons, resulting in several clinical variants. Despite the availability of immunotherapy, novel diagnostic techniques and disease-specific therapeutic strategies tailored to the needs of each patient are still needed.

USEFUL WEBSITES

INTERNATIONAL GBS OUTCOME STUDY
The International GBS Outcome Study (IGOS) is the largest and longest prospective trial that provided a forum for the collection of extensive data to identify clinical and biological determinants and predictors of disease course in patients with GBS.
gbstools.erasmusmc.nl

GBS/CIDP FOUNDATION INTERNATIONAL
This website offers details on GBS and CIDP, as well as support for patients and their families, news about activism, and volunteer opportunities.
gbs-cidp.org/

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