Guillain-Barré Syndrome

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ABSTRACT

Guillain-Barré syndrome (GBS) is an acute-onset, monophasic, immune-mediated polyneuropathy that often follows an antecedent infection. The diagnosis relies heavily on the clinical impression obtained from the history and examination, although cerebrospinal fluid analysis and electrodiagnostic testing usually provide evidence supportive of the diagnosis. The clinician must also be familiar with mimics and variants to promptly and efficiently reach an accurate diagnosis. Intravenous immunoglobulin and plasma exchange are efficacious treatments. Supportive care during and following hospitalization is also crucial.

KEYWORDS: Guillain-Barré syndrome, inflammatory neuropathy, demyelinating neuropathy, acquired demyelinating neuropathy, Miller Fisher syndrome, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy

Guillain-Barré syndrome (GBS) is an acute-onset, immune-mediated disorder of the peripheral nervous system. The term GBS is often considered to be synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but with the increasing recognition over the past few decades of variants, the number of diseases that fall under the rubric GBS has grown to include axonal variants and more restricted variants such as Miller Fisher syndrome (MFS).[1,2]

HISTORY

The clinical features of GBS were described by Landry in 1859.[3] Eichorst in 1877 and Leyden in 1880 described the lymphocytic inflammation of nerve in some cases of peripheral neuropathy. In 1916, Guillain, Barré, and Strohl described the characteristic cerebrospinal fluid (CSF) findings of increased protein concentration and normal cell count in two French soldiers (Guillain 1916). In 1949, Haymaker and Kernohan described the clinical and histopathological features, including inflammatory changes of the peripheral nerve in 50 fatal cases of GBS.[4] In the mid-1950s, Waksman and Adams produced experimental allergic neuritis in animals by injection of homologous or heterologous peripheral nerve tissue combined with Freund adjuvant. In the 1980s, plasma exchange was found to be an effective treatment,[5,6] and in the 1990s, efficacy was also demonstrated for intravenous immunoglobulin (IVIg).[7,8]

CLINICAL FEATURES AND DIAGNOSIS

The reported incidence rates for GBS are 1 to 2 per 100,000 population.[9–11] The lifetime likelihood of any individual acquiring GBS is 1:1000.[12] GBS is equally common in men and women and can occur at any age.

An otherwise unremarkable infection, such as an upper respiratory infection, often predates the onset of GBS by 10 to 14 days.[9,12] Many antecedent infections have been identified, including *Campylobacter jejuni*,

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cytomegalovirus (CMV), *Mycoplasma pneumonia*, Epstein-Barr virus, and influenza virus.[13,14] Surgery, immunization, and parturition have also been associated with GBS. GBS usually begins abruptly with distal, relatively symmetrical onset of paresthesias. Sensory disturbances are accompanied by or quickly followed by progressive limb weakness. Patients are able to identify a definite date of onset of sensory and motor disturbances. Progression is rapid, with ~50% of patients reaching clinical nadir by 2 weeks and more than 90% by 4 weeks.[15] Current diagnostic criteria include < 4 weeks of progression to clinical nadir. Approximately 80 to 90% of patients with GBS become nonambulatory during the illness.[5,16,17] Pain is prominent in ~50% of patients.[1,4,17–20] Neurological examination will demonstrate distal and often proximal, relatively symmetrical, weakness. Sensory examination is often normal in the early phase of disease.[21] Widespread areflexia or hyporeflexia is the rule.[15,22] GBS patients often develop cranial nerve weakness, usually in the form of facial or pharyngeal weakness.[4] Diaphragmatic weakness due to phrenic nerve involvement is also common. Approximately one third of hospitalized GBS patients require mechanical ventilation because of respiratory muscle or oropharyngeal weakness.[5,6,8,9,21,23–29] Autonomic disturbance is seen in more than 50%.[30–36] The autonomic disturbance usually manifests as tachycardia but more serious autonomic nervous system dysfunction may occur, including life-threatening arrhythmias, hypotension, hypertension, and gastrointestinal dysmotility.

Supportive ancillary testing for GBS includes CSF analysis and electrodiagnostic testing, both of which may be normal in the early phase of GBS. The limitations of ancillary testing in the early phase combined with the importance of prompt treatment of GBS mandates that the clinician at times make the diagnosis based solely on history and examination. An elevated CSF protein concentration (with normal cell count) is only found on initial CSF analysis in ~50% of patients; elevated CSF protein concentration occurs in more than 90% of patients at clinical nadir.[21] There is probably no reason to repeat the CSF analysis if the initial CSF is normal and there is a reasonable degree of certainty about the clinical diagnosis. CSF pleocytosis is not seen in GBS and raises the question of infectious (HIV, CMV, Lyme, sarcoid), carcinomatous, or lymphomatous polyradiculoneuropathy.

Electrodiagnostic testing is performed to support the clinical impression that the acute motor paralysis is caused by a peripheral neuropathy. Electrodiagnostic testing of GBS patients often also demonstrates features of demyelination, such as temporal dispersion, significantly slow conduction velocities, and prolonged distal and F-wave latencies.[37] Electrodiagnostic testing features of *acquired* demyelination (e.g., conduction block, temporal dispersion, nonuniform slowing of conduction velocities) are particularly helpful because these findings are characteristic of immune-mediated demyelinating neuropathies. In early GBS, prolonged distal compound muscle action potential (CMAP) latencies and temporal dispersion are more commonly demonstrated than are slow motor conduction velocities and conduction block.[38–40] For example, Gordon and Wilbourn reported that of 31 patients with GBS studied within the first week of symptoms, only 5 had nerve conduction velocities in the demyelinating range in at least one nerve and only 4 of them demonstrated conduction block in at least one nerve.[40] On the other hand, temporal dispersion was seen in at least one nerve in more than 50%, and significantly prolonged distal CMAP latencies were seen in at least one nerve of approximately two thirds of patients studied within the first week.[40] Another electrodiagnostic testing signature of GBS is the "sural-sparing" pattern; that is, the finding of a normal sural sensory nerve response in the setting of abnormal upper extremity sensory nerve results (e.g., ulnar or median antidromic sensory responses).[38,40] The sural-sparing pattern is seen in approximately one half to two thirds of patients with GBS studied within the first week of symptoms.[38,40] This pattern—normal lower extremity but abnormal upper extremity sensory nerve conduction studies—is very unusual for neuropathies other than GBS. Other electrodiagnostic testing abnormalities are frequently encountered in early GBS but they are less specific to GBS. These include absent H-reflexes, low motor nerve CMAP amplitudes on distal stimulation, and prolonged F-wave responses.[38–40] It is reported that the H-reflex was absent in 97% of GBS patients within the first week of symptom onset.[40] It should also be pointed out that motor electrodiagnostic testing findings are more often abnormal than sensory nerve results in early GBS. In one study, ~90% of GBS patients had motor nerve conduction abnormalities—often low CMAP amplitudes—but only 25% had sensory nerve conduction abnormalities in the first week of GBS.[38] Blink studies are very often abnormal in GBS patients with facial weakness.[39] Prolonged compound muscle action potential duration (> 8.5 msec) on distal stimulation may suggest distal demyelination and can be helpful in some cases.[41] Needle examination typically demonstrates the finding of reduced motor unit action potential recruitment in clinically weak muscles. With regard to prognosis, very low CMAPs on distal stimulation (i.e., mean distal CMAP [summated from peroneal, tibial, median and ulnar motor nerves] of 0 to 20% of the lower limit of normal) on initial electrodiagnostic testing has been shown to be associated with a markedly increased probability of a poor long-term outcome.[42,43]

Magnetic resonance imaging (MRI) of the spine or brain is commonly performed to rule out a mimic of GBS, such as myelopathy or infiltrative or compressive causes of polyradiculoneuropathy. Moreover, MRI can

support the diagnosis of GBS by revealing enhancement of involved nerve roots or cranial nerves.[44–46] Other than for cases of MFS (associated with anti-GQ1b antibodies), at the present time there is no diagnostic value in assaying antiganglioside antibody values in a patient with GBS.

VARIANTS

Commonly recognized variants include those with severe axon loss, variants in which one particular fiber type (sensory or autonomic) is predominantly affected, and MFS.[2] (See http://www.aanem.org/education/podcast/index.cfm to listen to a podcast interview with Dr. C. Miller Fisher discussing his 1956 New England Journal of Medicine article that described three cases of what later became known as MFS.) Variants with regional or a markedly asymmetric distribution also occur.[1] There are also differences in abruptness of onset and time to reach nadir, which can complicate diagnosis and decisions about treatment. For example, some patients have clinical features and disease course similar to GBS except for a slower progression (i.e., progression that lasts longer than 4 weeks); this disease is sometimes referred to as subacute inflammatory demyelinating polyradiculoneuropathy (SIDP)[47,48]; however, in many respects SIDP is like GBS and often should be treated as such.

Axonal injury occurs to some degree in many cases of GBS,[49] usually secondary to the pathological events of demyelination (e.g., "bystander" injury).[50] In the early phase of GBS, any axonal degeneration is almost always overshadowed by the manifestations of acquired demyelination. In many instances of severe GBS, significant secondary axonal damage will develop and impact the degree of residual damage, and thus the long-term outcome. Cases of GBS with primary demyelination and secondary axonal loss should not be confused with the acute axonal form of GBS, a distinct entity that probably represents 5 to 10% of cases of GBS in North America[51–54] but is more common in Japan and China.[55–57] Acute motor and sensory axonal neuropathy and acute motor axonal neuropathy are two variants characterized by immune attack directed at axons rather than Schwann cells and myelin.[51–53,55,56,58]

Acute motor axonal neuropathy occurs in large epidemics in the summer in northern China and more sporadically elsewhere, including North America, Europe, and Asia.[56,58] The summer epidemics in northern China mostly affect children, usually from rural areas. Onset of motor weakness is abrupt and is often preceded a few weeks by an upper respiratory or other infection.[59–61] In addition to acute motor paralysis, many patients have transient neck and back stiffness early in the course with resolution within days. There are no sensory symptoms or signs. CSF studies demonstrate elevated protein concentration without cells. Recovery usually begins within 3 weeks and is often complete. Mortality rate is roughly 3 to 5%. Sensory nerve conduction studies are normal and motor nerve studies are remarkable for low or absent CMAP amplitudes with normal conduction velocities. Denervating potentials are seen on needle electromyography.[59]

Acute motor and sensory axonal neuropathy shares many pathological features with acute motor axonal neuropathy but differs clinically from it in patient age of onset (usually adults rather than children), geographic distribution (can occur anywhere), time of onset (not only summertime), involvement of sensory nerves, course (protracted), and outcome (usually severe residual disability).[51–53,55,56,58] Onset is abrupt and progression rapid with most patients requiring mechanical ventilation within a few days of symptom onset. Motor nerves are electrically inexcitable early in the disorder. Sensory nerve conduction studies are also abnormal. Widespread denervation is seen on needle examination. The course is protracted and outcome poor, with only ~20% ambulating at 1 year.[52]

The most recognizable and distinct regional variant of GBS is MFS.[1,2,62] Like GBS, onset of MFS often follows an infection, for example *C. jejuni*.[63] MFS patients classically present with external ophthalmoparesis, areflexia, and ataxia,[2] although MFS patients often present with fewer components of the classical clinical triad[1,62,64–66] or with additional clinical features (facial weakness, oropharyngeal weakness, internal ophthalmoparesis, central nervous system involvement). Bickerstaff's brainstem encephalitis (BBE) is a related syndrome in which alteration of consciousness or corticospinal tract signs are seen in addition to ophthalmoparesis and ataxia. Facial weakness and dysarthria are particularly common in BBE and MFS. Many patients with MFS or BBE also have "overlapping GBS" with flaccid quadriparesis.[62,67] Anti-GQ1b antibodies are present in ~95% of patients with acute MFS[68,69] and in approximately two thirds of patients with BBE. The recognition of the various clinical presentations and the high sensitivity and specificity of anti-GQ1b antibody testing has prompted the suggestion that these conditions fall under the rubric of the "anti-GQ1b antibody syndrome."

Anti-GT1a antibodies are also commonly abnormal on serological testing of these patients.[70] Rarely, anti-GT1a antibody without anti-GQ1b reactivity is found in patients presenting with the pharyngeal-cervical-brachial (PCB) variant of GBS.[71,72] More than half of MFS patients will have cytoalbuminological dissociation on CSF analysis performed within the first 3 weeks of disease.[73] In MFS, motor nerve conduction studies in the limbs are usually normal or only mildly abnormal with slight reductions in compound muscle action potential amplitudes.[74] Motor conduction

velocities are usually normal or at most only very mildly abnormal in patients with MFS. Conduction block and temporal dispersion are not seen on testing of limb motor nerves of patients with MFS. Sensory nerve action potential amplitudes are usually moderately to severely reduced, more so in the upper extremity sensory nerves (e.g., median) than the sural nerve. Facial CMAP amplitudes are often reduced without discernible delay in conduction in patients with MFS. Blink reflex R1 latencies may be delayed, and R2 responses may be delayed or absent. Needle electromyelogram (EMG) changes are usually normal or only mildly abnormal.[74] MRI of the brain frequently demonstrates cranial nerve enhancement (e.g., oculomotor nerves) in MFS[75] and high-intensity abnormalities in the posterior fossa, white matter, or thalami in patients with BBE.[67] MFS is generally a benign, self-limiting condition. Almost all treated and untreated patients return to normal activities within 6 months of disease onset, usually with resolution of ophthalmoplegia within 1 to 2 months and ataxia within 3 to 4 months.[76] Other regional variants of GBS are those that affect other specific areas of the body, such as only the face or the afferent sensory and autonomic systems.[77]

MIMICS

To achieve a reasonable degree of certainty about a diagnosis of GBS, the neurologist must consider the mimics (Table 1), keeping in mind, however, that GBS will in fact be the diagnosis in the vast majority of acute-onset polyneuropathies. These mimics should be evaluated for, when appropriate, but whenever possible diagnosis and treatment of GBS should not be delayed because of an inappropriately extensive evaluation for less common mimics. Perhaps acute-onset myelopathy is the entity that most commonly mimics GBS. Acute myelopathy resembling GBS may be caused, for example, by transverse myelitis, acute spinal cord compression, or spinal cord infarct. Corticospinal tract findings, such as hyperreflexia, may not be evident in the acute phase, and thus urgent spinal cord or cauda equina imaging is sometimes indicated. The site of imaging should be based on clinical features. For example, if a patient has motor and sensory features in four extremities, imaging of the cervical cord may be appropriate. If a patient only has clinical features in the lower extremities, imaging more caudally may be indicated.

Vasculitic neuropathy may also resemble GBS, particularly if the distribution of neuropathy mimics GBS by appearing to be relatively symmetric or only slightly asymmetric. For this reason, the neurologist must not only examine the patient but also query the patient about the sequence of neuropathic symptoms to tease out whether the process followed a rapidly progressive multiple mononeuropathy (e.g., "overlapping mononeuritis multiplex") pattern typical of systemic vasculitis or a more symmetric pattern typical of GBS. Systemic symptoms (e.g., unexplained weight loss, fevers), multiorgan involvement (e.g., joints, skin, kidney, respiratory tract), serological markers (e.g., elevated sedimentation rate, rheumatoid factor), and absence of an antecedent illness would be some features that would point toward systemic vasculitis and away from GBS.[78] Chronic inflammatory demyelinating polyneuropathy (CIDP) may sometimes present with abrupt onset and rapid progression to clinical nadir (e.g., < 4 weeks) and thus may be indistinguishable from GBS in the early phase of disease.[79] Other mimics of GBS are less common (Table 1[1,80–93]).

PATHOPHYSIOLOGY

Acute Inflammatory Demyelinating Polyradiculoneuropathy

The most common form of GBS is AIDP, which is characterized pathologically by demyelination, lymphocytic infiltration, and macrophage-mediated clearance of myelin.[3,4,49] Approximately two thirds of GBS cases occur weeks after an infection such as *C. jejuni,* CMV, *Mycoplasma pneumonia*, or influenza virus.[13,21] These infectious agents have epitopes on their surface that are similar to epitopes on the surface of peripheral nerves (e.g., gangliosides, glycolipids), resulting in the peripheral nerve acting as a "molecular mimic" of the infectious agent.[14,94–98] For example, carbohydrate moieties of gangliosides (e.g., GM1, GD1a, GQ1b) found on the surface of the peripheral nerve are structural mimics of the lipooligosaccharides (LOSs) of *C. jejuni*.[12,77,97,99] During an otherwise trivial infection (e.g., *C. jejuni*), the complement-fixing immunoglobulin (Ig) G antibodies that arise to attack the infection also bind to peripheral nerve gangliosides, inducing autoimmune injury.[12,94]

Paranodal myelin, exposed axolemma at nodes of Ranvier, and the presynaptic component of the neuromuscular junction are sites of antibody attack of varying degrees for different GBS syndromes and individuals.[12] Macrophage-mediated stripping of myelin also occurs, mediated by antibody and complement deposition on Schwann cell and myelin membranes.[3,94] Demyelination may occur throughout the length of the nerve, especially and perhaps earliest at proximal nerve roots and distal intramuscular nerve twigs where the blood-nerve barriers are weak.[12,100] The nerve terminal axons are also damaged in AIDP. Nerve terminal damage follows antibody binding and complement fixation. Activation of the complement pathway leads to membrane attack complex (MAC) formation with degradation of the terminal axonal cytoskeleton and mitochondrial injury.[12] The perisynaptic Schwann cell, like the axonal element

Table 1 Mimics of Guillain-Barré Syndrome and Some of Their Distinguishing Characteristics

Acute myelopathy (e.g., transverse myelitis, cord compression, infarct)	Hyperreflexia, extensor plantar responses (although corticospinal tract findings may be absent early); trauma; absence of antecedent illness. Normal electrodiagnostic testing. Imaging of spine or cauda equina is often indicated to exclude spinal cord or cauda equina structural lesion.[1]
Vasculitic neuropathy	Asymmetric polyneuropathy or multifocal mononeuropathies; very painful, systemic symptoms (e.g., unexplained weight loss, fevers, rash); multiorgan involvement (e.g., joints, skin, kidney, respiratory tract); serologic markers (e.g., elevated sedimentation rate, rheumatoid factor); absence of an antecedent illness. Normal CSF. Axonal polyneuropathy on electrodiagnostic testing.[1,78]
Myasthenia gravis	Ocular (e.g., diplopia), bulbar (e.g., dysarthria), and limb weakness without sensory symptoms; fatigable, fluctuating symptoms; absence of an antecedent illness. Pattern of descending weakness. Normal CSF. Abnormal CMAP decrement on slow RNS studies.[80]
Botulism	Infants (most frequent) and at-risk adults (e.g., foodborne, such as exposure to home canned foods; from wound; injecting drug users). Nausea, vomiting, constipation, diplopia, ophthalmoplegia, ptosis, blurring of vision, dysphagia, dysarthria, urinary retention. Pattern of descending weakness. Normal CSF. Abnormal CMAP decrement on slow RNS studies. Abnormal CMAP facilitation on fast RNS.[1,81]
West Nile encephalomyelitis	Fever, meningoencephalitis (may be mild), rash, abdominal pain, back pain; acute-onset lower motor neuronopathy. No sensory disturbance. CSF pleocytosis. Lower motor neuronopathy on electrodiagnostic testing.[1,82,83]
Lyme neuroborreliosis	Endemic area during tick season; meningitis, fever, myalgias, arthralgias, facial weakness; tick bite and rash. CSF pleocytosis. Axonal polyradiculoneuropathy on electrodiagnostic testing.[84,85]
Heavy metals (e.g., arsenic) and other toxins	Known exposure; neuropathy is accompanied by systemic symptoms (e.g., abdominal pain, diarrhea, constipation, rash, alopecia, central nervous system involvement); absence of an antecedent illness; prominent small-fiber nerve component (e.g., ''burning'' neuropathic pain). Unremarkable CSF. Axonal polyneuropathy on electrodiagnostic testing.[1,86]
Tick paralysis	Children during tick season. Ataxic gait, diplopia, dysarthria, pupillary abnormalities (dilated pupils). No sensory complaints. Normal CSF. Low CMAPs and normal SNAPs on electrodiagnostic testing. Tick on scalp (e.g., behind the ear) or skin (e.g., nape of the neck).[87,88]
Acute intermittent porphyria	Accompanying autonomic symptoms (tachycardia, hypertension, constipation, urinary retention), abdominal pain (usually severe), psychiatric and other CNS manifestations; patient with a history of prior suggestive attacks; axonal polyradiculoneuropathy or neuronopathy, often asymmetric. CSF resembles GBS with cytoalbuminological dissociation.[89]
Buckthorn toxicity	Children living in the southwestern United States and Mexico; little or no sensory symptoms.[90]
Diphtheria	Patient (e.g., from a developing country) with recent sore throat, fever, and multiple cranial neuropathies (e.g., diplopia, ptosis, dysarthria, dysphagia, numb tongue, gingivae and face). CSF resembles GBS with cytoalbuminological dissociation. Axonal polyradiculoneuropathy on electrodiagnostic testing.[1,91]
HIV	GBS more common in HIV patients; occurs at seroconversion. Demyelinating polyradiculoneuropathy on electrodiagnostic testing. CSF pleocytosis.[92]
CMV polyradiculopathy	AIDS patient, late stages. Rapidly progressive lower extremity weakness and pain (sparing upper extremities). CSF pleocytosis. Axonal polyradiculopathy on electrodiagnostic testing.[1,93]
Poliomyelitis	Endemic area; sore throat, fever, nausea, vomiting, headache, acute-onset lower motor neuronopathy with myalgias and fasciculations. CSF pleocytosis. Lower motor neuronopathy on electrodiagnostic testing.[1]
Critical illness myopathy and polyneuropathy	Quadriparesis in critical care patients. Unremarkable CSF. Myopathic and/or axonal neuropathic features on electrodiagnostic testing.

CSF, cerebrospinal fluid; CMAP, compound muscle action potential; RNS, repetitive nerve stimulation; SNAP, sensory nerve action potential; CNS, central nervous system; GBS, Guillain-Barré syndrome; CMV, cytomegalovirus.

of the nerve terminal, also lies outside the blood-nerve barrier and is probably damaged by antiganglioside antibodies.

Anti-LOS/ganglioside antibodies exist within the natural antibody repertoire, acting as innate defense against bacteria.[12] The carbohydrate moieties of gangliosides elicit a T-cell–independent humoral response, and antiganglioside antibodies exist as low-affinity IgM isotypes in normal subjects. The level and affinity of these antibodies is controlled by tolerance in normal subjects, and 99% of humans infected with ganglioside-mimicking strains of *C. jejuni* do not develop significant anti-LOS/ganglioside antibodies or GBS.[12] In GBS, the antibody response has

class-switched from IgM to complement-fixing IgG1 and IgG3 isotypes.

Acute Axonal Neuropathy

Acute motor axonal neuropathy often follows infection with *C. jejuni*, which contain an epitope in their LOSs that is also present in GM1 gangliosides of nerve.[101,102] Like AIDP, acute motor axonal neuropathy is believed to be an IgG- and complement-mediated disorder.[56,58] The target epitopes are likely the constituents of the axolemma of motor fibers. Antibody binding may alter sodium channel function, causing conduction block. The relatively rapid improvement of many acute motor axonal neuropathy cases may be explained by reversal of IgG-mediated conduction block before development of significant axonal degeneration. Motor nerve terminal and intramuscular axon damage without more proximal degeneration also occurs in at least some cases of acute motor axonal neuropathy, and this might also explain rapid recovery in many patients.[103] However, in many cases, macrophages are attracted early in the process to the nodes of Ranvier by complement products. The macrophages dissect into the internodal periaxonal spaces, displacing axons from inner Schwann cell plasmalemma, and appear to cause axonal degeneration.[55,56,58] The extent of macrophage-mediated axonal degeneration likely predicts outcome, with more macrophage-mediated axonal degeneration leading to higher likelihood of mortality and protracted course and incomplete recovery for those who survive.[52]

Miller Fisher Syndrome

Miller Fisher Syndrome shares many pathophysiological events with AIDP and acute motor axonal neuropathy. Molecular mimicry between infection (e.g., *C. jejuni*) and surface components of peripheral nerve plays a key role leading to humoral and complement activation with MAC formation and nerve axon terminal damage.[12,63,104] A critical difference between MFS and AIDP or acute motor axonal neuropathy is the activation of anti-GQ1b and anti-GT1a antibodies in MFS that target oculomotor and bulbar nerves, which are nerves thought to have relatively high GQ1b and GT1a ganglioside densities.[12,68,69,104] The presynaptic nerve terminal axons and perisynaptic Schwann cells are damaged in MFS.[12,62]

MANAGEMENT

Immunotherapy

Plasma exchange (PE) and IVIg are effective immunotherapies for adult and pediatric patients with GBS if given during the first few weeks of disease.[6–8,105–116] For patients with GBS, PE is usually administered as one plasma volume, 50 mL/kg, on five separate occasions over 1 to 2 weeks.[5,6,8,107,108,113] In a meta-analysis of six class II trials comparing PE to supportive care alone for adults with GBS, 48 out of 321 in the PE group and 106 out of 325 in the control group were on a ventilator after 4 weeks (relative risk 0.56; 95% confidence interval [CI], 0.41 to 0.76; $p = 0.0003$).[107,117] In a meta-analysis of four trials, 135 of 199 PE and 112 of 205 control patients recovered full muscle strength after 1 year (relative risk 1.24 in favor of PE; 95% CI, 1.07 to 1.45; $P = 0.005$).[107] The cost of PE has been shown to be offset by the savings of a shorter hospital stay.[118,119] The Quality Standards Subcommittee of the American Academy of Neurology (AAN) concluded in 2003 that PE hastens recovery in nonambulant patients with GBS who seek treatment within 4 weeks of onset, and that PE hastens recovery of ambulant patients with GBS who are examined within 2 weeks.[107] The Quality Standard Subcommittee, therefore, recommends treatment with PE for nonambulant patients with GBS within 4 weeks (level A recommendation) and for ambulant patients within 2 weeks (level B recommendation) of symptom onset.[107] The optimum number of plasma exchanges has not been established, but many physicians use the protocol of the North America Trial in which a total of 200 to 250 mL/kg were exchanged over 7 to 10 days.[6,106] The French Cooperative Group on Plasma Exchange in GBS demonstrated that for adult patients with mild GBS (able to walk unaided but not run), two exchanges were better than none; and for patients with moderate (unable to walk) or severe (ventilated) GBS, four exchanges were better than two and six exchanges were no better than four.[111] In a small study looking at the effect of the number of exchanges on Ig levels in serum, including antiganglioside antibody levels, a significant decrease in Ig levels occurred during the first two exchanges but not with subsequent exchanges.[120]

Although IVIg and PE are probably of equal efficacy, nonsignificant trends toward faster recovery have been observed with IVIg in trials designed to compare it to PE.[7,8,105,107] No compelling evidence favors one treatment over the other.[106] For adult and pediatric patients with GBS, IVIg is usually administered as 2 g/kg total divided over 2 to 5 days.[106,107,112,115] The Quality Standards Subcommittee of the AAN concluded in 2003 that IVIg has equal efficacy in hastening recovery for GBS patients who require aid to walk if IVIg is started within 2 weeks of the onset.[107] The Quality Standard Subcommittee recommends treatment with IVIg for patients with GBS who require aid to walk within 2 weeks (level A recommendation) or 4 weeks (level B recommendation) of neuropathic symptom onset.[107]

The decision to use PE or IVIg must be based on multiple factors, including availability of treatments and

the side effect profiles in the context of the patient's course and comorbidities. In the major trials comparing IVIg to PE, slightly more complications were observed in the PE group than the IVIg group. Significant adverse events associated with PE include hypotension, septicemia, pneumonia, abnormal clotting, complications from central venous access, and hypocalcemia. Citrate infused for anticoagulation or as part of fresh-frozen plasma may lead to hypocalcemia or metabolic acidosis. Symptoms of hypocalcemia include paresthesias, muscle cramps, and, in severe cases, cardiac arrhythmias.[121] Major hemostatic disorders, unstable cardiovascular status, active infection, and pregnancy are contraindications to PE.[5] Significant adverse events associated with IVIg include renal failure, myocardial infarction, vomiting, and meningismus.[7,8,107] IVIg is not contraindicated in pregnancy. In general, adverse reactions to IVIg are usually minor and occur in less than 10% of patients. A slow rate of infusion is advised for patients with coronary artery disease or congestive heart failure to avoid fluid overload. IVIg increases serum viscosity, and this may increase the risk of thromboembolic events. IVIg may be relatively contraindicated for patients with elevated serum viscosity (such as that caused by serum cryoglobulins), high triglycerides, or hypergammaglobulinemia.[122,123] It should also be used judiciously in patients with recent deep vein thrombosis (DVT). Acute tubular necrosis occurs rarely in patients with preexisting kidney disease, especially the elderly and those with diabetes or poor hydration.[122,123] Acute tubular necrosis is most commonly associated with IVIg products with high concentrations of sucrose. Close monitoring of blood urea nitrogen (BUN) and creatinine and proper hydration are essential during IVIg treatment, particularly for patients at risk for renal tubular necrosis. Diluting the IVIg preparation, slowing the rate of infusion, and selecting products with low osmolality lessen the risk.[122,123] The prevalence of selective IgA deficiency is 1:1000. When these patients receive IVIg, the IgA in the IVIg may lead to an anaphylactic reaction. However, this is a rare complication occurring most frequently in patients with common variable immunodeficiency, and screening for IgA deficiency before treating a GBS patient with IVIg is not justified.[123,124]

Corticosteroid treatment is ineffective for treating GBS.[107,125–127] In a Cochrane systematic review of six trials with 587 patients, the overall evidence showed no significant difference between the corticosteroid- and non–corticosteroid-treated patients in disability grade.[127] In four trials of oral corticosteroids with 120 patients, there was significantly less clinical improvement after 4 weeks with corticosteroids than without corticosteroids, suggesting that oral corticosteroids may slow recovery. Intravenous methylprednisolone alone does not produce significant benefit or harm. In combination with IVIg, intravenous methylprednisolone (e.g., 500 mg per day for 5 days, administered within 48 hours of the first dose of IVIg) may hasten recovery but does not appear to significantly affect the long-term outcome.[127,128]

Immunoabsorption therapy is an alternative technique to PE that does not require using a human blood product as a replacement fluid, thereby reducing risk of infection or allergic reaction.[129–131] Immunoadsorption therapy removes Ig from the circulation without need for replacement with albumin or fresh-frozen plasma because of the lower loss of albumin. In one study, there were no differences in outcome between 13 patients with GBS treated with immunoadsorption and 11 patients treated with PE.[131] There was also no difference observed in clinical outcome in a retrospective review of patients with GBS treated with immunoadsorption, PE, or double-filtration plasmapheresis. Fewer complications were reported with immunoadsorption.[129] PE followed by IVIg was shown to provide no statistically significant additional benefit compared with PE alone or IVIg alone.[8] Immunoadsorption followed by IVIg also appears to be no more effective than IVIg alone.[131] In 2003, the Quality Standards Subcommittee of the AAN did not recommend sequential treatment with PE followed by IVIg or immunoadsorption followed by IVIg.[107]

Early relapses ("treatment-related fluctuations") occur in ~10% of patients with GBS following PE or IVIg therapy. Rate of relapse is similar for PE and IVIg.[7,8,14,132] A longer interval between onset and treatment[132] and longer time to nadir[133] may be associated with a greater chance of relapse, but these associations likely reflect the characteristics of a patient's immune activation more than the timing of immunotherapy. For instance, some patients initially diagnosed with GBS—with preceding infectious episode, abrupt onset of neuropathic symptoms, and progression to clinical nadir within 4 weeks—are later rediagnosed as having CIDP because of the persistence of neuropathy deficits, based on ongoing demyelination caused by an active autoimmune process.[134] It is occasionally challenging to determine whether persistent deficits are caused by ongoing autoimmunity and demyelination or the secondary, residual axonal damage of previously active GBS. In such instances, repeat electrodiagnostic testing can be helpful, and if testing suggests ongoing demyelination, CIDP and treatment for CIDP (e.g., corticosteroids) should be considered.[134]

Untreated patients with MFS generally recover completely within months.[62,74,76,134–136] Patients with MFS or a variant of MFS (e.g., BBE) are frequently treated with immunotherapy (e.g., PE or IVIg), but no randomized trials of immunotherapy for these conditions have been published,[62,136] and it is unknown whether immunotherapy hastens recovery or improves outcome in these patients. Clinical recovery was recently

analyzed retrospectively for 92 patients with MFS.[134] IVIg appeared to slightly hasten the start of amelioration of ophthalmoplegia and ataxia compared with PE or conservative therapy, but the times to disappearance of symptoms were similar for all three groups. Furthermore, at 1 year, only four (4%) patients with MFS had residual symptoms (three with diplopia, one with diplopia and ophthalmoplegia). Of the four patients who were not asymptomatic at 1 year, one had received IVIg, two had been treated with PE, and one had received conservative treatment. Patients with mild or uncomplicated MFS may perhaps be treated conservatively.[134] Patients with a more severe or complicated anti-GQ1b antibody syndrome, such as patients with BBE or with overlapping GBS, should probably be treated with immunotherapy.[62,134]

SUPPORTIVE CARE

Even with immunotherapy, mortality from GBS is ~5% and may be as high as 20% for ventilated patients.[137] Diligent supportive care is essential to minimizing risk of mortality.[21,23] Supportive care consensus guidelines have recently been published.[23]

Monitoring and Management for Respiratory Failure and Airway Compromise

Neuromuscular respiratory failure requiring mechanical ventilation occurs in 20 to 30% of GBS patients.[5,6,8,9,21,23–29] The neurologist must monitor for clinical signs of impending respiratory failure, including tachypnea, use of accessory muscles of respiration, asynchronous movements of the chest and abdomen, and tachycardia.[23] A vital capacity below 20 mL/kg, maximal inspiratory pressure (PI_{max}) less than 30 cm H_2O, or maximal expiratory pressure (PE_{max}) less than 40 cm H_2O predicts imminent respiratory arrest.[23,138–140] Time from onset to admission of less than 1 week, facial weakness, inability to cough, inability to lift head off of pillow, and atelectasis on chest radiograph are other factors associated with respiratory failure and need for mechanical ventilation.[25,141–143] Patients with demyelinating GBS also appear to be more likely to require mechanical ventilation.[142,144] GBS patients who require mechanical ventilation are at high risk of developing a significant complication such as pneumonia, tracheobronchitis, pulmonary embolus, or bacteremia.[145] In some GBS patients, mechanical ventilation is indicated because of severe bulbar dysfunction causing difficulty with clearing secretions, increasing the risk of aspiration, and impairing gas exchange.[23,25,28,29]

The mean duration of mechanical ventilation for GBS is 2 to 6 weeks.[5,6,8,110,141] Weaning from the ventilator should follow improvement in serial pulmonary function tests and strength.[23] The necessity and timing of tracheostomy should be based on the status of the individual in the context of an understanding that early tracheostomy improves patient comfort and airway safety and may help weaning, but that tracheostomy can result in permanent disfigurement and has been associated with life-threatening complications such as hemorrhage, infection, and inadvertent dislodgement of the tube.[23] Percutaneous dilatational tracheostomy may be advantageous over traditional tracheostomy by allowing less risk of accidental extubation and a better cosmetic outcome.[146] The decision to perform tracheostomy may wait 2 weeks following intubation, but if at 2 weeks the patient does not show significant improvement in pulmonary function tests and strength, then tracheostomy is probably indicated. If the pulmonary function tests are improving at 2 weeks, it may be preferable to wait 1 more week to allow an attempt at weaning from the ventilator. The ratio of an integrated pulmonary function score (VC [mL/kg] + PI_{max} [cm H_2O] + PE_{max} [cm H_2O]) calculated before intubation and then at day 12 after ventilation can be used to predict the need for tracheostomy.[141] A summated pulmonary function ratio (day 12 score divided by score day before intubation) greater than 1.0 (i.e., improving parameters) is predictive of weaning from ventilator before 3 weeks, whereas a score less than 1.0 (i.e., worsening parameters) predicts the need for ventilation beyond 3 weeks.

Monitoring and Management for Autonomic Nervous System Dysfunction

Acute autonomic dysfunction develops in the majority of patients with GBS and is a significant cause of death in these patients. Cardiac and hemodynamic disturbances are the most serious and frequent complications, but GBS patients also frequently experience dysautonomia of bowel and bladder function. Sympathetic overactivity with parasympathetic underactivity is the most frequent pattern of autonomic outflow imbalance,[30–33] but other patterns are seen, even throughout the disease course of an individual patient. Severe dysautonomia is most likely to occur in severe cases of GBS when patients are at their clinical nadir, such as the ventilated intensive care patient,[34,36,147,148] although dysautonomia can occur early in the disease and resolve when paralysis is most severe.[34] Cardiac and hemodynamic disturbance manifesting as hypertension, postural hypotension, and tachycardia occur in the majority of GBS patients.[32–35,149,150] Blood pressure and heart rate monitoring is strongly recommended for at least severely affected cases and should be considered for milder cases.[23,33] Cardiovascular monitoring should continue until the patient has begun to clinically improve or, if the patient required ventilation, until ventilatory support has been discontinued.[23] Disturbances of heart rate and blood pressure should not always be assumed to be secondary to autonomic

neuropathy, particularly if sustained or if the patient's GBS is otherwise not severe or near clinical nadir. Pulmonary embolus, sepsis, dehydration, undertreated pain, and electrolyte disturbance need to be considered.

Sinus tachycardia is the most commonly encountered manifestation of dysautonomia in GBS.[34] Tachycardia is usually in the range of 100 to 120 beats per minute and is of little clinical significance.[34,151] However, the presence of tachycardia signifies the presence of cardiac dysrhythmia in a GBS patient and may identify patients more at risk for severe bradycardia, heart block, and asystole. Severe bradycardia, heart block, and asystole that necessitates resuscitation and placement of a cardiac pacemaker occur infrequently.[32,34,147,148] Endotracheal suction and pharmacological agents may provoke bradycardia and asystole.[34,147] Hyperoxygenation before endotracheal suction minimizes the effects of severe bradycardia.

Hypertension occurs in approximately one third of GBS patients.[34,149] Hypertension is most frequently paroxysmal but may be sustained.[34] Systolic blood pressure fluctuations may be extreme.[32] Episodes of hypertension may be followed by hypotension or even sudden death.[32] However, in most cases the hypertension is mild and transient and doesn't warrant specific therapy, particularly because some GBS patients experience labile blood pressures with hypotension following hypertension.[34] If the hypertension is severe and sustained, specific therapy may be necessary. In such cases, antihypertensives with a short half-life that can be titrated should be considered.[34] Postural and episodic hypotension occurs in up to one third of GBS patients.[32,34] Maintenance of intravascular volume and avoidance of diuretics and other drugs that lower blood pressure, whenever possible, are important measures to minimize hypotension. GBS patients at risk for hypotension should not be left unattended in a sitting or upright position.[34]

Urinary retention may occur in up to one third of patients.[32–34] Bladder dysfunction is particularly common in GBS patients who are nonambulatory and require mechanical ventilation.[34] Urinary retention is likely secondary to sacral parasympathetic nerve and pudendal motor nerve dysfunction,[33,34,152] and may be managed by a sterile, closed urinary drainage system.[23,34,36]

Gastrointestinal motility disorders occur in ~15% of severely affected GBS patients.[34,36] Upper gastrointestinal ileus may manifest as abdominal distention, pain, and cramping. Lower gastrointestinal ileus may manifest as constipation. Ileus may occur during the acute phase of worsening motor strength or later during the plateau or recovery phase. When ileus occurs during the acute GBS phase, it is usually accompanied by other features of dysautonomia (urinary retention, tachycardia, hypertension), and is presumed to occur on the basis of autoimmune damage of the parasympathetic vagal nerve (stomach, small intestine, and much of the colon) and sacral parasympathetic nerves (distal colon). In the later phases of GBS, ileus is not associated with other dysautonomias but rather with prolonged immobility and mechanical ventilation.[36] Ileus is transient but may persist for days to weeks. Routine abdominal examination—including auscultation, measurement of abdominal girth, and, sometimes, abdominal radiography—should be standard for GBS patients, particularly those with other dysautonomias, and should continue for GBS patients who require mechanical ventilation.[36] Dysmotility can usually be effectively managed by suspension of enteral feeds, nasogastric suctioning, and erythromycin or neostigmine.[23,36] Parenteral nutrition may be necessary if ileus persists for more than a few days. Rectal tubes are sometimes employed. When possible, avoidance of narcotics is also helpful in lessening dysmotility.

Prophylaxis for Deep Vein Thrombosis

Immobilization caused by GBS is a risk factor for development of DVT and pulmonary embolus. Subcutaneous fractionated or unfractionated heparin and support stockings are recommended for nonambulatory GBS patients until they are able to walk independently.[23] These recommendations are based on the evidence that subcutaneous heparin (5000 U every 12 hours) or enoxaparin (40 mg every day) reduces the incidence of DVT in acutely ill medical patients and in orthopedic and urological surgical patients,[153,154] and the evidence that support stockings also reduce the risk of DVT.[155]

Pain Management

Pain is reported in the majority of GBS patients[4,17,19,20,23] and should be treated aggressively. In one prospective study of GBS patients,[19] 47% reported pain that was "distressing," "horrible," or "excruciating." The most common pain types are deep, aching back and lower extremity pain and dysesthetic extremity pain. Pain intensity correlated poorly with degree of disability. In this study, 75% of GBS patients required oral or parenteral opioid analgesics and 30% were treated with intravenous morphine infusions (range, 1 to 7 mg/h). Narcotics may exacerbate gastrointestinal dysmotility and bladder distention so clinicians should carefully monitor for these side effects.[23,36] Gabapentin (e.g., 15 mg/kg/d)[156] and carbamazepine (e.g., 300 mg daily)[157] are reported to be effective for pain reduction in patients with GBS. Other adjuvant therapy (e.g., mexiletine, tramadol, tricyclic antidepressant medications) may also be helpful in the short-term and long-term management of neuropathic pain.[23] Acetaminophen or nonsteroidal anti-inflammatory agents can also be tried as first-line treatment but are often not very effective.[19]

ISSUES FOLLOWING ACUTE CARE HOSPITALIZATION FOR PATIENTS WITH GUILLAIN-BARRÉ SYNDROME

Inpatient Rehabilitation

Approximately 40% of patients hospitalized with GBS will need inpatient rehabilitation.[158] Of patients who need inpatient rehabilitation, prior requirement for mechanical ventilation and other indicators of more severe GBS predict a longer rehabilitation stay. Rehabilitation management approaches for patients with GBS have been borrowed from the experiences of other neuromuscular diseases and also from the experiences of managing GBS patients during the acute care hospitalization. Many of the same issues that arise during the hospital stay remain during the inpatient rehabilitation stay. For instance, patients with GBS following inpatient hospitalization are likely to still be at increased risk for complications secondary to weakness and immobilization (e.g., DVT, decubitus ulcer, postural hypotension), sensory loss (e.g., compression neuropathy), dysautonomia (e.g., bladder overdistention), restrictive pulmonary function (e.g., sleep hypercapnia and hypoxia, pneumonia), weight loss (e.g., decubitus ulcer, compression neuropathy), and psychosocial concerns (e.g., depression). Muscle weakness may be associated with muscle shortening and joint contractures, complications that may be prevented by daily range-of-motion exercises.[158] Appropriate exercise regimens are used during rehabilitation to improve strength. Exercise regimens should avoid overworking muscle groups, which has been associated with paradoxical weakness and impedes recovery.[159,160] Orthotics should be prescribed to maximize motor function. For patients with significant proprioceptive loss and ataxia, therapy should include techniques for sensory reintegration and repetitive exercises to improve coordination.[158]

Five phases of recovery in GBS have been described: experiencing dependency, encountering helplessness, wanting to know more about GBS, discovering inner strength, and regaining independence.[161] GBS support groups often play an important role in the recovery following hospitalization, both for the patient and the family of the patient. Patients and others can find information online using various search engines. A few recommended Web sites are http://www.ninds.nih.gov/disorders/gbs/gbs.htm, http://www.gbsfi.com/, and http://www.gbs.org.uk/.

Persistent Symptoms and Disability

Guillain-Barré syndrome has a serious long-term impact on the patient's work and private life, even 3 to 6 years after the onset of the illness.[162] Recovery is usually slow and can take years. Patients and families need to be informed about the pace and extent of recovery to limit overly optimistic or pessimistic expectations. Patients experience most of the recovery during the first year, especially the first 6 months, but the majority of patients continue to experience recovery well into the second year and often beyond.[162,163] In one study of adult patients who were queried 1 year after onset, more than half felt that they were not yet back to baseline and were still improving.[163] At 1 year, two thirds still reported some disturbed sensation and/or loss of power; in many cases, these neuropathic symptoms were considered to be moderately or seriously annoying. Of those patients who reported feeling that they were cured at 1 year post-GBS (which was less than half the cohort), the mean time to the perception of cure was 230 days. At 1 year and even during the 3- to 6-year follow-up period, almost half the patients from this cohort reported an inability to function at home as well as before GBS and/or an alteration of leisure activity.[162,163] One fifth of patients still noticed improvement occurring 2.5 to 6.5 years after GBS.[162]

Persistent disability is seen in 20 to 30% of adult GBS patients[9,142,145,163–168] but is much less common in children.[169,170] Long-term disability in adults is more common with axonal GBS and severe GBS, for example, in mechanically ventilated patients.[9,23] The majority of adult patients resume work but approximately one third of patients either take a less demanding job or ultimately don't return to work.[162,163,166,171] In addition to electrophysiological characteristics, age, rapid progression, and disability at nadir are associated with long-term prognosis. A clinical prognostic scoring system (the Erasmus GBS Outcome Score [EGOS]) has recently been proposed.[168] This score takes into account the GBS disability score (Table 2) at 2 weeks after admission, absence or presence of antecedent diarrhea, and age at onset to determine the likelihood of not ambulating unassisted 6 months after GBS. To calculate the EGOS, a point is given for each GBS disability score point (i.e., 1 to 5) at 2 weeks (Table 2). Points are added to the GBS disability score as follows: 1 point is added for patients older than 60 years, 0.5 points for patients ages 41 to 60, and no points for patients 40 years and younger; 1 point is added if the patient experienced antecedent diarrhea. If the EGOS is 3, the data suggest there is a $<5\%$ chance the patient won't be walking independently at 6 months; if EGOS is 4, the chance is $\sim 7\%$; if EGOS is

Table 2 Guillain-Barré Syndrome Disability Score[125]

0 = healthy state
1 = minor symptoms and capable of running
2 = able to walk 10 m or more without assistance but unable to run
3 = able to walk 10 m across an open space with help
4 = bedridden or chairbound
5 = requiring assisted ventilation for at least part of the day
6 = dead

5, the chance is ~25%; if EGOS is 6, the chance is ~55%; and if EGOS is 7, the chance of not walking independently at 6 months is ~85%.[168]

Severe fatigue is a sequela of GBS in approximately two thirds of adult patients.[166,172,173] It can persist for years and is considered by most patients to be one of the most disabling residual symptoms.[173] Fatigue in patients who suffered GBS is significantly associated with reduced quality of life and is independent of muscle strength, sensory impairment, functional ability, and electrophysiological findings.[173,174] Fatigue appears to not be associated with level of functional disability at nadir, antecedent infections, and time to follow-up after GBS.[172] In a randomized, controlled trial of amantadine for severe fatigue following GBS, amantadine was not superior to placebo.[175] There are currently no additional published studies for other pharmaceutical agents, such as modafinil, for treatment of post-GBS fatigue. Another study of patients with severe fatigue 6 months to 15 years following GBS found that a 12-week bicycle exercise training program had positive effects on patient-reported fatigue, anxiety, depression, functional outcome, and quality of life. These patients performed three supervised sessions of bicycling per week for 12 weeks. Each session consisted of a five-minute warm-up and 30 minutes of cycling followed by 5 to 10 minutes of cool-down cycling.[176] Eighty-percent of patients in this cohort were motivated to continue with regular exercise. In general, clinicians should encourage patients with GBS to participate in an appropriate exercise program; for example, one that incorporates stationary bicycling, swimming, or walking.

Future Immunizations

There is either no or very minimal risk of GBS associated with routine immunization.[177–179] Any increased risk of GBS following influenza vaccination is likely not greater than 1 or 2 additional GBS cases per million vaccinations.[177–179] The potential benefits of influenza vaccination outweigh the possible risks for vaccine-associated GBS.[180]

Recurrence of GBS following immunization also appears to be rare.[23] However, only limited data are available to guide clinicians and patients about whether future immunizations, such as annual influenza vaccination, are prudent for patients who have had GBS. One patient with a history of severe GBS went on to have 15 annual influenza vaccinations without incident.[181] Of 311 patients in a British GBS patient organization who had received immunization after suffering GBS, 11 (3.5%) reported symptoms within 6 weeks of immunization.[182] Symptoms such as fatigue, weakness, paresthesias or numbness were almost always mild and always transient, although one patient reported loss of unassisted ambulation for 6 weeks. No patient needed hospitalization or treatment. Influenza, tetanus, and typhoid were the most common immunizations associated with relapse of GBS symptoms.

The current consensus guidelines state that immunizations are not recommended during the acute phase of GBS and probably "not during a period, possibly of 1 year" after onset of GBS.[23] Decisions about future immunizations should be made on a case-by-case basis, factoring in the benefits and risks of immunization and also the possibility that infection, such as influenza, may itself be associated with an increased risk of recurrence of GBS.[181] If GBS occurred within 6 weeks of a particular immunization, more consideration should be given to avoid that particular immunization in the future.[23]

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