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Rev Invest Clin. 2022;74(3):121-30 BRIEF REVIEW

Guillain-Barré Syndrome in Mexico: An Updated Review Amid the Coronavirus Disease 2019 Era

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ABSTRACT

Guillain-Barré syndrome (GBS) is the most frequent cause of acute flaccid paralysis and if not diagnosed and treated timely, a significant cause of long-term disability. Incidence in Latin America ranges from 0.71 to 7.63 cases/100,000 person-years. Historically, GBS has been linked to infections (mainly gastrointestinal by *Campylobacter jejuni*) and vaccines (including those against severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]); however, a trigger cannot be detected in most cases. Regarding SARS-CoV-2, epidemiological studies have found no association with its development. Acute motor axonal neuropathy is the most common electrophysiological variant in Mexico and Asian countries. Intravenous immunoglobulin or plasma exchanges are still the treatment cornerstones. Mortality in Mexico can be as high as 12%. Advances in understanding the drivers of nerve injury in GBS that may provide the basis for developing targeted therapies have been made during the past decade; despite them, accurate criteria for selecting patients requiring acute treatment, prognostic biomarkers, and novel therapies are still needed. The newly-developed vaccines against SARS-CoV-2 have raised concerns regarding the potential risk for developing GBS. In the midst of coronavirus disease 2019 and vaccination campaigns against SARS-CoV-2, this review discusses the epidemiology, clinical presentation, management, and outcomes of GBS in Mexico. (REV INVEST CLIN. 2022;74(3):121-30)

Keywords: Guillain-Barré syndrome. Polyneuropathy. Intravenous immunoglobulin. Plasma exchange. Areflexic flaccid paralysis. Anti-ganglioside antibodies.

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Received for publication: 07-01-2022
Approved for publication: 24-02-2022
DOI: 10.24875/RIC.22000006

INTRODUCTION

Guillain-Barré syndrome (GBS) is the most frequent cause of acute flaccid weakness worldwide, with an incidence of 1-2 cases/100,000 person-years[1]. GBS is classically considered an immune-mediated, ascending, symmetric polyradiculoneuropathy usually preceded by an infection that may occur at any age. However, its incidence and severity increase with age, generally associated with axonal damage, less involvement of cranial nerves, and slower functional recovery[2]. GBS represents a neurological emergency as, despite proper treatment, up to 20% of patients will become seriously disabled, and approximately 5% will die[1]. Regardless of recent advances in GBS knowledge, mortality in Mexico has been reported to be as high as 12%[3,4].

While vaccines have been historically linked to GBS, especially seasonal influenza vaccines, epidemiological studies indicate that they do not increase GBS incidence[5]. However, vaccination campaigns against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have raised questions of whether these newly-developed vaccines approved under emergency conditions may increase the risk of developing GBS[6,7]. This review discusses the current understanding in pathophysiology, clinical presentation, diagnostic criteria, and management of GBS, focusing on recent Mexican data, including the evidence of potential associations between SARS-CoV-2, anti-SARS-CoV-2 vaccines, and GBS.

EPIDEMIOLOGY AND POTENTIAL TRIGGERS

The overall incidence of GBS is higher in men than in women (0.86 vs. 0.57 cases/100,000 person-years)[1]. GBS epidemiology varies regionally. In Asian countries, incidence ranges from 0.44 to 3.25 cases/100,000 person-years, with acute motor axonal neuropathy (AMAN) being the predominant electrophysiological variant. In Europe, incidence ranges from 0.94 to 1.91 cases/100,000 person-years, and the predominant electrophysiological variant is acute inflammatory demyelinating polyneuropathy (AIDP). On the other hand, its epidemiology has marked variability in the Americas. For example, the United States reports 2.2 cases/100,000 person-years with AIDP predominance, while in Central and South America, the reported incidence ranges from 0.4 to 7.63/100,000 person-years[1].

In 2010, Mexico reported 4 cases/100,000 person-years of acute flaccid weakness, and by 2019, a much lower incidence of 0.71 cases/100,000 person-years[8]. These differences between the Americas and the rest of the world may be related to differences in operational definitions and because in most Latin American countries, GBS reports mostly depend on passive epidemiological surveillance systems. The most common electrophysiological variant in Mexico is AMAN, probably associated with the increased incidence of *Campylobacter jejuni* gastrointestinal infections[9,10]; despite this association, in Mexico, GBS has a seasonal distribution with a peak of axonal variants during the summer, while the AIDP variant is more frequent in winter, possibly associated to a higher incidence of respiratory infections[11].

About two-thirds of cases have a preceding infection 3-6 weeks before symptom onset. In case–control studies, *C. jejuni, Mycoplasma pneumoniae, Haemophilus influenzae,* Cytomegalovirus, Epstein-Barr virus, Hepatitis E virus, and Influenza A virus have been temporally associated with its development[10]. In addition, reports have demonstrated an increase in cases during outbreaks of specific pathogens such as Zika and Chikungunya. Interestingly, an association between Chikungunya, Zika, and GBS is unclear in Mexico[12].

CORONAVIRUS DISEASE 2019 (COVID-19) AND IMMUNIZATION AGAINST SARS-CoV-2

Throughout the COVID-19 pandemic, a link between GBS and SARS-CoV-2 remains controversial. A population-based epidemiological study from the United Kingdom reported that the surge of COVID-19 cases during the first pandemic wave did not correlate with an increase in the expected incidence of GBS compared to pre-pandemic records; nevertheless, this finding might be related to the lockdown measures imposed by the pandemic, reducing the transmission of GBS-inducing pathogens[13]. Still, several studies have reported GBS cases after SARS-CoV-2 infection,

suggesting a parainfectious mechanism[14,15]. However, a causal relationship is yet being debated[10].

Vaccines have been historically linked to GBS; however, the last epidemiological association occurred almost five decades ago in association with the H1N1 influenza vaccine, when the risk for GBS increased 7.3-fold among immunized people5. No other vaccines have been directly linked to GBS ever since. As for the SARS-CoV-2 vaccines, some reports suggest a lack of causal association between the currently available mRNA-based (BNT162b2 and mRNA-1273) vaccines and GBS[6,7,16].

A recent Mexican study conducted among 3,890,250 recipients of the BNT162b2 vaccine reported an observed incidence of 0.18/100,000 administered doses, suggesting that GBS among recipients of this vaccine may occur at the expected community-based rate[7]; however, current incidence among the unvaccinated population against COVID- 19 is still undetermined; therefore, these preliminary results should be taken with caution. On the other hand, epidemiological associations with the adenovirus-vectored Ad26. COV2.S (Janssen) and AZD1222 (AstraZeneca) anti-SARS-CoV-2 vaccines with GBS have been made, posing a red flag nonetheless[6,17].

It has been hypothesized that contaminating proteins or other vaccine components may elicit anti-ganglioside antibody production[18,19]; still, these potential mechanistic associations remain to be elucidated. There are no current recommendations on subsequent immunization for two-dose regimen vaccines or boosters after developing GBS as an adverse event. Decisions must be taken on a case-by-case basis; in patients with non-SARS-CoV-2 vaccine-related GBS, it has been suggested that subsequent immunizations should be administered no less than 3 months after the last dose[18]. In the case of anti-SARS-CoV-2 vaccines, we suggest using another vaccine different from the initial one if available.

PATHOPHYSIOLOGY

Historically, GBS was thought to be a single-mechanism disease affecting the peripheral nerves. Further electrodiagnostic testing and pathological analysis have proved that at least two mechanisms are involved, resulting in demyelinating and axonal injury. Despite the discovery of anti-ganglioside antibodies, which opened the pathway toward identifying specific antibodies directed against the neuronal axon[10,20], its exact cause and pathogenesis remain incompletely understood.

Gangliosides are glycolipids with one or more sialic acids, as n-acetylneuraminic acid (NANA) located within the cell surface that oversees cellular recognition and communication between cells. The number of NANAs determines the anti-ganglioside antibodies subtype: one = mono (GM), two = di (GD), three = T (GT), and four = Quattro (GQ)20. To date, there are no specific anti-ganglioside antibodies found in GBS demyelinating variants; those antibodies are only observed in axonal variants, as well as in Miller-Fisher syndrome (MFS) and Bickerstaff brainstem encephalitis (BBE) (Table 1). Some myelin proteins and neurofascin antibodies are currently being studied for AIDP. The anti-ganglioside antibodies found in AMAN and acute motor and sensory axonal neuropathy (AMSAN) electrophysiological variants are GM1 and GD1a, while GQ1b and GT1b are observed in MFS, BBE, and pharyngeal-cervical-brachial variants of GBS. GM1 and GD1a are found in patients who developed GBS after C. *jejuni* infection[20].

The most accepted mechanistic hypothesis for GBS development is molecular mimicry producing cross-reactivity between bacterial lipo-oligosaccharides and neuronal gangliosides. Peripheral nerve injury in GBS is mediated by T cells, macrophages, and complement activation. Patients with demyelinating features usually recover. On the other hand, the recovery for axonal variants is generally slower than in demyelinating forms, and it depends on the degree of nerve injury[20,21]. Some patients with axonal variants may have a quick recovery explained by a functional conduction block without axonal injury. The former may occur during the initial stages; however, if an axonal injury is already present, recovery depends on the extent of damage[22].

CLINICAL VARIANTS AND FEATURES

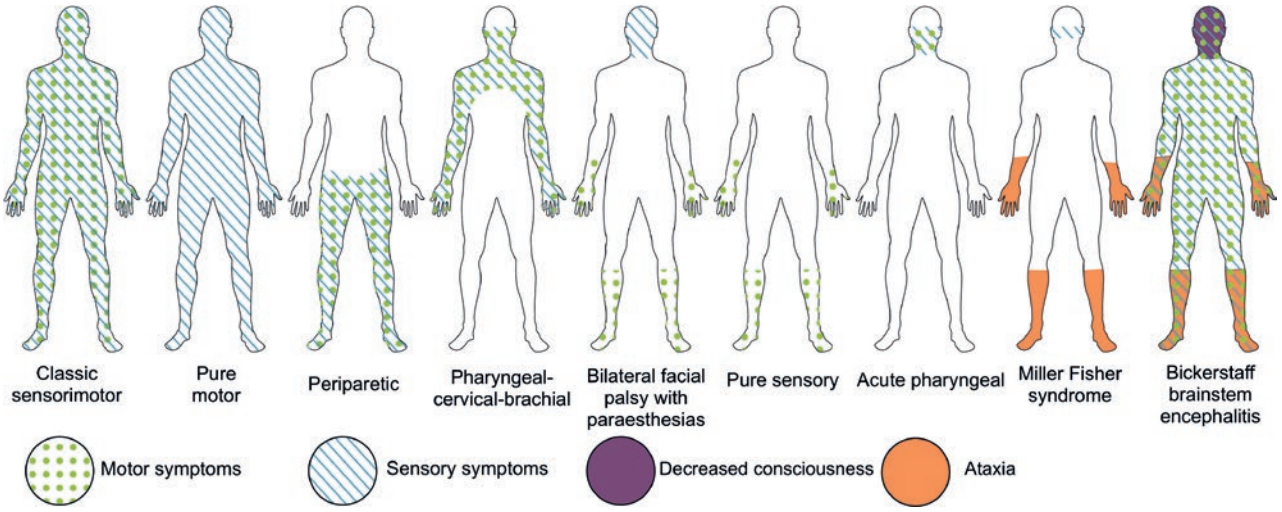
GBS is a heterogeneous disorder with several clinical variants. GBS presents in three stages; the first (progressive) is characterized by a monophasic, progressive

Table 1. Guillain-Barré syndrome, Miller-Fisher syndrome and Bickerstaff brainstem encephalitis spectrum variants, clinical features, and associated anti-ganglioside antibodies

Variant	Frequency	Clinical features	Possible cranial nerve involvement	Associated antibodies	Electrophysiological variant
Guillain-Barré syndrome spectrum variants					
Classic GBS	30-90%	Classic progressive symmetrical weakness with/without sensory signs and areflexia, usually with dysautonomia	Yes	Unknown	AIDP
Pure motor variant	5-70%	Progressive motor weakness without sensory signs	Yes	GM1, GD1a	AMAN
Paraparetic variant	5-10%	Progressive weakness restricted to the legs	No	GM1, GD1b	Axonal
Pure sensory variant	< 1%	Progressive sensory symptoms without weakness	No	GD1b	N/A
Pharyngeal-cervical-brachial variant	< 5%	Progressive weakness restricted to pharyngeal, cervical, and brachial muscles	Yes	GT1a, GQ1b	Equivocal
Bilateral facial palsy with paresthesia variant	< 5%	Progressive bilateral facial palsy, with limb paresthesia	Yes	Unknown	AIDP
Acute pharyngeal variant	< 1%	Progressive acute weakness restricted to pharyngeal muscles	Yes	GT1a	Equivocal
Miller-Fisher syndrome spectrum variants					
Classic Miller-Fisher variant	4-25%	Progressive ophthalmoparesis, ataxia and areflexia	Yes	GQ1b, GT1a	Normal
Acute ophthalmoparesis	< 1%	Progressive ophthalmoparesis	Yes	GQ1b	Normal
Acute ataxic neuropathy	< 5%	Progressive acute ataxia	No	GM1	Axonal
Acute ptosis	< 1%	Progressive acute ptosis	Yes (only ptosis)	GQ1b	Normal
Acute mydriasis	< 1%	Progressive acute mydriasis	Yes (only mydriasis)	GQ1b	Normal
Bickerstaff brainstem encephalitis spectrum variants					
Classic Bickerstaff brainstem encephalitis	< 5%	Progressive ophthalmoparesis, ataxia, areflexia, pyramidal signs and hypersomnolence	Yes	GQ1b, GT1a	Axonal/Normal
Acute ataxic hypersomnolence	< 1%	Progressive ataxia and hypersomnolence	No	GQ1b	Normal
Overlap syndromes	Unknown	Overlap between GBS/MFS/BBE clinical syndromes	Yes	GM1, GT1a, GQ1b	AIDP/Axonal/Normal

GBS: Guillain-Barré syndrome; MFS: Miller-Fisher syndrome; BBE: Bickerstaff brainstem encephalitis; AIDP: acute inflammatory demyelinating polyneuropathy; AMAN: acute motor axonal neuropathy. Modified from Shahrizaila N, Lehmann HC, Kuwabara S (2021)[20].

Figure 1. Clinical GBS variants.



course of symptoms, usually lasting 2-4 weeks; in the second (plateau) phase, symptoms gradually decrease but may persist from weeks to months. In the third (recovery) phase, symptoms gradually improve. Two-thirds of patients will have a preceding acute or subacute infection within 3-6 weeks before symptom onset[10,20].

The classical GBS clinical variant (sensorimotor) is the most common, occurring in 55% of cases (Table 1 and Fig. 1). It usually presents with acute weakness and sensory alteration of all limbs, cranial nerve involvement, and autonomic dysfunction. In most instances, the weakness starts in the lower limbs, ascending to the upper limbs within several days or weeks -generally < 4- (Fig. 1). By the time weakness reaches the knees, it can also be detected in the upper limbs[18,23]. Overall, up to 38% of patients may develop at least one feature of autonomic dysfunction, most common among those with demyelinating forms. Ileus (42%), hypertension (39%), hypotension (37%), fever (28%), tachycardia or bradycardia (27%), urinary retention (24%), pupillary dysfunction (14.1%), or loss of sweating (9.9%) are the most common signs of autonomic instability[24,25].

Other clinical variants of GBS include: pure motor, pure sensory, paraparetic, pharyngeal-cervical-brachial, acute pharyngeal variant, MFS, and BBE. Sometimes a variant may share characteristics with other variants (e.g., classic GBS with MFS features). These mixed variants are known as GBS overlap variants[23,26]. Usually, the pure motor, pharyngeal-cervical-brachial, and paraparetic variants have a more severe presentation, with gait loss and bulbar cranial nerve involvement leading to respiratory failure. Severe autonomic dysfunction is mostly seen in patients who develop severe weakness and respiratory failure[20,23].

Despite having clinical manifestations different from the classical syndrome, MFS and BBE are included within GBS because they share similar pathophysiological characteristics. Within MFS, a triad of ophthalmoparesis, ataxia, and areflexia, we can find incomplete forms, such as the acute ophthalmoplegia variant, acute ataxic neuropathy, acute ptosis, and acute mydriasis[20,23]. In 50% of cases, MFS presents with overlapping BBE and classic GBS[26]. BBE clinically presents with progressive ophthalmoparesis, ataxia, areflexia, upper motor neuron signs, and hypersomnolence, sharing the presence of anti-GQ1b antibodies with the MFS. Interestingly, in BBE, there is a high expression of GQ1b antibodies in oculomotor nerves, neuromuscular spindles, and reticular formation[20].

Cranial nerve involvement can be detected in up to 35% of cases, more frequently in the classic (sensorimotor) GBS variant. Bilateral facial palsy is the most common cranial nerve neuropathy (seen in 50% of patients presenting cranial nerve dysfunction). Ocular motor nerves involvement is more commonly associated with MFS, while the IX and X cranial nerves with

the acute pharyngeal and pharyngeal-cervical-brachial variants[20,23]. Radicular and muscle pain are also frequent initial signs. In some cases, reflexes may be normal during the early stages of the disease, especially in axonal variants, and in some sporadic cases, hyperreflexia can be seen. However, as the disease advances, reflexes are progressively abolished. Twenty-five percent of patients will require invasive mechanical ventilation[18,23]. *Forme fruste* GBS occurs when patients exhibit incomplete clinical variants such as paraparesis restricted to the legs without clinical repercussion in the arms[20].

DIAGNOSTIC CONSIDERATIONS

GBS is primarily a clinical diagnosis, although cerebrospinal fluid (CSF) analysis and nerve conduction studies (NCS) should always be performed. The US National Institute of Neurological and Communicative Disorders and Stroke (NINDS) published the first GBS diagnostic criteria precipitated in part by the increasing number of cases among recipients of swine flu vaccine in 1977, allowing an early diagnosis supported by clinical, laboratory, and electrodiagnostic features[23]. However, in 2011, the Brighton collaboration group developed updated case definitions for GBS and MFS occurring as adverse events following immunization, classifying patients according to the level of certainty depending on CSF analysis and NCS results into four levels, with level 1 representing the highest level of diagnostic certainty and 4 the lowest one[20].

On CSF analysis, most patients may have elevated protein levels, but it may not be evident until 3 weeks after symptom onset. Therefore, the diagnosis may only rely on clinical presentation and electrophysiological testing during the initial stages. Nonetheless, performing a lumbar puncture is recommended in all patients to detect red flags despite an early presentation. CSF cell count is usually low (≤ 5 cells/μL); however, in up to 15% of cases, cell counts may range from 5 to 50 cells/μL. Pleocytosis greater than 50 cells/μL should raise suspicion for infectious or neoplastic origins (e.g., cytomegalovirus infection, Lyme disease, human immunodeficiency virus infection, sarcoidosis, or carcinomatous meningitis, among others)[10,27].

All GBS patients should undergo electrophysiologic testing, not necessarily to confirm the diagnosis but to determine the nerve injury mechanism and prognosis. Timing of NCS is crucial as early studies may be normal or show very few signs of demyelination[18,27]. Pitfalls of electrophysiologic testing and diagnostic criteria will be addressed later in this review. Finally, we recommend testing all patients for serum anti-ganglioside antibodies to support the diagnosis and identify the disease immunophenotype. Anti-ganglioside antibody panels should include immunoglobulin G (IgG) and IgM for GM1, GM2, GD1a, GD1b, and GQ1b.

ELECTROPHYSIOLOGICAL VARIANTS AND CRITERIA

Electrophysiological studies are essential to define whether the injury mechanism is demyelinating or axonal. The demyelinating pattern is characterized by reduced nerve conduction velocity and prolonged latencies. On the other hand, the axonal pattern is characterized by reduced amplitudes, decreased compound motor action potentials (PAMC), conduction block, or an isolated prolonged latency or absence of F-waves[28]. Sural nerve-sparing is a key finding in GBS patients in the proper clinical setting[21]. The axonal variant has two subtypes: if involvement is limited to motor nerves, the variant is known as AMAN; if both motor and sensory nerves are involved, as ASMAN[18]. Table 2 shows the differences between axonal and demyelinating variants among the Mexican population.

The clinical and electrophysiological features of the various presentations can be seen in table 1. Interestingly, in MFS and BBE, electrophysiological studies are generally normal. However, acute ataxic neuropathy and classic BBE may have prolonged distal compound muscle action potentials (CMAP) in motor nerves without fulfilling axonal pattern criteria[26]. Some studies report that the most frequent electrophysiological variant is AMAN, which presents some clinical and paraclinical differences compared to the AIDP variant (Table 2)[9,20]. Although AMAN is the most prevalent variant in Mexico, only 35% of cases have preceding diarrhea, while respiratory tract infections precede in 25%. On the other hand, AIDP is preceded by diarrhea in 44.4% of cases or a respiratory tract infection in 26%[9]. AIDP is usually less severe and carries a better prognosis than AMAN, which has a faster course

Table 2. Clinical and paraclinical differences between axonal and demyelinating variants of Guillain-Barré syndrome in Mexican population

	Axonal	Demyelinating
Overall frequency	31-45%	29-41%
Preceding diarrhea*	35-47%	24-44%
Preceding respiratory tract infection	25-33%	26-45%
Severe disease (GDS ≥ 3 at admission)	85%	83%
Cranial nerve involvement	48%	57%
Facial nerve involvement	41%	57%
Bulbar cranial nerve involvement	27%	30%
Sensory symptoms	42-63%	58-76%
Autonomic dysfunction	25-31%	15-28%
CSF cytoalbuminologic dissociation	41-76%	72-88%
Campylobacter jejuni positive testing	44%	37%
IMV requirement	20-30%	12-33%
Good functional prognosis**	37%	49%

*Diarrhea < 4 weeks before symptoms onset.
**Able to walk 10 m independently at 3 months (GDS ≤ 2).
GDS: Guillain-Barré Disability Scale; IMV: invasive mechanical ventilation; CSF: cerebrospinal fluid.
Adapted from López-Hernández JC, et al. (2021)[9].

associated with an increased risk for invasive mechanical ventilation requirement[10].

The first electrophysiological criteria for GBS were published by Hadden et al. in 1998; however, the cutoff values they proposed had low specificity for the demyelinating variant, particularly for latencies and nerve conduction velocities[28]. Furthermore, studies with an axonal pattern in subsequent studies demonstrated a demyelinating pattern; therefore, a single NCS was not enough to make the diagnosis. In addition, in up to 38% of patients, the electrophysiologic classification may change in follow-up studies[29]. The aforementioned caveats led various authors to question these criteria and propose new cutoff values to determine the nerve injury mechanism in early NCS studies.

Rajabally et al., in 2014, proposed new criteria that allowed for an early (< 7 days) and more accurate determination of the electrophysiological findings' nature[29], obtaining results similar to those published by Hadden et al. when the study is conducted between 3 and 10 weeks after symptoms onset. Furthermore, they demonstrated a reduction in equivocal variants. In 2017, Uncini et al. proposed new electrophysiologic criteria, suggesting that dynamic changes occur in peripheral nerves, and some cases may benefit from serial testing[30].

For those reasons, we prefer using Rajabally's or Uncini's criteria to define the electrophysiological subtype with a single study. Within 3 to 8 weeks from disease onset, a second study is recommended in cases where the first study shows no clear demyelinating features, has low amplitude distal CMAP, or conduction block without temporal dispersion28. In addition to knowing the different criteria, the adequate performance of NCS should rely on an experienced electrophysiologist.

THERAPEUTIC CONSIDERATIONS

The first step in GBS treatment is to know which patients may benefit from immunotherapy or supportive treatment alone. The Guillain-Barré Disability Scale (GDS) allows clinical stratification of patients. This scale ranges from 0 to 6 and primarily assesses the gait and mechanical ventilation requirement[23].

However, as it only measures lower limb strength indirectly by evaluating gait, new scores should be sought to improve treatment selection.

Immunotherapy should be considered in patients unable to walk more than 10 m independently (GDS ≥ 3), those with severe autonomic dysfunction, rapid progression of weakness, bulbar muscles involvement, or respiratory failure within 4 weeks after symptoms onset. Treatment of mildly affected patients (GDS 1 or 2) is controversial as to whether it is cost- and risk-effective, as this subset of patients usually recovers faster due to a milder course. Patients with mild GBS should be observed and treated with immunotherapy only if severe clinical worsening occurs, for instance, if the patient is unable to walk unaided (GDS ≥ 3) due to rapidly progressive weakness, develops severe autonomic dysfunction, involvement of bulbar muscles, or respiratory failure[18,20,27]. MFS is considered a disease with a benign course; therefore, only supportive treatment is recommended unless an overlap variant is diagnosed or if the patient presents any of the previously listed features. In BBE, clinical severity always justifies acute treatment with intravenous Ig (IVIg) or plasma exchange (PLEX)[26].

Acute treatment options include IVIg and PLEX. IVIg is recommended at a total dose of 2 g/kg administered during 5 consecutive days; as for PLEX, five sessions on alternate days (total volume exchange of 200-250 mL/kg or 40-50 mL/kg each session) are the current recommendation. Both treatments are equally effective as they accelerate recovery. IVIg started within 2 weeks after symptoms onset hastens recovery as much as PLEX, has a similar rate of adverse events, and is likelier to be completed[18,20,27].

PLEX has been demonstrated to be effective when started within 4 weeks after symptoms onset10. Combining or switching therapy (PLEX followed by IVIg or vice versa) is not recommended as evidence is not clear on whether patients may benefit or not from switching therapies. Use of PLEX after IVIg is discouraged as PLEX may wash out IVIg[31]. Small volume PLEX (total exchange of 140 mL/kg over 8 days) is a safe and feasible treatment in low-income countries where IVIg and PLEX are unavailable or unaffordable[10]. In Mexico, the decision between IVIg and PLEX depends on treatment availability, and recent studies report that only 63-75% of patients are so treated[3,4,9].

A trial re-evaluating the efficacy and safety of this drug among patients with severe GBS is ongoing (ClinicalTrials.gov Identifier: NCT04752566). Corticosteroids are not recommended for acute GBS as they do not improve short- or long-term outcomes, as demonstrated in several clinical trials[27]. Patients should be considered for intensive care unit admission if they develop progressive respiratory distress, bulbar muscles involvement, rapidly progressive weakness, an Erasmus GBS Respiratory Insufficiency Score (EGRIS) > 4, or severe autonomic dysfunction[20,27].

Treatment-related fluctuations are characterized by clinical deterioration after initial improvement or stabilization within the first 8 weeks following treatment initiation, defined as a decrease of 1 or more points in the GDS. These can occur in 8-16% of patients, and the specific mechanism remains unclear. This subset of patients might benefit from receiving a second course of IVIg or PLEX[20,27]; however, further studies addressing this question are still needed. The benefits of a second course of IVIg were studied in the SID-GBS trial, which only included patients with a poor prognosis (score of ≥ 6) according to the modified Erasmus GBS Outcome Score (mEGOS), failing to demonstrate that patients with a poor prognosis benefit from a second IVIg course[33]. Even so, since that study only included patients with a severe course of the disease, further clinical trials are still needed to determine accurately if a subset of patients may benefit from this treatment strategy. Hence, with the available evidence, administering a second course of IVIg should be limited to research settings.

Supportive treatment must include continuous respiratory assessment, nasogastric tube placement if bulbar weakness is present to prevent aspiration pneumonia, management of autonomic dysfunction, early rehabilitation evaluation, delirium management, pain relief, and deep venous thrombosis prophylaxis. These conditions are essential to consider as they are the most common causes of death during the recovery phase[20,27]. In addition, pain management is fundamental since 89% of patients will develop this complication. Different kinds of pain have been reported, including radicular pain, paresthesia, muscle pain, visceral pain, and meningism. Gabapentin, pregabalin, and carbamazepine are recommended for neuropathic pain as these have proven to be effective for long-term management[34].

Management and monitoring of autonomic dysfunction are imperative, as dysautonomia may develop in up to 70% of patients, remaining as a potentially deadly complication to keep in mind. Tachycardia is the most common sign of dysautonomia in 25-38% of patients. For sinus tachycardia, only monitorization is recommended as sinus blockers may cause fatal bradyarrhythmias. Non-pharmacological bradyarrhythmias and conduction blocks are infrequent but may require atropine administration or pacemaker implantation in some instances[25].

Hypertension develops in 27% of patients. Therefore, for mild to moderate episodes of hypertension, only close monitoring of blood pressure is recommended and for severe hypertension, defined as a mean arterial pressure > 125 mmHg, treatment with either IV labetalol, esmolol, or nitroprusside is justified[35]. Patients presenting with fluctuations between hypertension and hypotension should be admitted to the intensive care unit, as antihypertensives may cause severe hypotension leading to circulatory collapse, and vasoactive agents can precipitate a hypertensive crisis. In that setting, the *start-low, go-slow approach* is recommended. Cardiovascular monitorization is vital in patients treated with PLEX, as it can lead to severe hypotension. Strength, gait, and swallowing rehabilitation provided by a specialist are mandatory in treating severe GBS cases[25].

PROGNOSIS

EGRIS and mEGOS are helpful tools to predict respiratory and functional prognosis during the acute phase, respectively. EGRIS estimates the risk of respiratory failure within the first week of admission, considering the days between symptom onset and admission and facial/bulbar weakness. The total MRC sum score and the mEGOS performed on the seventh day following hospital admission predict the probability of being unable to walk independently within the first 6 months of follow-up; this score considers patient age, history of diarrhea within the past 4 weeks before symptoms onset, and the MRC sum score[20,27].

Despite timely and proper treatment, up to 20% of patients will be unable to walk unaided at 6 months; however, some may still show functional improvement 3 to 6 years after the event. Risk factors for a poor functional outcome (inability to walk unaided) include older age, severe presentation, and mechanical ventilation requirement[18]. A recent Mexican study reported that patients aged >70 years had a delayed gait recovery compared to younger patients[4]. Mechanical ventilation directly impacts the functional outcome and prognosis. Rapid motor symptom progression and early cranial nerve involvement are predictors for mechanical ventilation and aspiration risk[3].

GBS is still a life-threatening illness. The reported mortality rate in Mexico of 10-12% is slightly higher than that described in other parts of the world[3,4,9]. Before IVIg and PLEX, GBS had a reported mortality rate ranging from 3-13% worldwide, with respiratory failure, pneumonia, cardiac arrest, and autonomic dysfunction being the most frequently described causes. Mortality risk factors include older age, severe presentation, and mechanical ventilation requirement. The leading causes of death during the progressive phase are mostly related to complications from autonomic dysfunction, while during the recovery phase, deaths are usually related to respiratory infections or cardiovascular complications[10,20,23].

CONCLUSION

GBS is often associated with unfavorable functional prognosis in patients who are not diagnosed and treated timely. During the past decade, several advances have been made in understanding the pathophysiological drivers of nerve injury in GBS that may support the development of targeted therapies. However, prognostic biomarkers and targeted treatments are still needed. A clear link between COVID-19, the currently available vaccines against SARS-CoV-2, and GBS is yet to be established in large-scale epidemiological studies. Hence, physicians should be aware of the diverse clinical presentations, diagnostic, and care protocols of GBS.

REFERENCES

1. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36:123-33.
2. Zhang B, Wu X, Shen D, Li T, Li C, Mao M, et al. The clinical characteristics and short-term prognosis in elderly patients with Guillain-Barré syndrome. Medicine (Baltimore). 2017;96:e5848.
3. Ruiz-Sandoval JL, Salvatella-Gutiérrez AP, López-Valencia G, Chiquete E, Ruiz-Herrera V, Pérez-Gómez HR, et al. Clinical charac-

teristics and predictors of short-term outcome in Mexican adult patients with Guillain-Barré syndrome. Neurol India. 2021; 69:107-14.
4. Briseño-Godínez ME, Arauz A, López-Hernández JC, de Saráchaga AJ, Pérez-Valdez EY, May-Más RN, et al. Prognostic factors in elderly patients with Guillain-Barré syndrome: does age matter? Neurohospitalist. 2021;11:303-9.
5. Arias LH, Sanz R, Sáinz M, Treceño C, Carvajal A. Guillain-Barré syndrome and influenza vaccines: a meta-analysis. Vaccine. 2015;33:3773-8.
6. Rosenblum HG, Hadler SC, Moulia D, Shimabukuro TT, Su JR, Tepper NK, et al. Use of COVID-19 vaccines after reports of adverse events among adult recipients of Janssen (Johnson and Johnson) and mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna): update from the advisory committee on immunization practices United States, July 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1094-9.
7. García-Grimshaw M, Michel-Chávez A, Vera-Zertuche JM, Galnares-Olalde JA, Hernández-Vanegas LE, Figueroa-Cucurachi M, et al. Guillain-Barré syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. Clin Immunol. 2021; 230:108818.
8. de Salud A, de México G. Incidencia de Casos Nuevos de Enfermedad por Grupos de edad Estados Unidos Mexicanos; 2019. Available from: https://epidemiologia.salud.gob.mx/anuario/2019/incidencia/incidencia_casos_nuevos_enfermedad_grupo_edad.pdf [Last accessed on 2021 Feb 02].
9. López-Hernández JC, Colunga-Lozano LE, García-Trejo S, Gómez-Figueroa E, Delgado-García G, Bazán-Rodríguez L, et al. Electrophysiological subtypes and associated prognosis factors of Mexican adults diagnosed with Guillain-Barré syndrome, a single center experience. J Clin Neurosci. 2020;80:292-7.
10. Papri N, Islam Z, Leonhard SE, Mohammad QD, Endtz HP, Jacobs BC. Guillain-Barré syndrome in low-income and middle-income countries: challenges and prospects. Nat Rev Neurol. 2021; 17:285-96.
11. Domínguez-Moreno R, Tolosa-Tort P, Patiño-Tamez A, Quintero-Bauman A, Collado-Frías DK, Miranda-Rodríguez MG, et al. Mortality associated with a diagnosis of Guillain-Barré syndrome in adults of Mexican health institutions. Rev Neurol. 2014;58:4-10.
12. Grijalva I, Grajales-Muñiz C, González-Bonilla C, Borja-Aburto VH, Paredes-Cruz M, Guerrero-Cantera J, et al. Zika and dengue but not chikungunya are associated with Guillain-Barré syndrome in Mexico: a case-control study. PLoS Negl Trop Dis. 2020;14:e0008032.
13. Keddie S, Pakpoor J, Mousele C, Pipis M, Machado PM, Foster M, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain J Neurol. 2021;144:682-93.
14. Sánchez-Morales AE, Urrutia-Osorio M, Camacho-Mendoza E, Rosales-Pedraza G, Dávila-Maldonado L, González-Duarte A, et al. Neurological manifestations temporally associated with SARS-CoV-2 infection in pediatric patients in Mexico. Childs Nerv Syst. 2021;37:2305-12.
15. Freire M, Andrade A, Sopeña B, Lopez-Rodriguez M, Varela P, Cacabelos P, et al. Guillain-Barré syndrome associated with COVID-19- lessons learned about its pathogenesis during the first year of the pandemic, a systematic review. Autoimmun Rev. 2021;20:102875.
16. García-Grimshaw M, Ceballos-Liceaga SE, Hernández-Vanegas LE, Núñez I, Hernández-Valdivia N, Carrillo-García DA, et al. Neurologic adverse events among 704,003 first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine in Mexico: a nationwide descriptive study. Clin Immunol. 2021;229:108786.
17. Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S, et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021;27:2144-53.
18. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388:717-27.
19. McKean N, Chircop C. Guillain-Barré syndrome after COVID-19 vaccination. BMJ Case Rep. 2021;14:e244125.
20. Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré syndrome. Lancet. 2021;397:1214-28.
21. Esposito S, Longo MR. Guillain-Barré syndrome. Autoimmun Rev. 2017;16:96-101.
22. Ohnari K, Okada K, Mafune K, Kusunoki S, Adachi H. Unclassified subtype of Guillain-Barré syndrome is associated with quick recovery. J Clin Neurosci. 2021;91:313-8.
23. Sheikh KA. Guillain-Barré syndrome. Continuum (Minneap Minn). 2020;26:1184-204.
24. Chakraborty T, Kramer CL, Wijdicks EF, Rabinstein AA. Dysautonomia in Guillain-Barré syndrome: prevalence, clinical spectrum, and outcomes. Neurocrit Care. 2020;32:113-20.
25. Zaeem Z, Siddiqi ZA, Zochodne DW. Autonomic involvement in Guillain-Barré syndrome: an update. Clin Auton Res. 2019; 29:289-99.
26. Bazán-Rodríguez L, López-Hernández JC, de Saráchaga AJ, Gómez-Figueroa E, Leon-Manriquez E, Briseño-Godinez ME, et al. Classic and overlapping Miller-Fisher syndrome: clinical and electrophysiological features in Mexican adults. Neurol Sci. 2021;42:4225-9.
27. Leonhard SE, Mandarakas MR, Gondim FA, Bateman K, Ferreira ML, Cornblath DR, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. Nat Rev Neurol. 2019;15:671-83.
28. Uncini A, Kuwabara S. The electrodiagnosis of Guillain-Barré syndrome subtypes: where do we stand? Clin Neurophysiol. 2018;129:2586-93.
29. Rajabally YA, Durand MC, Mitchell J, Orlikowski D, Nicolas G. Electrophysiological diagnosis of Guillain-Barré syndrome subtype: could a single study suffice? J Neurol Neurosurg Psychiatry. 2015;86:115-9.
30. Uncini A, Ippoliti L, Shahrizaila N, Sekiguchi Y, Kuwabara S. Optimizing the electrodiagnostic accuracy in Guillain-Barré syndrome subtypes: criteria sets and sparse linear discriminant analysis. Clin Neurophysiol. 2017;128:1176-83.
31. Oczko-Walker M, Manousakis G, Wang S, Malter JS, Waclawik AJ. Plasma exchange after initial intravenous immunoglobulin treatment in Guillain-Barré syndrome: critical reassessment of effectiveness and cost-efficiency. J Clin Neuromuscul Dis. 2010; 12:55-61.
32. Misawa S, Kuwabara S, Sato Y, Yamaguchi N, Nagashima K, Katayama K, et al. Safety and efficacy of eculizumab in Guillain-Barré syndrome: a multicentre, double-blind, randomised phase 2 trial. Lancet Neurol. 2018;17:519-29.
33. Verboon C, van den Berg B, Cornblath DR, Venema E, Gorson KC, Lunn MP, et al. Original research: second IVIg course in Guillain-Barré syndrome with poor prognosis: the non-randomised ISID study. J Neurol Neurosurg Psychiatry. 2020;91:113-21.
34. Liu J, Wang LN, McNicol ED. Pharmacological treatment for pain in Guillain-Barré syndrome. Cochrane Database Syst Rev. 2015; 2015:CD009950.
35. Verboon C, van Doorn PA, Jacobs BC. Treatment dilemmas in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry. 2017; 88:346-52.