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REVIEW ARTICLE

Guillain-Barré syndrome in pediatrics: a literature review

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Abstract

Objective: Guillain-Barré syndrome (GBS) is the most common cause of acute flaccid paralysis since poliomyelitis has been eradicated in some countries. This review aims to cover the clinical presentations, the most common causes and the effectiveness of treatments for GBS. **Methods:** This literature review included 15 articles published in the MEDLINE, Cochrane, and LILACS databases between 2010 and 2020. Literature review articles, systematic reviews, and meta-analyses written in English, Portuguese, or Spanish were included. Our review looked into the data of patients aged 18 years or less described in the included articles. **Results:** Pathology findings and clinical signs and symptoms vary according to the clinical subtype of the syndrome. Diagnosis is based on clinical findings, but tests may be required depending on the complexity of the case and for purposes of differential diagnosis. Treatment aims to accelerate recovery, decrease complications, and reduce residual neurological impairment in the long term. Intravenous immunoglobulin is considered the most effective mode of therapy. Plasmapheresis is considerably more affordable and more beneficial when started early. In developed countries, five percent of the patients with GBS die of medical complications. **Conclusion:** GBS is currently the leading cause of acute flaccid paralysis. Despite the existence of effective therapeutic options, death rate is significant, as are the sequelae resulting from incomplete recovery. More research about GBS is needed, since improving knowledge and management might lead to a reduction in morbidity and mortality.

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INTRODUCTION

Guillain-Barré syndrome is an acute onset immune-mediated disease of the peripheral nerves and nerve roots, characterized by progressive symmetrical ascending paralysis, decreased or abolished tendon reflexes, dysautonomia, and sensory deficits. Cranial nerves are also affected in 50% of the cases, along with branches that innervate respiratory muscles, which may, in some cases, cause acute respiratory failure. Some patients may begin with limb pain and numbness associated with difficulty walking or climbing stairs. Limb weakness is rapidly progressive, bilateral, and symmetrical, beginning in the legs and ascending to the arms within a period ranging from days to weeks. In rare cases, it may result in death^{1, 2, 3, 4}.

The syndrome has different clinical variants, the most common being acute inflammatory demyelinating polyradiculopathy (AIDP). Other subtypes include acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, Miller-Fisher syndrome, acute generalized dysautonomia, pharyngeal-cervical-brachial weakness, purely sensory symptoms, and cranial polyneuritis^{2, 9}.

The main treatments studied are intravenous immunoglobulin and plasmapheresis, which are used alone, depending on availability. Despite their positive effect, about 20% of patients remain with walking deficits six months after the onset of acute disease^{4, 7}.

METHODOLOGY

This literature review was based on articles published in the MEDLINE, Cochrane, and LILACS databases between 2010 and 2020. The search included literature review articles, systematic reviews, and meta-analyses published in English, Portuguese, or Spanish. Our review looked into the data of patients aged 18 years or less described in the included articles. Fifteen articles were found. Another six articles were used to set the historical background of the disease and diagnostic criteria.

DISCUSSION

EPIDEMIOLOGY, ETIOLOGY, AND PATHOPHYSIOLOGY

Guillain-Barré syndrome (GBS) was described almost a century ago, when the French neurologists Guillain, Barré, and Strohl reported the story of two soldiers who developed acute paralysis with areflexia and recovered spontaneously. In both cases, a combination of increased protein levels in cerebrospinal fluid (CSF) and normal cell counts - albuminocytological dissociation - was identified, which differentiated the observed condition from poliomyelitis⁴. The disease is characterized by peripheral nerve disorder, manifested as acute flaccid paralysis and decreased or abolished osteotendinous reflexes, with a rapidly progressive and ascending course, in which symptoms peak within four weeks of onset, often triggered by infection. The disease affects individuals of all ages, although it is more prevalent among adults between 30 and 50 years of age.

Moreover, it has become the most common cause of pediatric acute flaccid paralysis since the eradication of poliomyelitis in developed countries, even though it rarely occurs in individuals aged less than two years. Incidence varies by region and ranges from 0.89 to 1.89 cases per 100,000 population per year; males are preferentially affected^{2, 3, 4, 5, 6, 7, 8, 13}. In 50-70% of the cases, the disease can occur within 2-4 weeks of an episode of infection, most often bacterial infections caused by *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and most commonly by *Campylobacter jejuni*, which accounts for 20-30% of cases in the US and Europe. Viral agents involved include cytomegalovirus, Epstein-Barr virus, influenza virus, HIV, along with recent reports involving Sars-CoV-2^{3, 4}. After symptoms peak, the disease stabilizes and lasts for days to months. Then patients enter recovery, which may last for variable lengths of time.

Although rare, cases of disease triggered by vaccination, surgery, trauma, transplantation, lymphoma, and systemic lupus erythematosus have been described. In most cases, the infectious trigger occurs in the gastrointestinal or respiratory tract, with the disease manifesting within four weeks^{3, 4, 6, 9, 10, 11, 12}.

The causal link between GBS and vaccines was first described in 1976, relative to the development of disease after vaccination against the H1N1 influenza virus. Subsequently, other studies have emerged to dispute or support this correlation. In 2011, the Institute of Medicine stated that there is no adequate evidence to reject or accept the hypothesis that the vaccine causes GBS. Nevertheless, vaccination is still considered as a trigger for the onset of GBS, affecting one to six more people when the number of vaccinated and unvaccinated individuals is compared¹. The risk of developing the disease from infection by the virus itself is four to seven times higher, so the benefit of vaccination still outweighs the risk^{3, 11, 13}.

Seasonal increases in the incidence of GBS have not been confirmed¹³. Nevertheless, some papers discuss the variability of incidence, attributing it to factors such as temperature, which affects the distribution of other diseases that might trigger GBS, and other circulating respiratory viral infections¹.

The mechanisms by which it damages peripheral nerves is poorly explained, but some believe that the immune-mediated trigger might affect neural components by molecular mimicry^{4, 6, 7, 8}.

There is no agreement over the potential association between Zika virus infection during pregnancy and GBS, especially as the heterogeneity of the studies on this subject is considered. However, the WHO has described the Zika virus as a cause of congenital disorders and Guillain-Barré, although without further specifications¹⁴.

The first study that observed a relationship between Zika virus (ZIKV) infection and GBS was a case-control study, published in 2016 in the *Lancet*, following an outbreak in French Polynesia from October 2013 to April 2014.

The control groups included patients diagnosed with GBS during the outbreak (n=98) and patients with acute Zika virus infection but no neurological disorders (n=70). Ninety-three percent of the patients with GBS were positive for ZIKV IgM and 88% had transient symptoms of infection six days before the onset of neurological symptoms on average. The incidence of GBS was estimated at 0.24 per 1000 cases of Zika virus infection^{14, 15, 16}.

CLINICAL MANIFESTATIONS AND CLINICAL VARIANTS

The subtypes of GBS are defined according to the neuron groups involved. They are: acute inflammatory demyelinating polyradiculopathy (AIDP), which affects segments of the myelin sheath; acute motor axonal neuropathy (AMAN); acute motor and sensory axonal neuropathy (AMSAN); Miller-Fisher syndrome (MFS) - characterized by the triad ataxia, areflexia, and ophthalmoplegia, with minimal or no flaccidity; and acute generalized dysautonomia^{2, 3, 6, 7, 9, 10, 12}.

Classical cases of the disease manifest with pain – present in about 89% of the patients and usually difficult to locate. At the time of diagnosis, a third of the patients have severe or very severe pain¹¹, paresthesia or numbness, and limb weakness. The main mechanism of pain is inflammation and compression of the nerve roots, and demyelination and degeneration of the sensory nerves. In addition to nerve root and neuropathic pain, musculoskeletal and visceral pain may also occur. Weakness usually progresses rapidly in both legs, in a relatively symmetrical fashion – usually resulting in an inability to walk – and may or not involve muscles innervated by respiratory nerve branches or cranial nerves. Facial muscle weakness occurs in more than 50% of patients. Dysautonomia may also be present in about 70% of the cases, manifesting with sinus tachycardia, bradycardia, hypertension or hypotension, diaphoresis, among other symptoms. Presence of dysautonomia has been directly associated with sudden death. Weakness is observed in the first four weeks of disease, but most patients reach the peak of symptoms within the first two weeks. In 30% of patients, the progress of disease may be fulminant, with ventilatory support becoming required if muscles of the respiratory system are affected. In most cases respiratory symptoms develop slowly and accompany the pace of development of weakness of the legs, although there are some rare cases in which children present potentially fatal acute respiratory failure. In general, the disease develops in a monophasic way: after reaching a peak, patients reach a plateau, which can last for days or months; then a recovery phase follows, for varied lengths of time^{2, 3, 4, 7, 8, 9, 10, 11, 13}. Despite the recovery of normal mobility, pain was present in up to a third of the patients after two years of onset of the syndrome¹⁰.

AIDP is the most common subtype of GBS, accounting for 90-95% of cases of the disease in North America, Europe, and most developed countries. Incidence in pediatric populations is about 1.34 per 100,000 children under 15 years of age, with a slight predominance in males. In this subtype, paresthesia – numbness and tingling – are frequent, followed by weakness and distal symmetric hyporeflexia or areflexia of the lower extremities, which ascend in hours to days, compromising the arms and, in some cases, the respiratory musculature.

Most patients develop some form of gait disorder or become unable to walk and report neuropathic pain. Bilateral facial paralysis is the most common cranial neuropathy and is present mainly in children. The disease is usually monophasic and typically without recurrence. In addition, about 50% of the patients present with autonomic symptoms, particularly tachycardia, although bradycardia, blood pressure variability, urinary retention, and gastrointestinal symptoms may also occur. Early clinical signs may be mistaken for fatigue or growing pains^{3, 9, 13}.

GBS can also manifest with different patterns of disease, forming what we call clinical variants, which may pose greater difficulty at the time of diagnosis, since these variants can be very similar to other causes of acquired peripheral neuropathies. AMSAN, one of the axonal variants with associated sensory involvement, is a more severe form of disease that causes axonal degeneration with consequent motor and sensory deficits, with no or minimal demyelination. AMAN, a condition without a sensory component, is more frequently associated with *Campylobacter jejuni* infection. Severity depends on the extent of neuronal damage. Variants with an axonal pattern increase the overall risk of respiratory failure. MFS accounts for 3-5% of the cases of GBS in some countries – with other reports describing it in 10-25% of cases – and is associated with ataxia, ophthalmoplegia, and areflexia, a triad that presents over the course of a week. External ophthalmoplegia starts in the upper rectus muscles and ends in the lower rectus muscles. Bell's phenomenon is frequently observed. MFS develops more favorably and is not accompanied by respiratory failure or severe paresis of the extremities^{9, 13}. Cases characterized by encephalopathy and hyperreflexia – in some cases ataxia or ophthalmoplegia may be absent – occur consistently with Bickerstaff brainstem encephalitis and account for about 10% of the cases of Miller-Fisher syndrome⁹.

Other more localized forms of the disease are characterized by the involvement of certain nerve groups. They are: multiple cranial polyneuropathy with paralysis of multiple cranial nerves and severe peripheral sensory alteration; pharyngeal-cervical-brachial (PCB) variant of GBS; a combination of MFS and PCB variant; paraparesis; pure sensory paralysis with minimal or absent weakness; palpebral ptosis without ophthalmoplegia; ophthalmoplegia without ataxia; and cranial nerve six paresis with paresthesias^{9, 13}. The forms with palsy or paralysis tend to be more similar to classic AIDP, although they have incomplete anatomic distribution or variable degrees of miscellaneous motor, sensory, and autonomic symptoms. The clinical variants of GBS, despite the observed differences, also tend to present as a monophasic condition that generally responds well to immunomodulation⁹.

Pathology findings vary according to the clinical subtype of the syndrome. Motor and sensory nerve fibers are involved in AIDP, with predominance in the motor portion. There is marked segmental demyelination, with mononuclear cell infiltration in all levels of the peripheral nervous system, including sympathetic chains and ganglia, and cranial nerves.

Nerve repair occurs secondarily with Schwann cell proliferation. Findings in Miller Fischer Syndrome are similar to the ones in classic GBS. No inflammatory changes occur in axonal forms and the primary lesion is seen at the level of the nodes of Ranvier, which produce only axonal degeneration. It might be difficult to differentiate between clinical manifestations, but neurophysiological tests may be used to this end^{7,13}.

In rare occasions, children with severe GBS present with incarceration syndrome, quadriparesis, areflexia, and respiratory failure. In these cases, peripheral nerves are unresponsive and prognosis is poor.

DIAGNOSIS

The diagnosis of GBS is straightforward and based on clinical signs, especially when manifestations are preceded by infection with compatible incubation time, which is around one to three weeks in most cases. Progressive ascending weakness in arms and legs and areflexia are tell-tale signs of GBS. Weakness usually develops over a period of 12 hours to 28 days, and may affect respiratory muscles.

Some findings have been strongly correlated with GBS, such as progression of symptoms ranging from days to four weeks in a distal to proximal direction, relatively symmetric weakness and areflexia, pain, mild sensory symptoms or signs, cranial nerve involvement, recovery or stabilization of symptoms within two to four weeks of disease onset, autonomic dysfunction, absence of initial fever, high protein levels in CSF with a normal cell count (less than 100 cells/L), and typical electromyography findings. Signs that rule out the possibility of GBS include a diagnosis of botulism, myasthenia, poliomyelitis and toxic neuropathy, abnormal porphyrin metabolism, recent diphtheria, and purely sensory syndrome^{4, 6, 12, 13}.

Diagnosis becomes more complex in cases in which pain precedes weakness or when weakness is initially present only in the legs. A few other conditions must be watched for, such as marked asymmetry, urinary or bowel dysfunction (at onset or persistent), severe pulmonary dysfunction (with limited muscle weakness at onset or persistent), defined sensory level (possibly indicative of myelopathy), upper motor neuron syndrome symptoms (hyperreflexia, spasticity, cerebellar ataxia), proximal weakness (suggestive of myopathy), and increased counts of mononuclear or polymorphonuclear cells in the CSF. It is also worth noting that severe sensory alteration can cause sensory ataxia, which may be confused with weakness^{4,9}.

The most commonly used diagnostic tests are CSF analysis, electroneuromyography (EMG), and magnetic resonance imaging (MRI). The classic and essential CSF findings that allow differentiation from other possible conditions are increased protein levels with normal cell counts and lymphocyte predominance, a condition called albuminocytological dissociation. Despite this particular feature, 50% of the patients with GBS still have normal protein levels in the first week of disease, which means GBS cannot be ruled out yet.

Albuminocytological dissociation almost invariably presents in the second week of disease. It is seen in 75% of patients in the third week after the onset of symptoms. It is noteworthy that in patients with HIV, GBS may present with pleocytosis. EMG may show conduction abnormalities depending on the subtype of GBS, which can be differentiated between axonal, demyelinating, and mixed subtypes based on whether conduction block or increased distal latency and decreased nerve conduction velocity are found. MRI scans may show gadolinium enhancement of spinal nerve roots with a pattern of demyelination. MRI is a more sensitive than specific test, indicated in cases of diagnostic doubt^{3, 4, 6, 9}. Other important tests in diagnostic investigation for flaccid paralysis are plasma electrolytes, creatine phosphokinase, complete blood count, chest X-ray, electrocardiogram, electroencephalogram, serological studies, and toxicology panel¹³.

Anti-ganglioside antibodies, as monomers or complexes, can be isolated in a proportion of patients with the syndrome and are particularly identified in patients with AMAN. Individuals with AMAN are tested for anti-GM1 IgG, while patients with Miller Fisher syndrome are tested for anti-GQ1b, in addition to GD3 and GT1a. AMAN and AMSAN can also present with GM1b, GD1a, and GalNac-GD1a antibodies. Tests for antibodies can take days to weeks, which makes them of little use in medical practice^{4,9}.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes an extensive list of conditions. Similar conditions that must be ruled out vary depending on location. Intracranial and spinal cord diseases include encephalitis, carcinomatous meningitis, lymphomatosis, transverse myelitis, and spinal cord compression. Diseases of the anterior horn of the spinal cord include poliomyelitis and West Nile virus. Peripheral nerve disorders include drug-induced neuropathy, acute intermittent porphyria, critical illness polyneuropathy, vasculitis neuropathy, diphtheria, vitamin B1 deficiency, heavy metal poisoning, tick-borne paralysis, and metabolic disorders. Diseases of the neuromuscular junction include myasthenia gravis, botulism, and organophosphate poisoning. Muscle disorders include polymyositis, dermatomyositis, and acute rhabdomyolysis. In these cases, CSF analysis is especially useful in differentiation, as are electroneuromyography and MRI^{6, 9, 13}.

In cases of symptoms refractory to immunomodulatory therapy, alternative causes – or neurological origin or not – must be investigated. Non-classical forms of GBS, acquired chronic neuropathies, and inherited peripheral neuropathies must also be considered. About five percent of the patients initially diagnosed with Guillain-Barré are later found to have acute onset chronic inflammatory demyelinating polyneuropathy (CIDP) when symptoms persist for two months after onset⁹.

Disease with genetic etiologies usually develop silently, with chronic and persistent clinical signs alongside systemic symptoms that indicate the presence of an inherited condition.

In some situations, however, more acute onset and mild systemic symptoms may occur, in such a way that they may mimic GBS. Diagnosis is more challenging in cases of episodic or recurrent-remittent symptoms, with symptom-free periods that delay the understanding of these bouts as elements in one disease. Signs indicative of chronic neuropathy, such as muscle atrophy that is consistent with the duration of symptoms and limb deformities secondary to muscle weakness, may aid in diagnosis. Genetic tests are not performed, given the variety of inherited neuropathies and the multiple gene patterns they present⁹.

Charcot-Marie-Tooth disease (CMT) is the most common inherited condition and encompasses a spectrum of motor-sensory neuropathies with several clinical subtypes. The demyelinating form is the most common. It usually presents with similar clinical, CSF analysis, and electromyography test findings as the ones found in AIDP, MFS, and acute onset CIDP, although with symptoms refractory to immunomodulatory therapy. Clinical signs usually include weakness and paresthesia preceded by respiratory or gastrointestinal symptoms, with distribution of weakness in some cases following a mononeuropathy pattern⁹.

Other genetic forms are peripheral neuropathies secondary to mitochondrial diseases, in which systemic symptoms are usually associated. Infection may worsen pre-existing conditions, in exacerbations that may be confused with AIDP. Two conditions in particular deserve attention: mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) and POLG-related disorders. The former usually presents with gastrointestinal (dysmotility, pseudo-obstruction, poor growth) and neurological (ophthalmoplegia, ptosis, leukoencephalopathy, peripheral neuropathy) symptoms, with 10% of patients presenting with episodes of peripheral neuropathy. The latter usually presents with ptosis, ophthalmoplegia, stroke-like episodes, epilepsy, and ataxia, and varies quite substantially in terms of severity⁹.

TREATMENT

Early patient management involves monitoring motor, autonomic, and respiratory function. Treatment aims to accelerate recovery, reduce GBS complications, and decrease residual neurological impairment in the long term⁵. Immunotherapy with intravenous immunoglobulin is considered the most effective treatment mode, but it is reserved for severe cases of the disease, with muscle weakness that progresses faster than expected, respiratory involvement, bulbar symptoms, and inability to walk without assistance. The total dose for children is 2 g/kg, with 1 g/kg for two days or 400 g/kg for five days, in only one course of treatment. Immunotherapy works by suppressing inflammatory and immune-mediated responses. Management of mild cases of the disease is controversial. Some authors indicate the prescription of support therapy alone, while others advocate specific therapy for all patients. Once the condition has been stabilized, multidisciplinary care for functional recovery and rehabilitation must be initiated.

Respiratory kinesiotherapy is important to avoid atelectasis, and motor therapy has a role in reducing muscle atrophy due to prolonged paralysis. Studies indicate that patients with treatment started within the first two weeks of disease have better prognoses^{4, 6, 13}.

Plasmapheresis is another immunotherapy used in patients with the disease. It has been considered more beneficial when started early and considerably more affordable. The first uses of this treatment date from 1978 to 1981, and benefits have been reported since. Currently, the usual regimen of plasma exchange is one session every two days, adding up to a total of five sessions. A study published in France showed that two sessions of plasmapheresis were more effective than support therapy alone in mild cases of the disease, while another study recommended four sessions for severe cases of GBS. A study showed that this treatment alone can sustain results after 12 months of treatment, and two other studies recommended the use of plasmapheresis in moderate and severe cases of GBS. According to one of these studies, plasmapheresis led to shorter use of ventilatory support and lower risk of cardiac arrhythmia in hospitalized children. It was also observed that, although plasmapheresis is more beneficial if administered within the first two weeks of onset – although treatment can be initiated within up to four weeks – greater benefit was associated with administering plasmapheresis even seven to 30 days of the onset of GBS than not administering it at all. Measures such as prophylaxis against deep vein thrombosis and pain management must be emphasized^{4, 5, 13, 17}. The most commonly used analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, but evidence suggests that anticonvulsants, such as gabapentin and carbamazepine, and antidepressants are more effective than traditional analgesics in treating neuropathic pain¹⁰.

A study conducted in 1992 showed similar levels of efficacy when immunoglobulins and plasmapheresis were compared. Combination of the two treatments was not significantly superior to using one or the other^{4, 7, 8, 11, 18}. No proven difference has been found between immunoglobulin or plasmapheresis, with most services preferring the former due to ease of administration and availability^{4, 6, 13}. When it comes to MFS, a randomized clinical trial is yet to be organized to determine the effects of plasmapheresis or immunotherapy, or to compare them to the effects of support therapy⁴.

In theory, corticosteroids may benefit patients treated for GBS due to their ability to decrease the inflammatory response. Although animal studies have shown accelerated recovery with the use of corticosteroids in high doses, the results observed in studies in which patients with GBS were disappointing. It has been reported that corticosteroids do not improve the recovery of patients with Guillain-Barré when factors such as mortality, ICU admission, time on mechanical ventilation, clinical condition at discharge, or long-term residual disorders are considered^{7, 8}. A study indicated that oral corticosteroids might delay the resolution of neurological disease.

Another study found that intravenous corticosteroids associated with immunoglobulin therapy might decrease the time required for disease resolution when compared to immunoglobulin treatment alone⁸. Other studies reported that corticosteroids are not beneficial in treating patients with Guillain-Barré Syndrome and should not be included in the management of the disease^{19,20}.

In addition, it is important to bear in mind that corticosteroid therapy increases the risk of infection and requires a risk-benefit analysis based on the particularities of each case. According to the literature, serious adverse effects are rare and the most observed alteration was an increase in serum glucose levels of patients given intravenous corticosteroid therapy, an unsurprising finding. A finding, however, was contrary to what might be expected: patients receiving corticosteroids had lower rates of hypertension, indicating that the drug might have had a protective renal effect, given the reported association between GBS and glomerulonephritis⁸.

Alternative treatment options beyond established therapies with intravenous immunoglobulin and plasmapheresis have been studied. Although interferon beta-1a (IFNβ-1a) showed benefits in animal studies, no significant improvement in symptoms was found in human studies, as also seen in studies in which patients were given Eculizumab (anti-C5 antibody), mycophenolate mofetil, or CSF therapy (cerebrospinal fluid aspiration, filtration and reinfusion), all without significant differences in outcomes when compared to controls. Tripterygium polyglycosides have been used as an anti-inflammatory agent in traditional Chinese medicine, with potential symptom improvements for patients with GBS. BDNF (brain-derived neurotrophic factor) generated a neuroprotective effect and showed beneficial effects in the management of GBS when compared to placebo. Finally, studies with SDD (selective decontamination of the digestive tract) showed discordant results, with some indicating that it decreases time on mechanical ventilation and others showing no significant benefit. Available research has produced low levels of evidence (due to the design of the studies and the size and heterogeneity of the samples), so further studies are needed before scientific consensus about alternative therapies in the treatment of GBS can be achieved⁷.

PROGNOSIS

Some patients may deteriorate even after adequate treatment, with severe long-lasting immune attack resulting in axonal degeneration. The rationale and management for such conditions have not been established. Five to ten percent of patients may worsen after initial improvement or stabilization of symptoms. The role of a second prescription of immunoglobulins has not been evaluated, although it is often performed⁴.

A study indicated that 7% of the patients have recurrent seizures in the years following the initial onset of GBS symptoms, and 16% have symptoms with clinical fluctuations, even when on immunomodulatory treatment. In addition, about 20% of the patients remain with some level of residual impairment after the end of symptoms⁹.

A study cited a small but significant increase in relapse within the first six to 12 months of the onset of GBS in individuals treated with plasmapheresis, when compared to patients not prescribed this type of treatment⁵.

Disease mortality in developed countries is around 2 to 3% and higher in developing countries. Autonomic dysfunction and respiratory failure are important causes of death by GBS. In developed countries, five percent of GBS patients die from medical complications such as sepsis, pulmonary embolism, and unexplained cardiac arrest. Despite the low mortality rates, 25% of the patients require artificial ventilation due to impaired respiratory muscle innervation. Approximately 20% of survivors remain experiencing difficulty walking after the end of acute symptoms, and many are left with persistent fatigue. Prognostic models such as the Erasmus GBS Respiratory Insufficiency Scale (EGRIS) can predict the likelihood of ventilation being required based on admission criteria. Tools such as this may help in the making of decisions regarding the referral of patients to different care teams. Patients with accelerated progression of weakness and altered lung function, requiring mechanical ventilation, unable to swallow, with a high chance of developing aspiration pneumonia, and severe autonomic dysfunction must be referred to intensive care^{2, 4, 7, 8, 9, 13}. There are no controlled studies comparing the results of different modes of mechanical ventilation, but the most common approach is assist-control ventilation, with noninvasive ventilation as an alternative¹³. Long-term sequelae and impact on activities of daily living are not yet fully understood, but weakness and fatigue, sensory disorder, and psychosocial and quality of life effects can be long-lasting. A study conducted by Forsberg et al. reported that the impact of GBS on activities of daily living, social and quality of life was still considerable two years after the resolution of the disease^{2, 4, 21}. Old age and severity of symptoms are associated with poorer prognosis. Children generally recover better than adults: more than 80% of the children with the disease have excellent long-term recovery, regardless of disease subtype^{4, 6, 13}. The risk of disease recurrence has been estimated at 2-5%, with a mean interval of seven years between disease events⁶. More than 90% of the patients with AIDP and all with MFS recover fully. Patients with AMAN have more motor sequelae, and cases of AMSAN, rare in children, have been associated with poorer outcomes¹³.

Table 1. shows the findings evidenced in each analyzed article.

Title	Author(s)	Year of publication	Results
Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta - analysis	Salmon et al	2013	There are no definitive conclusions about the relationship between H1N1 vaccine and GBS to either determine or rule out the vaccine as a cause of disease. Therefore, GBS continues to be accepted as a post-vaccination effect. The authors describe factors such as temperature and respiratory viral infections as causes of variability in incidence.
Multidisciplinary care for Guillain - Barré syndrome	Khan et al	2010	Ventilatory support is needed since GBS affects the muscles of the respiratory system. Some prognostic models can predict the likelihood that ventilation will be required, which may assist in decision making regarding patient referral to specific care teams.
Pediatric Guillain - Barré syndrome	Ryan MM	2013	GBS is a common element in acute flaccid paralysis in children. Symptoms such as paresthesia, weakness and pain in limbs are common; in most cases, respiratory symptoms develop slowly; the disease is rarely fatal. Severe GBS can present with incarceration syndrome. The benefits of vaccinating against H1N1 outweigh the risks.
Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS)	van Doorn PA	2013	GBS is a post-infectious disorder, and <i>Campylobacter jejuni</i> , cytomegalovirus, Epstein-Barr virus, and <i>Mycoplasma pneumoniae</i> are major causes of infection. The disease has some diagnostic characteristics, such as symmetry of symptoms and weakness of facial muscles. Symptoms develop within days to four weeks - distal to proximal - with onset of recovery/ stabilization within two to four weeks after onset. Diagnosis can be complex if pain precedes weakness, or if weakness manifests first in the legs. Diagnostic doubt may occur when asymmetry, urinary or bowel dysfunction, and defined sensory level are present. Antibody screening can be used in diagnosis, with anti-ganglioside antibodies especially identified in patients with AMAN and Miller Fisher syndrome. Better prognosis is obtained if treatment is started within the first two weeks of illness onset. The studies reviewed here have shown similar efficacy of immunoglobulins compared to plasmapheresis.
Plasma exchange for Guillain-Barré syndrome	Chevret et al	2017	In the initial management of GBS, motor, autonomic, and respiratory function must be monitored; treatment aims to recover function and decrease complications and long-term residual neurological impairment.
Guillain-Barré Syndrome	Chung A e Deimling M	2018	GBS is a rapidly progressive, ascending peripheral nerve disorder. The mechanism of peripheral nerve damage is poorly explained, but the immune-mediated trigger is believed to act by molecular mimicry. Diagnosis is made based on clinical signs. Relative symmetry of weakness and sweating, pain, cranial nerve involvement, among other symptoms, strongly indicate a diagnosis of GBS. Cerebrospinal fluid analysis, electroneuromyography and MRI may assist in diagnosis.
Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome	Doets et al	2020	The peripheral nerve damage mechanism is related to the autoimmune system. Alternative therapies such as interferon beta-1a (IFNβ-1a), Eculizumab (anti-C5 antibody), Mycophenolate mofetil and CSF therapy (CSF aspiration, filtration, and reinfusion) have not significantly improved symptoms. BDNF (brain-derived neurotrophic factor), on the other hand, showed a beneficial effect in the management of GBS.
Differentiating Familial Neuropathies from Guillain-Barré Syndrome	Bordini BJ e Monrad P	2017	The following are clinical variants of GBS: AIDP, AMAN, AMSAN, MFS, with 10% being Bickerstaff brainstem encephalitis. Some conditions raise doubt in the diagnosis of GBS, such as upper motor neuron syndrome symptoms, proximal weakness, chronic or persistent symptoms, systemic symptoms, as well as cases of symptoms refractory to immunomodulatory therapy. In cases of symptoms refractory to immunomodulatory therapy, alternative causes that explain the condition should be investigated, such as non-classical forms of GBS and inherited or chronic acquired neuropathy.
Pharmacological treatment for pain in Guillain-Barré syndrome	Liu et al	2015	Vaccination and surgery may trigger GBS. Pain has inflammation and compression of the nerve roots and the demyelination and degeneration sensory nerves as its main mechanisms. It can occur in radicular, neuropathic, musculoskeletal, and visceral forms. Most commonly used analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, but evidence suggests that anticonvulsants, such as gabapentin and carbamazepine, and antidepressants are more effective in treating neuropathic pain.
Acute polyradiculoneuritis: Guillain-Barré syndrome	Korinthenberg R	2013	Classic cases of the disease include difficult-to-locate pain. GBS manifests itself initially with weakness, ataxia, and paresthesia, and may progress to respiratory failure. Symptoms develop gradually to a peak, followed by a plateau, and then by recovery. Treatment involves immunoglobulin or plasmapheresis.
Guillain-Barre Syndrome	Rosen BA	2012	The incidence of GBS is 0.5-1.5/100,000 population per year. Progression occurs from distal to proximal, taking up to four weeks; high protein levels and normal cell counts in the CSF and typical electromyography findings are strongly suggestive of GBS. Botulism, myasthenia, poliomyelitis, toxic neuropathy, porphyria, or diphtheria rule out a diagnosis of GBS.

Continued **Table 1.**

Gullain-Barré Syndrome	João P	2014	The risk of developing GBS from H1N1 infection is higher than the risk of developing it due to the vaccine. There is no conclusion about the increased incidence of GBS in relation to seasonality. Weakness is a symptom that usually progresses rapidly, in both limbs, symmetrically. Its subtypes are: AIDP, AMSAN, AMAN; and MFS. GBS is the most common etiology of acute flaccid paralysis in children, with incidence of 0.89-1.89 cases per 100,000 population per year. Bilateral facial paralysis constitutes the most frequent cranial neuropathy. Immunotherapy with intravenous immunoglobulin is considered the most effective treatment; the ideal dose for children is 2 g/kg - 1 g/kg for 2 days or 400 g/kg for 5 days. Assist-control ventilation is the most common treatment provided to patients with respiratory failure, although there are no studies comparing the results of different modes of mechanical ventilation. The prognosis of cases of AIDP and MFS is good, with full recovery in most cases.
Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barré syndrome: A living systematic review	Counotte et al	2019	There is no general agreement about the association between Zika virus infection during pregnancy and the development of GBS. However, the virus has been indicated as a cause of GBS by the WHO.
Zika virus- associated Guillain - Barré syndrome: a warning for critical care physicians	Thiery et al	2016	93% of GBS patients are ZIKV IgM positive and 88% had transient symptoms of infection six days before the onset of neurological symptoms on average.
Ineffectiveness of high-dose intravenous methylprednisolone in Guillain-Barré syndrome	Hughes R	1991	Corticosteroid therapy in patients with GBS did not yield the expected results, with no benefit to patient recovery. Some patients had lower rates of hypertension, suggesting a renal protective effect. Risk-benefit analysis must be performed in each case.

CONCLUSION

Guillain-Barré syndrome is currently the main cause of acute flaccid paralysis. Although the available therapeutic options are considered effective in its management, the death rate resulting from the disease is still significant, as well as the sequelae resulting from incomplete recovery of a significant portion of the patients.

In view of these facts, further studies about this condition are still required in order to improve the practical knowledge of this condition and allow, in the future, the introduction of better management practices with lower morbidity and mortality and higher quality of life for patients.

REFERENCES

- Salmon DA, Proschan M, Forshee R, Gargiullo P, Bleser W, Burwen DR, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. *The Lancet*. 2013 Apr;381(9876):1461-8.
- Khan F, Ng L, Amatya B, Brand C, Turner-Stokes L. Multidisciplinary care for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews*. 2010 Oct 6;1-24.
- Ryan MM. Pediatric Guillain-Barré syndrome. *Current Opinion in Pediatrics*. 2013 Dec;25(6):689-93.
- van Doorn PA. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS). *La Presse Médicale*. 2013 Jun;42(6):e193-e201.
- Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews*. 2017 Feb 27;1-51.
- Chung A, Deimling M. Guillain-Barré Syndrome. *Pediatrics in Review*. 2018 Jan;39(1):53-4.
- Doets AY, Hughes RA, Brassington R, Hadden RD, Pritchard J. Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews*. 2020 Jan 25;1-61.
- Hughes R, Swan A, and van Doorn P, 2010. Corticosteroids for Guillain-Barré syndrome. *Cochrane Database Of Systematic Reviews*, pp. 1-31
- Bordini BJ, Monrad P. Differentiating Familial Neuropathies from Guillain-Barré Syndrome. *Pediatric Clinics of North America*. 2017 Feb;64(1):231-52.
- Liu J, Wang L, McNicol ED. Pharmacological treatment for pain in Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews*. 2015 Apr 9;1-36.
- Korinthenberg, Rudolf. Acute polyradiculoneuritis: Guillain-Barré syndrome. *Handbook of Clinical Neurology*, vol. 112, Elsevier, 2013, p. 1157-62.
- Rosen BA. Guillain-Barre Syndrome. *Pediatrics in Review*. 2012 Apr 1;33(4):164-71.
- João P, 2014. Síndrome de Gullain-Barré. *PROTIPED (Programa de Atualização em Terapia Intensiva Pediátrica)*, 1, p.9-56.
- Counotte MJ, Meili KW, Taghavi K, Calvet G, Sejvar J, Low N. Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barré syndrome: A living systematic review. *F1000Res*. 2019 Aug 14;8:1433.
- Cao-Lormeau V, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *The Lancet*. 2016 Apr;387(10027):1531-9.
- Thiery G, Valentino R, Meddhaoui H. Zika virus-associated Guillain-Barré syndrome: a warning for critical care physicians. *Intensive Care Med*. 2016 Sep;42(9):1485-6.
- Appropriate number of plasma exchanges in Guillain-Barré syndrome. *Ann Neurol*. 1997 Mar;41(3):298-306.
- van der Meché F, Schmitz P. A Randomized Trial Comparing Intravenous Immune Globulin and Plasma Exchange in Guillain-Barré Syndrome. *N Engl J Med*. 1992 Apr 23;326(17):1123-9.
- Korinthenberg R, Monting JS. Natural history and treatment effects in Guillain-Barre syndrome: a multicentre study.. *Archives of Disease in Childhood*. 1996 Apr 1;74(4):281-7.
- Hughes R. Ineffectiveness of high-dose intravenous methylprednisolone in Guillain-Barré syndrome. *The Lancet*. 1991 Nov;338(8775):1142.
- Forsberg A, Press R, Einarsson U, de Pedro-Cuesta J, Holmqvist LW. Disability and health-related quality of life in Guillain-Barré syndrome during the first two years after onset: a prospective study. *Clin Rehabil*. 2005 Dec;19(8):900-9.