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Current guidelines & treatment of Guillain-Barre's syndrome: A review

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Abstract
Guillain-Barre Syndrome (GBS) is one of the rarest syndrome whose treatment and understanding of the syndrome were very challenging for about past 10 years. It has been clear throughout the certain years that this syndrome differing in seriousness so that it can cause respiratory paralysis and death in its serious form. GBS is a diversified syndrome. Current epidemiological studies suggested the occurrence in between 1 and 2/100000 with somewhat more male individual affected than females. Recent epidemiological data recommend that the Varicella zoster and influenza virus may precede GBS in a remarkable fraction of cases. In the pathogenesis of GBS the progress of certain neurological signs antiganglioside antibody can function and through its binding to ganglioside antigens in peripheral nerves. First diagnostic standard for GBS was from 1978, and were revised in 1990 by Asbury and Kornbluth. GBS patient needs excellent care to prevent and manage fatal complications. This study reviewed all the guidelines & treatments of GBS and conducted that current treatment options are largely equal to those which was already in use 20 years ago in comparison with the recent advances in to the novel treatment in GBS. Hoping that some more approaches by the international GBS research community will be discovered for the goal to optimize the care for GBS patients.

Keywords: GBS, antiganglioside, treatment, varicella zoster, influenza

Introduction
Guillain-Barre Syndrome remains one of the most compulsive yet challenging condition despite considerable advances in its understanding and treatment for about 10 years in the past. During the First word war in sixth army camp, French physicians were working so this was originally described by them [1]. It has continue to exist as the rarest syndrome, but so obvious in the presentation that the clinical features will not be remembered by some of the doctors. If the autonomic nervous system is intricate and respiratory muscles are affected than GBS can lead to deadly problems and weakness because to this, reaches its worst in 2-4 weeks. Over 5 percent of the patient die and some more patients with a disabling motor deficiency and /or fatigue are left [2].

It has been clear throughout the certain years that this syndrome differing in seriousness so that it can cause respiratory paralysis and death in its serious form. GBS is a diversified syndrome [3]. Current epidemiological studies suggested the occurrence in between 1 and 2/100000 with somewhat more male individual affected than females [4]. Men are affected approximately 1.5 times more than woman [5]. As the age increases the incidences due to this GBS also rises, although there is a minor apex among young adults [6]. There are no incidences based studies of GBS in the Indian population but some case-based studies reported [7]. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in the western world is the most recurrent subtypes with a primarily demyelinating pathology and various degree of secondary axonal damage. Acute motor neuropathy (AMAN), the next most recurrent and visible to be a primary axonal disorder have an effect on motor nerves [8]. Several clinical variants can be distinguished such as then miller fisher syndrome (MFS), the pharyngeal-cervical-brancical variant and paraparetic GBS [9]. CSF and NCS (Cerebrospinal fluid & nerve conduction studies) are normal in a subset of patients especially early in the course of the disease, emphasizing the need for new diagnostic technique [10]. Nerve ultrasound and MRI have been suggested as potentially useful diagnostic techniques for GBS [11-14].

Clinical feature
GBS has an occurrence of about 1/100,000 throughout the several studies in a number of countries. Incidences Because of GBS can increases as the age increases and there is a small prevalence of males [15, 16].

Most commonly are the unremarkable infections, such as upper respiratory infections, commonly antecede that the onset of GBS by 14 days [17, 18]. Majority of the ancestor infections have been identified including Campylobacter jejuni, cytomegalovirus (CMV), Mycoplasma pneumonia, Epstein - Barr virus, influenza Virus JEV [19, 20]. GBS usually begins suddenly with distal relatively symmetrical beginning of paraesthesia and quickly followed by progressive limb weakness. The ongoing diagnostic norm include <4 weeks of progression to clinical nadir approximately 80%-90% of patientssuffered from GBS becomes non-ambulatory illness [21]. Painis prominent in 50% of the patients [22]. GBS is a critical motor neuropathy, sensory dysfunction which is observed in some patients and in a demyelinating form of GBS it is observed more [23, 24]. Few number of patients evolve abnormal signs such as papilledema considered to be secondary to cerebral edema and hyponatremia. Mortality in most population studies in between 5-10 %**.** Most recent epidemiological surveys show the risk of immunization triggering GBS to be very low [25, 29].

Antecedent events

GBS is a rare event after vaccination. In most cases, GBS follows an infection of GIT or Upper respiratory infection. Campylobacter jejuni enteritis, one of the most ordinary antecedent infection causes include cytomegalovirus, Epstein-Barr virus and mycoplasma pneumonia [30, 33]. In about 30% to 50% of cases of serological studies disclose the confirmation of antecedent infection. In about 30% of patients with GBS, serological confirmation of C. jejuni infections exist and observed to be related with few more severe disease and with acute motor axonal neuropathy (AMAN)) Variants. Serological studies suggested that Campylobacter jejuni, Epstein Bar virus and cytomegalovirus are the most recurring antecedent infections. Secretion of Jejuni can be continued sometimes in the stool of the patients for up to 3 months which is followed by the beginning of GBS [34, 39].

Recent epidemiological data recommend that the Varicella zoster and influenza virus may precede GBS in a remarkable fraction of cases [40, 44].

Table 1: Clinical case definitions of GBS [45].

Diagnostic certainty level 1	Diagnostic certainty level 2	Diagnostic certainty level 3
Bilateral AND flaccid weakness of the Limbs AND Decreased or absent deeptendonre flexes in weak limbs AND Monophasic illness pattern AND the interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau AND Electrophysiological findings consistent with GBSAND Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/l)AND Absence of an identified alternative diagnosis for weakness	Bilateral AND flaccid weakness of the Limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern AND the interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau AND CSF total white cell count<50 cells/l (with or without CSF protein elevation above laboratory normal value)OR If CSF not collected or results not available, electrophysiological studies consistent with GBSAND Absence of an identified alternative diagnosis for weakness	Bilateral AND flaccid weakness of the Limbs AND Decreased or absent deep tendon reflexes in weak limbs AND Monophasic illness pattern AND the interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau AND Absence of identified alternative diagnosis for weakness

CSF=CEREBROSPINAL FLUID; GBS=GUILLAIN –BARRE SYDROME

Epidemiology

GBS is a uncommon disease. The annual incidences rates range from 0.35 to 1.34 per 100,000 which is reported and are resembled throughout the world. GBS is 1:1000 obtained by any individual in the lifetime probability. In North-America and Europe, in90% of the cases AIDP is a dominant contributor and AMAN being the most common subtypes in China and Japan [45-52]. In India the incidences of AIDP and AMAN are almost equal, although AMAN is more common in younger patients [53]. Majority of the source data about the epidemiology of the GBS stem from the duration between 1980 and 2000 [48]. Swine flu experience in the United States when the national influenza immunization programed was interrupted because of the occurrence of GBS cases in vaccine recipients [54]. The alliance between GBS and influenza vaccination was again revitalized in 2009 during the swine flu influenza A (H1N1) virus pandemic and the upcoming launch of mass immunization campaigns in several countries. Since then, several cases of GBS and miller fisher syndrome after influenza vaccination have been reported**[55]**. Recently, age and gender-specific background rates for GBS have been reported for the countries like Brazil, Finland, UK, United States and Canada [56, 57, 58].

Pathophysiology

In the progress of certain neurological signs antiganglioside antibody can function and through its binding to ganglioside antigens in peripheral nerves in the pathogenesis of GBS**[51]**. Because of the patient's death, autopsy studies are rare in GBS. Edema of the peripheral nerves with spares inflammatory infiltrate was reported by the previous studies of GBS. The presence of perifascicular lymphocytic cuffs of small vessels in the endoneurium and perineurium, considered the authentication of GBS by the well- known studies of colleagues and Asburg, this become noticeable to be related with demyelination, which is expected to be macrophages associated [59, 60]. The microscopic studies related to nerve biopsy have demonstrated macrophages associate demyelination, macrophages which relate to invade the Schwann cell basement membrane and phagocytic myelin debris [61, 62]. Some cases of GBS are related with a primarily axonal process in which macrophages may be observed in a close proximity to the axon with sparing of myelin [63]. In AMAN the pathological studies describes the relative paucity of inflammatory infiltrate with axonal destruction but this time macrophages were located between axons and the myelin especially in the region of the node of Ranvier [64]. Some other cases in which GBS appear that involved both sensory and motor axons and these type of cases can be called as the acute motor and sensory axonal neuropathy (AMSAN). In AMSAN condition it involves both motor and ventral nerve roots but pathological changes are similar [65].

Diagnosis

First diagnostic standard for GBS was from 1978, and were revised in 1990 by Asbury and Kornbluth. For the diagnosis, both limb (upper and lower) in GBS syndrome along with areflexia within 4 weeks is a necessary demand and in some

patients, diagnosis is very difficult in some patientsespecially when pain already presentor weakness started in legs [66,67].

- **Cerebrospinal fluid:** CSF examination helpful for the patient weakness, if CSF total protein is high with cellular reaction this may help to make diagnosis especially when there are some non-typical features. CSF protein level is highly dependent on the timing of lumbar puncture. When lumbar puncture was performed within 1 day from the onset of weakness, 49% of patients had elevated protein level which increased to 88% of patients after 2 weeks [68]. Recently age-specific references values for CSF protein level were defined for children [12, 69]. In children younger than 6 months of age, the additional value of CSF total protein determination was considered nil because of large physiological variation in protein levels [70].
- **EMG Examination:** It's helpful for polyneuropathy in clinically not yet invades areas, for example when signs of polyneuropathy in the arms of the patients observed with weakness only in the legs. It also enables to differentiate GBS in AMAN (axonal features) and AIDP (demyelinating features) [71].
- **Nerve conduction studies (NCS):** Many electrophysiology criteria have been developed for GBS. However much debates are ongoing concerning the validity of these criteria and on the optimal frequency of NCS for GBS subtypes diagnosis [72, 73].
- NCS for GBS in current clinical practice to confirm diagnosis especially in atypical cases such as paraparetic GBS by finding either sign of demyelination or abnormalities in the region that are clinically not affected [74, 75].
- **MRI and Nerve ultrasound:** this is commonly used in diagnostic tool in mononeuropathies and traumatic neuropathies and it is used especially in the diagnosis of chronic immune-mediated polyneuropathies is increasing. Nerve ultrasound and MRI techniques currently used in especially children in GBS cases. GBS reported to be present 1-3 days following symptom onset but is usually mild and segmentally disturbed. Cervical nerve root enlargement has been described in both demyelinating and axonal form of GBS and in MFS. MRI indicates the swelling of the nerve root that may add to the diagnosis of GBS [76]. In few cases GBS is caused by autoantibodies current evidences suggested and that autoantibodies arising via microbial molecular mimicry [77].
- **Anti-ganglioside antibodies:** It is a monomer or as complexes which can be found in a fraction of GBS patients especially with AMAN (IgG anti-GM1 antibodies) and in patients with MFS (anti-GQ1b) that cross-react with campylobacter. The various gangliosides have been found in human peripheral nerves including (LM1, GM1, GM1b, GM2, GD1a, GalNAc-GD1a, GD1b, GD2, GD3, GT1a, and GQ1b) in about half of patient with GBS, serum antibodies [78, 82]. Antibodies to GM1, GM1b, GM2, GD1a, and GalNAc-GD1a are related with the pure motor or axonal variants of GBS. Antibodies presence, clinical symptoms and GBS severity, the pathological importance of some of these antibodies have yet to be established. In GBS patients Antibodies to other glycolipids and T cells to peripheral nerve proteins have also been observed**.**

The presence of anti-GQ1b antibodies can be helpful in making the diagnosis in patients with MFS as mentioned below [28, 29]:

Table 2: Showing the diagnosis by the help of antibodies

Diagnosis	Antibodies
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)34,36,44,55	Unknown
Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)10,34,36,39,41,44,47,48,55,56	GM1, GM1b, GD1a, GalNAc-GD1a
MFS and GBS overlapping syndrome34,36,40,44,45,55	GD3, GT1a, GQ1b

Treatment of Guillain-Barre syndrome

GBS patient needs excellent care to prevent and manage fatal complications. Most treatments have been tried in GBS disease. GBS does not respond to treatment with oral or intravenous steroids. Many clinical trial both plasma exchange and intravenous immunoglobulin shorten recovery when its use in the early stage of neuropathy [82, 83, 84].

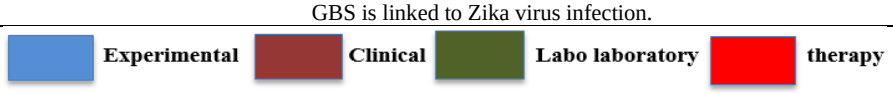
- **Immunotherapies:** GBS is an acute immune-mediated disorder of peripheral nerves and nerves roots, immunotherapies generally administered to improve outcome and prevent the disability in GBS syndrome. Many randomized clinical trials (RCTs) established that plasma exchange (PE) and intravenous immunoglobulin (IVIg) are effective in the GBS immunotherapies. Early utilization of PE and IVIG to improve neurological outcomes. Two small clinical trials showed some positive effect of PE in 1984, but in 1985 large study confirmed the effect of PE [85-90].
- **Plasma exchange (PE):** In GBS syndrome therapy related to PE is proved but the treatment not always the direct and with autonomic disturbance having the particular risk for patients, which is common in GBS syndrome. According to a case in 1959 a patient with thrombocytopenia purpura recovered after the treatment with fresh frozen plasma exchange. Indicate that PE may be advantageous for an autoimmune disorder. In carrier, particular RCTs with 245 patients PE was established and treatment with confirmation of the efficacy by subsequent larger clinical trials. In GBS case the first use of PE in 1978 treat patient with acute polyneuropathy who rapidly recovered advocating potential efficacy in GBS [91, 86].

  According to the quality standards subcommittee of the America Academy of Neurology (AAN) in 2003 provided for physician practice': when PE hasten recovery in no ambulant patients who get treatment within 4 weeks of onset and PE hasten recovery of ambulant patients with GBS who are examined within 2 weeks. PE usually administered as on plasma volume, 50Ml/kg on 5 separate occasions over 1-2 weeks [92]**.** The like hood and duration of mechanical ventilation has been reduced by the PE and also reduce the time needed to walk with assistance and increase the likelihood of fully recovering muscle strength after one year [93, 94, 95]. The mode of action of PE is not clear. It may nonspecifically remove circulating autoantibodies immune complex complement factors, proinflammatory factors like cytokines that contribute to GBS syndrome. Adverse event of PE like hypertension, septicemia, pneumonia, abnormal clotting [15, 95].

- **Intravenous immunoglobulin (IVIg):** The first RCT on the use of IVIg is effective as PE these resultant IVIG in a regimen of 0.4g/kg body weight daily for 5 consecutive days has replaced PE as the preferred treatment in many centers mainly because of convenience and availability. The use of IVIg in GBS contained 4 additional trials according to the Cochrane review. IVIgs is a hypothesized mode of action to modulate the immune system in GBS in several ways; restraints of autoantibody production and autoantibody neutralization via anti-idiotypic antibodies, inhibiting of complement activation and membrane attack complex formation modulating the expression and function of Fc receptor on macrophages and other effector cells, suppression of cytokines, chemokine and adhesion molecule modulation of T cell function and interference with pathogenic recognition and clinical observations is reduce in demyelination and axonal injury with resultant hastening of clinically recovery and better outcomes**.** Many adverse events during clinical trials of IVIg like mi, renal failure, vomiting and headache due to meningeal irritation [96-102].
- **Steroids:** It has been shown by the Cochrane systemic review of 6 trials with 587 patients that corticosteroid therapy is ineffective for treating GBS syndrome [100].
- **Ayurveda treatment:** currently many herbsise used for management of GBS cases according to the reported studies. As per *Ayurvedic* classics, this condition is correlated with *sarvāṅgagatavātavyādhi* (~*vāta* affecting all parts of the body), which is *apatarpaṇa* in nature (~diseases which are associated with deprived growth of body tissue). Hence, the choice of treatment is *santarpaṇa cikitsā* (~nourishing treatment). *Santarpaṇa bahyopakramas* (~nourishing external treatment modalities) such as *candanabalalākṣādi tailamabhyaṅga* (~oleation therapy) and *ṣaṣṭikaśālipiṇḍa sveda* (~application of processed rice) were administered along with *karma basti* (~*pittaghna* drugs processed in *kṣīra*), *śirodhārā* (gentle pouring of medicated liquid over forehead), and *bṛhatvātachitamani kalpa* whose main ingredients include *bṛhatavātachitamani*, *guḍūci* (*Tinospora cordifolia*) *sattva*, *rajatabhasma* and *sūtaśekhara rasa*. Remarkable improvement in the muscle power from zero to five of all four limbs with improvement in speech that were seen by using various mineral compounds and Ayurvedic herbs. There was no difficulty post-treatment in deglutition, sitting, standing and walking; and now the patient has near to normal movement [103-110].
- **Noval therapies:** Much effort has been made in the evolution of therapeutics that prevent the complement-dependent neuronal damage underlying GBS. Two randomized, double-blind, placebo-controlled phase 2 trials have evaluated the safety and efficacy of eculizumab – a complement factor 5 inhibitor in GBS. In the Inhibition of Complement Activation in GBS study, patients were randomized to receive IVIg with eculizumab or placebo. The small patient number precluded conclusions on efficacy, but eculizumab was deemed safe and well tolerated[111-113]. For GBS the Japanese Eculizumab Trial used the same study protocol, and randomized 23 patients to IVIg with eculizumab and 12 patients to IVIg with placebo. The predefined response rate threshold for the eculizumab group was not reached, but a larger proportion of patients in the eculizumab group were able to run at 24 weeks (74%), than in the placebo group (18%). In most patients, eculizumab was well tolerated, although a causality with two serious adverse events could not be excluded. These studies implicate that eculizumab seems safe and well tolerated, and might potentially improve outcome in GBS as add on treatment to IVIg, but larger trials are required [114].

Table 3: Showing the major milestones in Guillain–Barré syndrome (GBS) [20].

1859	**In case report of ascending paralysis, core clinicl feature is explained by Landry.**
1889	The lumbar puncture technique is developed by Essex Wynter.
1916	A report on two patients with radiculoneuritis syndrome and high level of CSF protein but low CSF white cell count a hallmark of GBS and establish the condition as distinct from other cause of flaccid paralysis by Guillain, barre and strohl.
1949	Humorally mediated injury in GBS was suggested in the pathology study of Haymaker and Kernohan's.
1955	The EAN mouse model of immune-mediated peripheral nerve inflammation is developed.
1956	Miller Fisher reports on three patients with areflexia, ophthalmoplegia and ataxia, a condition that he suggested was a variant of GBS.
1969	Cell-mediated demyelination in GBS is demonstrated by pathology study of Asbury's.
1976	Exogenous ganglioside administration in humans is linked to excess cases of GBS &Swine flu vaccination triggers fears of its association with GBS.
1978	Publication of the Asbury diagnostic criteria for GBS.
1982	Demonstration that sera from EAN mice and humans with GBS can induce experimental conduction block &Campylobacter jejuniis isolated from patients with GBS.
1984	Trials for plasma exchange establish which is effective for GBS.
1986	The first report on pure axonal GBSpublished by Feasby.
1988	Anti-ganglioside antibodies are detected in patients with GBS.
1992	Anti-GQ1b antibodies are detected in patients with Miller Fisher syndrome &Trials of IVIg show that it is effective for GBS.
1993	Campylobacter jejuni lipooligosaccharides are shown to have ganglioside-like domains &steroids are shown to be ineffective.
1996	Study demonstrates that the pathology of Chinese paralytic syndrome is the same as that of pure axonal GBS.
1997	Trials of IVIg and plasma exchange in combination demonstrate no additional benefit for GBS.
2004	Yuki develops a rabbit model of GBS induced by Campylobacter jejuni lip oligosaccharides,Anti-gangliosidecomplex antibodies are detected in patients with GBS &Trials of IVIg and steroids in combination demonstrate no additional benefit.
2005	Complement inhibitors are tested in animal model of GBS.
2012	The International Guillain–Barré Outcome Study is commenced.
2014	The Inhibition of Complement Activation in GBS study is commenced.
2015	The Japanese Eculizumab Trial for GBS is commenced.
2016	GBS is linked to Zika virus infection.



Management

- **Supportive care:** the major factors in improving mortality in GBS with the occurrence of good care and modern method. Once the initial acute stage appears passive movement of limbs and active physiotherapy, beneficial although it has never been subjected to a controlled clinical trials [93]. The backbone of the treatment is the active immune modulation with IVIg or plasma exchange in most situations because of its ease of availability and greater in patients with the unstable B.P and pulse rate [97]. In case of GBS syndrome immunotherapy has not reduced the mortality. Mortality can be caused by various reasons i.e. prolonged hospitalization or disease-related issue. The mortality can be reduced by meticulous and attentive care. Supportive care consensus guidelines have been published [101].
- **Respiratory failure in GBS:** Neuropathy respiratory paralysis can be caused by the most common peripheral i.e. GBS. In the case of respiratory failure mechanical ventilation mostly required by one-third of the patients. In this case some factors associated with facial weakness, bulparesis and neck weakness by the onset of admission of less than one week. In general, it takes 2-6 weeks to wean out of ventilator support. If pulmonary function improves it may be preferable to wait 1 more week to attempt at weaning from the ventilator.
- **Nutrition:** the introduction of the Gastric tube or nasogastric tube should be early and slowly. High energy (40-45 non-protein kcal) and high protein diet (2-2.5g/kg) have been recommended to reduce muscle wasting and assists respiratory weaning. In comparison with bolus feeding in these patients the continuous enteral feeding seems to be better tolerated.
- **Pain:** In GBS Patients pain and sensory symptoms reported in majority, but hypo motility and sedation may become a problem. NSAIDs are tried for treatment like gabapentin, carbamazepine acetaminophen [101, 103-105].

Management of dysautonomia

The significant cause of death in GBS patients is acute dysautonomia. Hypertension, postural hypotension and tachycardia is occurred by the cardiac and hemodynamic disturbances in a majority of GBS patients, this is due to excessive sympathetic over activity and parasympathetic under activity. At the peak of the deficit severe dysautonomia occurs in severe cases [115]. In the range of 100-120/min tachycardia is most common which does not require treatment. Situation to inserting a pacemaker for serious bradycardia or sinus arrest has assorted widely because of the uncertainty that exists in anticipating such events at the bedside by different ways. However, in systolic blood pressure tachycardia increased daily variation which reduced normal respiratory-induced heart rate variation and the first episode of severe Brady arrhythmia reduces the threshold for insertion of pacemaker [116, 117]. Hyperoxygenation may lead to reduction of the bradycardia or systole provoked by the endotracheal suction. In one-third of GBS patients, hypertension is seen and can be labile or be followed by hypotension. Hypertension is severe (mean pressure greater than approximately 125 mmHg) and sustained, specific therapy may be necessary. Antihypertensive with short half-lives (labetalol, esmolol or nitroprusside infusions) should be considered [118, 119]. With caution the beta-adrenergic or calcium channel blockers should be used, especially if episodes of hypertension alternate with hypotension. By maintaining intravascular volume and avoid using diuretics hypotension can be managed. Patients with a risk of hypotension should not be left unattended in a sitting or upright position. Identifiable and determined hypotension should justify the searches for other causes, such as sepsis myocardial infarction and pulmonary thromboembolism or use of narcotics or positive pressure ventilation. In 15% of severely affected GBS patients gastrointestinal motility disorder occur. Ileus is related with other features of dysautonomia (tachycardia and hypertension). Dysmotility can be effectively managed by a suspension of enteral feeds, nasogastric suctioning and erythromycin or neostigmine [97, 115].

Conclusion

On GBS, over a certain period of time significant progress has been achieved in different areas of research, which included epidemiological aspects as well as its pathogenesis. The current treatment options are largely equal to those which was already in use 20 years ago in comparison with the recent advances in to the novel treatment in GBS which has been less straightforward. Hoping that the more coordinated approaches by the international GBS research community like the formation of the inflammatory neuropathy consortium will result in new treatment and outcome trials to determine novel immunomodulatory and perhaps Neuroprotective or repair promoting agent with the goal to optimize the care for GBS patients. In the last 100 years since the first landmark description of GBS, considerable progress in understanding the nature of the disease and the mechanism that lead to its development have been made.

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