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PHYSICIANS' BOOKLET ON

GUILLAIN-BARRÉ SYNDROME

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Author's note

This booklet serves as a quick reference to provide an easy explanation regarding Guillain-Barré syndrome to doctors and medical practitioners. We hope the important and updated information that has been included in this booklet will be beneficial to everyone treating patients with Guillain-Barré syndrome.

We would like to thank CSL Behring for the support in the production of this first edition of GBS physician booklet.

CONTENTS

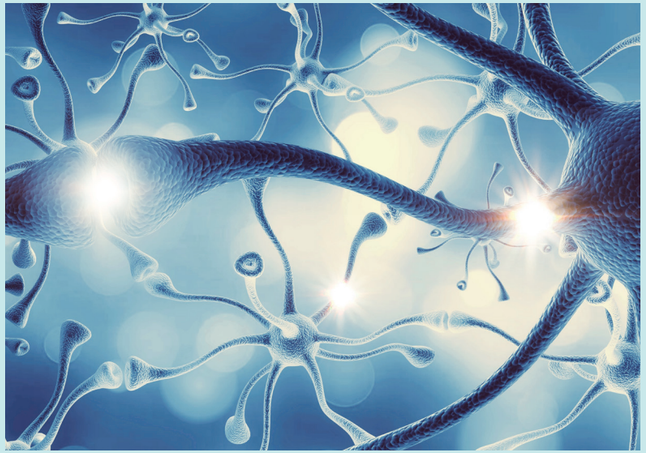
What is Guillain-Barré Syndrome?

Introduction

Guillain-Barré syndrome (GBS) is a rare, but potentially fatal, immune-mediated disease of the peripheral nerves and nerve roots that is usually triggered by infections. GBS is the most common cause of acute flaccid paralysis, monophasic illness characterized by symmetrical weakness of the limbs, and hyporeflexia or areflexia, which reaches a maximum severity within 4 weeks. Sensory disturbances and cranial nerve deficits occur in some patients.

Patients with GBS typically present with weakness and sensory signs in the legs that progress to the arms and cranial muscles, although the clinical presentation of the disease is heterogeneous and several distinct clinical variants exist. About 25% of patients develop respiratory insufficiency and many show signs of autonomic dysfunction.[1]

Diagnosis of GBS is based on the patient history and neurological, electrophysiological and cerebrospinal fluid (CSF) examinations.[2-4] Most patients with GBS do well with immunotherapy, but a substantial proportion are left with disability, and death can occur.



Epidemiology of GBS

Up to 70% of cases of GBS were caused by antecedent infections, most frequently respiratory or gastrointestinal infections. Possible links between vaccinations and the occurrence of cases of GBS have been proposed, although the evidence for this link is not strong.

Generally, no contraindication to the vaccination of patients who previously have had GBS seems to exist, except for patients who had had the disorder in the past 3 months or had vaccination-related GBS, although risk and benefit might be discussed on a case-by-case basis. The issue of seasonal variation in incidence was raised in some studies although none reported significant differences in levels of onset of GBS between seasons. Some found more cases in colder months although a cluster of cases was reported in spring and summer in Brazil, during the winter and June in the Netherlands and during autumn in Sweden.[5]

The overall incidence of GBS was between 1.1/100,000/year and 1.8/100,000/year. The incidence of GBS increased with age after 50 years from 1.7/100,000/year to 3.3/100,000/year. Lower rates reported in children (<16 years) of around 0.6/100,000/year. Unusually for an autoimmune disease, higher incidence rates have been reported in males than females.[5]

Studies have shown that the most frequent subtype in North America, Europe, USA, Canada, and Australia, up to 90% of GBS cases present as the Acute Inflammatory Demyelinating Polyneuropathy (AIDP) variant, and only 5% correspond to motor axonal variants. In Asia, South America, and Central America, however, the axonal variants of GBS [Acute Motor Axonal Neuropathy (AMAN) and Acute Motor Sensory Axonal Neuropathy (AMSAN)] account for 30% to 47% of cases.[1-3] In Asia, 70% of cases are of the axonal type (AMAN), whereas <25% of cases are the AIDP variant or other types.[4]

What are the Clinical Features of GBS?

History

A careful history indicates that there are antecedent upper respiratory or gastrointestinal infective symptoms in over 70% of patients who develop GBS. *Campylobacter jejuni*, the most common cause of acute bacterial gastroenteritis, is consistently identified as the most frequent antecedent infection, occurring in up to 30% of patients. However, only one in 1000 patients with *C. jejuni* infection develop GBS. The median time interval between onset of diarrhoea and development of neurological symptoms is 10 days, but may be as short as 3 days or as long as 6 weeks.[5]

Several other bacterial and viral infections are associated with the development of GBS. These include: *Haemophilus influenzae*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein–Barr virus and varicella zoster virus, Zika virus, and in 2020, the severe acute respiratory syndrome coronavirus 2.[7] Some of the remaining patients with no antecedent infectious symptoms may still be harbouring asymptomatic infection. For example, half the patients with *C. jejuni* do not develop gastrointestinal symptoms.

There are also non-infective associations which include parenteral gangliosides for treating peripheral neuropathy and various vaccines (eg, H1N1 influenza vaccine), which have the potential to induce molecular mimicry. Other associations include autoimmune diseases (eg, systemic lupus erythematosus), immunosuppressive drugs (e.g., anti-tumor necrosis factor [anti-TNF]) and surgery, probably reflecting the increased susceptibility to known infective triggers, some of which are asymptomatic.[5]

Association with GBS

Viral Infections
Cytomegalovirus, Zika virus Epstein–Barr virus and varicella zoster virus

Bacterial Infections
Campylobacter jejuni, Haemophilus influenzae, Mycoplasma pneumoniae

Non Infective Associations
Autoimmune disease (eg. systemic lupus erythematosus) immunosuppressive drugs, surgery and vaccines

What is the Clinical Course of GBS?

The clinical journey through GBS follows a typical pattern that can be readily divided into its constituent phases and components (figure 1).[6] The majority of patients with GBS report an infection before the onset of weakness. Antiganglioside antibodies are often detected; their levels decrease over time. Different types of antibodies are related to the preceding infection and the GBS subtype. Progressive weakness reaches its maximum within 4 weeks (often within 2 weeks). The recovery phase may last many weeks, months or even years.

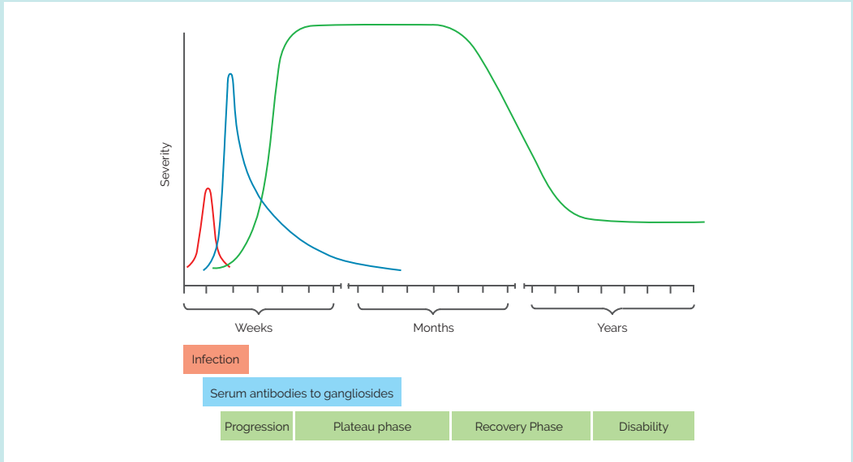


Figure 1: Guillain-Barré syndrome time course. Adapted from Hugh J Willison, Bart C Jacobs, Pieter A van Doorn. Guillain-Barré syndrome. Lancet 2016; 388: 717–27

What is the GBS Pathophysiology and Correlation with Clinical Spectrum?

Immunopathogenesis of GBS

Pathophysiology of GBS is rather complex. Molecular mimicry, antiganglioside antibodies and, likely, complement activation are believed to be involved in the pathogenesis of GBS. Infections with pathogens, such as *Campylobacter jejuni*, can trigger humoral immune and autoimmune responses that result in nerve dysfunction and the symptoms of GBS.

Lipo-oligosaccharides on the *C. jejuni* outer membrane may elicit the production of antibodies that cross react with gangliosides, such as GM1 and GD1a on peripheral nerves. The antigens targeted in AMAN are located at or near the node of Ranvier. The anti-GM1 and anti-GD1a antibodies bind to the nodal axolemma, leading to complement activation followed by membrane attack complex (MAC) formation and disappearance of voltage-gated sodium channels. This damage can lead to detachment of paranodal myelin, and nerve conduction failure.

Macrophages then invade from the nodes into the periaxonal space, scavenging the injured axons. The antigens targeted in AIDP are, presumably, located on the myelin sheath. The antibodies can activate complement, which leads to formation of the MAC on the outer surface of Schwann cells, initiation of vesicular degeneration, and invasion of myelin by macrophages (figure 2).[6]

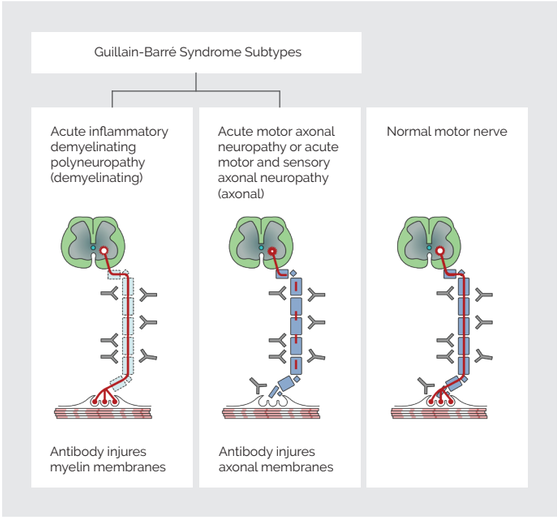


Figure 2: Major Guillain-Barré syndrome subtypes in which antibody-mediated effector pathways, including complement activation, cause glial or axonal membrane injury with consequent conduction failure. Adapted from Hugh J Willison, Bart C Jacobs, Pieter A van Doorn. Guillain-Barré syndrome. Lancet 2016; 388: 717–27

How Do You Diagnose GBS?

Diagnosis of GBS is clinical, supported by relevant investigations such as CSF analysis, electrodiagnostic studies (nerve conduction study), radiological findings (ultrasound/MRI) or anti-gangliosides testing. The most widely applied set of diagnostic criteria for GBS are the National Institute of Neurological Disorders and Stroke (NINDS) in 1978 (revised in 1990) and the Brighton Collaboration in 2011.[8,9,10] In 2019, NINDS criteria was further improved with new adaptations for a clearer description.[11]

Modified National Institute of Neurological Disorders and Stroke (NINDS) criteria for GBS [8,9,11]

Features required for diagnosis

- Progressive bilateral weakness of arms and legs (initially only legs may be involved)
- Absent or decreased tendon reflexes in affected limbs (at some point in clinical course)

Features that strongly support diagnosis

- Progressive phase lasts from days to 4 weeks (usually <2 weeks)
- Relative symmetry of symptoms and signs
- Relatively mild sensory symptoms and signs (absent in pure motor variant)
- Cranial nerve involvement, especially bilateral facial palsy
- Autonomic dysfunction
- Muscular or radicular back or limb pain
- Increased protein level in CSF; normal protein levels do not rule out the diagnosis
- Electrodiagnostic features of motor or sensorimotor neuropathy (normal electrophysiology in the early stages does not rule out the diagnosis)

NINDS criteria also included features that cast doubts on diagnosis of GBS [8,9,11]

Features that case doubt on diagnosis of GBS
• Increased numbers of mononuclear or polymorphonuclear cells in CSF (>50 × 106/l)
• Marked, persistent asymmetry of weakness
• Bladder or bowel dysfunction at onset or persistent during disease course
• Severe respiratory dysfunction with limited limb weakness at onset
• Sensory signs with limited weakness at onset
• Fever at onset
• Nadir <24 h
• Sharp sensory level indicating spinal cord injury
• Hyperreflexia or clonus
• Extensor plantar responses
• Abdominal pain
• Slow progression with limited weakness without respiratory involvement
• Continued progression for >4 weeks after start of symptoms
• Alteration of consciousness (except in Bickerstaff brainstem encephalitis)

GBS diagnostic criteria by The Brighton Collaboration GBS Working Group[10]

Due to variable availability of diagnostics resources, the group proposed 3 levels of diagnostic certainty based on available supportive laboratory testing. Highest diagnostic certainty requires the presence of a monophasic illness reaching nadir within 28 days, cerebrospinal fluid cytoalbuminologic dissociation, and electrodiagnostic evidence of neuropathy.

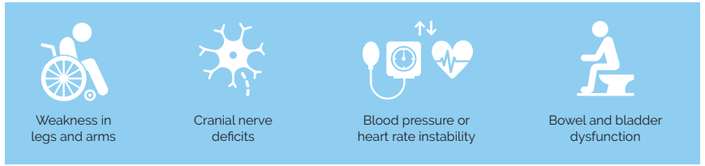
Diagnostic criteria	Level 1	Level 2	Level 3	Level 4
Bilateral and flaccid weakness of limbs	+	+	+	+/–
Diminished or absent deep tendon reflex in weak limbs	+	+	+	+/–
Monophasic course and time between onset and nadir, 12 hours to 28 days	+	+	+	+/–
Absence of alternative diagnosis for weakness	+	+	+	+
Cytoalbuminologic dissociation (ie elevation of CSF protein level above laboratory normal value and CSF total white cell count < 50cells/microL)	+	+/–	–	+/–
Electrophysiologic findings consistent with GBS	+	+/–	–	+/–

When Do You Suspect GBS?

Clinician should consider the diagnosis of GBS in patients with rapidly progresive weakness of upper or lower limbs, which may affect the cranial and respiratory muscles, in the presence of reduced or areflexia with no obvious CNS involvement or metabolic cause. GBS presentation can be heterogenous.[12] In most patients (up to two-third), there is associated history of antecedent infective illness or preceding events.[13] Majority of the GBS patient present with classical presentation of the syndrome.
A smaller proportion of GBS present as atypical variants which can be easily misdiagnosed as other neurological conditions.[11]

Classical GBS presentation

Classical GBS presents as ascending sensorimotor weakness begins in the legs and may progress to involve the arms and cranial nerves with reduced or absent of reflexes. However, tendon reflexes can be normal or even exaggerated in the initial stages.[14] More than half of the patients may develop cranial nerve deficits including facial, bulbar or extraocular motor weakness.[13]
Up to 25% of patients with classical GBS develop dysautonomia, manifests as blood pressure or heart rate instability, pupillary dysfunction, and bowel or bladder dysfunction.[14] Neuropathic pain is not uncommonly seen.[15] Typically, most patient progress to reach maximal disability within 2-4 weeks before eaching a plateau state and followed by recovery. GBS has a monophasic clinical course, although treatment related fluctuations (TRFs) and relapses occur in a minority of patients.[16]



GBS variants

Atypical GBS presentation includes those with localised weakness of a classical GBS or those with a distinct clinical presentation. In addition, atypical features of GBS also include those with asymmetry weakness and sensory signs, predominantly proximal or distal weakness and in some, normal or exaggerated reflexes. In rarer condition, GBS can also present as overlap syndrome, making diagnosis particularly challenging.[17]

Clinical classification of GBS, MFS and BBE [7]

Guillain-Barré syndrome (GBS) spectrum	Classical GBS
	Pure Motor GBS
	Pure sensory variant
	Paraparetic variant
	Bilateral facial palsy with paraesthesias
	Pharyngeal–cervical–brachial weakness
	Acute bulbar palsy
	GBS with hyperreflexia
Miller Fisher Syndrome (MFS) spectrum	Classical MFS: Ophthalmoplegia, areflexia and ataxia
	Acute opthalmoplegia
	Acute ataxic neuropathy
	Acute ptosis
	Acute mydriasis
	Acute vestibular syndrome
Bickerstaff brainstem encephalitis (BBE)	Classical BBE
	Acute ataxic hypersomnolence

Differential Diagnoses of GBS

Differential diagnoses of GBS are wide, considering the heterogenous presentation of GBS from classical ascending weakness to variants of GBS.

Classical GBS	Chronic inflammatory demyelinating polyneuropathy, Critical illness polyneuropathy, Nutritional neuropathy, Metabolic or electrolytes abnormality, Paraneoplastic neuropathy, Diphtheria neuropathy, Lyme disease, Acute flaccid myelitis, Myasthenia gravis, Porphyria, Botulism
Pure Motor GBS	Anterior horn cell disease, Multifocal motor neuropathy, Poliomyelitis
Pure sensory variant	Nutritional neuropathy, Metabolic abnormality (e.g diabetic neuropathy), Paraneoplastic neuropathy, Vasculitic neuropathy, Connective tissue related neuropathy (E.g Sjogren syndrome)
Paraparetic variant	Transverse myelitis, Cauda equina syndrome, lumbosacral radiculopathy
Bilateral facial palsy with paraesthesias	Muscle disorders, Neuromuscular junction disorders
Pharyngeal–cervical–brachial weakness	Brachial plexopathy, Motor neuron disease variants, Neuralgic amyopathy
Acute bulbar palsy	Neuromuscular junction disorders, Motor neuron disease variants
GBS with hyperreflexia	Transverse myelitis, Spinal cord lesions
Miller Fisher syndrome (MFS)	Myasthenia gravis, Central nervous system demyelinating diseases
Pure sensory ataxia	Cerebellar pathology, Paraneoplastic neuropathy, Metabolic neuropathy
Bickerstaff brainstem encephalitis	Meningitis, Encephalitis, Brainstem stroke, CNS demyelination

Laboratory investigations in GBS

In most cases of GBS, laboratory studies are not required for diagnosis. However, if available these studies are helpful in supporting and speeding up the diagnosis, especially in patients with atypical presentation.

General laboratory testing

For exclusion of infective and metabolic causes: Full blood counts, blood glucose, electrolytes, kidney and liver functions.

For identifying associated infections (Optional): Zika virus, *C. jenuni* serology, Mycoplasma serology, Hepatitis A, B, C and E, Haemophilus ınfluenzae, Epstein-Barr Virus, Cytomegalovirus.

Anti-gangliosides antibodies

With the establishment of relationship between infective pathogens, in particular *C. jejuni* infection and ganglioside antibodies in patients with GBS, serological tests to detect these antibodies are increasingly used.[1]

However, it is still largely not accessible in lower income countries.[18] Absent of anti-gangliosides antibodies does not rule out GBS. In addition, such serology tests have variable sensitivity and diagnosis accuracy depending on laboratory methods.

CSF examination

Elevated CSF protein level and a normal CSF cell count (known as albumin- cytological dissociation) is typically seen in patient with GBS.[22]

However, a normal CSF protein levels do not rule out a diagnosis of GBS. Up to 50% of the patient have normal CSF at first week after disease onset and up to 30% in the second week. [13, 19, 23]

Some patients with GBS have mild pleocytosis although this must be interpreted with care. A marked pleocytosis (>50 cells/µl) suggests other infective or inflammatory pathologies.[13,20]

Electrodiagnostic studies: Nerve conduction study (NCS) and Electromyogram

Electrodiagnostic studies are helpful in supporting the diagnosis of GBS and to classify into electrophysiology subtypes of GBS: AIDP, AMAN, and AMSAN.[21]

The typical electrodiagnostic findings in GBS reveal sensorimotor polyradiculoneuropathy or polyneuropathy, in the present of 'sural sparing pattern'.[22] In demyelinating form of GBS (AIDP), NCS typically shows prolonged latencies, reduced conduction velocities, abnormal temporal dispersion and/or partial motor conduction blocks whilst axonal form of GBS (AMAN and AMSAN) shows reduced sensory and motor evoked amplitudes.

Although ascending paralysis is seen among most GBS patient where lower limbs are affected more than the upper limbs, sural sparing pattern is the reverse, with normal sural sensory nerve action potential and an abnormal or absent median and ulnar sensory nerve action potentials. Electrodiagnostic findings are dependent on timing of the study, in which measurement can be normal when test is performed within the first week of symptoms onset. Clinician should be aware that in variants GBS such as those with localised disease, NCS findings might be unremarkable. In these patients, a repeat electrodiagnostic study 2–3 weeks is recommended.[23, 24, 25] In MFS, results of electrodiagnostic studies are usually normal or demonstrate only a reduced amplitude of sensory nerve action potentials.[17]

Imaging in GBS

Imaging in GBS include the use of Magnetic Resonance Imaging scan (MRI) (Brain, spinal cord and nerve roots) and ultrasound of peripheral nerve. MRI is helpful in excluding differential diagnosis such as central nervous system infection, inflammation or infiltrative lesions. In some GBS cases, MRI of the nerve roots may demonstrate gadolinium-enhancement which is supportive of GBS, although it is a GBS specific features and may be seen in other causes of acute flaccid myelitis.[26] Recently, ultrasound of the peripheral nerves has gained much attention as it is cheap and easily performed. On nerve ultrasound, cervical root enlargement can be seen especially in early GBS onset.[27]

How Do You Manage GBS?

Managing GBS

Intravenous immunoglobulin (IVIG) is usually the treatment of choice as it is easier to administer and more widely available. However, it is not without its complications. Reported adverse effects of IVIG include headache, liver dysfunction, hyponatraemia, acute renal failure, haemolytic anaemia and exfoliative dermatitis.

1

Whenever possible, patients should be treated in intensive care unit (ICU), where adequate resources would allow continuous cardiac and respiratory monitoring.

2

IVIG (0.4 g/kg daily for 5 days) and plasma exchange (200-250 ml plasma/kg alternate day for 5 sessions) are equally effective, started within the first 4 (preferably 2) weeks from onset who are unable to walk unaided.[28]

3

Plasma exchange may be unsuitable for patients with autonomic instability because of the large shift in fluid balance. It has also come with the cost of catheter-related sepsis.

4

Plasma exchange followed by IVIG or vice versa is not more effective than either treatment alone.[29]

5

Several randomised controlled trials had shown no significant benefit of corticosteroids for GBS.[29,30]

6

Insufficient evidence to support the efficacy of add-on intravenous methylprednisolone to IVIG-treated patients.[30]

Monitoring

- Routine measurement of respiratory function is mandatory.
- Respiratory monitoring should include observation of usage of accessory respiratory muscles, frequent check of vital capacity and arterial blood gas if necessary.[31,32]
- Monitoring with peak expiratory flow rate is not reliable as frequently this group of patients will have facial weakness that they will not be able to seal the mouthpiece tightly.
- Patient is deemed at risk of respiratory failure if the vital capacity is <15 ml/kg or <1.5 L.[32]
- Muscle strength in the neck, arms and legs should be assessed with Medical Research Council (MRC) grading scale and functional disability with GBS disability scale.[33]
- Patients should also be monitored for swallowing and coughing difficulties.
- Autonomic dysfunction (arrhythmias, blood pressure fluctuations) should be assessed with continuous heart rate and blood pressure monitoring, and cardiac rhythm monitoring with electrocardiography/telemetry. Regular monitoring of bowel and bladder function also should not be overlooked.
- Two-third of the mortality of patients with GBS occur during the recovery phase. Mostly are mostly caused by cardiovascular dysrhythmias and respiratory dysfunction including pulmonary embolism.[34,35]
- Clinicians to be vigilant during this phase and monitor the patient closely, especially those who have recently left the ICU and those with cardiovascular risk factors.

Managing complications

- Complications including sacral sores, pressure ulcers, hospital-acquired infections (for example, orthostatic pneumonia or urinary tract infections) and deep vein thrombosis can occur in bed-bound patients.
- Complications more specific to GBS, for example, the inability to swallow safely in patients with bulbar palsy; corneal ulceration in patients with facial palsy; and limb contractures, and ossification in patients with limb weakness.
- Standard practice preventive measures and treatment are recommended.
- Pain, hallucinations, anxiety and depression are also frequent in patients with GBS.
- Adequate management of complications is best undertaken by a multidisciplinary team includes nurses, physiotherapists, rehabilitation specialists, occupational therapists, speech therapists and dietitians.

Managing clinical progression

- **Insufficient response**
  Approximately 40% of patients treated with plasma exchange or IVIG do not improve within the first 4 weeks of treatment.[29,35]

  Clinicians may consider retreating the patient with the same treatment or changing to an alternative treatment, but no evidence to support this approach will improve the outcome.[36,37]

- **Treatment-related fluctuations (TRFs)**
  TRFs can occur in 6–10% of patients with GBS and are defined as disease deterioration occurring within 2 months following an initial treatment-induced clinical improvement or stabilization.[16]

  This condition might benefit from further treatment. A common practice is to repeat the full course of IVIg or plasma exchange in these patients.[16]

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- In about 5% of patients with GBS, repeated clinical deteriorations suggest a more chronic form of disease, termed acute-onset CIDP.[16]
- Acute-onset CIDP typically presents with three or more TRFs and/or clinical deterioration ≥8 weeks after disease onset.[16]

How Do You Predict the Outcome of Patients With GBS?

About 80% of patients with GBS regain the ability to walk independently at 6 months after disease onset.[13]

The probability of regaining independent walking ability can be predicted using the modified Erasmus GBS outcome score (mEGOS), based on the age at onset, preceding diarrhea and MRC sum score.[38]

GBS carries a mortality rate of 5%. Most commonly due to cardiovascular and respiratory complications, which can occur in both the acute and the recovery phase.[34]

Risk factors for mortality include advanced age and severe disease at onset.[34]

Long-term management of GBS (rehabilitation)

Patients with GBS can experience a wide range of long-term residual problems, including incomplete recovery of motor and sensory function, fatigue, pain and psychological distress.[39]

Physical function: Arranging a rehabilitation programme with a rehabilitation specialist, physiotherapist and occupational therapist is crucial towards recovery.

Fatigue: Fatigue occurs in 60–80% of patients with GBS and is often one of the most disabling complaints.[40] A graded and supervised exercise programme might be useful in reducing fatigue.[41]

Pain: Severe pain is reported in one-third of patients with GBS 1 year after disease onset.[44] Management includes encouragement of mobilization and administration of drugs for neuropathic pain.[15]

Psychological distress: Rapid loss of physical function in previously healthy individuals can be severely traumatised and cause anxiety and/or depression.

Referral to a psychologist or psychiatrist will be beneficial.[43]

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