BMJ Best Practice

Guillain-Barre syndrome

Straight to the point of care

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Summary

Guillain-Barre syndrome (GBS) is an acute inflammatory polyneuropathy that is classified according to symptoms and divided into axonal and demyelinating forms.

Two-thirds of patients have a history of gastroenteritis or influenza-like illness weeks before onset of neurological symptoms.

GBS is associated with outbreaks of Zika virus. As with other viral infections, there are occasional reports of GBS associated with coronavirus disease 2019 (COVID-19) infection, although this is very rare.

Approximately 20% to 30% of patients with GBS will develop respiratory muscle weakness requiring ventilation.

Neurophysiology is confirmatory and is abnormal in most patients, even early in the disease.

Lumbar puncture is useful, and the classic finding is elevated protein with normal cell count (albuminocytological dissociation).

Treatment combines supportive and disease-modifying therapy (high-dose immunoglobulin or plasma exchange).

Definition

Guillain-Barre syndrome (GBS) is an acute inflammatory neuropathy.[1] [2] It is a clinically defined syndrome characterised by motor difficulty, absence of deep tendon reflexes, paraesthesias without objective sensory loss, and increased cerebrospinal fluid albumin with a normal cell count (albuminocytological dissociation).[1] [3] Acute inflammatory demyelinating polyradiculoneuropathy is the most commonly encountered variant.[4]

Epidemiology

Guillain-Barre syndrome (GBS) is identified throughout the western hemisphere without geographical clustering, but with minor seasonal variations.[10] Population-based studies give crude mean annual incidence rates varying from 0.6 to 1.9 per 100,000 population. A few outbreaks have been reported, including the 1976 outbreak in the US after the swine influenza programme (although the link between the influenza immunisation and incidence of GBS is unclear).[11] [5]

GBS is slightly more common in men than women, with an estimated male-female ratio of 1.78.[5] [12]

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form in North America and Europe and accounts for 85% to 90% of cases.[13] [14] AIDP can occur at any age, although rarely in infancy, and incidence increases with age; mean age of onset is approximately 40 years.[12] [15] GBS is the most common cause of acute flaccid paralysis in children.[16]

The acute motor axonal neuropathy (AMAN) subtype of GBS is more common in Japan and China, particularly in young people. It occurs more frequently during summer.[17] Sporadic AMAN worldwide affects 10% to 20% of patients with GBS.[18]

Miller-Fisher syndrome affects between 5% and 10% of patients with GBS in western countries, but is more common in eastern Asia, affecting 25% of patients with GBS in Japan and 19% in Taiwan.[19]

GBS is associated with Zika virus outbreaks. One meta-analysis estimated that 1.23% of people with Zika virus develop GBS, and another estimated that incidence of GBS in Latin America and the Caribbean rose 2.6-fold during Zika virus outbreaks.[20] [21] One study in the Americas found that just under half of 51 deaths associated with Zika virus were related to GBS.[22]

There have been multiple reports from a number of countries of patients with confirmed coronavirus disease 2019 (COVID-19) infection developing GBS.[23] [24] [25] The reported mean age (55 to 59 years) and male predominance of patients developing GBS appear to be typical of hospitalised COVID-19 patients.[23] [24] [25] More evidence is needed about whether the incidence of GBS in patients with COVID-19 is higher than that in the general population.[24] There have also been reports of GBS after COVID-19 vaccination.[26]

Aetiology

Guillain-Barre syndrome (GBS) is characterised by an immune-mediated attack on the myelin sheath or Schwann cells of sensory and motor nerves. This is due to cellular and humoral immune mechanisms, frequently triggered by an antecedent infection.

Although genetic predisposition has not been fully established, the acute motor axonal neuropathy (AMAN) type of the disease occurs more commonly in Japan and China than in North America or Europe. Polymorphisms in genes encoding macrophage mediators (matrix metalloproteinase-9 and tumour necrosis factor-alpha) have been associated with severe weakness and poorer outcome in patients with GBS.[27] One meta-analysis suggested an association between GBS and FcgammaRIIa gene polymorphisms, and to a lesser extent with exon 2 of CD1E polymorphism, in white people.[28]

Two-thirds of patients with GBS have had infections in the 6 weeks before symptom onset, most commonly upper respiratory tract infection or gastroenteritis. The acute infectious illness is usually viral (cytomegalovirus [CMV], Epstein-Barr virus [EBV], hepatitis E), but sometimes bacterial (*Campylobacter jejuni* , *Mycoplasma* species). The most commonly identified infectious triggers include *C jejuni* (in 13% to

39% of cases), CMV (5% to 22%), EBV (1% to 13%), and *Mycoplasma pneumoniae* (5%).[29] [30] [31] *C jejuni* infection precedes about 60% to 70% of AMAN and acute motor-sensory axonal neuropathy (AMSAN) cases and up to 30% of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) cases.[32] [33]

GBS has been demonstrated in patients with confirmed coronavirus disease 2019 (COVID-19) and other human coronavirus infections.[34] All variants of GBS have been reported in COVID-19 patients.[23] [24] [25] The median interval between onset of COVID-19 symptoms and development of GBS was 11.5 days and 14 days in two systematic reviews.[23] [25] This time interval suggests a post-infectious immune-mediated mechanism, but the details have yet to be established.[23] [35]

Immunisations have been proposed to trigger GBS, but this suggestion is controversial, and was based primarily on data relating to the no longer used swine influenza vaccines (US in 1976) and the rabies vaccine containing brain material.[36] [37] However, one study found no evidence of increased risk of GBS after seasonal influenza vaccine, and cohort studies found no risk of GBS following meningococcal conjugate vaccine A, C, Y, and W135 (MCV4).[38] [39]

Epidemiological evidence indicates that the relative risk of GBS after immunisation is far lower than that following an infectious disease, especially for influenza.[40] [41] There is a comparatively higher risk for pandemic vaccines than for seasonal vaccines.[42] Similarly, there are occasional case reports of GBS associated with vaccination against COVID-19, but considering the number of vaccinations across the globe this is likely to be a relatively rare occurrence.[26]

Cases of GBS were reported following the outbreak of Zika virus in 2013, possibly secondary to molecular mimicry, with a proposed putative role for gangliosides.[43] [44] [20] [45] Several other mosquito-borne viral infections such as dengue, chikungunya, and Japanese encephalitis have also been linked to GBS.[46] [47] [48] [49]

Pathophysiology

Guillain-Barre syndrome (GBS) is an autoimmune disorder in which antibodies to gangliosides play an important role. They trigger an attack on various components of peripheral nerve myelin and sometimes even the axons.[50] [51] The mechanism for this is unclear but may be a consequence of molecular mimicry, whereby antibodies or T cells stimulated by antigenic epitopes on the infecting microbe cross-react with neural epitopes.[52] Host-generated antibodies against GM1-, GD1a-, GalNac-Gd1a-, and GD1b-related gangliosides are strongly associated with a subtype of AMAN, AMSAN, and Miller-Fisher syndrome (MFS).[17] [53] [54] [55] [56] [57] AMAN is strongly associated with antibodies against GM1, GD1a, GalNac-GDa1, and GD1b.[53] [54] [58] [59]

Pure sensory GBS may be associated with antibodies against GD1b.[9] Ganglioside complexes have been found to influence the phenotype. Antibodies against GD1a/GD1b or GD1b/GT1b may cause severe GBS, and antibodies against complexes containing GQ1b or GT1a are more likely to cause ophthalmoplegia in both GBS and MFS patients.[60]

In *C jejuni* -related infections, carbohydrate mimicry between the bacterial capsular lipooligosaccharide and specific myelin gangliosides and glycolipids is thought to induce antibodies against myelin.[61] [62]

An immune cascade occurs in AIDP with early lymphocytic infiltrates in spinal roots and peripheral nerves. Subsequent macrophage-mediated segmental stripping of myelin occurs leading to segmental demyelination and mononuclear cellular infiltration.[5] Segmental loss of the insulating properties causes profound defects

in the propagation of electrical nerve impulses, resulting in conduction block and the functional correlate of flaccid paralysis.[63] Once the immune reaction stops, repair and remyelination promptly begin, which correlate with a quick and, in most cases, complete recovery from the flaccid paralysis.[5]

AMAN can be differentiated from AIDP by autopsy findings of axonal denervation of motor and sensory nerves with no demyelination and minimal inflammation.[64] [65] The earliest demonstrable pathological change seems to be the binding of IgG and activated complement components to axolemma at nodes of Ranvier in large motor fibres.[66] Macrophages become attracted to these nodes and track underneath the detached myelin lamellae along the periaxonal space. This dissects the axon from the overlying Schwann cell and compact myelin. Axolemmas in contact with invading macrophages are focally destroyed, while axons show progressive denervative changes to the point of total disintegration.[65] *C jejuni* strains associated with the AMAN pattern of GBS are known to have GM1-like epitopes in the liposaccharide membrane.[7] Pathological studies suggest severe and selective loss of terminal motor axons, whereas the distal sensory fibres are completely intact.[67] [68]

Classification

Variants of Guillain-Barre

GBS is classified according to symptoms and is divided into axonal and demyelinating forms.

- Sensory and motor: AIDP (most common) or AMSAN.[5]
- Motor: acute motor demyelinating neuropathy or AMAN.[5]
- Miller-Fisher syndrome: ophthalmoplegia, ataxia, and areflexia (also referred to as Fisher's syndrome).
- Bickerstaff's brainstem encephalitis: similar to Miller-Fisher syndrome but also includes altered consciousness (encephalopathy) or hyper-reflexia, or both.[6]
- Pharyngeal-cervical-brachial: acute arm weakness, swallowing dysfunction, and facial weakness.[5]
- Acute pandysautonomia: diarrhoea, vomiting, dizziness, abdominal pain, ileus, orthostatic hypotension and urinary retention, bilateral tonic pupils, fluctuating heart rate, decreased sweating, salivation, and lacrimation.[7] [8]
- Pure sensory: acute sensory loss, sensory ataxia, and areflexia but no motor involvement.[9]

Case history

Case history #1

A 20-year-old woman with no significant past medical history presents with lower back pain and bilateral foot and hand tingling. Her symptoms rapidly progress over 4 days. She develops lower extremity weakness, to the point that she is unable to mobilise her legs. She reports coryzal symptoms 2 weeks ago. On examination, she has 0/5 power in her lower extremity with areflexia, but despite the paraesthesias she does not have sensory deficits. Her aminotransferases are elevated, and lumbar puncture reveals mildly elevated protein with no cells and normal glucose. She weighs 70 kg and her admission vital capacity is 1300 mL, maximum inspiratory pressure is -30 cmH_2O, and maximum expiratory pressure is 35 cmH_2O.

Approach

Diagnosis is made by pattern recognition.[86] The classic presentation is a progressive symmetrical muscle weakness affecting lower extremities before upper extremities, and proximal muscles before distal muscles, accompanied by paraesthesias in the feet and hands.[87] [88] [11] The paralysis is typically flaccid with areflexia and progresses acutely over days, with around 80% of patients reaching a nadir by 2 weeks and 97% by 4 weeks.[89]

The progressive phase is followed by a plateau phase of persistent, unchanging symptoms lasting a variable duration before recovery begins. Mild dysautonomia occurs in approximately two-thirds of patients and causes sinus tachycardia, labile blood pressure, postural hypotension, urinary retention, ileus, and very rarely life-threatening cardiac arrhythmia.[90]

Initial tests include neurophysiological evaluation, lumbar puncture for cerebrospinal fluid (CSF) analysis, spirometry, and hepatic aminotransferases.

History

Two-thirds of patients have a history of influenza-like or respiratory illness or gastroenteritis in the 6 weeks before onset of neurological symptoms.[15] [69] The most commonly presenting symptoms include a respiratory tract or gastrointestinal tract infection that has resolved by the time neurological symptoms begin, which is around 1 to 3 weeks (mean 11 days in several large studies) after the initial illness.[15]

Other reported anecdotal triggers include history of trauma, surgical procedures, immunisations, malignancy, and HIV infection.

GBS is more common in the older age groups and in males.[11]

Cases of GBS were reported following the outbreak of Zika virus in 2013.[43] [44] [20] [45] [21] Several other mosquito-borne viral infections such as dengue, chikungunya, and Japanese encephalitis have been linked to GBS.[46] [47] [48] [49] GBS has been reported in patients with confirmed coronavirus disease 2019 (COVID-19) infection and after vaccination against COVID-19.[23] [24] [25] [26]

Symptoms and signs: general

Paraesthesias in hands and feet frequently precede the onset of weakness.[11] These are usually mild and may extend proximally in the extremities. Most patients experience pain, which typically begins in the back and legs. It occurs at onset and during disease course.[91] Presence of back pain and paralysis is easily misinterpreted as cord compression, sometimes leading to unnecessary surgical intervention. Pain is a much more prominent symptom in children than in adults.[92]

Hyporeflexia or areflexia can be seen at the onset in both GBS and cord compression, but the presence of bowel or bladder dysfunction early on or the finding of a sensory level should alert the clinician to the prospect of acute myelopathy. Facial, oropharyngeal, and extraocular weakness may also occur. These cranial nerve deficits usually occur after trunk and limb involvement, but may precede them.[12]

Mild dysautonomia is common and results in sinus tachycardia, hypertension, and postural hypotension in approximately two-thirds of patients.[90] Other autonomic symptoms such as urinary retention and ileus can also occur.[93] Life-threatening cardiac arrhythmias are relatively rare.[11]

Around 20% to 30% of patients develop respiratory muscle weakness requiring mechanical ventilation.[11] [94] In children, autonomic dysfunction may be an independent risk factor for mechanical ventilation.[92] Typical signs may include dyspnoea on exertion and shortness of breath, but respiratory muscle weakness can often be asymptomatic.

Symptoms and signs: acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

Typical symptoms include acute polyradiculoneuropathy, causing progressive weakness of 2 or more limbs with reduced or absent tendon reflexes.[87] Time of onset is not more than 4 weeks, and alternative aetiologies should be absent.[87] Symptoms are predominantly proximal but may affect distal muscles. There may be motor, sensory, or mixed disturbances, with or without autonomic features. These usually follow an antecedent influenza-like illness, or respiratory or gastrointestinal infection.[51] [95]

Symptoms and signs: acute motor axonal neuropathy (AMAN)

AMAN presents as acute weakness or paralysis without any sensory loss and with reduced or absent reflexes. Most cases are preceded by *Campylobacter jejuni* infection.[17] [96] It is distinguished from AIDP by selective involvement of motor nerves, preservation of sensory fibres, and electrophysiology showing axonal features. AMAN has a more rapid progression and earlier lowest point than AIDP.[17] [97]

Symptoms and signs: acute motor-sensory axonal neuropathy (AMSAN)

This is associated with sensory and motor deficits with axonal loss.[33] [98] It often presents with fulminant paralysis and sensory loss with incomplete recovery.[64]

Symptoms and signs: Miller-Fisher syndrome (MFS)

This is characterised by impaired eye movements (ophthalmoplegia), abnormal coordination (ataxia), and loss of tendon reflexes (areflexia).[99] Occasionally ophthalmoplegia may be absent.[100] Patients with MFS may have bilateral tonic pupils.[101] [102] Up to nearly half of patients with MFS have sluggish pupils and mydriasis.[103] [102] Ptosis, and bulbar and facial palsy may occur.[103]

MFS does not cause limb or respiratory muscle weakness.[51] It is usually a self-limiting, benign condition.[103] The median period between neurological symptom onset and the disappearance of ataxia/ophthalmoplegia is between 32 and 88 days.[103]

Occasionally, an MFS-GBS overlap syndrome may give rise to limb weakness, which has a similar prognosis to that of GBS. Overlap syndromes, such as the pharyngeal-cervical-brachial variant of GBS or Bickerstaff's brainstem encephalitis, occur in 50% of patients with MFS within 7 days of disease onset.[104]

Symptoms and signs: Bickerstaff's brainstem encephalitis (BBE)

Clinical features are similar to those of MFS but also include altered consciousness (encephalopathy) or hyper-reflexia, or both.[6] BBE may be a separate clinical entity secondary to its clinical features of drowsiness, coma, hyper-reflexia, and extensor plantar responses.[105] Alternatively, it may also be a variant of MFS.[106] [107] If the MFS triad presents with drowsiness and extensor plantar response, BBE is the likely underlying disease process.[108] [109]

Symptoms and signs: pharyngeal-cervical-brachial

This presents with acute arm weakness, swallowing dysfunction, and facial weakness.[5]

Symptoms and signs: acute pandysautonomia

Presenting symptoms and signs include diarrhoea, vomiting, dizziness, abdominal pain, ileus, orthostatic hypotension, and urinary retention. GBS may be associated with bilateral tonic pupils and may involve both parasympathetic and sympathetic postganglionic neurons.[8] Other signs of dysautonomia, including fluctuating heart rate, decreased sweating, salivation, and lacrimation, may be present.[7]

Symptoms and signs: pure sensory

This presents with acute sensory loss, sensory ataxia, and areflexia, but no motor involvement.[9] It mostly affects the large sensory fibres, and may be associated with antibodies to GD1b.[9]

Investigations

If the diagnosis remains unclear despite clinical examination, anti-ganglioside antibodies, CSF analysis, and neurophysiological tests can be performed to differentiate subtypes.[108] [110] [111]

Neurophysiological evaluation

Nerve conduction studies are routinely performed and play an important role in diagnosis, subtype classification, and confirming that the disease is a peripheral neuropathy. A neurophysiological examination should be done as soon as possible.[88] [112] [113] [12] [11] At least 3 sensory nerves and 3 motor nerves with multisite stimulation F waves and bilateral tibial H reflexes need to be evaluated.[108] Early abnormalities typically include prolonged distal and F-wave latencies and reduced conduction velocities. H reflex is also prolonged or absent.[108] Evidence of demyelination is present in 85% of patients with early testing.[112]

Retrospective data indicate that a single neurophysiological examination may be diagnostically useful, provided that accurate neurophysiological criteria are employed.[114] [115] Serial electrophysiology studies may be unhelpful.[115] However, a second examination (although not always practical) is recommended in patients showing no clear demyelinating features, low amplitude distal compound muscle action potentials, or conduction block without temporal dispersion.[116] Given the dynamic nature of the disease, a second study may be of benefit in determining the subtype of GBS.[116]

Cerebrospinal fluid analysis

CSF analysis is an important laboratory aid in excluding other infectious causes and should be performed early.[11] Elevated CSF protein with normal cell count (albuminocytological dissociation) is the classic finding. However, CSF protein may be normal during the first 2 weeks of the illness, and the extent of albuminocytological dissociation may vary in different populations and with different GBS variants.[5] [89] [11] [117] Repeat lumbar puncture is warranted if the diagnosis remains in question. A retrospective study has suggested a correlation between the level of CSF protein elevation and the amount of electrophysiologically demonstrable demyelination.[118]

Cell counts are typically <5 cells/mm^3. However, up to 15% of patients with GBS may have mild pleocytosis of 5 to 50 cells/mm^3.[89] If CSF pleocytosis is present, further evaluation for HIV, Lyme disease, sarcoidosis, meningitis, or carcinomatous meningitis should be initiated.[108] [109] These tests would include HIV enzyme-linked immunosorbent assay (ELISA), Lyme serology and Western blot, CSF

Lyme antibody, CSF angiotensin-converting enzyme and a chest x-ray, CSF VDRL, CSF cytology and flow cytometry, CSF Gram stain, CSF culture, and CSF West Nile polymerase chain reaction. Further viral studies should be considered if immunosuppression is a concern.

Spirometry

Bedside spirometry should be performed every 6 hours initially. This will help triage the patient to the intensive care unit (ICU) or the regular ward. A forced vital capacity of <20mL/kg is an indication for ICU admission.[11]

Patients with bulbar dysfunction and high risk of aspiration should be intubated for airway protection and impending respiratory failure. Risk factors for progression to mechanical ventilation include rapid disease progression, bulbar dysfunction (odds ratio 17.5), bilateral facial nerve weakness, and dysautonomia.[125] [126] Other risk factors include inability to lift head (odds ratio 5.0) or inability to cough (odds ratio 9.09).[127] Algorithms or tools that predict a patient's risk of respiratory failure at admission (e.g., the Erasmus GBS Respiratory Insufficiency Score [EGRIS]) may be more reliable than individual variables.[128] [129] [11] Pulse oximetry and arterial blood gases should not be relied on, as either hypoxia or hypercapnia is a late sign and patients will decompensate very quickly.

Serology and stool culture

An increase in titres for infectious agents, including cytomegalovirus, Epstein-Barr virus, *Mycoplasma* , *Haemophilus influenzae* , and *C jejuni* , may help in establishing aetiology for epidemiological purposes but is of limited clinical use. Some data suggest that positive serological markers for *C jejuni* are associated with worse prognostic outcome.[30] [130]

Testing for *C jejuni* may be considered if there is an antecedent history of diarrhoea or if the patient has been in a region where AMAN is prevalent. Treatment with antibiotics may be indicated if there is persistent faecal excretion of the bacteria.

Anti-ganglioside antibodies

Measuring serum levels of anti-ganglioside antibodies has limited diagnostic value. A positive test result may be helpful in supporting a diagnosis, but a negative result does not rule out GBS.[11]

If clinical features suggest a less common variant, particularly MFS or the pharyngeal-cervical-brachial variant, testing for the anti-ganglioside antibodies anti-GQ1b and anti-GT1a, respectively, may have some diagnostic utility. Anti-GQ1b IgG antibodies are found in up to 90% of patients with MFS.[131] The evidence for clinical utility of other anti-ganglioside antibodies is less robust.[11]

Hepatic aminotransferases

Hepatic aminotransferases may be elevated during the first few days in patients with GBS, and often normalise by 1 to 2 weeks.[132] Presence of elevated liver enzymes also correlates with increased severity of disease and should be routinely tested and monitored.[133] If transaminases remain persistently elevated, evaluation for viral hepatitides should be considered.

Imaging

Spinal magnetic resonance imaging (MRI) may be useful when the diagnosis is unclear and electrophysiological abnormalities are equivocal. It can also be performed to exclude a disease process

involving the spinal cord (i.e., epidural abscess, transverse myelitis, spinal stenosis, spinal cord stroke, or tumour). Brain MRI abnormalities are present in 30% of patients with BBE.[106]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include preceding viral or bacterial infection.

muscle weakness (common)

- Progressive symmetrical muscle weakness usually affecting lower extremities before upper extremities and proximal muscles before distal muscles accompanied by paraesthesias in the feet and hands is typical.[87] [88] [11] The paralysis is typically flaccid with areflexia and progresses acutely over days, with around 80% of patients reaching a nadir by 2 weeks and 97% by 4 weeks.[89] Weakness evolving over >4 to 8 weeks is more consistent with chronic inflammatory demyelinating polyradiculoneuropathy.[87] [88]

paraesthesia (common)

- Paraesthesias in hands and feet occur in most GBS patients and frequently precede the onset of weakness.[5] Paresthesias may extend proximally in the extremities, but sensory abnormalities on examination are usually mild. If a distinct sensory level is noted on examination, this is unlikely to be GBS and is more likely a spinal cord process.

back/leg pain (common)

- Pain is a common feature of GBS, and may precede muscle weakness; back and leg pain is typical.[91] The presence of back pain and paralysis is easily misinterpreted as cord compression.
- Pain is a much more prominent symptom in children than in adults.[92]

respiratory distress (common)

- Typical signs may include dyspnoea on exertion and shortness of breath, but respiratory muscle weakness can often be asymptomatic. Approximately 20% to 30% of patients develop respiratory muscle weakness requiring mechanical ventilation.[11] [94]

speech problems (common)

- Facial weakness and oropharyngeal weakness occurs in around two-thirds of patients.[134] [135] Typical signs include slurred speech.

areflexia/hyporeflexia (common)

- The majority of patients are areflexic on admission, with ankle jerks and knee jerks being the most commonly affected. In some patients the areflexia/hyporeflexia may be present only in the weakest limbs. Plantar reflex should be downgoing or absent but never upgoing. Tone should be flaccid. However, all GBS variants and subtypes can present with hyper-reflexia, although this is rare.[136]

facial weakness (common)

- Occurs in around two-thirds of patients.[134] [135]

bulbar dysfunction causing oropharyngeal weakness (common)

- Together with bilateral facial weakness, bulbar dysfunction is associated with increased risk of progression to mechanical ventilation.[125] Oropharyngeal weakness occurs in around 50% of patients.[134] Typical signs include swallowing difficulty.

extra-ocular muscle weakness (common)

- Occurs in around 15% of patients.[134]

facial droop (common)

- Often occurs after trunk and limb involvement but occurs before in a small number of patients.

diplopia (common)

- Often occurs after trunk and limb involvement but occurs before in a small number of patients.

dysarthria (common)

- Often occurs after trunk and limb involvement but occurs before in a small number of patients.

dysphagia (common)

- Often occurs after trunk and limb involvement but occurs before in a small number of patients.

dysautonomia (common)

- Mild dysautonomia is common and results in sinus tachycardia, hypertension, and postural hypotension in approximately two-thirds of patients.[90] Other autonomic symptoms such as urinary retention and ileus can also occur.[93] Bladder disturbance is usually mild or absent early in the disease; if severe, cord compression should be excluded. Life-threatening cardiac arrhythmias are relatively rare.[11]
- Autonomic dysfunction in children may be an independent risk factor for mechanical ventilation.[92]

pupillary dysfunction (uncommon)

- GBS may be associated with bilateral tonic pupils and may involve both parasympathetic and sympathetic post-ganglionic neurons.[8] Up to nearly half of patients with Miller-Fisher syndrome have sluggish pupils and mydriasis.[103] [102]
- Although uncommon, light-fixed dilated pupils in GBS have been described.[137] [138] If pupils are fixed and dilated, the possibility of botulism needs to be considered.[139]
- Anisocoria (unequal pupils) may occasionally be seen; tends to accompany severe ophthalmoparesis and ptosis.

ophthalmoplegia (uncommon)

- Ataxia, areflexia, and ophthalmoplegia are the classic triad for Miller-Fisher syndrome (MFS), although not all patients with MFS have ophthalmoplegia.[99] [100] Around 30% of patients with MFS develop extremity weakness manifesting as an overlapping syndrome with classic GBS.[5]

Other diagnostic factors

ptosis (common)

- May occur in Miller-Fisher syndrome.

altered level of consciousness (common)

- Encephalopathy and hyper-reflexia may be the presenting features of Bickerstaff's brainstem encephalitis.

ataxia (uncommon)

- Characteristic feature of Miller-Fisher syndrome (MFS). A few patients with MFS present with ataxia and hyporeflexia without ophthalmoplegia.[99]

Risk factors

Strong

preceding viral illness

- Two-thirds of patients with GBS have a history of gastroenteritis or influenza-like illness in the weeks before onset of neurological symptoms.[15] [69]

preceding bacterial infection

- Approximately 60% to 70% of acute motor axonal neuropathy and acute motor-sensory axonal neuropathy cases and up to 30% of acute inflammatory demyelinating polyradiculoneuropathy cases are preceded by *Campylobacter jejuni* infection.[32] [33] *Campylobacter* -associated GBS appears to have a worse prognosis, manifested by slower recovery and greater residual neurological disability.[13] A study in Sweden estimated that the risk of developing GBS during the 2 months following *C jejuni* infection is approximately 100-fold higher than in the general population.[70]

preceding mosquito-borne viral infection

- Cases of GBS were reported following the outbreak of Zika virus in 2013.[43] [44] [45] [20] [21] A case control study from French Polynesia found that 98% of patients with GBS harboured anti-Zika virus IgG or IgM, and that the risk of GBS was 0.24 per 1000 Zika virus infections.[71] However, this risk is lower than that associated with *Campylobacter jejuni* (0.25 to 0.65 per 1000 cases) or cytomegalovirus infections (0.6 to 2.2 per 1000 cases).[5] Guidelines have been updated regarding the risk of GBS following Zika virus infection.[72] [73] Several other mosquito-borne viral infections such as dengue, chikungunya, and Japanese encephalitis have been linked to GBS.[46] [47] [48] [49]

hepatitis E infection

- There is evidence that hepatitis E virus is a risk factor for the development of GBS.[74] [75] Of patients with GBS in the Netherlands, 5% had preceding acute hepatitis E infection; in Bangladesh (where hepatitis E is endemic), this figure was 11%.[76]

Weak

immunisation

- There is some suggestion of increased risk of GBS following vaccination.[36] However, one study found no evidence of increased risk of GBS after seasonal influenza immunisation, and cohort studies found no risk of GBS following meningococcal conjugate vaccine A, C, Y, and W135 (MCV4).[39] [38] Epidemiological evidence indicates that the relative risk of GBS after immunisation is far lower than that following an infectious disease, especially for influenza.[40] [41] There is a comparatively

higher risk for pandemic vaccines than for seasonal vaccines.[42] There have been reports of GBS associated with vaccination against coronavirus disease 2019 (COVID-19).[26]

cancer and lymphoma

- Case reports link GBS with Hodgkin's disease.[77] Less commonly, other malignancies have been associated with GBS.[78] [79] [80]
- Several immune-mediated neurological complications, including GBS, have been reported in patients with cancer who are prescribed checkpoint inhibitors (eg., anti-CTLA-4 antibodies); clinicians should be aware of this risk when using these therapies.[81] [82]

older age

- Incidence increases with age. For people <30 years of age, the incidence is <1:100,000. For people >75 years of age, incidence is 4:100,000.[30] [69] The mean age of onset is approximately 40 years.[15]

HIV infection

- Anecdotal: several cases of GBS have been reported in people with HIV.[83] [84] [85]

COVID-19 infection

- GBS has been reported in patients with confirmed COVID-19 infection; more evidence is needed about whether the incidence of GBS in patients with COVID-19 is higher than that in the general population.[23] [24] [25]

male

- GBS is slightly more common in males, with an estimated male-female ratio of 1.78.[5] [12]

Investigations

1st test to order

Test	Result
nerve conduction studies • Interpretation of electrophysiology can be difficult, especially in early stages. However, clear electrophysiological evidence of demyelinating polyneuropathy is useful for outcome prediction.[112] [140] • Retrospective data indicate that a single neurophysiological examination may be diagnostically useful, provided that accurate neurophysiological criteria are employed.[114] [115] Serial electrophysiology studies may be unhelpful.[115] However, a second examination (although not always practical) is recommended in patients showing no clear demyelinating features, low amplitude distal compound muscle action potentials, or conduction block without temporal dispersion.[116] Given the dynamic nature of the disease, a second study may be of benefit in determining the subtype of GBS.[116]	**prolonged distal and F-wave latencies and reduced conduction velocities; H reflex prolonged or absent**
lumbar puncture • Classic finding is elevated cerebrospinal fluid (CSF) protein with normal cell count (albuminocytological dissociation).[11] However, CSF protein may be normal during the first 2 weeks of the illness, and the extent of albuminocytological dissociation may vary in different populations and with different GBS variants.[5] [89] [11] [117] • Extremely high protein levels (10 g/L [1000 mg/dL]) are associated with development of high intracranial pressure and papilloedema. • Cell counts are typically <5 cells/mm^3. However, up to 15% of patients with GBS may have mild pleocytosis of 5 to 50 cells/mm^3.[89] •	**elevated CSF protein, normal/slightly high lymphocytes (<50 cells/mm^3)**
LFTs • Hepatic aminotransferases may be elevated during the first few days, and often rapidly normalise by 1 to 2 weeks.[132] Elevation of hepatic enzymes is associated with more severe disease.[133] The cause is unclear. Epstein-Barr virus and cytomegalovirus infection have been suggested, but serological markers are often negative.[132]	**elevated aspartate aminotransferase and alanine aminotransferase as high as 500 U/L; bilirubin may be transiently elevated but rarely high enough to cause jaundice**
spirometry • Should be carried out at 6-hour intervals initially at the bedside. Intensive care unit monitoring and elective intubation should be considered if any of the following is present: vital capacity <20 mL/kg (odds ratio 15.0); maximal inspiratory pressure worse than -30 cmH_2O; maximal expiratory pressure <40 cmH_2O; or reduction of 30% or more of vital capacity, maximal inspiratory pressure, or maximal expiratory pressure.[125]	**may show reduced vital capacity, maximal inspiratory pressure, or maximal expiratory pressure**

Other tests to consider

Test	Result
anti-ganglioside antibody • The presence of subtype-specific anti-ganglioside antibodies may be useful when the diagnosis remains unclear despite clinical examination, cerebrospinal fluid analysis, and electrodiagnostic tests.[108] [110] [111] However, a negative result does not rule out GBS.[11] • If clinical features suggest a less common variant, particularly Miller-Fisher syndrome (MFS) or the pharyngeal-cervical-brachial variant, testing for the anti-GQ1b and anti-GT1a, respectively, may have some diagnostic utility. Anti-GQ1b antibody is found in up to 90% of patients with MFS.[131]	**MFS: GQ1b, GT1a GQ1b; MFS/GBS overlap syndrome: GQ1b, GM1, GM1a, GD1a, GalNac-GD1a; pharyngeal-cervical-brachial variant, GT1a; acute motor-sensory axonal neuropathy: GM1, GM1b, GD1a; acute motor axonal neuropathy: GM1, GM1a, GD1a, GalNac-GD1a; acute inflammatory demyelinating polyradiculoneuropathy: antibodies unknown**
serology • An increase in titres for infectious agents including cytomegalovirus (CMV), Epstein-Barr virus (EBV), *Mycoplasma* , *H influenzae* , and *C jejuni* may help in establishing aetiology for epidemiological purposes but is of limited clinical use. Some data suggest that positive serological markers for *C jejuni* are associated with worse prognostic outcome.[30] [130]	**presence of *Campylobacter jejuni* , CMV, EBV, *Mycoplasma pneumoniae* , or *Haemophilus influenzae***
stool culture • Testing for *C jejuni* may be considered if there is an antecedent history of diarrhoea or if the patient has been in regions where acute motor axonal neuropathy is prevalent.	**presence of *Campylobacter jejuni* or poliovirus (pure motor syndrome)**
HIV antibodies • Indicated if the patient is at high risk of HIV or if cerebrospinal fluid lymphocytic pleocytosis is detected (>10 cells/mm³).	**positive in HIV infection**
spinal MRI • Sensitive but non-specific. • Enhancement of the cauda equina nerve roots with gadolinium on lumbosacral MRI was found to be 83% sensitive for acute GBS and was present in 95% of typical cases.[144] • May be useful when diagnosis is unclear and electrophysiological abnormalities are equivocal. Can exclude disease processes involving the spinal cord (i.e., epidural abscess, transverse myelitis, spinal stenosis, spinal cord stroke, or tumour).	**may show enhancement of cauda equina nerve roots with gadolinium**
Borrelia burgdorferi serology • Should be performed early to aid exclusion of other causes.	**positive in Lyme disease**
cerebrospinal fluid (CSF) meningococcal polymerase chain reaction • Should be performed early to aid exclusion of other causes.	**positive in meningococcal meningitis**
CSF cytology • Should be performed early to aid exclusion of other causes.	**positive in carcinomatous meningitis**

Test	Result
CSF angiotensin-converting enzyme • Should be performed early to aid exclusion of other causes.	**positive in sarcoidosis**
chest x-ray • Should be performed early to aid exclusion of other causes.	**bilateral hilar lymphadenopathy in sarcoidosis**
CSF VDRL • Should be performed early to aid exclusion of other causes.	**positive in neurosyphilis**
CSF West Nile polymerase chain reaction • Should be performed early to aid exclusion of other causes.	**positive in West Nile virus infection**

Emerging tests

Test	Result
ultrasound imaging of peripheral nerves • An emerging technique that may help to diagnose inflammatory neuropathies, including GBS.[145] Serial nerve ultrasound studies could be useful for demonstrating nerve recovery in GBS.[146] Currently this is only available in a research setting.	**morphological alterations of the nerves may be visible, e.g., enlargement of cross-sectional area**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Transverse myelitis	• Spinal cord disorders including transverse myelitis present with asymmetrical motor or sensory loss usually involving lower extremities, early bowel or bladder dysfunction with persistent incontinence, and segmental radicular pain. • Physical examination demonstrates upper motor neuron signs (hyper-reflexia, positive Babinski's response) and a sensory level.	• Cerebrospinal fluid analysis: pleocytosis with modest number of lymphocytes and increase in total protein. • MRI shows focal demyelination with possible enhancement at the appropriate level.
Myasthenia gravis	• Early involvement of muscle groups including extra-ocular, levator, pharyngeal jaw, neck, and respiratory muscles. Sometimes presents without limb weakness. • Excessive fatigability and variation of symptoms and signs through the day is common. • Reflexes are preserved, and sensory features, dysautonomia, and bladder dysfunction are absent.	• Electrophysiological study shows normal nerve conduction and presence of decremental response to repetitive nerve stimulation. • Electromyogram shows abnormal jitter and blocking.
Lambert-Eaton myasthenic syndrome (LEMS)	• Can be difficult to differentiate because of similar clinical characteristics. • Characteristics more typical of LEMS include slower development of clinical symptoms, dry mouth, lack of objective sensory loss, rare involvement of respiratory muscle group, and potentiation of reflexes after exercise or contraction.[147]	• Electrophysiological study: hallmark is a low amplitude compound muscle action potential (CMAP) after single nerve stimulus, increase in CMAP amplitude after voluntary contraction, or repetitive stimulation at high frequencies.[147]
Botulism	• History of ingesting food tainted with botulinum toxin. • Descending paralysis begins in the bulbar muscles then the limbs, face, neck, and respiratory muscles.	• Electrophysiological study: reduced amplitude of evoked muscle potentials, increase in amplitude with repetitive nerve stimulation, and increased number of

Condition	Differentiating signs / symptoms	Differentiating tests
	• Respiratory muscles are involved with mild limb weakness, and reflexes are usually preserved. • Ptosis, dilated non-reactive pupils are present. Dilated non-reactive pupils are uncommon in GBS, but more common in botulism. • Constipation is also a characteristic feature of botulism.[147]	myopathic units, which is atypical for GBS.[147]
Polymyositis	• Presence of pain and muscle tenderness usually in the shoulder and upper arm, involvement of flexor neck muscle disproportionate to limb weakness, absence of sensory symptoms, preservation of reflexes, absence of dysautonomia, and presence of skin lesions, which are uncommon presentation for GBS.[147]	• Elevated erythrocyte sedimentation rate and creatine kinase, normal nerve conduction study, and myopathic changes with fibrillation on electromyogram. • Muscle biopsy shows muscle fibre destruction and regeneration, and lymphocyte infiltrates.[147]
Vasculitic neuropathy	• Common features include painful asymmetrical presentation of muscle weakness, uncommon involvement of cranial nerves, respiratory paralysis, and sphincter dysfunction. • Usually patients report fever, fatigue, weakness, and arthralgia.[147]	• May have elevated erythrocyte sedimentation rate. • Cerebrospinal fluid does not show albuminocytological dissociation. • Electrophysiological study shows evidence of denervation. • Nerve biopsy shows signs of inflammation and scarring.[147]

Criteria

Assessment of current diagnostic criteria for Guillain-Barre syndrome[87] [148]

Required features

- Progressive weakness in both arms and legs
- Areflexia (or hyporeflexia).

Features supportive of diagnosis

- Progression of symptoms over days to 4 weeks

- Relative symmetry
- Mild sensory signs or symptoms
- Cranial nerve involvement, especially bilateral facial weakness
- Recovery beginning 2 to 4 weeks after progression ceases
- Autonomic dysfunction
- Absence of fever at onset
- Typical cerebrospinal fluid (CSF) and electromyogram/nerve conduction studies features.

Features casting doubt on the diagnosis

- Asymmetrical weakness
- Persistent bladder and bowel dysfunction
- Bladder or bowel dysfunction at onset
- >50 mononuclear leukocytes/mm^3 or presence of polymorphonuclear leukocytes in CSF
- Distinct sensory level.

Features that rule out the diagnosis

- Hexacarbon abuse
- Abnormal porphyrin metabolism
- Recent diphtheria infection
- Lead intoxication
- Other similar conditions: poliomyelitis, botulism, hysterical paralysis, toxic neuropathy.

Electrophysiological classification of Guillain-Barre syndrome[108] [112]

Neurophysiological criteria for acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor-sensory axonal neuropathy (AMSAN), and acute motor axonal neuropathy (AMAN).

At least 3 sensory nerves and 3 motor nerves with multi-site stimulation F waves, and bilateral tibial H reflexes, need to be evaluated.

AIDP

At least 1 of the following in each of at least 2 nerves, or at least 2 of the following in 1 nerve if all others inexcitable and distal compound muscle action potential (dCMAP) >10% lower limit of normal (LLN):

- Motor conduction velocity <90% LLN (85% if dCMAP <50% LLN)
- Distal motor latency >110% upper limit of normal (ULN) (>120% if dCMAP <100% LLN)
- Proximal compound muscle action potential (pCMAP)/dCMAP ratio <0.5 and dCMAP >20% LLN
- F-response latency >120% ULN.

Newer criteria have been proposed for AIDP, which increase the sensitivity of diagnosis, and include:[114]

- At least 1 of the following in at least 2 nerves: mean corpuscular volume <70% LLN; distal motor latency >150% ULN; F-response latency >120% ULN, or >150% ULN (if distal CMAP <50% of LLN); or
- F-wave absence in 2 nerves with dCMAP ≥20% LLN or greater, with an additional parameter, in 1 other nerve; or

- pCMAP/dCMAP ratio <0.7 (excluding the tibial nerve) in 2 nerves, with an additional parameter in 1 other nerve.

AMSAN

- Diminution of muscle and sensory action potentials[64]
- None of the features of AIDP except 1 demyelinating feature allowed in 1 nerve if dCMAP <10% LLN
- Sensory action potential amplitudes less than LLN.

AMAN

- Reduction in distally evoked motor action potential amplitudes, early signs of denervation on needle, normal action potential on sensory nerves, and relatively preserved motor nerve conduction velocity.[51] [67] [68]
- None of the features of AIDP except 1 demyelinating feature allowed in 1 nerve if dCMAP <10% LLN
- Sensory action potential amplitudes normal.

Inexcitable

- dCMAP absent in all nerves or present in only 1 nerve with dCMAP <10%.

Miller-Fisher syndrome

- Reduced or absent sensory action potential response without slowing of sensory conduction velocity.[149]

Electrodiagnostic criteria for acute inflammatory demyelinating polyradiculoneuropathy[113]

Different sets of criteria have been published, including the following (sensitivity 64% to 72%):

- 150% prolongation of motor distal latency above ULN
- 70% slowing of motor conduction velocity below LLN
- 125% (150% if the distal negative-peak CMAP amplitude was 80% of LLN) prolongation of F wave latency above ULN
- Abnormal temporal dispersion (peak CMAP duration increase) in ≥2 nerves.

Hughes Scale[150]

0 - healthy

1 - minor symptoms or signs of neuropathy but capable of manual work

2 - able to walk without support of a stick but incapable of manual work

3 - able to walk with a stick, appliance, or support

4 - confined to bed or chair-bound

5 - requiring assisted ventilation

6 - dead

Identification of patients with GBS at risk of respiratory failure using the 20/30/40 rule[125]

In patients with no bulbar dysfunction, or with mild bulbar dysfunction without aspiration risk, the 20/30/40 rule should be used.

Intensive care unit monitoring and elective intubation should be considered if any of the following is present:

- Vital capacity <20 mL/kg (odds ratio 15.0)
- Maximal inspiratory pressure worse than -30 cmH_2O
- Maximal expiratory pressure <40 cmH_2O
- Reduction of 30% or more of vital capacity, maximal inspiratory pressure, or maximal expiratory pressure.

Approach

A multidisciplinary approach to the acute phase is required, combining supportive therapy and disease-modifying therapy with either high-dose intravenous immunoglobulin (IVIG) or plasma exchange.[12] IVIG and plasma exchange are equally efficacious.

Supportive therapy: respiratory management

Respiratory failure is common in GBS, and approximately 20% to 30% of patients need ventilatory support in an intensive care unit (ICU).[12] [129]

Risk factors for progression to mechanical ventilation include: short time from symptom onset to hospital admission, bulbar, neck, or facial weakness, severe muscle weakness at hospital admission, and autonomic instability.[128] [129] Algorithms or tools that predict a patient's risk of respiratory failure at admission (e.g., the Erasmus GBS Respiratory Insufficiency Score [EGRIS]) may be more reliable than individual variables.[128] [129] [11] Pulse oximetry and arterial blood gases should not be relied on, as hypoxia or hypercapnia is a late sign and patients will decompensate very quickly.

There is insufficient evidence to recommend specific methods for monitoring respiratory function, but respiratory status should be monitored in all patients.[151] Bedside spirometry, including measurement of forced vital capacity, should be performed every 6 hours initially. Early spirometry will also help triage the patient between the ICU and regular ward.

Patients with bulbar dysfunction, high risk of aspiration (i.e., infiltrates on chest x-ray), and new atelectasis on chest x-ray should be intubated early for airway protection and impending respiratory failure.

In patients with no bulbar dysfunction, or with mild bulbar dysfunction without aspiration risk, the 20/30/40 rule should be used.[125] The patient should be monitored in the ICU and elective intubation considered if any of the following is present:

- Vital capacity is <20 mL/kg
- Maximal inspiratory pressure is worse than -30 cmH_2O (negative inspiratory force)
- Maximal expiratory pressure is <40 cmH_2O
- Vital capacity, maximal inspiratory pressure, or maximal expiratory pressure is reduced by 30% or more from baseline.[125]

The reported mean duration of ventilation is 15 to 43 days, and weaning should be guided by serial pulmonary function tests (PFTs) and assessment of strength.[151] The need for tracheostomy should be addressed from week 2 onwards, especially if PFTs do not show improvement. If there is improvement of PFTs above baseline, tracheostomy may be delayed by an additional week before reassessment.[151]

Supportive therapy: cardiovascular management

Haemodynamic monitoring of pulse and blood pressure (BP) should be started on admission. Telemetry is prudent, especially if there is evidence of dysautonomia. If dysautonomia is present, continuous cardiac monitoring and placement of a Foley catheter should be initiated on admission. There are insufficient data for methods and setting of monitors, but all patients with severe disease should have their pulse and BP monitored until they are off ventilator support and have begun to recover.[17] [151]

Fluid balance should be monitored carefully, because the autonomic dysfunction renders clinical determination of hydration status very difficult. Hypotensive episodes can be managed with fluid boluses.

If BP is very labile, intra-arterial BP monitoring should be initiated. Hypertensive episodes should be treated with short-acting agents (e.g., labetalol, esmolol, nitroprusside) to prevent abrupt hypotension.

Other factors that may potentiate dysautonomia include manoeuvres such as suctioning and changing position (i.e., lying to sitting), and medicines (antihypertensive drugs, succinylcholine).[154]

Supportive therapy: deep vein thrombosis (DVT) prophylaxis

Immobility and hypercoagulability from treatments such as IVIG can increase the risk of DVT in these patients.[155] Appropriate prophylactic anticoagulation (e.g., a direct oral anticoagulant, subcutaneous unfractionated heparin or a low molecular weight heparin) and support stockings are recommended for non-ambulatory patients until they are able to walk independently.[151]

Supportive therapy: pain management

Various medications (e.g., gabapentin, carbamazepine, amitriptyline) may be helpful in the acute and long-term management of neuropathic pain associated with GBS.[151] Opioids may aggravate autonomic gut dysmotility and bladder distension, and should be used with caution.[156] [151] [157]

Choice of immunotherapy

Immunotherapy comprises IVIG or plasma exchange.

IVIG and plasma exchange are equally efficacious.[158] [11] One Cochrane review found moderate-quality evidence that, in severe disease, IVIG given within 2 weeks of disease onset expedites recovery to a similar extent as plasma exchange.[52] Combination therapy (plasma exchange followed by IVIG) is not recommended.[52] [158] [11]

IVIG is administered via peripheral intravenous infusion. It is used more frequently than plasma exchange because plasma exchange requires central venous access and is associated with tolerability issues.[159] Treatment-related complications occur less frequently with IVIG than with plasma exchange.[158]

IVIG is a pooled blood product and is associated with the risk of pathogen transmission (e.g., HIV, hepatitis B or C, Creutzfeldt-Jakob disease), although the risk is low.

IVIG can precipitate anaphylaxis in an IgA-deficient person, and is contraindicated in these patients. Plasma exchange is preferred in the presence of ongoing renal failure.

Large randomised clinical trials have established the effectiveness of plasma exchange in severe disease.[14] [160] [161] Plasma exchange is recommended for ambulatory patients >2 weeks from onset of neurological symptoms because trials with IVIG did not include these patients.[158] [162]

Evidence suggests that in adults with GBS, plasma exchange is superior to supportive care with respect to:[50]

- Mean time to recover walking with aid (primary outcome)
- Shorter time to onset of recovery (primary outcome)
- Improvement by one disability grade by 4 weeks (secondary outcome).

There is no evidence concerning the relative efficacy of plasma exchange and IVIG for treating axonal forms of GBS.

Corticosteroid monotherapy does not significantly shorten time to recovery or prevent long-term disability in patients with GBS; oral corticosteroids delay recovery compared with placebo, possibly due to harmful effects on denervated muscle.[163] [Evidence B]

Intravenous immunoglobulin (IVIG)

IVIG is recommended for:[52] [158]

- ambulatory patients ≤2 weeks from the onset of neurological symptoms
- patients who require help to walk within 2 to 4 weeks from the onset of neurological symptoms.

One small retrospective study did not find a difference in outcomes for two groups given IVIG either within 7 days of symptom onset or 7 days or more after symptom onset.[164]

A randomised controlled trial found no evidence of any benefit of a second IVIG course for patients with GBS with a poor prognosis, and there was a risk of serious adverse events. Therefore a second course of IVIG is not recommended.[165]

Plasma exchange (plasmapheresis)

Plasma exchange should be performed as early as possible:[158]

- Within 4 weeks of symptom onset for non-ambulatory patients
- Within 2 weeks of symptom onset for ambulatory patients.

Plasma exchange is most effective if started within 7 days of symptom onset, but improvement in outcome has been observed when plasma exchange was initiated up to 30 days after onset.[50] [166]

Plasma exchange should be initiated in parallel with supportive care. Two to five plasma exchanges are often needed, depending on the severity of GBS.[50] Patients undergoing plasma exchange should be closely monitored for electrolyte abnormalities and coagulopathies.

The risk of relapse during the first 6 to 12 months after symptom onset is higher with plasma exchange compared with those not treated.[50]

Rehabilitation

This is recommended in the acute phase. It comprises gentle strengthening involving isometric, isotonic, isokinetic, and manual resistive and progressive resistive exercises. Rehabilitation should be focused on proper limb positioning, posture, orthotics, and nutrition.[151] [11] A multi-disciplinary approach has been shown to improve disability and quality of life, as well as reduce fatigue.[167]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)			
ambulatory within 2 weeks of onset or non-ambulatory within 4 weeks of onset			
	without IgA deficiency or renal failure	**1st**	**intravenous immunoglobulin (IVIG)**
		plus	**supportive treatment**
		1st	**plasma exchange**
		plus	**supportive treatment**
	with IgA deficiency or renal failure	**1st**	**plasma exchange**
		plus	**supportive treatment**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

ambulatory within 2 weeks of onset or non-ambulatory within 4 weeks of onset

without IgA deficiency or renal failure

1st **intravenous immunoglobulin (IVIG)**

Primary options

» normal immunoglobulin human: 400 mg/kg/day intravenously for 5 days

» Plasma exchange and IVIG are equally efficacious. The choice between them is often institution-dependent. Combination therapy (plasma exchange followed by IVIG) is not recommended.[52] [158] [11]

» IVIG is a pooled blood product and is associated with the risk of pathogen transmission (e.g., HIV, hepatitis B or C, Creutzfeldt-Jakob disease), although low. IVIG can precipitate anaphylaxis in an IgA-deficient person. However, it is much easier to administer than plasma exchange because it is a peripheral intravenous infusion. Treatment-related complications occur less frequently with IVIG than with plasma exchange.[158]

» A randomised controlled trial found no evidence of any benefit of a second IVIG course for patients with GBS with a poor prognosis, and there was a risk of serious adverse events. Therefore a second course of IVIG is not recommended.[165]

plus **supportive treatment**

Treatment recommended for ALL patients in selected patient group

» All patients with severe disease should have their pulse and blood pressure (BP) monitored until they are off ventilator support and have begun to recover.

» Deep vein thrombosis prophylaxis: appropriate prophylactic anticoagulation (e.g., a direct oral anticoagulant, subcutaneous unfractionated heparin, or a low molecular weight heparin) and support stockings are recommended for non-ambulatory patients until they are able to walk independently.[151]

Acute

» Respiratory management: risk factors for progression to mechanical ventilation include short time from symptom onset to hospital admission, bulbar, neck, or facial weakness, severe muscle weakness at hospital admission, and autonomic instability.[128] [129] Algorithms or tools that predict a patient's risk of respiratory failure at admission (e.g., the Erasmus GBS Respiratory Insufficiency Score [EGRIS]) may be more reliable than individual variables.[128] [129] [11] Pulse oximetry and arterial blood gases should not be relied on, as hypoxia or hypercapnia is a late sign and patients will decompensate very quickly. Early intubation should be performed for patients with bulbar dysfunction, high risk of aspiration, and new atelectasis on chest x-ray. Elective intubation should be considered for patients with no or mild bulbar dysfunction if any of the following is present: vital capacity is <20 mL/kg; maximal inspiratory pressure is worse than -30 cmH_2O; maximal expiratory pressure is <40 cmH_2O; or vital capacity, maximal inspiratory pressure, or maximal expiratory pressure is reduced by 30% or more from baseline.[125] Once the patient is intubated, the need for tracheostomy should be addressed from week 2 onwards. If there is no improvement of pulmonary function tests (PFTs), percutaneous tracheostomy should be performed. If there is improvement of PFT above baseline, tracheostomy may be delayed for an additional week before reassessment.[151]

» Pain: various medications (e.g., gabapentin, carbamazepine, amitriptyline) may be helpful in the acute and long-term management of neuropathic pain associated with GBS.[168] Opioids may aggravate autonomic gut dysmotility and bladder distension, and should be used with caution.[156] [168] [157]

» Hypotension: can be managed with fluid boluses. Intra-arterial BP monitoring should be started if BP is very labile.

» Hypertension: should be treated with short-acting agents (e.g., labetalol, esmolol, or nitroprusside) to prevent abrupt hypotension.

» Rehabilitation: all patients should undergo an individual programme of rehabilitation in the acute phase, comprising gentle strengthening involving isometric, isotonic, isokinetic, and manual resistive and progressive resistive exercises. The focus is on proper limb positioning, posture, orthotics, and nutrition.[168] [11] A multi-disciplinary approach has been

Acute

shown to improve disability and quality of life, as well as reduce fatigue.[167]

1st **plasma exchange**

» Plasma exchange and intravenous immunoglobulin (IVIG) are equally efficacious. The choice between them is often institution-dependent. Combination therapy (plasma exchange followed by IVIG) is not recommended.[52] [158] [11]

» Plasma exchange should be performed as early as possible. It is most effective if started within 7 days of symptom onset, but improvement in outcome has been observed when initiated up to 30 days after onset.[50] [166]

» Two to five plasma exchanges are often needed, depending on the severity of GBS.[50]

» The dose for plasma exchange, given through a central venous catheter, is 50 mL/kg bodyweight every other day for 7 to 14 days.[169]

» During administration, patients should be closely monitored for electrolyte abnormalities and coagulopathies.

» Complications include severe infection, blood pressure instability, cardiac arrhythmias, and pulmonary embolus.[170] [171] Compared with IVIG, plasma exchange showed more instances of pneumonia, atelectasis, thrombosis, and haemodynamic difficulties.[169] Other adverse effects include hypocalcaemia.

plus **supportive treatment**

Treatment recommended for ALL patients in selected patient group

» All patients with severe disease should have their pulse and blood pressure (BP) monitored until they are off ventilator support and have begun to recover.

» Deep vein thrombosis prophylaxis: appropriate prophylactic anticoagulation (e.g., a direct oral anticoagulant, subcutaneous unfractionated heparin, or a low molecular weight heparin) and support stockings are recommended for non-ambulatory patients until they are able to walk independently.[151]

» Respiratory management: risk factors for progression to mechanical ventilation include short time from symptom onset to hospital

Acute

admission, bulbar, neck, or facial weakness, severe muscle weakness at hospital admission, and autonomic instability.[128] [129] Algorithms or tools that predict a patient's risk of respiratory failure at admission (e.g., the Erasmus GBS Respiratory Insufficiency Score [EGRIS]) may be more reliable than individual variables.[128] [129] [11] Pulse oximetry and arterial blood gases should not be relied on, as hypoxia or hypercapnia is a late sign and patients will decompensate very quickly. Early intubation should be performed for patients with bulbar dysfunction, high risk of aspiration, and new atelectasis on chest x-ray. Elective intubation should be considered for patients with no or mild bulbar dysfunction if any of the following is present: vital capacity is <20 mL/kg; maximal inspiratory pressure is worse than -30 cmH_2O; maximal expiratory pressure is <40 cmH_2O; or vital capacity, maximal inspiratory pressure, or maximal expiratory pressure is reduced by 30% or more from baseline.[125] Once the patient is intubated, the need for tracheostomy should be addressed from week 2 onwards. If there is no improvement of pulmonary function test (PFT), percutaneous tracheostomy should be performed. If there is improvement of PFT above baseline, tracheostomy may be delayed for an additional week before reassessment.[151]

» Pain: various medications (e.g., gabapentin, carbamazepine, amitriptyline) may be helpful in the acute and long-term management of neuropathic pain associated with GBS.[151] Opioids may aggravate autonomic gut dysmotility and bladder distension, and should be used with caution.[156] [168] [157]

» Hypotension: can be managed with fluid boluses. Intra-arterial BP monitoring should be started if BP is very labile.

» Hypertension: should be treated with short-acting agents (e.g., labetalol, esmolol, or nitroprusside) to prevent abrupt hypotension.

» Rehabilitation: all patients should undergo an individual programme of rehabilitation in the acute phase, comprising gentle strengthening involving isometric, isotonic, isokinetic, and manual resistive and progressive resistive exercises. The focus is on proper limb positioning, posture, orthotics, and nutrition.[151] [11] A multi-disciplinary approach has been shown to improve disability and quality of life, as well as reduce fatigue.[167]

Acute

with IgA deficiency or renal failure

1st **plasma exchange**

» If there is a contraindication to intravenous immunoglobulin - namely, IgA deficiency or ongoing renal failure - plasma exchange is preferred over IVIG.

» Ambulatory patients: plasma exchange is recommended within 2 weeks from the onset of neurological symptoms.

» Non-ambulatory patients: plasma exchange is recommended within 4 weeks from onset.[158]

» Plasma exchange should be performed as early as possible. It is most effective if started within 7 days of symptom onset, but improvement in outcome has been observed when initiated up to 30 days after onset.[50] [166]

» Two to five plasma exchanges are often needed, depending on the severity of GBS.[50]

» The dose for plasma exchange, given through a central venous catheter (Mahurkar), is 50 mL/kg bodyweight every other day for 7 to 14 days.[169] During administration, patients should be closely monitored for electrolyte abnormalities and coagulopathies.

» Complications include severe infection, blood pressure instability, cardiac arrhythmias, and pulmonary embolus.[170] [171] Compared with IVIG, plasma exchange showed more instances of pneumonia, atelectasis, thrombosis, and haemodynamic difficulties.[169] Other adverse effects include hypocalcaemia.

plus **supportive treatment**

Treatment recommended for ALL patients in selected patient group

» All patients with severe disease should have their pulse and blood pressure (BP) monitored until they are off ventilator support and have begun to recover.

» Deep vein thrombosis prophylaxis: appropriate prophylactic anticoagulation (e.g., a direct oral anticoagulant, subcutaneous unfractionated heparin, or a low molecular weight heparin) and support stockings are recommended for non-ambulatory patients until they are able to walk independently.[151]

» Respiratory management: risk factors for progression to mechanical ventilation include

Acute

short time from symptom onset to hospital admission, bulbar, neck, or facial weakness, severe muscle weakness at hospital admission, and autonomic instability.[128] [129] Algorithms or tools that predict a patient's risk of respiratory failure at admission (e.g., the Erasmus GBS Respiratory Insufficiency Score [EGRIS]) may be more reliable than individual variables.[128] [129] [11] Pulse oximetry and arterial blood gases should not be relied on, as hypoxia or hypercapnia is a late sign and patients will decompensate very quickly. Early intubation should be performed for patients with bulbar dysfunction, high risk of aspiration, and new atelectasis on chest x-ray. Elective intubation should be considered for patients with no or mild bulbar dysfunction if any of the following is present: vital capacity is <20 mL/kg; maximal inspiratory pressure is worse than -30 cmH_2O; maximal expiratory pressure is <40 cmH_2O; or vital capacity, maximal inspiratory pressure, or maximal expiratory pressure is reduced by 30% or more from baseline.[125] Once the patient is intubated, the need for tracheostomy should be addressed from week 2 onwards. If there is no improvement of pulmonary function test (PFT), percutaneous tracheostomy should be performed. If there is improvement of PFT above baseline, tracheostomy may be delayed for an additional week before reassessment.[151]

» Pain: various medications (e.g., gabapentin, carbamazepine, amitriptyline) may be helpful in the acute and long-term management of neuropathic pain associated with GBS.[151] Opioids may aggravate autonomic gut dysmotility and bladder distension, and should be used with caution.[156] [168] [157]

» Hypotension: this can be managed with fluid boluses. Intra-arterial BP monitoring should be started if BP is very labile.

» Hypertension: should be treated with short-acting agents (e.g., labetalol, esmolol, or nitroprusside) to prevent abrupt hypotension.

» Rehabilitation: all patients should undergo an individual programme of rehabilitation in the acute phase, comprising gentle strengthening involving isometric, isotonic, isokinetic, and manual resistive and progressive resistive exercises. The focus is on proper limb positioning, posture, orthotics, and nutrition.[151] [11] A multi-disciplinary approach has been shown to improve disability and quality of life, as well as reduce fatigue.[167]

Emerging

Complement activation inhibitors

A number of biological agents that inhibit various stages of complement activation are being evaluated in patients with GBS.[172] Eculizumab, a humanised monoclonal antibody that specifically binds to complement component 5, did not reach the pre-defined response rate in one small phase 2 randomised clinical trial of patients with severe GBS.[173] [174]

Other therapies

Small controlled trials of interferon beta-1a, brain-derived neurotrophic factor, and cerebrospinal fluid filtration failed to demonstrate significant benefit in patients with acute GBS.[175] One Chinese herbal product, tripterygium polyglycoside, hastened recovery compared with corticosteroids; however, given that corticosteroids are not usually beneficial in GBS, the significance of this finding is unclear.[175] Imlifidase, a cysteine protease derived from the IgG-degrading enzyme of *Streptococcus pyogenes* , is being investigated for GBS.[176] [177]

Secondary prevention

Recurrent episodes of GBS are rare, affecting 2% to 5% of patients, and no definite preventative action is recommended. However, immunisation is not recommended during the acute phase of GBS and is not suggested for a period of up to 1 year after onset. After 1 year the need for immunisation should be reviewed on an individual basis.[11]

Patient discussions

- Advise patients to contact their physician straight away with any worsening symptoms of weakness, numbness, paraesthesia, facial weakness, difficulty with swallowing or breathing, or worsening bladder function.
- Advise patients to continue with physiotherapy and occupational therapy.
- Provide information about possible long-term effects of GBS, such as fatigue, pain, and psychological problems, and encourage the patient to contact their physician if they experience any of these problems.
- Provide information about patient organisations, such as GBS/CIDP Foundation International (the international patient association for GBS). [CBS/CIPD Foundation: International patient association for GBS] (https://www.gbs-cidp.org)

Monitoring

Monitoring

Most patients show continued disease progression for up to 2 weeks, followed by a plateau phase of 2 to 4 weeks, and then recovery of function. Patients should have follow-up within 2 weeks after the acute syndrome to evaluate for relapse, at which point plasma exchange can be considered. Thereafter, follow-up is every 4 to 6 weeks for 6 months, then to 6 months for 1 year, and then yearly.

Patients should continue to have access to physiotherapy and occupational therapy, and monitoring for psychological problems should be ongoing.

Complications

Complications	Timeframe	Likelihood
respiratory failure	**short term**	**medium**
Neuromuscular respiratory function is compromised in some patients with GBS.[108] [94] Bulbar dysfunction may cause difficulty with clearing secretions, adversely affecting gas exchange and increasing the risk of aspiration. Tachypnoea, sweating, tachycardia, asynchronous movements of the chest and abdomen, and episodic use of accessory muscles of respiration indicate fatigue of respiratory muscles.[151] In the case of worsening respiratory failure, the patient should be started on invasive or non-invasive mechanical ventilation.		
bladder areflexia	**short term**	**medium**
Bladder areflexia and disturbed bladder sensation occurs secondary to dysfunction of peripheral types of parasympathetic and somatic nerve.[93] Voiding is more frequently compromised with axonal type GBS. Patients exhibit evacuation and storage disorders, bladder areflexia, and disturbed bladder sensation indicative of peripheral types of parasympathetic and somatic nerve dysfunction.[93] Maintaining an indwelling urethral catheter during the acute phase is helpful.[151]		
adynamic ileus	**short term**	**medium**
Adynamic ileus occurs secondary to dysfunction of the autonomic nervous system. Daily abdominal examination and auscultation should be performed to facilitate early detection.[151] Feeding should be suspended and nasogastric tube placed. Nasogastric feeds can be given at 10 mL/hour if the ileus is not severe. Opioids should be avoided and promotility agents are contraindicated with dysautonomia. Erythromycin or neostigmine may be helpful.[183] [184]		
paralysis	**short term**	**medium**
Up to 80% of patients are able to walk independently 6 months after disease onset, with or without treatment.[11] Treatment in the acute phase should include an individual programme of gentle strengthening involving isometric, isotonic, isokinetic, and manual resistive and progressive resistive exercises. Rehabilitation should be focused on proper limb positioning, posture, orthotics and nutrition.[151] [11]		
fatigue	**long term**	**high**
The cause and contributing factors are not fully known, but fatigue appears in part to be a sequel of forced inactivity and general muscle deconditioning.		

Complications	Timeframe	Likelihood
Supervised exercise programmes are recommended for both fatigue and functional abilities, which were measurably improved in studies.[151]		
immobilisation hypercalcaemia	**long term**	**low**
This may become evident approximately 4 months after the onset of paralysis, as in other states of immobilisation that favour resorption of the calcium.[181] Subcutaneous calcitonin combined with oral etidronate disodium has been found to be useful if sodium infusions fail.[182]		
deep vein thrombosis (DVT)	**variable**	**medium**
Immobilisation is a risk factor for the development of DVT.[185] Anticoagulation is the mainstay of therapy for the treatment of DVT. The choice of agent depends on patient factors such as hepatic function, renal function, pregnancy, presence of cancer, obesity, concomitant medications and the ability to monitor drug-drug interactions, and the risk of bleeding. Choice may also depend on individual physician or patient preference or recommendations in local guidelines. Appropriate prophylactic anticoagulation (e.g., a direct oral anticoagulant, subcutaneous unfractionated heparin, or a low molecular weight heparin) and support stockings are recommended for non-ambulatory patients until they are able to walk independently.[151]		
psychological problems	**variable**	**medium**
Distress, anxiety and depression have been reported following GBS. Early recognition and management of psychological problems is important.[11] Referral to a psychologist or psychiatrist may benefit some patients. Psychological problems may persist after physical recovery is complete.[168]		

Prognosis

The overall prognosis for patients with GBS is good, with approximately 85% of survivors making a good functional recovery. Miller-Fisher syndrome has a better prognosis than other GBS subtypes, and most patients recover completely without treatment within 6 months.[11]

Recovery from severe disease may be prolonged, but most patients regain the ability to walk independently.[178] Up to 80% of patients are able to walk independently 6 months after disease onset, with or without treatment.[11] A majority of severely disabled patients with acute motor axonal neuropathy have been found to walk independently within a few years.[2]

Factors associated with poorer outcome include more severe weakness, rapid onset, older age, muscle wasting, electrically inexcitable nerves, and preceding diarrhoeal illness.[1] [179] [69]

Most patients with a poor outcome have been mechanically ventilated. Mortality of 20% has been demonstrated in these patients.[178]

Acute and long-term disability appear to be associated with axonal involvement and a Hughes score ≥2 at the lowest point.[180]

Long-term symptoms reported by patients who have recovered from acute GBS include neuropathic pain, fatigue, and muscle weakness.[11]

Diagnostic guidelines

United Kingdom

Zika virus and Guillain-Barré syndrome (https://www.gov.uk/guidance/zika-virus-and-guillain-barre-syndrome)

Published by: Public Health England **Last published:** 2017

Electrophysiological classification of Guillain-Barré syndrome (https://www.ncbi.nlm.nih.gov/pubmed/9818934)

Published by: Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group **Last published:** 1998

Europe

Diagnosis and treatment of Guillain-Barre syndrome in childhood and adolescence: an evidence- and consensus-based guideline (https://pubmed.ncbi.nlm.nih.gov/31941581)

Published by: German-Speaking Society of Neuropediatrics (GNP); Association of Scientific Medical Societies (AWMF) **Last published:** 2020

Diagnostic and classification criteria for the Guillain-Barré syndrome (https://www.ncbi.nlm.nih.gov/pubmed/11306855)

Published by: GBS-consensus group of the Dutch Neuromuscular Research Support Centre **Last published:** 2001

International

Diagnosis and management of Guillain-Barré syndrome in ten steps (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6821638)

Published by: ZikaPLAN **Last published:** 2019

Assessment and management of Guillain-Barré syndrome in the context of Zika virus infection (https://www.who.int/publications/i)

Published by: World Health Organization **Last published:** 2016

Treatment guidelines

United Kingdom

Zika virus and Guillain-Barré syndrome (https://www.gov.uk/guidance/zika-virus-and-guillain-barre-syndrome)

Published by: Public Health England **Last published:** 2017

Europe

Diagnosis and treatment of Guillain-Barre syndrome in childhood and adolescence: an evidence- and consensus-based guideline (https://pubmed.ncbi.nlm.nih.gov/31941581)

Published by: German-Speaking Society of Neuropediatrics (GNP); Association of Scientific Medical Societies (AWMF)

Last published: 2020

International

Diagnosis and management of Guillain-Barré syndrome in ten steps (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6821638)

Published by: ZikaPLAN

Last published: 2019

Assessment and management of Guillain-Barré syndrome in the context of Zika virus infection (https://www.who.int/publications/i)

Published by: World Health Organization

Last published: 2016

North America

Practice parameter: immunotherapy for Guillain-Barré syndrome (https://www.aan.com/Guidelines/Home/ByTopic?topicId=19)

Published by: American Academy of Neurology

Last published: 2003 (reaffirmed 2022)

Online resources

1. CBS/CIPD Foundation: International patient association for GBS (https://www.gbs-cidp.org) *(external link)*

Evidence tables

What are the benefits and harms of corticosteroids in people with Guillain-Barre syndrome?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Clinical Answers

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.1497/full)

Evidence B *

Confidence in the evidence is moderate or low to moderate where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes.

Population: Adults with Guillain-Barre syndrome
Intervention: Corticosteroids (oral prednisolone or intravenous methylprednisolone)
Comparison: Placebo or no treatment

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Disability grade change after four weeks	No statistically significant difference	Moderate
Disability grade change after four weeks: oral regimens	Favours comparison	Very Low
Disability grade change after four weeks: intravenous regimens	No statistically significant difference	Moderate
Death or disability (inability to walk without aid) after one year	No statistically significant difference	Moderate
Proportion of patients who relapsed during the first year	No statistically significant difference	GRADE assessment not performed for this outcome
Adverse events: diabetes mellitus requiring insulin	Occurs more commonly with corticosteroids compared with placebo or no treatment (favours comparison)	High
Adverse events: hypertension	Occurs more commonly with placebo or no treatment compared with corticosteroids (favours intervention)	High

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Other adverse events: new infection treated with antibiotics or gastrointestinal haemorrhage [a]	No statistically significant difference	GRADE assessment not performed for this outcome

Note

The Cochrane Clinical Answer (CCA) notes that adults with Guillain-Barre syndrome were given oral prednisone (4 RCTs, N=120) or intravenous methylprednisolone (2 RCTs, N=467). See the CCA for more information on the different dosing regimens.

[a] Results reported narratively

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016 Aug 13;388(10045):717-27. Full text (https://www.doi.org/10.1016/S0140-6736(16)00339-1) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26948435?tool=bestpractice.bmj.com)
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