Guillain-Barré syndrome

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Guillain-Barré syndrome is the most common and most severe acute paralytic neuropathy, with about 100 000 people developing the disorder every year worldwide. Under the umbrella term of Guillain-Barré syndrome are several recognisable variants with distinct clinical and pathological features. The severe, generalised manifestation of Guillain-Barré syndrome with respiratory failure affects 20–30% of cases. Treatment with intravenous immunoglobulin or plasma exchange is the optimal management approach, alongside supportive care. Understanding of the infectious triggers and immunological and pathological mechanisms has advanced substantially in the past 10 years, and is guiding clinical trials investigating new treatments. Investigators of large, worldwide, collaborative studies of the spectrum of Guillain-Barré syndrome are accruing data for clinical and biological databases to inform the development of outcome predictors and disease biomarkers. Such studies are transforming the clinical and scientific landscape of acute autoimmune neuropathies.

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Introduction

The clinical journey through Guillain-Barré syndrome follows a typical pattern that can be readily divided into its constituent phases and components (figure 1).[1] Demyelinating and axonal forms of the syndrome occur in varying proportions across different geographical regions, and clinical variants, such as Miller Fisher syndrome, are readily definable.[2] Within the typical disease course are many less well understood biological variations, which are considered chronologically in this Seminar.

First, Guillain-Barré syndrome is usually preceded by infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots.[3,4] Molecular mimicry between microbial and nerve antigens is clearly a major driving force behind the development of the disorder, at least in the case of *Campylobacter jejuni* infection. However, the interplay between microbial and host factors that dictates if and how the immune response is shifted towards unwanted autoreactivity is still not well understood.[5] Furthermore, genetic and environmental factors that affect an individual's susceptibility to develop the disease are unknown.[6] Unwanted autoimmunity does not arise in most individuals (>99%) exposed to an immune stimulus as a result of Guillain-Barré syndrome-associated infections such as *C jejuni*.[7]

The acute progression of limb weakness, often with sensory and cranial nerve involvement 1–2 weeks after immune stimulation, proceeds to its peak clinical deficit in 2–4 weeks.[8] When patients present with rapidly progressive paralysis, the diagnosis of Guillain-Barré syndrome needs to be made as soon as possible. Although establishment of the diagnosis in typical cases is usually straightforward, there are many clinical and investigative components to consider, especially in atypical cases. The diagnosis is largely based on clinical patterns, because diagnostic biomarkers are not available for most variants of the syndrome. Identification of biomarkers and establishment of their pathophysiological roles, if any, in experimental models has been a major research challenge.[9,10] All patients with Guillain-Barré syndrome need meticulous monitoring and supportive care.[11] Early initiation of intravenous immunoglobulins (IVIg) or plasma exchange is of proven benefit and crucial, especially in patients with rapidly progressive weakness.[12] Because a quarter of patients need artificial ventilation and many develop autonomic disturbances, many patients need admission in the high or intensive care setting. Symptoms peak within 4 weeks, followed by a recovery period that can last months or years, as the immune response decays and the peripheral nerve undergoes an endogenous repair process.

Efforts focus on the measurement and prediction of clinical course and outcome to improve the care and treatment of individual patients.[13] Good prognostic models have been developed, but additional studies are needed to investigate whether these prognostic factors differ between different disease subgroups and areas in the world. In parallel, prognostic biomarkers now need to be developed to better predict outcomes and guide action, such as personalised treatment refinements in acute management.[14] Finally, the impact of Guillain-Barré syndrome on individuals and as a global health issue is discussed alongside efforts to create evidence-based uniformity in the management of affected patients in different health-care settings.

Epidemiology and preceding infections

Most studies that estimate incidence rates of Guillain-Barré syndrome were done in Europe and North America, and showed a similar range of 0·8–1·9 (median 1·1) cases per 100 000 people per year.[15] The annual incidence rate of

Search strategy and selection criteria

We searched the entire Cochrane Library, MEDLINE, and PubMed using the search term "Guillain-Barré syndrome". We mainly selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those papers we judged relevant. Review articles are cited to provide readers with more details and references than can be provided in this Seminar.

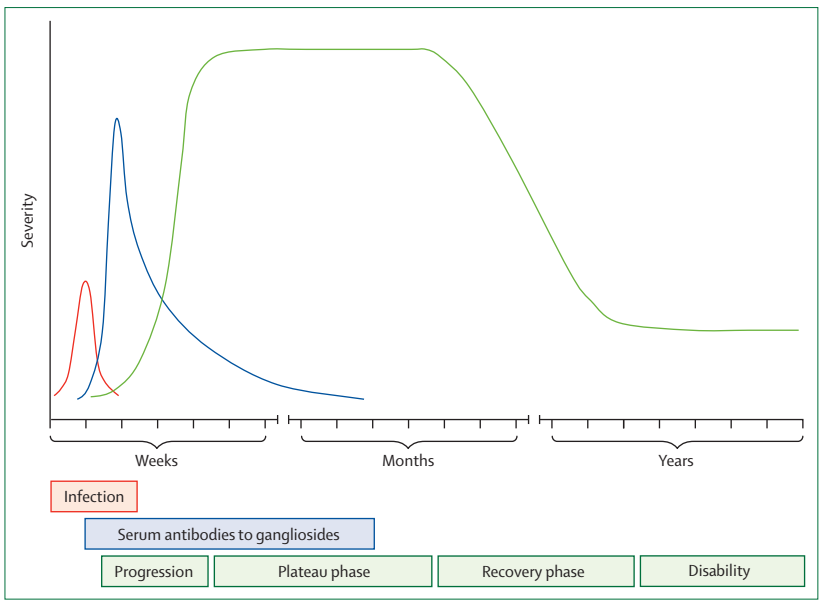

Figure 1: **Guillain-Barré syndrome time course**

Guillain-Barré syndrome increases with age (0·6 per 100 000 per year in children and 2·7 per 100 000 per year in elderly people aged 80 years and over) and the disease is slightly more frequent in males than in females. Seasonal fluctuations, presumably related to variations in infectious antecedents, have been reported, but these observations are rarely statistically significant.[16] Reports from several geographical areas have been published in the past 5 years suggesting that the local incidence rate of the disorder could be higher in some areas, which is possibly related to higher rates of exposure to infectious organisms.[17] Several outbreaks of Guillain-Barré syndrome have been reported, most recently in relation to *C jejuni* infections.[18] The disorder can affect several family members, but this is very unusual, might represent a chance finding, or might be caused by a common antecedent infectious history or unknown heritable factors.[19,20] Equally, few infected individuals (estimated at <1%) will mount the specific humoral immune response that drives the development of Guillain-Barré syndrome in *C jejuni* outbreaks.[21] Overall, based on the incidence rate and life expectancy, the estimated lifetime risk of developing Guillain-Barré syndrome for any individual is less than one in 1000.

Guillain-Barré syndrome is a typical post-infectious disorder, as shown by the rapidly progressive, monophasic disease course (<1 month) shortly after infection, usually without relapse. Two-thirds of adult patients report preceding symptoms of a respiratory or gastrointestinal tract infection within 4 weeks of onset of weakness.[22] Many different preceding infections have been identified in patients with the disorder, but only for a few microorganisms has an association been shown in case-control studies. *C jejuni* is the predominant infection, found in 25–50% of the adult patients, with a higher frequency in Asian countries.[23,24] Other infections associated with Guillain-Barré syndrome are cytomegalovirus (CMV), Epstein-Barr virus, influenza A virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*.[22,25] An association of Guillain-Barré syndrome with hepatitis E has been identified in patients from both the Netherlands and Bangladesh.[26,27] An emerging relation between Guillain-Barré syndrome and acute arbovirus infection including Zika and chikungunya is being closely monitored and is the subject of major interest as the global epidemic spreads. As further information emerges from epidemiological monitoring in case-control studies, the precise incidence data for arbovirus-associated Guillain-Barré syndrome will become clear.[28] The nature of the preceding infection affects the clinical phenotype and prognosis—for example, *C jejuni* infections are usually associated with a pure motor axonal form of Guillain-Barré syndrome, more severe limb weakness, and a serological antibody response directed against GM1 and GD1a gangliosides.[29,30] These patients generally have a poorer outcome. Whether the preceding infections of childhood Guillain-Barré syndrome are different has not been established.

Cases of Guillain-Barré syndrome have also been reported shortly after vaccination with Semple rabies vaccine and various types of influenza A virus vaccine. During the 1976 vaccination campaign for H1N1 influenza A virus, roughly one in 100 000 people who had been vaccinated developed Guillain-Barré syndrome.[31] Although a similar association was suggested for the H1N1 influenza A vaccination in 2009, extensive studies showed only 1·6 excess cases of Guillain-Barré syndrome per 1 000 000 people vaccinated, a frequency similar to all seasonal flu vaccinations.[32,33] Vaccination might, in fact, reduce the chance of an individual developing Guillain-Barré syndrome after natural infection with influenza A, which is itself a possible candidate to precipitate the disorder. A commonly asked clinical question is whether vaccination increases the risk of Guillain-Barré syndrome recurrence in previously affected individuals; this hypothesis seems not to be the case.[34] In a survey, none of the 106 patients with Guillain-Barré syndrome who had been vaccinated against influenza (range of vaccinations per person 1–37 times, total 775 vaccinations) reported a recurrence of Guillain-Barré syndrome after the vaccination.[35]

Generally, no contraindication to the vaccination of patients who previously have had Guillain-Barré syndrome seems to exist, except for patients who had had the disorder in the past 3 months or had vaccination-related Guillain-Barré syndrome, although risk and benefit might be discussed on a case-by-case basis.

Pathophysiology and immunopathology

Until 20 years ago Guillain-Barré syndrome was regarded as a homogeneous disorder, the outcome of which varied according to severity. This variation was believed to be largely caused by the extent of bystander axonal injury

arising secondarily to adjacent demyelination, rather than fundamental pathophysiological differences in the types of Guillain-Barré syndrome between individuals.[36] Peripheral nerve remyelination is a functionally effective, natural repair process, whereas axonal regeneration is slow, and can be irreversible if widespread along the whole length of a nerve fibre. The advance in understanding that changed this viewpoint was the appreciation that distinct, clinical-pathological phenotypes could be delineated within the Guillain-Barré syndrome spectrum, the main phenotypes of which are termed acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy (figure 2). Although this distinction of Guillain-Barré syndrome phenotypes does not negate the idea of bystander axonal injury, it does clarify the point that axons themselves can be the primary target for autoimmune injury, rather than being injured as a secondary phenomenon.[37] Clinical variants such as Miller Fisher syndrome are now classified within the Guillain-Barré syndrome family of disorders. As shown by the descriptive terms, immune injury specifically takes place at the myelin sheath and related Schwann-cell components in acute inflammatory demyelinating polyneuropathy, whereas in acute motor axonal neuropathy, membranes on the nerve axon (the axolemma) itself are the primary target for immune-related injury. Classification into acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy was first based on electrophysiological and pathological studies, and was subsequently supported by the identification of specific antibody biomarkers for acute motor axonal neuropathy, directed against neuronal membrane gangliosides (notably GM1 and GD1a).[38] This polarisation has been the cornerstone on which many detailed clinical and basic studies were based, many of which were done on cohorts from Asia, where acute motor axonal neuropathy seems to be more prevalent than in western Europe, owing in part to different geographical patterns of *C jejuni* infection. However, this cannot be the whole explanation as in the UK and the Netherlands at least 25% of Guillain-Barré syndrome cases are preceded by *C jejuni* infection, yet axonal cases are proportionally fewer than demyelinating ones, a finding that cannot be explained by differences in serological assays as comparative studies have shown.[39]

In parallel with, and in part due to the dichotomisation of Guillain-Barré syndrome into acute motor axonal neuropathy and acute inflammatory demyelinating polyneuropathy, the existing body of evidence has emerged that the disorder is mainly a humorally-mediated, rather than T-cell-mediated disorder, at least in the progressive phase of nerve injury. The extent to which T cells might be involved in the induction phase of the disease, during which the immune response is generated, remains uncertain, and continues to be explored in new models.[40] Few studies now use the myelin protein-specific T-cell-mediated experimental allergic neuritis model of Guillain-Barré syndrome that dominated the preclinical field for 20 years, compared with newer antibody-mediated models

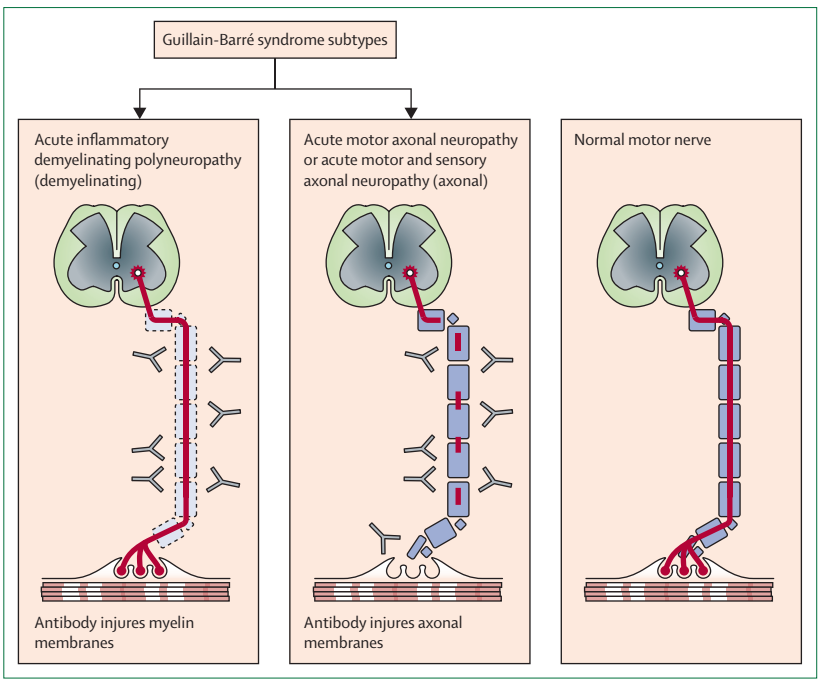

Figure 2: **Major Guillain-Barré syndrome subtypes in which antibody-mediated effector pathways, including complement activation, cause glial or axonal membrane injury with consequent conduction failure**

in rabbit and mouse. Because of these data from the new models, acute motor axonal neuropathy is thought of as an antibody-mediated attack on the nerve axolemma driven by molecular mimicry between microbial and axolemmal surface molecules.[41,42] The molecular mimics are glycans (ie, sugars) expressed on lipooligosaccharides (LOS) of preceding infectious organisms, notably *C jejuni*, that are capable of inducing antibody responses to these carbohydrate antigens.[5] Anti-carbohydrate antibody responses are believed to be largely independent of T cells. Anti-LOS antibodies can then bind to structurally identical glycans present on nerve gangliosides. Anti-ganglioside antibodies in acute motor axonal neuropathy are complement-fixing, of IgG1 and IgG3 subclass, and mainly bind to GM1 and GD1a gangliosides.[43] In animal models, they induce axonal injury by fixing complement, recruiting macrophages, and depositing membrane attack complex in the axolemmal membrane.[44] This immunological cascade disrupts the anatomical and physiological integrity of exposed nerve membranes in nerve terminals and nodes of Ranvier, causing a nerve conduction blockade that is either reversible or, in severe cases, results in severe, widespread axonal degeneration with poor recovery. A similar model is proposed for Miller Fisher syndrome associated with anti-GQ1b antibodies,[45] in which GQ1b ganglioside is the antigenic target, and is disproportionately enriched in the motor nerves that innervate extraocular muscles.[46]

In view of the high incidence of *C jejuni* infections in the general population, one might ask why so few people develop acute motor axonal neuropathy after *C jejuni*

infection. Two possible reasons could account for the low number of people who develop acute motor axonal neuropathy. First, only a small proportion of *C jejuni* strains have ganglioside mimics on their LOS—most strains bear other glycans.[47] Second, most individuals who have been exposed to *C jejuni* maintain immunological tolerance to the self-glycans on LOS, and instead mount a projective immune response against other components of the bacterial surface. Why certain individuals break tolerance and enter an autoreactive state is not known at present. Unlike T-cell tolerance, the mechanisms underlying B-cell tolerance to T-cell-independent antigens, including gangliosides, are not well studied.[5]

By contrast with acute motor axonal neuropathy, the immunological cascade involved in acute inflammatory demyelinating polyneuropathy is less well understood for various reasons. First, a wider range of immune stimulants cause acute inflammatory demyelinating polyneuropathy compared with acute motor axonal neuropathy, which includes bacterial and viral infections, and vaccines. Second, specific antibody biomarkers have yet to be characterised, despite widespread screening efforts to identify the putative nerve antigens. At present, a wider range of anti-nerve autoantibodies directed at both proteins and glycolipids could be responsible for acute inflammatory demyelinating polyneuropathy immunopathology than is the case for acute motor axonal neuropathy or Miller Fisher syndrome. Alternatively, nerve specific T cells, directed against as yet unknown antigens might play a greater part in acute inflammatory demyelinating polyneuropathy than is known at present. Historically, few studies have shown T-cell and B-cell responses to compact myelin proteins, including P0, P2, and PMP22, although these responses have been found in small numbers of cases.[48] Antibodies against proteins in the specialised domains at the node of Ranvier, including gliomedin, contactin, TAG-1, moesin, and neurofascin have been identified.[49] For example, a high proportion of antibodies against moesin, a component of the ezrin–radixin–moesin cytoplasmic complex in Schwann-cell microvilli that surround the nodal axolemma, have been reported in cases of acute inflammatory demyelinating polyneuropathy triggered by CMV infection,[50] although this result has not been replicated.[51] Nerve glycolipids expressed in glial membranes, including myelin, are prime candidates as important antigens in acute inflammatory demyelinating polyneuropathy.[52] Antibodies against the glycolipid LM1, sulphoglucuronosyl paragloboside, galactocerebroside, and sulfatide are found in a small proportion of patients with acute inflammatory demyelinating polyneuropathy.[53] In addition to being present in axonal membranes, some gangliosides (including GM1 and GQ1b) are expressed in glial membranes at the node of Ranvier, where they might mediate paranodal demyelination that causes the pathophysiological features of acute inflammatory demyelinating polyneuropathy.[54]

An intriguing, new area for exploration that originally emerged from Japanese Guillain-Barré syndrome studies has highlighted the notion that glycolipid domains, composed of multiple glycolipid and lipid components, can associate to form neoantigens that are not present in any single molecule.[55] These so-called anti-complex antibodies only bind heteromeric or multimeric lipid complexes and are difficult to detect. In addition to being found in some cases of acute motor axonal neuropathy, they might be widely present, but as yet, undiscovered in acute inflammatory demyelinating polyneuropathy. Studies investigating these antibodies are continuing and involve the development of both technical platforms and study design.[56,57]

Although the distinction between acute motor axonal neuropathy and acute inflammatory demyelinating polyneuropathy is conceptually clear, the margins might be more blurred than originally thought.[58] Electrophysiological methods are the mainstay of clinical investigation. A substantial proportion of acutely diagnosed patients with Guillain-Barré syndrome cannot be classified into a category, either because the tractable nerves (ie, the upper and lower limb nerves that can be readily accessed by surface electrodes used in clinical electrophysiology) are so severely affected that they are inexcitable, or are physiologically normal; both states are uninformative for classification as acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy. Furthermore, electrophysiological recordings are ambiguous, change during the clinical course in any one individual, and yield an acute inflammatory demyelinating polyneuropathy pattern early on and an acute motor axonal neuropathy pattern later (reversible conduction block).[59,60] Thus, inflammatory injury of either glial or axonal membranes (or both simultaneously) in the nodal complex might result in very similar electrophysiological features of reversible conduction failure.

The molecular architecture of the nodal complex, which consists of specialised nodal, paranodal, and juxtaparanodal domains that mediate glial–axonal interactions, has been well characterised and provides a foundation for the study of the fine details of Guillain-Barré syndrome pathogenesis from a nodal perspective.[61] Although yet to be established, immune responses focused on the nodal complex probably underlie much of the pathogenic cascade that takes place in Guillain-Barré syndrome, and the term nodo-paranodopathy has been coined to emphasise the focus on this site.[62] As noted previously, the nodal area is richly decorated with potential antigens, including proteins and glycolipids, and is functionally very sensitive to pathological perturbations induced by antibody deposits, complement activation, and macrophage recruitment. Nodal conduction block, of glial or axonal origin, can arise quickly, but functionality can be restored in equally short time periods through local repair of injured membranes. Conversely, complete axonal

transaction (which is always followed by Wallerian degeneration of the distal stump),[63] especially if proximally located in the nerve roots at a long distance from the innervation target, will be a permanent irreparable injury because regeneration cannot effectively occur over long distances. Although these considerations have clinical relevance, prediction of how they might affect outcome in individual cases is difficult, and there are no specific therapeutic implications at present.

Clinical classification and diagnosis

In typical Guillain-Barré syndrome, rapidly progressive bilateral weakness is the key presenting symptom in most patients (panel 1).[1,8,65,66] Weakness is classically described as ascending, and usually starts in the distal lower extremities, but can start more proximally in the legs or arms. The latter pattern can give the false clinical impression of a pyramidal lesion (ie, at the level of the spinal cord or above), but can be easily explained by focal conduction block at the level of the lumbar and cervical nerve roots, rather than along the length of the nerve fibre. A small number of patients present with paraparesis, which can remain during the course of the disease.[67] Others might present with cranial nerve involvement resulting in facial, oculomotor, or bulbar weakness, as in Miller Fisher syndrome, which might then extend to involve the limbs. In addition to weakness, patients might initially have sensory signs, ataxia, and features of autonomic dysfunction. Muscle pain or radicular pain, often but not always in the spinal region, is another frequent initial sign, which can complicate the diagnosis because pain can precede weakness in about a third of patients.[68] Symptoms of preceding infection might be too vague to add to the clinical presentation, but could be more informative, especially in the case of florid gastroenteritis. Most patients have, or develop, reduced tendon reflexes in the affected limbs. Reflexes can initially be normal especially in pure motor and axonal forms of the disorder or in a few cases, even be hyper-reflexic.[69] According to various diagnostic criteria for Guillain-Barré syndrome, patients can have progression of weakness within 4 weeks. Most patients, however, reach the nadir within 2 weeks.[8] Progression can last up to 6 weeks after onset (subacute Guillain-Barré syndrome) in some rare cases.[70] During the progressive phase, 20–30% of patients develop respiratory failure and need ventilation at an intensive care unit (ICU).[8] The clinical condition of at least 25% of patients deteriorates during or shortly after treatment with IVIg or plasma exchange—the inference of which is that they would be worse without therapy, rather than an indication of complete treatment resistance.[12] The severity and duration of disease is highly diverse in patients and can range from mild weakness, from which patients recover spontaneously, to patients becoming quadriplegic and ventilator-dependent without signs of recovery for several months or longer. Eventually, however, all patients start improving, although recovery could follow a protracted course and result in severe, permanent disability. During the acute phase, the stable phase, or even during recovery, patients might have signs or symptoms of autonomic dysfunction like cardiac arrhythmia that occasionally necessitates a pacemaker, excessive sweating, blood pressure instability, or ileus.[4]

Guillain-Barré syndrome is a clinical diagnosis, but additional investigations can be helpful or even needed for confirmation. Examination of the cerebrospinal fluid

Panel 1: Diagnostic criteria for Guillain-Barré syndrome[1]

Features needed for diagnosis of Guillain-Barré syndrome in clinical practice

- Progressive weakness in legs and arms (sometimes initially only in legs).
- Areflexia (or decreased tendon reflexes) in weak limbs.

Additional symptoms

- Progressive phase lasts days to 4 weeks (often 2 weeks).
- Relative symmetry.
- Mild sensory symptoms or signs (not present in acute motor axonal neuropathy).
- Cranial nerve involvement, especially bilateral weakness of facial muscles.
- Autonomic dysfunction.
- Pain (common).

Features that should raise doubt about the diagnosis of Guillain-Barré syndrome

- CSF: increased number of mononuclear cells or polymorphonuclear cells (>50 cells per μL).
- Severe pulmonary dysfunction with little or no limb weakness at onset.
- Severe sensory signs with little or no weakness at onset.
- Bladder or bowel dysfunction at onset.
- Fever at onset.
- Sharp spinal cord sensory level.
- Marked, persistent asymmetry of weakness.
- Persistent bladder or bowel dysfunction.
- Slow progression of weakness and without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or acute onset chronic inflammatory demyelinating polyneuropathy).

Nerve conduction studies

- Can be helpful in clinical practice, but are generally not required to diagnose Guillain-Barré syndrome.
- Needed to meet all Brighton criteria for Guillain-Barré syndrome.[8]
- Essential for classification of Guillain-Barré syndrome in acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy.
- Acute inflammatory demyelinating polyneuropathy: features of demyelination (decreased motor nerve conduction velocity, prolonged distal motor latency, increased F-wave latency, conduction blocks, and temporal dispersion).[58]
- Acute motor axonal neuropathy: no features of demyelination (one demyelinating feature in one nerve, if distal CMAP amplitude is less than 10% LLN, can be found; distal CMAP amplitude less than 80% LLN in at least two nerves.[58] Transient motor nerve conduction block might be present.[64]

Classification of Guillain-Barré syndrome as either acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy is not required for diagnosis of Guillain-Barré syndrome, whether acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy require different treatments is unknown. The amount of conduction slowing required to define demyelination differs between classification systems.

CSF=cerebrospinal fluid. CMAP=compound muscle action potential. LLN=lower limit of normal.

(CSF) is important especially to exclude other causes of weakness associated with an increase in CSF cell count.[4] The disorder is classically known for its cytoalbuminological dissociation—the combination of a normal cell count and increased protein level. However, normal protein level (especially when determined in the first week after onset of disease) does not make the diagnosis unlikely or even exclude Guillain-Barré syndrome.[71] Additionally, 15% of patients with the disease have a mild increase in CSF cell count (5–50 cells per µL).[8]

Variants, formes frustes, and paediatric presentations

Guillain-Barré syndrome is a remarkably clinically diverse disorder and includes several clinically distinctive variants, formes frustes, and atypical cases. The frequency of these variant forms in part relates to the geographical area in which the disease is reported. Guillain-Barré syndrome can be restricted to specific nerve fibres, as 15% of patients with a pure motor form do not have any sensory deficits.[4] Pure motor Guillain-Barré syndrome can occur both in patients with acute motor axonal neuropathy or acute inflammatory demyelinating polyneuropathy. Acute pure sensory neuropathies are well recognised, but do not meet existing diagnostic criteria of Guillain-Barré syndrome.[72] Whether or not acute pure sensory neuropathies can be considered a variant of Guillain-Barré syndrome is unclear. Miller Fisher syndrome is a variant of Guillain-Barré syndrome accounting for 5% of cases in western Europe, although prevalence might be higher in other areas, such as Taiwan and Japan.[73] Miller Fisher syndrome is characterised by the triad of ophthalmoplegia, ataxia, and areflexia. In practice, Miller Fisher syndrome is frequently accompanied by other cranial nerve involvement and can progress to weakness of the limbs (Miller Fisher-Guillain-Barré overlap syndrome).[74] Equally, Miller Fisher syndrome, as defined by the presence of anti-GQ1b antibody, can present solely as an isolated, ocular nerve palsy. Another regional form is the so-called pharyngeal-brachial variant of Guillain-Barré syndrome. A typical forme fruste is the paraparetic variant of the disease in which the paresis is restricted to the legs, but most patients later develop involvement of the arms shown by sensory signs, low or absent reflexes, or electrophysiological changes in these nerves.[67] Guillain-Barré syndrome can be difficult to diagnose in children, especially preschool children, because they present their complaints atypically and neurological examination is more challenging.[75,76] Thus, although the diagnosis of Guillain-Barré syndrome is usually straightforward, it can be challenging especially in young children, atypical cases, patients with severe pain preceding weakness, or in low-income countries with poor diagnostic facilities and a broader differential diagnosis. A widespread, differential diagnosis of Guillain-Barré syndrome exists, which depends on the clinical presentation, age, and country of origin of the patients (panel 2).

Panel 2: Differential diagnosis of rapidly progressive limb weakness (with or without respiratory failure)

CNS
Encephalitis, acute disseminated encephalomyelitis, transverse myelitis, brainstem or myelum compression, leptomeningeal malignancy

Motor neurons
Poliomyelitis, West Nile virus anterior myelitis, amyotrophic lateral sclerosis, progressive spinal muscular atrophy

Plexus
Neuralgic amyotrophia, diabetes mellitus

Nerve roots
Guillain-Barré syndrome, acute onset chronic inflammatory demyelinating neuropathy, Lyme disease, cytomegalovirus-related radiculitis, HIV-related radiculitis, leptomeningeal malignancy

Peripheral nerves
Guillain-Barré syndrome, acute onset chronic inflammatory demyelinating neuropathy, iatrogenic, toxic, critical illness myopathy-neuropathy, vasculitis, diphtheria, porphyria, thiamine deficiency, porphyria, Lyme disease, metabolic or electrolyte disorders (hypokalaemia, phosphataemia or magnesaemia, hypoglycaemia)

Neuromuscular junction
Myasthenia gravis, botulism, intoxication

Muscles
Critical illness myopathy-neuropathy, mitochondrial disease, acute rhabdomyolysis, polymyositis, dermatomyositis

Electrophysiological classification: current considerations

Guillain-Barré syndrome is a clinically diagnosed disorder, but nerve conduction studies (NCS) can help to support the diagnosis, to discriminate between axonal and demyelinating subtypes, and could relate to prognosis. Nerve conduction abnormalities are most pronounced 2 weeks after start of weakness.[58] NCS findings can be normal especially early in the course of disease. To increase the diagnostic yield, at least four motor nerves, three sensory nerves, F-waves, and H-reflexes, should be examined. NCS enables clinicians to divide Guillain-Barré syndrome into acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, or acute motor and sensory axonal neuropathy.[77] NCS in patients with acute inflammatory demyelinating polyneuropathy show features of demyelination, including prolonged distal motor latency, reduced nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion, and conduction blocks. The sural sensory potential is often preserved.[78] Features of axonal Guillain-Barré syndrome (acute motor axonal neuropathy or acute motor and sensory axonal neuropathy) are decreased

motor, sensory amplitudes, or both. Some patients turn out to have transient conduction blocks or slowing that rapidly recovers during the course of the disease, so-called reversible conduction failure.[64,79] This transient feature might initially suggest acute inflammatory demyelinating polyneuropathy instead of acute motor axonal neuropathy, and shows that serial NCS over weeks are needed to reliably distinguish between these two forms of Guillain-Barré syndrome. Transient blocks are probably caused by impaired conduction at the node of Ranvier, because of the effects of anti-ganglioside antibodies in those cases in which they are found. NCS might also have prognostic value because patients with features of demyelination more often need mechanical ventilation, and low compound muscle action potentials (CMAPs) are the most consistent findings predictive of poor outcome. Patients diagnosed with acute motor axonal neuropathy can either improve very slowly and incompletely, or recover rapidly, probably because of restoration of transient conduction blocks. Based on clinical trial evidence so far, distinguishing between acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy does not imply that a patient needs a specific or tailored immunological treatment. Additional studies are needed to further establish the electrophysiological criteria for Guillain-Barré syndrome and its subgroups, and to precisely delineate the relation between these conduction blocks, the presence of anti-ganglioside antibodies, the effect of treatment, and outcome.[80]

Approaches to treatment and clinical trials

Guillain-Barré syndrome is a potentially life-threatening disease. Both general medical care and immunological treatment are essential (figure 3). Meticulous attention to supportive care is needed to prevent or to manage complications.[4,11] Measures include monitoring of respiratory function by frequent measurement of vital capacity and other clinical outcomes, and timely transfer to ICU when needed. To help this decision making process, the Erasmus GBS Respiratory Insufficiency Score (EGRIS) can be used on hospital admission, because it determines the chance a patient will need artificial ventilation.[81] Among the other issues that need attention are cardiac and haemodynamic monitoring (autonomic dysfunction), prophylaxis for deep vein thrombosis, management of possible bladder and bowel dysfunction, early initiation of physiotherapy and rehabilitation, and psychosocial support. Two-thirds of patients with Guillain-Barré syndrome have pain, which can be very severe and persist for many months.[68] However, not enough evidence exists to support the use of any specific pharmacological intervention in these patients.[82]

Several randomised controlled trials (RCTs) studying the effect of immunotherapy in Guillain-Barré syndrome have been done in the past few decades. IVIg and plasma exchange have proved effective.[12,83] However, most of these studies were done in Europe and North America where most patients have the acute inflammatory demyelinating polyneuropathy variant of the disorder. If IVIg or plasma exchange will be started, they should, in principle, be started as soon as possible, before irreversible nerve damage has taken place. Five plasma exchange sessions (each exchange comprising 2–3 L of plasma according to bodyweight) over 2 weeks is the accepted, beneficial regimen, when started within the first 4 (preferably 2) weeks from onset in patients with Guillain-Barré syndrome who are unable to walk unaided (Guillain-Barré syndrome disability score >2).[83,84] Patients with Guillain-Barré syndrome who are still able to walk might improve more rapidly after two plasma exchange sessions than without plasma exchange. IVIg is proven to be effective, in patients unable to walk unaided, when started within the first 2 weeks after onset of weakness. Whether the total IVIg dose (2 g/kg bodyweight) given in 2 days (1 g/kg per day) is more beneficial than when given in 5 days (0·4 g/kg per day) is not known. In our centres, we usually give the total IVIg dosage in 5 days, because this regimen might induce fewer side-effects and because children who receive a faster IVIg regimen are reported to have treatment-related fluctuations (TRFs) more frequently.[85]

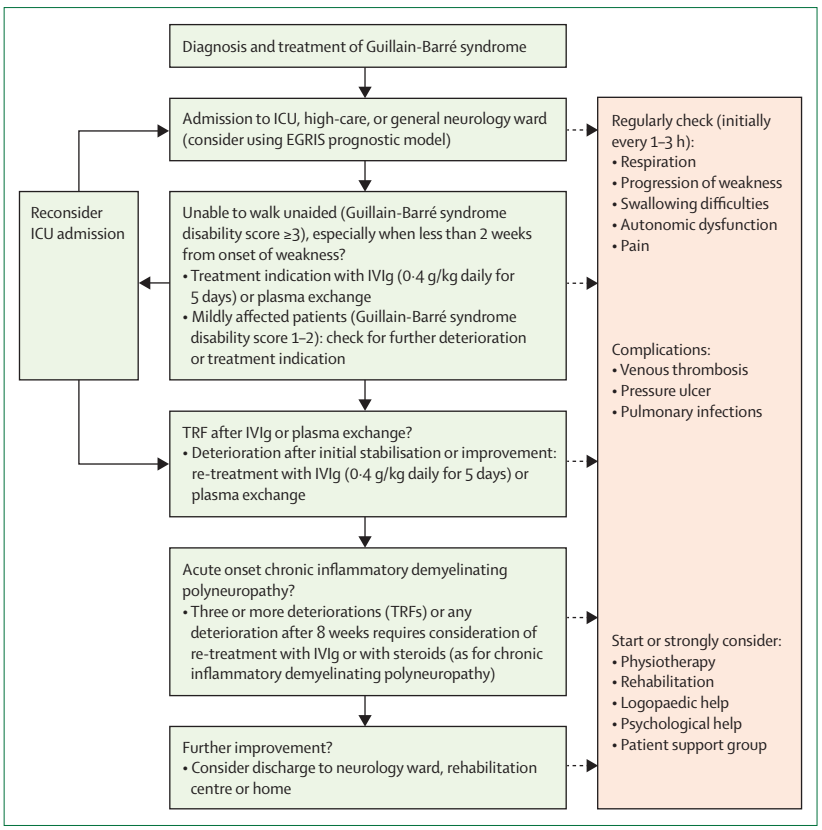

Figure 3: **Treatment approach for Guillain-Barré syndrome**
Modified with permission from van den Berg and colleagues.[4] Solid lines are treatment flow; dashed lines are issues that need to be considered. ICU=intensive care unit. EGRIS=Erasmus GBS Respiratory Insufficiency Score. IVIg=intravenous immunoglobulin. TRF=treatment related fluctuation.

Although IVIg and plasma exchange have proved effective, many patients with Guillain-Barré syndrome still develop severe weakness and have a long disease course, often with incomplete recovery, pain, and fatigue. A better treatment is therefore needed. Rather surprisingly, both oral steroids and intravenous methylprednisolone are not beneficial in the disorder.[86] The combination of IVIg and methylprednisolone is not more effective than IVIg alone, although there might be some additional short-term effect after correction for known prognostic factors.[87] Combination of plasma exchange followed by IVIg is not significantly better than plasma exchange or IVIg alone.[88] No evidence exists that shows a second course of IVIg is effective in patients with Guillain-Barré syndrome who continue to deteriorate. Researchers in the Netherlands are investigating whether patients with Guillain-Barré syndrome with a poor prognosis, defined using the modified Erasmus GBS outcome scale (mEGOS), might benefit from a second IVIg course when given shortly after the first IVIg course (SID-GBS RCT trial).[14,89] Investigators of an international variant of the SID-GBS trial (I-SID-GBS) are studying this effect using an observational, prospective open study design. The I-SID-GBS study is being done as part of the International Guillain-Barré syndrome Outcome Study (IGOS), supported by the Inflammatory Neuropathy Consortium, which aims to contribute to a broader understanding of the major causal factors in the disease. A completely new approach is being investigated in an RCT of the drug, eculizumab—a humanised monoclonal antibody that binds with high affinity to the complement factor C5 and prevents its cleavage to C5a and the proinflammatory, cytolytic C5b-9 complex.[90,91] Yet, at present only IVIg and plasma exchange are proven effective treatments for Guillain-Barré syndrome. Because IVIg is more convenient to give, widely available, and generally has only minor side-effects, it has replaced plasma exchange as the preferred treatment in many centres. A disadvantage of IVIg is the high cost—a major reason why some centres still use plasma exchange. In low-income countries, both IVIg and standard plasma exchange treatment might be too expensive for a large proportion of patients. New studies to improve the course and outcome of Guillain-Barré syndrome are still urgently needed.

For more on the **International Guillain-Barré syndrome Outcome Study (IGOS)** see https://www.gbsstudies.org/

TRFs and acute onset chronic inflammatory demyelinating neuropathy

About 10% of patients treated with IVIg or plasma exchange will deteriorate after initial improvement or stabilisation—ie, they will have a TRF.[12,92] These TRFs usually occur within the first 8 weeks after start of treatment. Repeated treatment (2 g IVIg/kg in 2–5 days) has been observed to be beneficial in these patients. Although no RCTs have shown that re-treatment is beneficial in case of a TRF, it is common practice in many centres to do so.[66] Patients with Guillain-Barré syndrome with a TRF are likely to have a prolonged immune response that causes sustained nerve damage or functional blockade, which needs more prolonged treatment than standard care.

Some patients initially diagnosed with Guillain-Barré syndrome can have several episodes of deterioration. Others initially have a rapidly progressive course like Guillain-Barré syndrome, but subsequently have further progression exceeding 4 weeks. In these patients, the question often arises as to whether the diagnosis is still consistent with Guillain-Barré syndrome, or the patient has chronic inflammatory demyelinating polyneuropathy with acute onset. In a prospective study series, about 5% of patients initially diagnosed with Guillain-Barré syndrome were eventually found to have acute onset chronic inflammatory demyelinating neuropathy.[89,93] The diagnosis of acute onset chronic inflammatory demyelinating neuropathy should especially be considered in patients initially diagnosed with Guillain-Barré syndrome who have three or more periods with clinical deterioration, or when there is a new deterioration after 8 weeks from onset of weakness. These secondary deteriorations should be recognised because patients with Guillain-Barré syndrome with a TRF might improve after re-treatment, and patients with acute onset chronic inflammatory demyelinating neuropathy usually need chronic maintenance treatment with IVIg or a switch to corticosteroid treatment.

Outcome and prediction of outcome

Guillain-Barré syndrome is still a life-threatening disorder with frequent morbidities, even with the best treatment available. Mortality rates in Europe and North America vary between 3% and 7%, and more widely in other countries where data are available.[23,94–96] Patients can die in the acute progressive stage, most probably because of ventilatory insufficiency or pulmonary complications, or from autonomic dysfunction including arrhythmia. However, death can occur at a late stage when a patient is discharged from an ICU to a general neurology ward, which further shows the importance of prolonged accurate monitoring and general care.[57,96] Emergency situations can occur after delayed diagnosis, especially in young children.[76] Patients who survive Guillain-Barré syndrome frequently have residual complaints and deficits, which can have a substantial effect on daily activities and quality of life.[97] About 20% of patients with Guillain-Barré syndrome cannot walk unaided 6 months after onset. Most patients have residual pain and fatigue, which can in part be attributed to persistent axonal loss.[98,99] Many patients have to change their work and daily activities, even after reaching a good functional level.[75,100] Most improvement happens in the first year, but patients might show further recovery even after 3 or more years.

To improve the outcome of Guillain-Barré syndrome, more effective treatments and good outcome assessments are needed.[101] However, the clinical course and outcome of the disease is highly variable and early recognition of patients with poor outcome is needed to personalise and improve treatment. Prognostic models could help to identify patients who need additional treatment and monitoring. Patient characteristics consistently related to poor prognostic outcome in Guillain-Barré syndrome are high age (aged 40 years and over), preceding diarrhoea (or *C jejuni* infection in the past 4 weeks), and high disability at nadir. The EGOS, which is based on these three clinical characteristics, can be used 2 weeks after admission to predict the ability of the patient to walk at 6 months.[102] The mEGOS requires the Medical Research Council (MRC) Scale for Muscle Strength score instead of disability and can predict outcome as soon as 1 week after admission, when therapeutic interventions are probably even more effective.[14] The risk of respiratory failure is associated with rate of disease progression, severity of limb weakness, peroneal nerve conduction block, and low vital capacity. This risk can be predicted for individual patients using EGRIS; based on the severity of weakness (expressed as MRC sum score); onset of weakness; and facial palsy, bulbar weakness, or both.[81] These models need to be validated for use in children and patients with axonal forms of Guillain-Barré syndrome.

Conclusions

In 2016, we approach the centenary of the first description of Guillain-Barré syndrome with some comfort in the knowledge that our rapidly advancing understanding of the pathological mechanisms of the disease is informing new treatment strategies and approaches to clinical care.[103] Treatments have been developed and proved effective, but these are not sufficient in many patients. Although there have been major steps forward, this is no time for complacency as the research area continues to face deep, unsolved issues around pathogenesis of Guillain-Barré syndrome, especially for the acute inflammatory demyelinating polyneuropathy form of the disorder. Newly emerging post-infectious forms of Guillain-Barré syndrome, such as those associated with arboviruses including Zika, need to be closely monitored as global epidemics spread. Biomarkers, prognostic models, and better therapies are needed. Many of these issues are being addressed through multicentre, collaborative efforts such as IGOS. Prevention of severe axonal injury early in the course of the disease remains a major focus, because it is an important limiting factor in achieving a good, long-term outcome.

Contributors
All authors contributed equally.

Declaration of interests
We declare no competing interests.

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