Guillain-Barré syndrome

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Guillain-Barré syndrome is the most common cause of acute flaccid paralysis worldwide. Most patients present with an antecedent illness, most commonly upper respiratory tract infection, before the onset of progressive motor weakness. Several microorganisms have been associated with Guillain-Barré syndrome, most notably *Campylobacter jejuni*, Zika virus, and in 2020, the severe acute respiratory syndrome coronavirus 2. In *C jejuni*-related Guillain-Barré syndrome, there is good evidence to support an autoantibody-mediated immune process that is triggered by molecular mimicry between structural components of peripheral nerves and the microorganism. Making a diagnosis of so-called classical Guillain-Barré syndrome is straightforward; however, the existing diagnostic criteria have limitations and can result in some variants of the syndrome being missed. Most patients with Guillain-Barré syndrome do well with immunotherapy, but a substantial proportion are left with disability, and death can occur. Results from the International Guillain-Barré Syndrome Outcome Study suggest that geographical variations exist in Guillain-Barré syndrome, including insufficient access to immunotherapy in low-income countries. There is a need to provide improved access to treatment for all patients with Guillain-Barré syndrome, and to develop effective disease-modifying therapies that can limit the extent of nerve injury. Clinical trials are currently underway to investigate some of the potential therapeutic candidates, including complement inhibitors, which, together with emerging data from large international collaborative studies on the syndrome, will contribute substantially to understanding the many facets of this disease.

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Introduction

Guillain-Barré syndrome is an immune-mediated polyradiculoneuropathy that accounts for an estimated 100 000 new cases annually worldwide.[1] In most patients, the acute onset of neurological symptoms is preceded by an infective illness,[2] followed by progressive limb weakness, which can last up to 4 weeks before reaching plateau. Several infections are associated with Guillain-Barré syndrome, but *Campylobacter jejuni* is the most common and extensively reported.[3] In *C jejuni*-related Guillain-Barré syndrome, robust evidence suggests that molecular mimicry exists between nerve and microbial antigens, leading to the development of Guillain-Barré syndrome.[4]

The classic presentation of the syndrome does not typically pose a diagnostic challenge, but atypical variants are missed when not considered. To support diagnosis, polyradiculoneuropathy can be detected on nerve conduction studies, and cerebrospinal fluid analysis can show albumincytological dissociation, although both tests can be normal in the early stages.[5] Patients with Guillain-Barré syndrome require close monitoring for disease progression, in particular for bulbar weakness, respiratory insufficiency, and autonomic dysfunction. Prognostic scales have been developed to predict patient outcome and to stratify treatment. To date, intravenous immunoglobulin and plasma exchange are the only recognised immunotherapeutic drugs that can accelerate recovery in Guillain-Barré syndrome.[5] However, the syndrome is still a serious disease. Even when treated with standard immunotherapies, approximately 5% of people die, and up to 20% cannot walk independently at 1 year from disease onset.

The past 5 years have seen advances in our understanding of Guillain-Barré syndrome, which is the focus of this Seminar. We now have improved understanding of Zika virus-associated Guillain-Barré syndrome,[6] improved insight into the global burden of the syndrome through the International Guillain-Barré Syndrome Outcome Study (IGOS),[7] and new therapeutic drugs have entered early clinical development.

Epidemiology and antecedent events

Epidemiology

Guillain-Barré syndrome has been reported in many countries and has a wide range of reported incidences (figure 1).[1,8] Population-based studies from North America and Europe suggest that incidence ranges from 0·81 to 1·91 cases per 100 000 person-years (median 1·11). There is a 20% increase in incidence for every 10-year increase in age, and unlike other autoimmune diseases, the risk of Guillain-Barré syndrome is higher in men than in women.[1]

Although not designed to study populations, IGOS reported similar findings following recruitment of more than 900 patients with Guillain-Barré syndrome worldwide.[7] IGOS found a medium age of 51 years and patient numbers peaked at 50–69 years, including a male-to-female

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and PubMed using the search term "Guillain-Barré syndrome". Publications from January, 2015, to April, 2020, were primarily selected, but we also included older publications that provided some of the seminal works in Guillain-Barré syndrome. We also searched the reference lists of articles identified by this search strategy, and selected papers that were relevant to the subject matter. Review articles are cited to provide readers with more details and references than can be provided in this Seminar. All articles were returned by the search term and cited if they provided relevant information for the purposes of the Seminar.

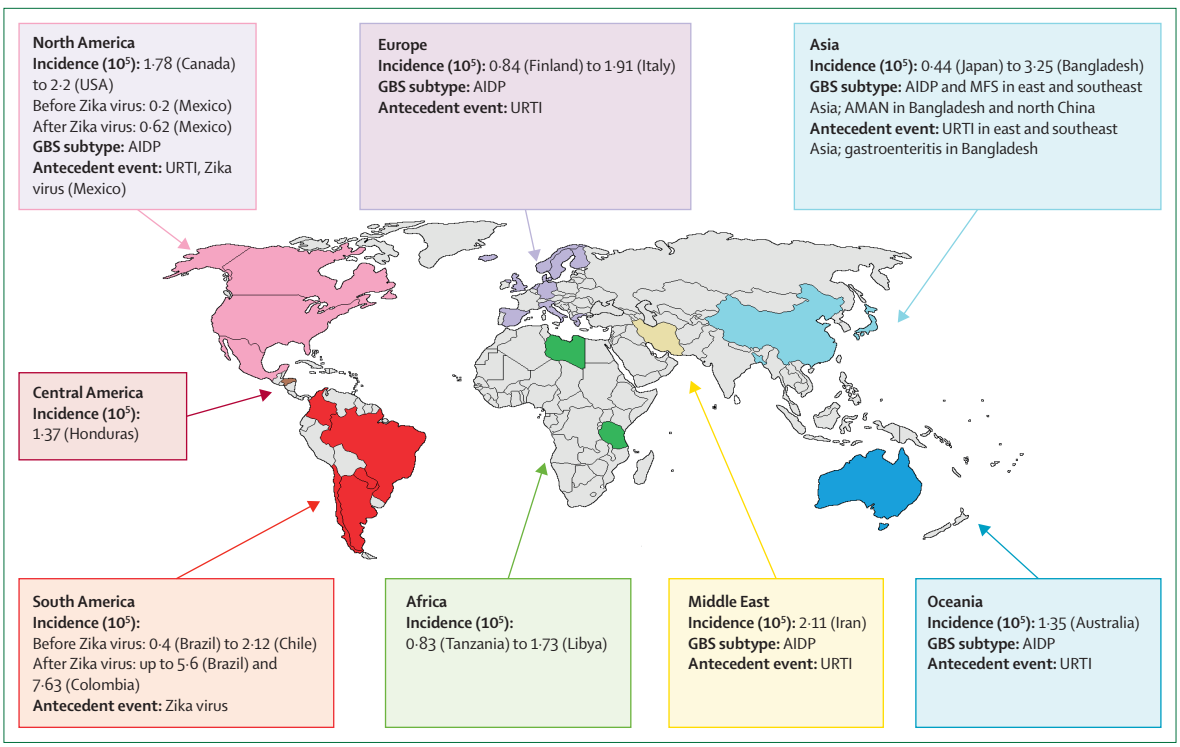

Figure 1: **The epidemiology of Guillain-Barré syndrome**
The map highlights countries that have reported incidence of Guillain-Barré syndrome, the subtype of Guillain-Barré syndrome that predominates, and the antecedent infections associated with Guillain-Barré syndrome. AIDP=acute inflammatory demyelinating polyneuropathy. AMAN=acute motor axonal neuropathy. MFS=Miller Fisher syndrome. URTI=upper respiratory tract infection.

ratio of 1·5. In comparison to North America and Europe, population-based studies in east Asia report lower incidences of Guillain-Barré syndrome with 0·44 cases per 100 000 person-years in Japan,[9] and 0·67 in China.[10] In Bangladesh, the incidence was 1·5–2·5 cases per 100 000 person-years in adults, and 3·25 in children.[11] Single-centre studies in the Middle East report similar incidences to western countries,[12] whereas in Latin America, the reported background incidences were highest in Chile (2·12 cases per 100 000 person-years) and lowest in Brazil (0·40).[13]

Seasonal variation of incidence have close association with infections.[14] Studies in western countries suggest suggest a peak in winter, whereas northern China, India, Bangladesh, and Latin America witness a summer peak. Reports from northern China and Bangladesh are linked to *C jejuni* infections and the acute motor axonal neuropathy (AMAN) phenotype.[15,16] Although strict hygiene measures preventing campylobacteriosis can reduce the incidence of Guillain-Barré syndrome,[17] the growing prevalence of *Campylobacter* infection worldwide could result in persistent, or even increased, incidence of Guillain-Barré syndrome in the future.[18]

Clinical features

GBS is clinically heterogeneous: the classic presentation of Guillain-Barré syndrome features progressive (ascending) limb weakness associated with reduced or absent reflexes. However, patients can present with localised weakness and these variants include a pharyngeal–cervical–brachial variant and facial diplegia with paraesthesia. Patients can also present with completely different sets of clinical features to classic Guillain-Barré syndrome but can share similar serological biomarkers. These disorders related to Guillain-Barré syndrome include Miller Fisher syndrome and Bickerstaff brainstem encephalitis. Recognising the clinical patterns categorised under the wide umbrella of Guillain-Barré syndrome allows for more timely and accurate diagnosis, and for treatment to be initiated without delay.

Antecedent events

Most patients with Guillain-Barré syndrome have an antecedent event up to 4 weeks before developing neurological symptoms. In IGOS, an antecedent event was reported in 76% of patients, mainly upper respiratory tract infections (35%) in Europe, North America, and east and southeast Asia, whereas gastroenteritis (27%) was more common in Bangladesh.[7] Guillain-Barré syndrome has also been associated with particular vaccinations[19] and in immune checkpoint inhibitor therapy.[20,21] Other less common triggers include ganglioside administration[22,23] and surgery.[24]

Antecedent infections

The prevalence of Guillain-Barré syndrome is linked to infections that are endemic to specific regions and can show a transient rise in outbreaks. An example is the surge and subsequent decline of Guillain-Barré syndrome following the 2014–16 Zika virus outbreak in French Polynesia,[6] Latin America, and the Caribbean, in which the syndrome's incidence increased transiently by 2·6 times the background incidence.[13] In 1991, McKhann and colleagues reported on the summer epidemic of acute so-called Chinese paralysis syndrome.[25] This landmark publication subsequently led to the recognition of AMAN and acute motor-sensory axonal neuropathy (AMSAN) as part of the clinical spectrum of Guillain-Barré syndrome related to *C jejuni* infection.

Prospective case-control studies remain the gold standard in establishing an epidemiological association of the syndrome with pathogens. Such studies have implicated *C jejuni*, cytomegalovirus, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, Epstein-Barr virus, hepatitis E virus, influenza A virus, and Zika virus.[2,6,16,26–32] Other arboviruses, including dengue and chikungunya, have been reported in regions where infections are endemic[33] or in outbreaks.[34] *C jejuni*-induced Guillain-Barré syndrome typically results in axonal neuropathy,[35] whereas infections with cytomegalovirus or Epstein-Barr virus usually trigger a demyelinating neuropathy.[36] In Zika virus-related Guillain-Barré syndrome, patients present with sensorimotor deficits, facial palsy, respiratory insufficiency, and a demyelinating electrophysiological subtype. In most patients, the onset suggests a postinfectious illness, rather than parainfectious illness.[37,38]

The COVID-19 pandemic has also seen emerging reports of Guillain-Barré syndrome and Miller Fisher syndrome in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection,[39–46] although a causal relationship has not been shown. Patients who develop Guillain-Barré syndrome have a classic phenotype with varying severity, typically occurring within 2 weeks of infection. In one report, Guillain-Barré syndrome was a parainfectious occurance.[39] Most patients have cerebrospinal fluid albumincytological dissociation and neurophysiological evidence of demyelinating neuropathy, although axonal neuropathy was described in three Italian patients.[41] Two of the patients had Miller Fisher syndrome, and the third had IgG against GD1b.[44] They were treated with either intravenous immunoglobulin or plasma exchange together with standard COVID-19 treatment. A management challenge is determining the cause for respiratory decline, which could be due to Guillain-Barré syndrome or COVID-19 pneumonia, or both diseases. Case-controlled studies are warranted to establish a causal relationship.

Vaccines and Guillain-Barré syndrome

A heightened surveillance of Guillain-Barré syndrome associated with vaccine administration was prompted by reports of an increased risk of Guillain-Barré syndrome (approximately one in 100 000 vaccinations) in individuals receiving the 1976 H1N1 influenza vaccine.[19] However, the risk of developing Guillain-Barré syndrome with other influenza vaccines, including the 2009 p(H1N1) vaccine, is low (<1 per million vaccinations).[47] By contrast, the attributable risk of Guillain-Barré syndrome with an influenza infection is considerably higher (17 per million infections) than with influenza vaccinations.[48] Other reports of polyneuritis or Guillain-Barré syndrome have originated in recipients of the previous brain-derived Semple rabies vaccine, but not the current rabies vaccine. In the former, it was hypothesised that exposure to brain proteins resulted in antibodies against neural antigens, leading to Guillain-Barré syndrome.[49]

In a large case-control study of 1056 Chinese patients with Guillain-Barré syndrome and 4312 controls, no significant association was detected from vaccination against multiple pathogens, including influenza and rabies viruses.[50] Vaccination also did not increase the risk of developing a recurrence in individuals who had previously been afflicted with Guillain-Barré syndrome.[51] Resistance and hesitancy towards vaccination can lead to the re-emergence of life-threatening diseases that have previously been eradicated, such as measles. Natural influenza A infection can potentially trigger Guillain-Barré syndrome, and vaccination has resulted in a marked reduction in complications, including Guillain-Barré syndrome.[27] When considering the risks and benefits of vaccination, this point should be emphasised.

Immune checkpoint inhibitors and Guillain-Barré syndrome

With the introduction of immune checkpoint inhibitors as therapeutics in oncology, cancers that were previously incurable now have improved prognoses. Neurological adverse events, although rare, have been reported, including a Guillain-Barré syndrome-like condition. Based on a large case-series,[20,21] more than 1% of patients developed peripheral neuropathy, which includes an isolated cranial neuropathy. The typical presentation of an ascending paralysis reminiscent of Guillain-Barré syndrome was seen in 0·1% of patients. The median time of onset in patients with Guillain-Barré syndrome was typically after three cycles of immune checkpoint inhibitor therapy, and disease progression was rapid. Cerebrospinal fluid analysis showed albumincytological dissociation, and electrophysiology was supportive of a demyelinating neuropathy.[52] The current treatment recommendation for neurological complications induced by therapy with immune checkpoint inhibitors is to stop the causative drug and initiate steroids.[53] However, as the clinical course of Guillain-Barré syndrome induced by immune checkpoint inhibitors appears to be similar to classic Guillain-Barré syndrome, intravenous immunoglobulin or plasma exchange should be considered. Of note, patients with pre-existing Guillain-Barré syndrome

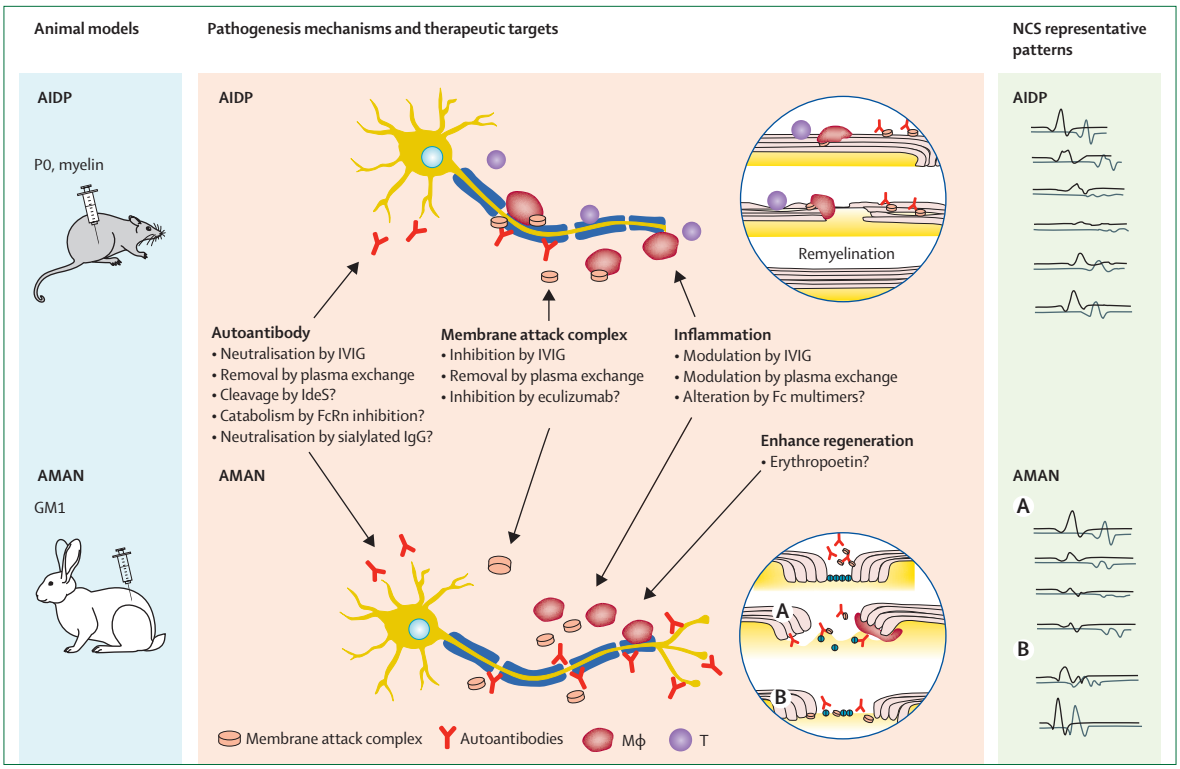

Figure 2: **Overview of the pathogenesis and therapeutic targets of the two major Guillain-Barré syndrome subtypes, AIDP and AMAN**
Rat models of experimental autoimmune neuritis have been used to investigate AIDP, and AMAN has been modelled in rabbits immunised with GM1. In AIDP, inflammatory infiltrates containing T cells and macrophages are present, with macrophages involved in stripping myelin. Antibodies and membrane attack complexes can also be detected on Schwann cells. In AIDP, segmental demyelination and subsequent remyelination result in progressively slow nerve conduction velocities, prolonged distal latencies, and temporal dispersion. AMAN is primarily an antibody-mediated condition, with IgG and activated complement proteins deposited on the nodal and internodal axolemma. Macrophages contribute to axonal injury by invading the periaxonal space between axon and myelin. Antibodies could also interfere with nerve regeneration. In AMAN, axonal involvement might result in axonal degeneration (A), or rapid resolution of conduction block and abnormal nodal lengthening (B). In AMAN, depending on the extent of axonal injury, the NCS pattern can show axonal degeneration with gradual reduction of CMAP amplitude (A), or reversible conduction failure with rapid resolution of conduction slowing or or conduction blocks (B). The various therapeutics currently in use and in development target different sites, resulting in neutralising or removing autoantibodies, inhibiting membrane attack complexes, modulating inflammation, and enhancing neural regeneration. AIDP=acute inflammatory demyelinating neuropathy. AMAN=acute axonal motor neuropathy. EAN= experimental autoimmune neuritis. Fc=fragment crystallisable. FcRn=neonatal FC receptor. GM1=monosialotetrahexosylganglioside. IdeS=*Streptococcus pyogenes*-derived IgG protease. IVIg=intravenous immunoglobulin. Mϕ=macrophages. NCS=nerve conduction study. P0=myelin protein zero. T=T cells.

could be at increased risk of relapse or worsening when exposed to immune checkpoint inhibitors.[54]

The mechanism by which immune checkpoint inhibitors induce Guillain-Barré syndrome is not well understood, but it is possible that the abrogation of self-tolerance could activate cytotoxic T lymphocytes, along with a reduced suppression of antibody-producing B lymphocytes. Notably, neurological complications following immune checkpoint inhibitors do not have autoantibodies associated with the related conditions, suggesting a T-cell-mediated pathogenesis.[55]

Pathogenesis

Overview

Up to the late 1980s, Guillain-Barré syndrome was considered to be a single disease entity with immune-mediated attack on myelin components, resulting in demyelination and secondary axonal damage. It subsequently became clear that Guillain-Barré syndrome could be broadly classified into acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and AMAN, depending on the site of target antigen.[25,56] This classification, together with the discovery of anti-glycolipid antibodies, expanded the understanding of Guillain-Barré syndrome pathogenesis (figure 2).

Post-mortem studies found that AIDP is characterised by the presence of inflammatory infiltrates containing T cells and macrophages involved in macrophage-mediated demyelination.[57,58] Deposition of activated complement products can be detected on Schwann cells, suggesting nerve injury that is antibody-mediated.[59] Some of these histopathological features can be reproduced in susceptible animals (figure 2) when actively immunised with myelin, myelin proteins (PMP22, P0, or P2), galactocerebroside, or by adoptive transfer of P0-specific and P2-specific T cells, resulting in a monophasic disease resembling Guillain-Barré syndrome, such as experimental autoimmune (allergic) neuritis.[60–63] Experimental

depletion of cellular components prevent disease, which implicates T cells and macrophages as essential in this experimental autoimmune neuritis model; however, the pathogenic mechanisms identified in experimental autoimmune neuritis might not always be relevant to Guillain-Barré syndrome.[64]

By contrast with AIDP, patients with AMAN show primary axonal injury without substantial T-cell inflammation or demyelination. IgG and activated complement are deposited on nodal and internodal axolemma.[65] Macrophages appear to invade the periaxonal space, and there is nodal lengthening following paranodal myelin detachment (figure 2),[66] leading to slowing of conduction due to an increase in nodal membrane capacitance. Immunisation of rabbits with GM1 ganglioside can produce disease that resembles AMAN, with circulating anti-GM1 antibodies, motor neuropathy, and pathological findings of IgG deposition on motor axons and periaxonal macrophages.[67]

The different underlying pathogenesis of AMAN and AIDP results in different patterns of clinical and neurophysiological recovery. In AIDP, recovery depends on the remyelination process (figure 2) and the degree of secondary axonal degeneration. In AMAN, recovery depends on the degree of axonal alterations caused by the deposition of antibodies (figure 2). This process is further complicated by antibody binding at axonal sprouts that prevents axonal regeneration.[68] In a small proportion of patients with AMAN, recovery is rapid when there is resolution of autoantibody-mediated conduction block.

The role of antibodies

Gangliosides are sialic acid-containing glycolipids enriched in the mammalian nervous system, particularly at the nodes of Ranvier and motor nerve terminals. Their importance as targets has been shown in transgenic mice that express complex gangliosides exclusively in neurons.[69] The underlying mechanism for antibody-mediated neuropathy includes modulation of ion channel function at the nodes of Ranvier, complement-dependent cytotoxicity at the nodes and motor nerve terminals, and interference with nerve regeneration.[70–74]

Guillain-Barré syndrome subtypes are often associated with specific antiganglioside antibodies suggesting a disproportionate enrichment of target glycolipids in different nerves. For instance, patients with AMAN often have IgGs against GM1, GD1a, and GalNAc-GD1a. Although studies suggest similar amounts of GM1 and GD1a in human sensory and motor nerves, the fine specificity and structural orientation of glycolipids can contribute to the preferential involvement of motor nerves.[75] Patients with Miller Fisher syndrome have reactivity against GQ1b, which is expressed at the paranodal regions of extraocular motor nerves.[76] Antibodies can also target clusters of gangliosides or ganglioside complexes.[77] These antibodies appear to have substantial associations with AMAN,[78] and can result in severe disease.[79]

The target antigens in AIDP are currently unknown. Studies in experimental autoimmune neuritis suggest myelin proteins (PMP22, P0, and P2) and the nodal protein, neurofascin, are probable targets. However, autoantibodies against myelin proteins have not been detected in patients, and antineurofascin antibodies are rare in patients with AIDP.[80–82] Antibodies against galactocerebroside have been reported in *M pneumoniae*-related AIDP.[29,83] Other potential myelin target epitopes include moesin in AIDP[84] and LM1 in AMAN and AIDP.[85–87]

The molecular mimicry theory

Proving the concept of molecular mimicry in autoimmune conditions requires sufficient evidence to support a causal relationship between the pathogenic microorganism and the disease.[88,89] In *C jejuni*-related AMAN, studies have supported the role of molecular mimicry in disease pathogenesis as follows: case-control studies have shown that approximately 26% of patients with Guillain-Barré syndrome versus 2% of household controls had *C jejuni* infection, establishing an epidemiological link;[90] patients with *C jejuni*-related AMAN also had anti-GM1 and anti-GD1a antibodies;[91,92] structural similarities were detected between the sugar components of lipo-oligosaccharides of *C jejuni* strains associated with AMAN and gangliosides on peripheral nerves;[93,94] and sensitising susceptible animals with GM1 and *C jejuni* lipo-oligosaccharides resulted in AMAN.[4,95]

Diagnostic criteria

Several criteria have been developed to aid clinicians in making a diagnosis of Guillain-Barré syndrome. In response to the swine flu vaccination campaign of 1976–77, the US National Institute of Neurological Disorders and Stroke (NINDS) commissioned diagnostic criteria to determine if there was a genuine increase in the prevalence of Guillain-Barré syndrome after vaccination.[96] These criteria were later reaffirmed with comments on its interpretation.[97] In 2011, the Brighton Collaboration Guillain-Barré Syndrome Working Group published case definitions for Guillain-Barré syndrome and Miller Fisher syndrome[98] that were aimed at standardising data collection globally as part of post-vaccination Guillain-Barré syndrome surveillance. The group recognised the resource limitations in many settings, proposing diagnostic certainty instead on the basis of available data.

Both the NINDS and the Brighton criteria have continued to be widely used (table 1). At minimum, a diagnosis of Guillain-Barré syndrome requires the presence of symmetrical flaccid weakness and decreased reflexes in the absence of alternative causes. The Brighton criteria also considered a separate case definition for Miller Fisher syndrome, which requires the presence of

	Modified NINDS criteria[97]		Brighton Collaboration (level of diagnostic certainty)[98]			
	Required	Supportive	Level 1 (highest)	Level 2	Level 3	Level 4 (lowest)
Classic Guillain-Barré syndrome						
Clinical features						
Bilateral and flaccid weakness of limbs	Yes	..	Yes	Yes	Yes	..
Decreased or absent deep tendon reflexes	Yes	..	Yes	Yes	Yes	..
Absence of alternative diagnosis	Yes	..	Yes	Yes	Yes	Yes
Additional clinical features						
Monophasic course, time between onset to plateau 12 h to 28 days	..	Yes	Yes	Yes	Yes	..
Relative symmetry	..	Yes	..	..	..	..
Mild sensory symptoms or signs	..	Yes	..	..	..	..
Progress (usually after 2–4 weeks of plateau)	..	Yes	..	..	..	..
Cranial nerve involvement (facial, bulbar, and oculomotor)	..	Yes	..	..	..	..
Autonomic dysfunction	..	Yes	..	..	..	..
Absence of fever at the onset of neuritic symptoms	..	Yes	..	..	..	..
CSF analysis						
CSF white cell count <50 /µl (usually <10)	..	Yes	Yes	Yes*	..	..
CSF protein raised (after week 1)	..	Yes	Yes	Yes*	..	..
Nerve conduction studies						
Consistent with conduction slowing and block	..	Yes	Yes	Yes*	..	..
Miller Fisher syndrome						
Clinical features						
Bilateral opthalmoparesis	..	..	Yes	Yes	Yes	..
Ataxia	..	..	Yes	Yes	Yes	..
Absent limb weakness	..	..	Yes	Yes	Yes	..
No altered consciousness or corticospinal tract signs	..	..	Yes	Yes	Yes	Yes
CSF analysis						
CSF cell count <50 (usually <10)	..	..	Yes	Yes*	..	..
CSF protein raised (after week 1)	..	..	Yes	Yes*	..	..
Nerve conduction studies						
Normal or only sensory abnormalities	..	..	Yes	Yes*	..	..

NINDS=National Institute of Neurological Disorders and Stroke. *To reach level 2 of the Brighton Collaboration criteria, either CSF or nerve conduction study results must be available.

Table 1: **Diagnostic criteria for Guillain-Barré syndrome**

the clinical triad of bilateral ophthalmoplegia, decreased reflexes, and ataxia, together with the absence of limb weakness and CNS involvement to fulfil a Level 3 diagnostic certainty. Reaching higher diagnostic certainties in both Guillain-Barré syndrome and Miller Fisher syndrome requires the presence of a monophasic illness reaching nadir within 28 days, cerebrospinal fluid albumincytological dissociation, and electrodiagnostic evidence of neuropathy.

In practice, the clinical characteristics of Guillain-Barré syndrome are variable. Although not included in either set of diagnostic criteria, there is an antecedent illness in the preceding 4 weeks in up to 76% of patients. The pattern of weakness in Guillain-Barré syndrome is also not restricted to the limbs and can extend to include cranial-innervated muscles, respiratory muscles, and autonomic involvement.[7] Rarely, these atypical patterns could be the first presentation of Guillain-Barré syndrome.

Natural history and the prognostic model

Historically, Guillain-Barré syndrome is associated with spontaneous recovery occurring shortly after plateau is reached. The advent of immunotherapy has led to quicker and more complete recoveries. Most publications on the natural history of Guillain-Barré syndrome have arisen from high-income and middle-income countries, where patients have access to immunotherapy and high standards of supportive care. In settings with restricted resources, such as Bangladesh, mortality (17%) is higher than in high-income countries (5%), which is probably owing to an increased proportion of patients with axonal forms of Guillain-Barré syndrome and inadequate access to ventilators, intensive care facilities, and immunotherapy.[99]

	Distinguishing clinical features	CSF findings	Neural conduction findings	Other supportive tests
Brain				
Encephalitis	Drowsiness, seizures	Pleocytosis	Normal	Brain MRI for hyperintense lesions, EEG for slowing epileptiform discharges
Brainstem stroke	Hyperacute sudden onset, cranial and limb weakness	Normal	Normal	Brain MRI and magnetic resonance angiography for corresponding infarct and vascular occlusion
Spinal cord				
Transverse myelitis	Sensory level, brisk reflexes	Normal	Normal	Abnormal spine MRI for hyperintense lesions
Malignant infiltration	Cauda equina syndrome	Malignant cells	Normal	Abnormal spine MRI for enhancing lesions, investigations for primary lesions
Anterior horn cell				
Infection with Poliovirus, enterovirus 71, or enterovirus D68	Fever, flaccid paralysis	Pleocytosis	Motor neuronopathy	Presence of virus
Plexus				
Neuralgic amyotrophy	Asymmetry, pain, and findings limited to affected nerves	Normal	Abnormal in affected nerves	Brachial plexus MRI for nerve enhancement
Nerve roots				
Cytomegalovirus and HIV radiculitis	Subacute presentation	Pleocytosis	Delayed or absent F waves and H waves	HIV and cytomegalovirus serology
Chronic inflammatory demyelinating polyneuropathy	Subacute presentation and relapsing–remitting pattern	Albumin-cytological dissociation	Demyelinating neuropathy	Nerve ultrasound for enlarged nerve roots
Peripheral nerves				
Chronic inflammatory demyelinating polyneuropathy	Subacute presentation and relapsing–remitting pattern	Albumin-cytological dissociation	Demyelinating neuropathy	Nerve ultrasound for enlarged nerve roots, and proximal and distal nerves
Porphyria	Family history, concomitant psychiatric and abdominal pain	Normal	Axonal neuropathy	Increased urinary porphobilinogen
Lyme disease or other tick-borne diseases	History of exposure, characteristic rash (erythema migrans in Lyme disease)	Normal	Axonal neuropathy	Antibodies against *Borrelia burgdorferi* (Lyme disease) or the related tick species
Thiamine deficiency	Predisposing factors (eg, hyperemesis gravidarum, alcohol misuse, nutritional deficiency, and other neurological features such as Wernicke encephalopathy)	Normal	Axonal neuropathy	Reduced blood thiamine and erythrocyte transketolase activity
Diphtheria	Laryngeal infection	Increased total protein	Demyelinating neuropathy	Isolation of *Corynebacterium diphtheriae* on cultures
Critical illness polyneuropathy	Prolonged illness or ventilation	Normal	Axonal neuropathy	Overlap with myopathy
Metabolic or electrolyte imbalance	Predisposing factors	Normal	Normal	Low serum concentrations of abnormal electrolyte
Neuromuscular junction				
Myasthenia gravis	Fatigable weakness, relapsing–remitting pattern	Normal	Repetitive nerve stimulation for a decremental response	Acetylcholine receptor antibodies
Botulism	Rapid progression, pupillary abnormalities, dysautonomia, and descending paralysis	Normal	Rapid repetitive nerve stimulation for an incremental increase	Botulism toxin
Lambert-Eaton syndrome	Proximal weakness, depressed tendon reflexes, and autonomic changes	Normal	Repetitive nerve stimulation for post-tetanic facilitation	Antibodies against voltage-gated calcium channels
Muscle				
Inflammatory myositis	Proximal weakness, normal reflexes and sensation	Normal	Normal sensory potentials	Increased serum creatine kinase, myopathic electromyography
Critical illness myopathy	Prolonged illness or ventilation	Normal	Normal sensory potentials	Overlap with neuropathy
Hypokalaemic periodic paralysis	Transient weakness, family history, triggering factors (eg, fasting, exercise, and carbohydrate-rich meals)	Normal	Abnormal exercise test	Low serum potassium concentrations, genetic mutation
Miscellaneous				
Functional disorder	Inconsistent, variable presentation	Normal	Normal	Psychological evaluation

Table 2: **Differential diagnosis of Guillain-Barré syndrome by anatomical site and illness**

Based on IGOS,[7] clinical nadir was reached within 2 weeks in 96% and 4 weeks in 99% of patients. Cranial nerve involvement was described in 50% of patients, autonomic dysfunction in 25%, and ventilator support required in 19% of patients. At nadir, 76% of patients were unable to walk independently. Following immunotherapy,

	Patterns of limb weakness	Sensory involvement	Cranial nerve involvement	CNS involvement	Serial neural conduction	IgG against ganglioside type	Proportion of patients with Guillain-Barré syndrome
Guillain-Barré syndrome spectrum							
Classic							
Demyelinating	Upper and lower limbs	Yes	Yes	No	AIDP	Unknown	69–90%
Axonal	Upper and lower limbs	Yes in AMSAN, no in AMAN	Yes	No	AMSAN, RCF	GM1, GD1a	<22%
Pure motor	Upper and lower limbs	No	Yes	No	AMAN, RCF	GM1, GD1a	5–70%
Pure sensory	None	Yes	No	No	Abnormal SNAPs	GD1b	<1%
Paraparetic	Lower limbs	Yes	No	No	Axonal	GM1, GD1b	5–10%
Facial diplegia and paraesthesia	None	Yes (distal)	Facial	No	AIDP	Unknown	<5%
Pharyngeal, cervical, brachial	Proximal upper limbs	Supportive	Bulbar	No	Equivocal	GT1a, GQ1b	<5%
Acute bulbar palsy	None	Supportive	Bulbar	No	Equivocal	GT1a	<1%
Guillain-Barré syndrome with hyperreflexia	Upper and lower limbs	Yes	Yes	No	Axonal	GM1	<1%
Miller Fisher syndrome spectrum							
Classic	None	Ataxia	Ocular motor nerves	No	Abnormal SNAPs	GQ1b, GT1a	4–25%
Acute ophthalmoplegia	None	Supportive	Ocular motor nerves	No	Normal	GQ1b	<1%
Acute ataxic neuropathy	None	Ataxia	No	No	Axonal	GM1	<5%
Acute ptosis	None	Supportive	Ptosis only	No	Normal	GQ1b	<1%
Acute mydriasis	None	Supportive	Dilated pupils	No	Normal	Unknown	<1%
Acute vestibular syndrome	None	Supportive	Nystagmus	Nystagmus	Normal	GQ1b	<1%
Bickerstaff brainstem encephalitis							
Classic	None	Supportive	Ocular motor nerves	Yes	Axonal	GQ1b, GT1a	<5%
Acute ataxic hypersomnolence	None	Ataxia	No	Yes	Normal	GQ1b	<1%

AIDP=acute inflammatory demyelinating polyneuropathy. AMAN=acute motor axonal neuropathy. AMSAN=acute motor and sensory neuropathy. RCF=reversible conduction failure. SNAP=sensory nerve action potential.

Table 3: **Clinical classification of Guillain-Barré syndrome**

most patients made a good recovery, with 77% able to walk independently at 6 months and 81% at 12 months.

The overall prognosis in Guillain-Barré syndrome is good, but there are patients who die from it or are left with substantial disabilities. Predictors of poor outcome include advanced age, antecedent *C jejuni* infection, the need for ventilation, and an axonal Guillain-Barré syndrome subtype. Prognostic models of Guillain-Barré syndrome have been developed to facilitate patient care, notably the modified Erasmus Guillain-Barré Syndrome Outcome Score (mEGOS) and Erasmus Guillain-Barré Syndrome Respiratory Insufficiency Score (EGRIS).[100,101] After assessment with mEGOS on admission and at week 1, patients who were older and had diarrhoea and a lower Medical Research Council sum score had a decreased probability of walking independently at 6 months. EGRIS predicted an increased probability of early ventilation in patients who, on admission, had a shorter duration of weakness from onset of symptoms, a lower Medical Research Council sum score, and the presence of facial weakness, bulbar weakness, or both. The models have since been validated in other Guillain-Barré syndrome patient cohorts.[102,103] Serum biomarkers, including low albumin, small rise in immunoglobulin, and high serum neurofilament light chain, have also been associated with inferior outcomes.[104–106]

Clinical classification of Guillain-Barré syndrome-related disorders and variants

The NINDS and Brighton Collaboration criteria have been helpful in diagnosing most patients with Guillain-Barré syndrome, but a substantial number or patients have minimal or regional patterns of weakness, and would not fulfil either set of criteria. To achieve complete case ascertainment of Guillain-Barré syndrome, all variants should be included.

Once other possible mimic syndromes have been excluded (table 2), particular clinical features will suggest the possibility of a Guillain-Barré syndrome-related disorder, as follows:[107] the neurological pattern is part of typical Guillain-Barré syndrome or Miller Fisher syndrome, electrophysiology suggests a sensorimotor neuropathy, cerebrospinal fluid analysis shows albumincytological dissociation, a monophasic illness is present with onset duration similar to Guillain-Barré syndrome, there is a history of antecedent illness up to 4 weeks before symptom onset, and the presence of IgG against neural antigens.

Table 3 shows the key features of the clinical spectrum of Guillain-Barré syndrome.[108,109] Each variant is described

on the basis of the extent of the pattern of weakness. For instance, paraparetic Guillain-Barré syndrome is a less extensive variant of classic Guillain-Barré syndrome with clinical features of bilateral lower limb weakness, whereas acute opthalmoplegia is a less extensive variant of classic Miller Fisher syndrome. A unique entity is Bickerstaff brainstem encephalitis, in which patients have CNS involvement with reduced consciousness, hyper-reflexia, or both.[110,111] The CNS involvement has been hypothesised to be due to the breakdown of the blood–brain barrier.[112] Some argue that Bickerstaff brainstem encephalitis should be considered a separate disease, but reports of Bickerstaff brainstem encephalitis overlapping with symptoms of Guillain-Barré syndrome suggest a link to Guillain-Barré syndrome.

Electrodiagnostic classification

Studies on nerve conduction are important in supporting a diagnosis of Guillain-Barré syndrome and in establishing the electrodiagnostic classification of demyelinating or axonal subtypes. At the early stages of disease, nerve conduction can be normal, but in most patients there is evidence of a neuropathy. Some early studies on nerve conduction changes in Guillain-Barré syndrome include absent Hoffmann reflexes and F waves, and abundant A waves.[113,114]

Several electrodiagnostic criteria of Guillain-Barré syndrome have become available, primarily defining parameters that indicate demyelination.[15,97,115–117] However, it has subsequently become clear that the most widely referenced criteria[15,115] have their limitations and can underestimate axonal pathology. Guillain-Barré syndrome electrophysiology is a dynamic process, and a single nerve conduction study might not reflect the true underlying pathophysiology. This shortcoming was shown in patients with a positive anti-GM1 antibody where the target antigens are localised primarily at the nodal and paranodal regions.[118,119] Antibodies against target antigens at these sites lead to myelin detachment, which is reflected on nerve conduction studies as slowing and block of conduction. However, subsequent changes at these sites (figure 2) leave the myelin intact with two possible outcomes depending on the extent of axonal involvement. Serial nerve conduction studies can show reduction in distal compound muscle action potential amplitude with relatively preserved velocities (axonal degeneration; figure 2). Such studies can also show rapid resolution of compound muscle action potential amplitude and conduction velocities, referred to as reversible conduction failure (figure 2). By contrast, repeated nerve conduction studies of AIDP show progressively slower parameters with prolongation of distal latencies and slower conduction velocities, even in the recovery stages, reflecting the remyelinating process (figure 2).

It is not always possible to do serial nerve conduction studies and thus, more stringent criteria have been proposed on the basis of studies that are typically done within 2 weeks of disease onset.[116,117] However, reversible conduction failure can only be detected on a second study completed within 6–8 weeks of disease onset. To overcome some of these limitations, the use of electrodiagnostic probabilities based on mathematical modelling has been recommended.[117,120]

Neuroimaging

Peripheral nerve imaging is an emerging area of disease biomarkers. In one study, MRI evidence of cauda equina and lumbar root enhancement had a sensitivity of 83% in patients with acute Guillain-Barré syndrome.[121] Nerve ultrasound offers a cheaper, more practical alternative to MRI. On nerve ultrasound, cervical root enlargement can be seen in early Guillain-Barré syndrome, especially when weakness is substantial.[122,123] In differentiating from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), one study found the application of ultrasound features of sensory sparing pattern, enlarged cervical roots or the vagus nerve had sensitivity, specificity, and positive predictive value of over 85%.[124] Another feature that supports Guillain-Barré syndrome is an improvement in nerve enlargement with clinical recovery.[124,125]

Paediatric Guillain-Barré syndrome

Making a diagnosis of Guillain-Barré syndrome in children can be challenging.[126,127] Their clinical features and disease progression are similar to adult Guillain-Barré syndrome; however, there is substantial pain associated with paediatric Guillain-Barré syndrome that could mask limb weakness, causing delays in diagnosis. When nerve conduction studies are not tolerated in children, neuroimaging with MRI or ultrasound can facilitate diagnosis. Children with Guillain-Barré syndrome tend to have a good prognosis, but as there have been reports of mortality from autonomic dysfunction, treatment strategies, as recommended in adult Guillain-Barré syndrome, are advocated.[128,129]

Treatment-related fluctuations and acute-onset CIDP

The neurological symptoms of a small proportion of patients with Guillain-Barré syndrome and Miller Fisher syndrome worsen after initial stabilisation. Treatment-related fluctuations, defined as a worsening of at least one grade on the Guillain-Barré syndrome disability scale or a decrease in Medical Research Council sum score within 8 weeks of treatment, occur in up to 16% of patients.[109,130,131] It is hypothesised that ongoing immunopathogenic processes are transiently halted during treatment, leading to a pseudo-nadir. Treatment-related fluctuations are different from acute onset of CIDP, in which patients have more than three relapses with one or more occurring after 8 weeks of disease onset.

Management

Approach to treatment

The management of patients with Guillain-Barré syndrome can be stratified according to the different

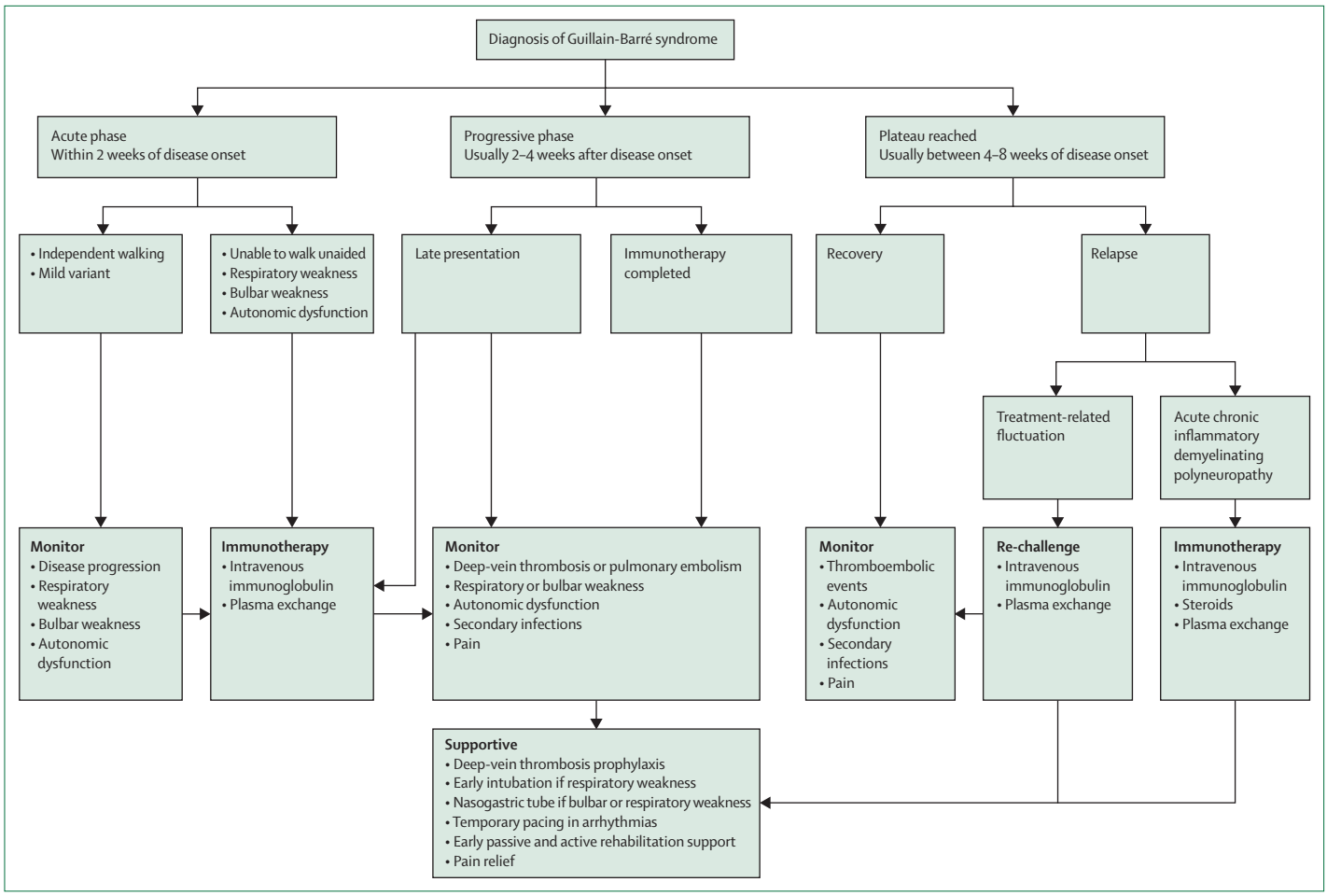

Figure 3: **The management of Guillain-Barré syndrome**
Depending on the time of symptom presentation from disease onset, patients can be managed according to the disease phase. Immunotherapy with either intravenous immunoglobulin or plasma exchange is recommended when the patient cannot walk unaided. Supportive management includes monitoring for disease progression and early intervention when there is evidence of autonomic dysfunction, respiratory weakness, or bulbar weakness. Owing to prolonged immobility, patients are also at risk of deep-vein thrombosis and pulmonary embolism, warranting preventive prophylaxis. After plateau is reached, some patients can have a relapse, which could be due to treatment-related fluctuation, or an acute onset of chronic inflammatory demyelinating polyneuropathy.

stages of the disease (figure 3). In the acute phase, typically within the first 2 weeks of disease onset, patients are at risk of developing complications and extensive nerve damage. In patients with potential respiratory and autonomic failure, admission to a high-dependency unit is advisable for close monitoring of disease progression. Immunotherapy should be initiated as soon as patients show features of disability.[132–135]

Currently, intravenous immunoglobulin and plasma exchange have been shown to be equally effective in improving disease outcome by accelerating recovery, but do not halt disease progression or alter the extent of nerve damage. Both treatments are associated with few adverse events. Rarely, liver dysfunction and thromboembolic events can occur with intravenous immunoglobulin, whereas plasma exchange should be avoided in patients with autonomic instability because the large shifts in fluids lead to a hypotensive state. Steroids are not effective when used on their own but could be beneficial in combination with intravenous immunoglobulin.[136] In patients with autonomic dysfunction and in children, intravenous immunoglobulin is preferred. A dose of 2 g/kg administered over 5 days has shown efficacy in accelerating recovery. A shorter 2-day course was effective in children, but associated with more frequent treatment-related fluctuations.[137] For plasma exchange, four sessions (50 mL/kg plasma per session) have been shown to be effective, but in most clinical practice, five sessions are done.[138]

During the progressive phase, patients are at risk of indirect complications including aspiration, pneumonia, and deep vein thrombosis. These complications can be prevented with supportive measures, such as enteral tube feeding, regular respiratory physiotherapy, and deep vein thrombosis prophylaxis. Physiotherapy should commence as early as possible. Symptoms of pain, fatigue, and low mood require appropriate management. Close monitoring should

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continue as Guillain-Barré syndrome mortality is highest during the recovery phase.[139] The causes of death are typically from respiratory, cardiovascular, or autonomic complications.

Other therapeutic considerations

There are scenarios when the correct decision to treat is not clear. Patients with mild forms of Guillain-Barré syndrome have a good prognosis, but there is some evidence to suggest that two plasma exchange sessions can accelerate recovery when compared with supportive care.[138] In Miller Fisher syndrome, patients eventually recover, but when there is overlap with classic Guillain-Barré syndrome, immunotherapy is recommended to prevent further complications. In treatment-related fluctuations, although there is no evidence to support a further course of treatment, most clinicians would opt for a second course of either treatment that was initially given.[131]

In a third of patients, clinical improvement is not apparent after symptoms reach a plateau.[131] The decision to treat patients with a further course of immunotherapy has largely been at the discretion of the treating clinicians. Sub-analysis of treatment in IGOS showed that in patients with a Guillain-Barré syndrome disability score of more than 3 (unable to walk independently), there were no differences in the 4-week or 24-week scores between patients who received a single course versus two courses of intravenous immunoglobulin.[140] However, this was a non-randomised observation, and prospective randomised trials are ongoing.[100] Other potential combinations that have not shown efficacy include plasma exchange followed by intravenous immunoglobulin, and intravenous immunoglobulin followed by plasma exchange. The latter sequence of the two treatments should be avoided, especially within the first 2 weeks of intravenous immunoglobulin therapy, as plasma exchange would remove intravenous immunoglobulin.

Potential therapeutic compounds

Despite the availability of immunotherapy, the substantial mortality and morbidity of Guillain-Barré syndrome necessitates the need for more effective treatment. Emerging therapeutic approaches target innate and adaptive immunity, and aim to promote regeneration. Some of these promising therapies have only been evaluated in preclinical models (figure 2), whereas others have entered clinical trials.

In a murine Guillain-Barré syndrome model, recombinant antibodies that bound to FcRn with increased affinity enhanced degradation of circulating antiganglioside antibodies, thus preventing antibody-mediated neuronal injury.[141] In other studies, sialylated intravenous immunoglobulin was also effective in preventing antibody-mediated nerve injury in rodents at lower doses than standard intravenous immunoglobulin.[142] In an AMAN rabbit model, IdeS, a *Streptococcus pyogenes*-derived protease, reduced the frequency of axonal motor degeneration and improved recovery.[143,144] Its efficacy in Guillain-Barré syndrome is currently being investigated in a phase 2 clinical study of imlifidase (NCT03943589). Following evidence that monoclonal antibodies, including antiC1q and anti-C5, can attenuate axonal injury and improve respiratory function in mouse models of Guillain-Barré syndrome,[69,145] a phase 2 clinical trial of eculizumab (an anti-C5 monoclonal antibody) was done. Although the study was limited by the small number of patients (n=34), patients who received eculizumab in addition to a course of intravenous immunoglobulin were more likely to run at 6 months of disease onset, suggesting earlier recovery than patients who received only a course of intravenous immunoglobulin.[134]

Controversies, uncertainties, and future directions

Despite the advances in the understanding of Guillain-Barré syndrome, many uncertainties remain. To date, IGOS has impressively recruited almost 2000 patients with Guillain-Barré syndrome, but most patients have been recruited from high-income countries. Published data on Guillain-Barré syndrome in Africa, the Middle East, and many parts of Asia are scarce. To fully comprehend the global burden of Guillain-Barré syndrome and factors associated with the disease, active global engagement with health-care providers from these regions is needed.

Studies support Guillain-Barré syndrome as an autoimmune disease, but the higher incidence reported in men than in women is unusual. Also unusual is that most individuals with *C jejuni* infection do not develop Guillain-Barré syndrome despite its established association. These irregularities suggest that there are likely to be other factors that are involved in causing disease, such as host genetic susceptibility. Axonal Guillain-Barré syndrome and Miller Fisher syndrome are more frequent in Asia than in other settings, whereas AIDP is more common in Europe and North America.[66] This disparity could partly be due to regional variations in infections (infective organisms), but in distinguishing between axonal versus demyelinating subtypes, there could be differences in electrodiagnostic approaches, which can be overcome with serial studies.[146]

The existing Guillain-Barré syndrome diagnostic criteria exclude many variants, including Guillain-Barré syndrome with preserved or brisk tendon reflexes.[97,98] Although uncommon, this group of patients typically present with AMAN, an antecedent diarrhoeal illness, and antiganglioside antibodies.[123] The recognition of Guillain-Barré syndrome variants is clinically important to avoid delayed treatment, and this and other atypical features should be considered in future diagnostic criteria for Guillain-Barré syndrome.

There is a preference in high-income countries for initiating intravenous immunoglobulin as first-line therapy,[131] but the cost-effectiveness of plasma exchange

in treating Guillain-Barré syndrome should not be overlooked. Further analysis comparing the health economics and treatment burden between intravenous immunoglobulin and plasma exchange is warranted, especially when there is a growing global shortage of blood products.[147] Small-volume plasma exchange in treating patients with Guillain-Barré syndrome has seen a resurgence[148,149] and has been shown to be a safe and cheaper alternative to standard plasma exchange. In low-income countries, where patients would receive only supportive treatment resulting in increased morbidity and mortality, this course of treatment should be considered.[150] Another potential therapy that merits further study is pleiotropic cytokine erythropoietin, which has been found to be neuroprotective and proregenerative in animal models of antibody and T-cell-mediated Guillain-Barré syndrome.[151,152]

Conclusion

Since its initial description in 1916 by Georges Guillain, Jean Alexandre Barré, and André Strohl, there continues to be substantial developments in Guillain-Barré syndrome. IGOS has provided some clarity on geographical variations with more information likely to follow. The transient surge in patients with Guillain-Barré syndrome during the 2016 Zika virus outbreak and emerging reports of Guillain-Barré syndrome in SARS-CoV-2 infection add to the growing list of antecedent infections. With the changing landscape in cancer therapy, reports of Guillain-Barré syndrome associated with immune checkpoint inhibitors have emerged. The medical community is continuously reminded of the need to remain vigilant of potential neurological complications with infective outbreaks and with the rise in novel immunotherapies. As new therapies enter clinical trials, and research is done into overcoming axonal degeneration and enhancing neural regeneration, the future outlook for Guillain-Barré syndrome is positive.

Contributors

All authors contributed equally and approved the final version of the manuscript.

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