Guillain-Barré Syndrome: Multifactorial Mechanisms versus Defined Subgroups

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The clinical spectrum of Guillain-Barré syndrome (GBS) is summarized in relation to antecedent infections and anti-ganglioside antibodies. Associations exist between a pure motor form of GBS, diarrhea, *Campylobacter jejuni* infection, and anti-GM_1 antibodies; between cranial nerve involvement and Miller Fisher syndrome, *C. jejuni* infection, and anti-GQ_{1b} antibodies; and between variants, such as severe sensory involvement and cytomegalovirus infection. These three clinical variants are suggested to form the extremes of a continuous spectrum; they are discussed in relation to the more pathologically defined patterns of acute motor axonal neuropathy and acute motor-sensory axonal neuropathy. In particular, patients with a clinically pure motor variant of GBS, diarrhea, anti-GM_1 antibodies, or *C. jejuni* infection seem to respond better to early treatment with high-dose immunoglobulins than to plasma exchange.

Recently, attempts have been made to subdivide the clinical patterns of Guillain-Barré syndrome (GBS). The primary criteria for a diagnosis of GBS are an acute or subacute more-or-less symmetrical paresis, a loss of myotatic reflexes, and a lack of other causes for the existing polyneuropathy [1]. Clinical, physiologic, pathologic, immunologic, and microbiologic factors may vary between patients [1]. In 1988, my colleagues and I reported on two patterns of nerve conduction failure in GBS [2]. In 1 group of patients, clinical deficit was purely motor, and conduction block was found in motor nerves early in the clinical course. Weakness was predominantly distal. In the other pattern, the motor and sensory systems were equally involved clinically and physiologically. Compound muscle action potentials (CMAPs) were low in most subjects after distal stimulation of the nerve, and weakness in proximal muscles sometimes occurred. Similar differences were demonstrated in another analysis of 8 very severe GBS cases with presumed extensive axonal damage [3]. In 3 of these patients, the sensory system was completely normal, and in 2 others, it was relatively unaffected. Conduction block was present initially in most of the subjects, suggesting initial demyelination, and in 3 patients, only low CMAPs could be recorded after distal stimulation of the nerve, indicating either primary axonal degeneration or initial distal demyelination.

On the basis of these experiences, we questioned whether clinical, physiologic, immunologic, or microbiologic factors have an effect on the outcome of GBS, especially with regard to treatment. Consequently, we incorporated these questions into a clinical trial comparing high-dose intravenous immunoglobulin (IVIG) and plasma exchange (PE) therapies in 147 GBS patients [4]. The results are the basis of this review.

In general, it has not been possible to define distinct subgroups in clinically defined GBS; instead, a clinical spectrum seems to exist with extremes, including the pure motor, severe sensory, and cranial nerve forms of GBS (table 1). Variants suggested by others [5] can also be included in this spectrum. In addition, associations have been found within the extreme groups (e.g., a high incidence of *Campylobacter jejuni* infection, the presence of anti-GM_1 antibodies, and other clinical features associated with the pure motor form of GBS) [6]. GBS patients with increased sensory involvement are more likely to have had an antecedent cytomegalovirus infection than are patients without sensory involvement; sensory-involved patients also have other specific clinical associations [7]. It is important to note that in our studies, patients with the pure motor form of GBS more often had anti-GM_1 antibodies and a preceding *C. jejuni* infection than did patients with other neurologic diseases or normal controls [8]. However, the association between *C. jejuni* and anti-ganglioside antibodies is not absolute [8], and molecular mimicry as a pathogenic mechanism therefore is likely in only part of the patients [9, 10].

Herein, we review our data supporting the point of view that strictly defined subgroups are not easily distinguished in GBS, that extremes of the spectrum of clinical symptoms are of great value for elucidating specific mechanisms, and that more than one specific mechanism may contribute to a ''composite'' GBS in those individual patients who form the majority with symptoms between the extremes. Moreover, we will discuss the effect of IVIG versus PE therapy for the treatment of these GBS extremes and the finding that IVIG treatment may be more effective than PE in some patients.

The Clinical Spectrum of GBS

The spectrum of GBS can be described at at least three levels: the clinical level, the level of antecedent infections, and

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Table 1. Extreme patterns in the clinical spectrum of clinically defined GBS.

Clinical characteristics	Clinicopathological characteristics
Pure motor	Acute inflammatory demyelinating polyradiculoneuropathy
	Acute motor axonal neuropathy
Severe sensory	Acute inflammatory demyelinating polyradiculoneuropathy
	Acute motor-sensory axonal neuropathy
Cranial nerves	Miller Fisher syndrome
	Lower bulbar variant
	(All demyelinating?)

the level of immunologic disturbances. Figure 1 attempts to describe the association between these three levels [11] in our population of 147 patients. Clinically, 18% of the patients had pure motor GBS [6]. The majority (80%) had sensory motor involvement, which varied from mild to very severe. A small proportion (3%) of patients had a deficit starting in the oculomotor nerves, resulting in Miller Fisher syndrome, which is defined as oculomotor weakness, ataxia, and areflexia. Not indicated are those patients in whom the paresis started in the lower bulbar muscles. Of note, in 26 of our patients with either Miller Fisher syndrome or the lower bulbar variant, about half of the Miller Fisher patients developed lower bulbar weakness and vice versa. Also, about half of them went on to develop paresis in the extremities [12].

Some of the GBS patients were thought to have very severe axonal involvement, either primary or secondary. In figure 1, this has been indicated in the pure motor and sensory motor segments. The exact proportion is difficult to establish since it is very difficult to estimate the contribution of axonal degeneration versus demyelination with certainty using conventional electrophysiologic techniques [13]. Further clinical characteristics are associated with these subgroups; in general, the pure motor form more often involves distal weakness and a more rapid onset, whereas patients with more severe sensory involvement more often have global and more proximal weakness and a slower onset [6, 7].

Antecedent Infections and Antibodies Related to Clinical Extremes

As indicated in figure 1, *C. jejuni* is the infection that most frequently precedes GBS, and it is strongly but not absolutely associated with the pure motor form [6, 8]. Cytomegalovirus infection is the second most frequently occurring antecedent infection and is associated with severe sensory involvement [6]. Anti-GM_1 antibodies are frequently associated with the pure motor form of GBS and with *C. jejuni* infection, and there is an association between *C. jejuni,* the pure motor form of GBS, Miller Fisher syndrome, and anti-GQ_{1b} antibodies [9].

These findings lead to the general conclusion that in GBS, infectious agents, such as *C. jejuni,* may be associated with different clinical patterns and different autoantibodies and that none of the associations are absolute. There is no simple connection between *C. jejuni* infection, the development of anti-GM_1 antibodies (41% of *C. jejuni*–positive patients), and a pure motor form of GBS (30% of *C. jejuni*–positive patients). Conversely, about two-thirds of the patients with either a pure motor form of GBS or GM_1 antibodies have positive *C. jejuni* serology [6, 8].

In a further attempt to distinguish subgroups, we performed a cluster analysis of electrophysiologic data: No distinct groups could be identified despite the large variation of findings for individual patients [14], supporting the concept of a continuum in which extremes may be identified. These clinical and laboratory findings provide background information for our general view that strictly defined subgroups are not easily distinguished in GBS, that extremes of the spectrum are of great value for elucidating specific mechanisms, and that more than one specific mechanism may contribute to a ''composite'' GBS in those individual patients who form the majority with symptoms between the extremes.

The Effect of PE or IVIG in Relation to GBS Subgroups

Of interest, there was a difference between the effect of treatment with PE and IVIG in the cluster of patients with pure motor syndrome, anti-GM_1 antibodies, or *C. jejuni* antibodies [6, 8]. In this group of patients, IVIG treatment was more effective than PE. This difference was most pronounced in the patient group with a pure motor syndrome and *C. jejuni* infection; none of the 6 patients treated with PE were able to walk after 6 months, whereas 9 of 10 IVIG-treated patients could walk independently 6 months after treatment [6]. Diarrhea was

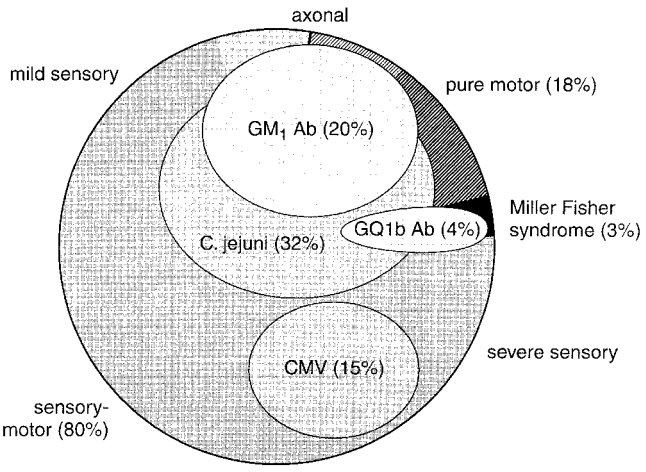

Figure 1. Distribution of subpatterns of clinically defined GBS among 147 patients. Axonal damage may occur in pure motor and sensory motor forms. Most common infections associated with specific subpatterns and association with antiganglioside antibodies (Ab) are indicated. CMV, cytomegalovirus. (Reprinted with permission from [11]).

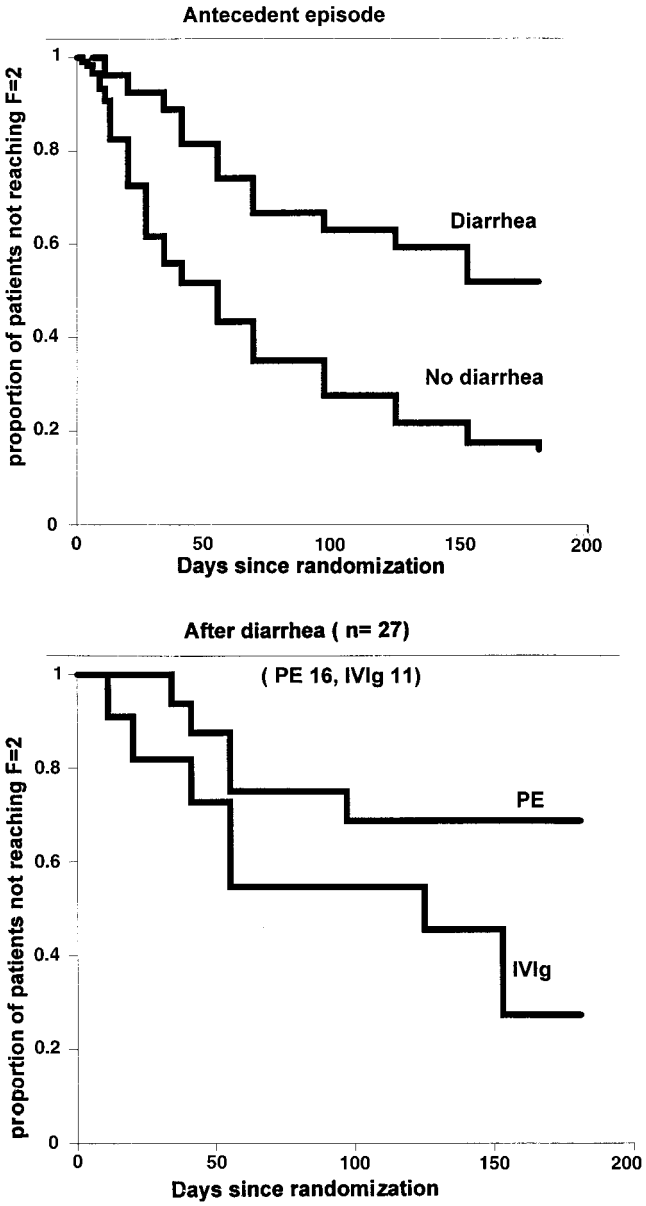

Figure 2. Kaplan-Meier curves indicating chance of being able to walk independently at different time points during 182-day follow-up. Top, patients with or without diarrhea and irrespective of treatment ($P < .001$). Bottom, patients with diarrhea and receiving plasma exchange or intravenous immunoglobulin treatment ($P = .04$).

also associated with the pure motor GBS, *C. jejuni* infections, and anti-GM_1 antibodies, and also the effect of the two treatments was similar: IVIG patients again did respond better (figure 2). Of note, in our analysis of these four factors (i.e., diarrhea, pure motor syndrome, anti-GM_1 antibodies, and *C. jejuni* antibodies) as predictive factors, diarrhea had the strongest predictive value in relation to outcome at 8 weeks or 6 months but only in the PE-treated group. In the IVIG-treated group, none of the factors were of prognostic value (Visser LH et al., unpublished data).

Discussion

The World Health Organization meeting on flaccid paresis (1992, in Geneva) suggested a primarily clinical definition for GBS: symmetric paresis with a typical time course and decreasing myotatic reflexes [15]. By use of such a broad definition, it is possible to study the association of GBS with a large variety of clinical and laboratory factors. As shown here, it has not yet been possible to define distinct subgroups. Extremes within the large clinical spectrum are, however, clearly associated with serologic findings. It is anticipated that within these extreme groups, the mechanisms will be elucidated in more detail and that these better-defined mechanisms will be found to occur in different combinations in individual GBS patients. One example of such a combination may be found in patients with early severe oculomotor involvement and classic ascending weakness, a situation in which a mechanism resulting in classic ascending GBS and a mechanism leading to Miller Fisher syndrome may be combined. Both mechanisms may result from a *C. jejuni* infection and the formation of anti-GQ_{1b} and anti-GM_1 antibodies, presumably due to molecular mimicry [9].

In fact, all combinations of the mechanisms of the clinical extremes might result in the full spectrum of what we observe in the clinic as GBS. The effect of treatment as described here only reinforces this concept, stressing the importance in clinical trials of collecting more data than seem necessary in order to evaluate outcome. The information we gathered enabled us to define subpatterns and subsequently to define a different effect of treatment in these subgroups. It may be that the ongoing discussion concerning the effect of *C. jejuni* will soon be extended to cytomegalovirus infection; we are completing a search for antiperipheral nerve antibodies in this group of infections, which ranks as the second most common precedent to GBS.

In contrast to our approach of looking for associations in a large group of clinically defined GBS patients in the Western world, a US-Chinese group defined GBS subgroups as determined on the basis of autopsies of Chinese patients [5, 16]. Such small studies are ideal for demonstrating specific pathologic patterns. Acute motor axonal neuropathy and acute motor-sensory axonal neuropathy patterns, as shown in table 1, are not easily determined in the usual clinical setting, in which autopsy is rare. In general, it is difficult to distinguish demyelination from axonal degeneration by use of electrodiagnostic methods [13, 14, 17, 18], and therefore it is even more difficult to define whether it is primary or secondary axonal degeneration [6, 19, 20]. Thus, in the Western clinical setting, there is need for validated criteria for subgroups based on clinical, electrophysiologic, and especially, microbiologic and immunologic data.

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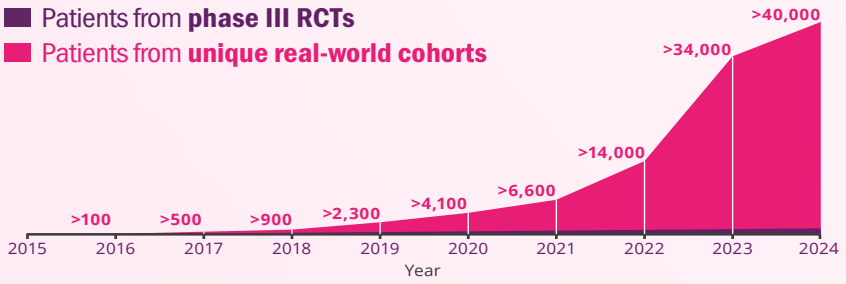

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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