Teaching Course 10

Current treatments in neurology - Level 1

Current treatment in Guillain-Barré Syndrome and myasthenia gravis

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Conflicts of interest
PA van Doorn has received unrestricted departmental research grants from Baxter/Baxalta to conduct 3 RCT’s in GBS or CIDP: Gammagard S/D with or without methylprednisolone in GBS, Gammagard S/D versus Kiovig in CIDP (DRIP), and a dose-finding study with Kiovig in CIDP (CIC). An unrestricted grant from Sanquin to conduct the second-dose IVIg RCT in GBS (SJD-GBS), and a grant from Grifols to conduct an international prospective study on the effect of a second-dose IVIg in GBS (I-SJD-GBS). Departmental payments for consultancy/ RCT trial boards, from Talecris, CSL, Baxalta, Kedrion, Octapharma. Received government research support ZonMW, and received support from the non-profit foundations Prinses Beatrix Spierfonds and Janivo Foundation, unrelated to this study.

Abbreviations

AIDP = acute inflammatory demyelinating polyradiculoneuropathy
AMAN = acute motor axonal neuropathy
AMSAN = acute motor and sensory axonal neuropathy
CIDP = chronic inflammatory demyelinating polyradiculoneuropathy
GBS = Guillain-Barré syndrome
IVIg = intravenous immunoglobulin
TRF = treatment-related fluctuation
MFS = Miller Fisher syndrome
MG = myasthenia gravis
PE = plasma exchange
RCT = randomized controlled trial
Abstract

Intravenous immunoglobulin (IVIg) and plasma exchange (PE) are effective in Guillain-Barré syndrome (GBS). Steroids alone are ineffective. Mainly for practical reasons, IVIg is the preferred treatment. It is yet unknown whether GBS patients who remain able to walk (‘mildly affected GBS patients’), or patients with Miller Fisher syndrome (MFS) also benefit from IVIg. Despite current treatment, GBS remains a severe disease, and 20% is still unable to walk after half a year, many patients have pain, fatigue or other residual complaints that may persist for months or years. Prognostic models for GBS are now available. The Erasmus GBS Respiration Insufficiency Scale (EGRIS) predicts the chance for artificial ventilation. The modified Erasmus GBS Outcome Scale (mEGOS) predicts the chance to be able to walk unaided after 6 months. GBS patients with a poor prognosis potentially might benefit from a more intensified treatment. A larger increase in serum IgG levels after standard IVIg treatment (0.4 g/kg/day for 5 consecutive days) seems to be related with an improved outcome. The SID-GBS trial investigates whether a second IVIg course improves outcome in GBS patients with a poor prognosis, when administered already early in the course of disease when nerve damage potentially is reversible. This RCT is now almost finished. As there is a lot of laboratory evidence that complement activation plays a role in GBS, the complement C5 inhibitor Eculizumab, has recently been investigated in a small RCT in GBS. This small RCT did not show significant differences for the primary endpoint, but indicated that Eculizumab potentially may be an effective treatment for GBS, but additional studies need to be done. In myasthenia gravis (MG), the mainstay of treatment is acetylcholine esterase inhibitors. There are additional treatments available like corticosteroids, mycophenolate, and azathioprine. PE and IVIg can be helpful,
mainly for acute exacerbations. Thymectomy was shown to be effective in a large controlled trial. Rituximab may also be effective, especially in MUSK positive patients. There is evidence that complement activation at the neuromuscular junction plays a role in MG. A recent large RCT (REGAIN study) in patients with refractory and generalized MG with anti-acetylcholine receptor antibodies investigated the effect of Eculizumab. Although the primary efficacy endpoint, improvement in activities of daily living (MG-ADL) compared with the placebo group, was not met, several secondary endpoints showed potential benefit for Eculizumab. This drug is extremely expensive. It can be an alternative drug for some patients with MG, but the precise role of this very expensive drug in the treatment of patients with MG in whom the currently used drugs did not work, needs to be established.

**Guillain-Barré syndrome**

**Introduction**

GBS most frequently is a post-infectious disorder, often with *Campylobacter jejuni*. Hepatitis E can also provoke the start of GBS[1, 2]. In typical cases, among the first symptoms are pain, numbness, paraesthesia, or weakness in the limbs[3]. The main features of GBS are rapidly progressive bilateral and relatively symmetric weakness of the limbs with or without involvement of respiratory or cranial nerve-innervated muscles[4-6]. Rapidly progressive weakness is the core clinical feature of GBS. By definition, maximal weakness is reached within four weeks, but most patients have reached their maximal weakness already within two
weeks[6]. Patients then have a plateau phase of variable duration ranging from days to several weeks or months. This phase is followed by a recovery phase of variable duration. Despite the effect of intravenous immunoglobulin (IVIg) or plasma exchange (PE) treatment, about 20% of the ‘severely affected patients’ remain unable to walk after half a year[7-9]. Moreover, many patients remain otherwise disabled or severely fatigued. Even 3-6 years after onset, GBS had great impact on social life and the ability to perform activities. It is clear that GBS often remains a severe disease for which better treatment is required, at least in a proportion of patients[10].

**Importance of general care in GBS**

Patients with GBS specially need excellent multidisciplinary care to prevent and manage potential fatal complications. This indicates the need for careful monitoring of cardiac and respiratory function and the prevention of infections[11, 12]. Since about 25% of severely involved patients require ventilation, the need for this procedure needs carefully and regularly be evaluated. This means at least the regular measurement of vital capacity and respiratory frequency, and timely transfer to an intensive care unit. (Table 1). A new simple scale that can be used already at hospital admission helps to predict the chance to need artificial ventilation[13]. Among other issues that need attention already early in the course of disease are prophylaxis for deep vein thrombosis, cardiac and hemodynamic monitoring (among other symptoms of autonomic dysfunction), pain management, management of possible bladder and bowel dysfunction, psychosocial support and rehabilitation. Patients can die from GBS. Severe complications leading to death can also occur after discharge form an ICU, likely due to acute choking or airway obstruction,
or to autonomic failure[14]. Many patients and their relatives benefit from joining a patient organisation such as The GBS/CIDP Foundation International (www.GBS-CIDP.org).

**The beneficial effect of immunotherapy**

It has been shown that plasma exchange (PE) is beneficial when applied within the first four weeks from onset, but the largest effect was seen when started early (within the first two weeks)[9]. The usual regimen is a five times PE during two weeks, with a total exchange of about five plasma volumes. The first RCT on the use of IVIg (0.4 gram IVIg/kg bodyweight/day for five consecutive days) was published in 1992, demonstrating that IVIg is as effective as PE[15]. After these results were published, IVIg has replaced PE as the preferred treatment in many centres, mainly because of its greater convenience and availability. The Cochrane review on the use of IVIg in GBS showed that there was no difference between IVIg and PE with respect to the improvement in disability grade after 4 weeks, the duration of mechanical ventilation, mortality, or residual disability[7]. The combination of PE followed by IVIg was not significantly better than PE or IVIg alone[16]. It appeared that oral steroids, or intravenous methylprednisolone 500 mg/day for 5 consecutive days) alone are not beneficial in GBS. The combination of IVIg and intravenous methylprednisolone was not more effective than IVIg alone, but there might be some additional short term effect of this combined treatment when a correction was made for known prognostic factors[17]. In a pilot-study, we studied the additional effect of a six-week treatment of mycophenolate in GBS, which did not show a positive effect[18]. There definitely is an effect of immunotherapy on the course of GBS, but new studies improving also the final outcome of GBS remain
urgently needed. A RCT (SID-GBS) studying the effect of a second dose IVIg in GBS patients with a poor prognosis, currently running in the Netherlands, is now almost finished (PA van Doorn, personal communication). The results of the international prospective study on the effect of a second dose IVIg in GBS patients with a poor prognosis (I-SID-GBS) are expected soon (PA van Doorn, personal communication). This study is part of the International GBS Outcome Study (IGOS).

There is a lot of evidence mainly from laboratory studies that complement activation plays an important role in GBS. The effect of the complement C5 inhibitor Eculizumab was initially investigated in Scotland [19].

The Japanese Eculizumab Trialist recently investigated the effect of Eculizumab (JET-GBS) [20]. This small RCT did not show significant differences for the primary endpoint. This trial however indicated that Eculizumab potentially may be an effective treatment for GBS, but additional studies need to be done.
**Table 1: Management of GBS during course of disease**

**Diagnosis**
Diagnosis of GBS is mainly based on clinical features and CSF. Laboratory investigations include blood studies and EMG.

**Give good general care**
Monitor progression, and prevent and manage potential fatal complications, especially:
- regular monitor pulmonary function (vital capacity, respiration frequency) initially every 2-4 hours, in stable phase every 6-12 hours.
- check for autonomic dysfunction (blood pressure, heart rate, pupils, ileus)
- check for swallowing dysfunction
- recognize and treat pain (WHO guideline). Try to avoid opioids
- prevent and treat infections and pulmonary embolism
- prevent decubitus and contractures

**Consider specific treatment with IVIg or PE**
- **Indication to start IVIg or PE**
  Severely affected patients (inability to walk unaided = GBS disability scale ≥3).
  Start preferable within first 2 weeks from onset
  IVIg: 0.4g/kg for 5 days (unknown whether 1.0g/kg for 2 days is superior)
  PE: standard 5x PE with total exchange of five plasma volumes
- **Unknown whether IVIg is effective**
  Mildly affected patients (GBS disability scale ≤2) or MFS patients
- **Indication for re-treatment with IVIg?**
  Secondary deterioration after initial improvement or stabilization (treatment-related fluctuation): treat with 0.4g/kg for 5 days
  No proven effect of re-treatment with IVIg in patients who continue to worsen

**Is there an indication for ICU admission?**
- Rapidly progressive severe weakness often with impaired respiration (vital capacity < 20 ml/kg), and or direct need for artificial ventilation
- Insufficient swallowing with high chance for pulmonary infection
- Severe autonomic dysfunction

**Fluctuations during course of disease or continued slow progression?**
- Consider treatment related fluctuation (TRF): repeat treatment
- Consider acute-onset CIDP (A-CIDP) and treat accordingly

**Rehabilitation and fatigue**
- Start physiotherapy early during course of disease
- Start rehabilitation as soon as improvement starts
- Consider a physical training program for severe fatigue
- Consider to contact patient organization for additional information and help
When should treatment be started?

The North-American PE trial showed an effect of PE when applied within the first four weeks after onset/weakness[21]. Most effect however was observed when PE was started within the first two weeks from onset. After the publication of this trial, most RCT’s have enrolled patients being within the time window of two weeks from onset of weakness and unable to walk without assistance[8].

Should mildly affected patients be treated?

Mildly affected is arbitrarily defined as being able to walk, with or without assistance. A retrospective study demonstrated that these patients frequently have residual disabilities. The RCT’s evaluating the effect of IVIg did not study the effect in mildly affected patients. One large French trial studied the effect of PE also in patients who could walk-with or without aid, but not run [22]. Onset of motor recovery was faster in patients who received two PE sessions compared to no PE. Based on this study there could be an indication also to treat mildly affected GBS patients with PE, but one must keep in mind that no randomized placebo controlled studies have evaluated the effect of PE or IVIg in these mildly affected GBS patients.

Should patients with Miller Fisher syndrome (MFS) be treated?

No RCT’s have been performed on the effect of PE or IVIg in patients with MFS. Observational studies suggested that the final outcome in patients with MFS generally is good[23]. From a large Japanese uncontrolled observational study it was found that IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia, but the times of disappearances of these symptoms were similar among the IVIg, PE and no-treatment group. It was
concluded that IVIg and PE seem not to have influenced MFS patients’ outcome, presumably because of good natural recovery.

**What to do if a patient continues to deteriorate after treatment?**

A proportion of GBS patients continue to deteriorate after PE or a standard course of IVIg. In these cases, it is unknown what would be the best option: wait and see, or to start additional treatment [24]. The reason why some patients continue to deteriorate and may be paralytic for months is not known. These patients might have a severe or prolonged immune attack causing severe axonal degeneration. Treatment might act insufficiently in these individuals. It is presently not known how to treat patients who continue to deteriorate. Do these patients need PE after they have been treated with IVIg? This has not been investigated, but it has been shown that the combination of PE followed with IVIg is not superior compared to PE or IVIg alone. A small open study suggested that a repeated course of IVIg may be effective in severe unresponsive GBS patients. The international trial studying the effect of a second IVIg dose in patients with a poor prognosis, based upon the modified Erasmus Guillain-Barré Outcome score (mEGOS) has been started[25].
What to do if a patient deteriorates after initial improvement?

About five to ten percent of GBS patients deteriorate after initial improvement or stabilization following IVlg treatment, a condition named “treatment-related clinical fluctuation”. Although no RCT has evaluated the effect of a repeated IVlg dosage in this condition, it is common practice to give a second IVlg course (2 g/kg in 2-5 days), since these patients are likely to improve after re-initiating this treatment. It is considered that these patients may have a prolonged immune-response that causes ongoing nerve damage needing treatment for a longer period of time. Some of these GBS patients may even have several episodes of deterioration. This often raises the question whether these patients may have chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP) [26].
### Table 2: Treatment dilemmas in GBS and recommendations

<table>
<thead>
<tr>
<th>Dilemma</th>
<th>Current personal view</th>
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<tbody>
<tr>
<td>Start of treatment</td>
<td><strong>Time window</strong></td>
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<tr>
<td></td>
<td>Treatment should be initiated as soon as possible after diagnosis to prevent further nerve damage (LOE: 3). The effect of IVIg started after 2 weeks and of PE after 4 weeks onset of weakness is unknown (LOE: 4).</td>
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<tr>
<td>Mild forms</td>
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<td></td>
<td>Consider treating mildly affected patients with a rapidly progressive course or with additional features such as autonomic dysfunction, bulbar or facial weakness (LOE: 2).</td>
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<tr>
<td>Variants</td>
<td>Patients with typical MFS likely require supportive care only (LOE: 3). In complicated MFS (limb weakness, bulbar weakness) and BBE, treatment with IVIg or PE should be considered (LOE: 4). Other GBS variants should be treated according to local guidelines until results of specific treatment trials show otherwise (LOE: 4).</td>
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<tr>
<td>Children</td>
<td></td>
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<td></td>
<td>Treatment with IVIg is beneficial in children and IVIg is preferred over PE because it is easier to administer (LOE: 2).</td>
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<td>Repeat or change of treatment</td>
<td><strong>Insufficient clinical response</strong></td>
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<td>There is not enough evidence that switching to IVIg after PE is effective in patients who are severely affected (LOE: 2). IVIg followed by PE should probably be avoided (LOE: 4). The effect of a 2nd IVIg course in patients with a poor prognosis is currently investigated.</td>
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<tr>
<td>TRF</td>
<td></td>
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<td>Although there are no RCTs, there is some rationale to re-treat patients who experience a TRF with either IVIg or PE (LOE: 4). When a patient develops 3 or more TRFs or deteriorates 8 weeks after onset, A-CIDP should be considered.</td>
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A-CIDP = acute-onset CIDP; BBE = Bickerstaff’s brainstem encephalitis; GBS = Guillain-Barré syndrome; IVIg = intravenous immunoglobulin; LOE = level of evidence; MFS = Miller Fisher syndrome; PE = plasma exchange; RCT = randomised controlled trial; TRF = treatment-related fluctuation.

Adapted from: C. Verboon, PA van Doorn, BC Jacobs. J Neurol Neurosurg Psychiatry 2017;88:346-352
How many deteriorations would alter the diagnosis from GBS to A-CIDP?

This is an important question, but the answer is not fully known yet. We have evaluated our series of patients and concluded that the diagnosis of A-CIDP should be suspected when patients initially diagnosed with GBS, do have three or more of these deteriorations or when they have a subsequent deterioration after nine weeks from onset of GBS. It is important to look for these secondary deteriorations because GBS patients may improve after a new course of IVIg and some of these patients turn out to have a variant of CIDP with acute onset (A-CIDP) needing chronic maintenance treatment[26].

Importance of pain in the acute and chronic phase of GBS

Pain is a common and severe symptom in patients with GBS. Recognition of pain is important, especially in patients unable to communicate due to intubation. Pain as a presenting symptom of GBS, before the onset of weakness, may be misleading in making the diagnosis of GBS. Pain has been described in up to 89% of patients with GBS. Recognition of the presence and type of pain is important because specific treatments can be offered[27].

Autonomic failure.

Autonomic dysfunction, like labile blood pressure, tachycardia or heart rate disturbances, often occurs in GBS patients. Recognition of autonomic dysfunction is important, because it seems to be an important cause of death in GBS. About 3% of patients die, presumable partly due to (sudden) autonomic- or respiratory failure[14]. It is yet not well possible to predict which patients will develop serious autonomic failure and therefore need
continue monitoring. From observational studies it seems that patients not only die while being admitted on an ICU due to serious autonomic failure or pulmonary problems, but also the first period after discharge from an ICU can be a high-risk period especially when a patient has a tracheostomy and develops a bronchopneumonia or when there are other reasons for hypoventilation.

The presence and treatment of severe fatigue after GBS

Fatigue after GBS is an important problem. It was found that severe fatigue was even present in 60-80% of patients [28]. Eighty percent of patients reported fatigue as being among their three most disabling symptoms. A 12 week bicycle exercise training however was likely to be effective in 16 severely fatigued but neurologically well recovered GBS and 4 stable CIDP patients [29]. The rather intensive, three-times weekly training program we used was well tolerated, and self-reported fatigue scores decreased significantly. Physical fitness, functional outcome, and quality of life were also improved. A RCT however still needs to be done[30]. Although the effect of the physical training program cannot fully be explained yet, it seems to help, possible also by ensuring and changing life-style.

Myasthenia gravis

Patients with myasthenia gravis (MG) often have good outcome after treatment with acetylcholine esterase inhibitors, and when needed immunosuppressive and immunomodulatory therapies like corticosteroids, mycophenolate, and azathioprine. PE and IVIg can be helpful, mainly for acute exacerbations. Thymectomy was found to be effective in patients 18-65 years of age with generalized nonthymomatous myasthenia gravis
with a disease duration of less than 5 years, with moderate-severe disease (class II-IV on a scale from I-V) and acetylcholine-receptor antibodies [31]. Rituximab, a chimeric mouse/human anti-CD20 monoclonal antibody, may also be effective, especially in patients with antibodies to muscle-specific thyrosine kinase (anti-MUSK positive) [32]. There is evidence that complement activation at the neuromuscular junction plays a role in MG. A recent large RCT (REGAIN study) in patients with refractory and generalized MG with anti-acetylcholine receptor antibodies investigated the effect of Eculizumab. Although the primary efficacy endpoint, improvement in activities of daily living (MG-ADL) compared with the placebo group, was not met, several secondary endpoints showed potential benefit for Eculizumab [33,34]. This drug is extremely expensive. It can be an alternative drug for some patients with MG, but the precise role of this very expensive drug in the treatment of patients with MG in whom the currently used drugs did not work, needs to be established.

Future directions

New treatment options in GBS are absolutely necessary because the prognosis in a large group of GBS patients is still far from good. One option in the acute phase could be a second IVIg treatment in patients with a poor prognosis. The results of the I-SID GBS prospective study and the SId-GBS RCT need to be awaited. The evidence of complement activation in the acute phase of GBS and the results of the first small RCT with Eculizumab in GBS are promising and warrant further studies with drugs that prevent complement activation in GBS.

There are multiple treatment option for patients with MG. Evidence from a recent study showed the effect of thymectomy in patients with generalized MG with acetylcholine receptor antibodies. Especially anti-
MUSK positive patients may improve after treatment with Rituximab. The role of new, but very expensive treatments like Eculizumab in the care of patients with refractory MG in daily practise needs to be established.


