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Review article

Diagnosis and treatment of Guillain-Barré Syndrome in childhood and adolescence: An evidence- and consensus-based guideline

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ABSTRACT

This evidence- and consensus-based practical guideline for the diagnosis and treatment of Guillain-Barré Syndrome (GBS) in childhood and adolescence has been developed by a group of delegates from relevant specialist societies and organisations; it is the result of an initiative by the German-Speaking Society of Neuropediatrics (GNP), and is supported by the Association of Scientific Medical Societies (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften). A systematic analysis of the literature revealed that only a few adequately-controlled studies exist for this particular age group, while none carries a low risk of bias. For this reason, the diagnostic and therapeutic recommendations largely rely on findings in adult patients with GBS, for which there are a higher number of suitable studies available. Consensus was established using a written, multi-step Delphi process. A high level of consensus could be reached for the crucial steps in diagnosis and treatment. We recommend basing the diagnostic approach on the clinical criteria of GBS and deriving support from CSF and electrophysiological findings. Repetition of invasive procedures that yield ambiguous results is only recommended if the diagnosis cannot be ascertained from the other criteria. For severe or persistently-progressive GBS treatment with intravenous immunoglobulin (IVIG) is recommended, whereas in cases of IVIG intolerance or inefficacy we recommended treatment with plasmapheresis. Corticosteroids are ineffective for GBS but can be considered when acute onset chronic inflammatory demyelinating polyneuropathy (A-

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CIDP) is suspected due to a prolonged disease course. The full German version of the Guideline is available on the AWMF website (https://www.awmf.org/leitlinien/detail/ll/022-008.html).

Contents

1. Introduction

Guillain-Barré Syndrome (GBS) is an immune-mediated rapidly progressive polyneuropathy whose aetiology and pathogenesis are not yet fully understood. Auto-antibodies against nerve gangliosides are suggested to play a central role in the pathogenesis in many cases. Epidemiological analyses have demonstrated that the incidence of GBS increases linearly with age, peaking at 70–80 years, with a maximum of 4–5 cases per 100,000 person years (PYs). In contrast, the disease is much rarer in children and adolescents, with an incidence of 0.62 cases per 100,000 PYs (95%CI 0,52–0,75) in 0-9-year-olds, and 0.75 cases per 100,000 PYs (95%CI 0.60–0.97) in 10–19-year-olds [1].

GBS can be subclassified into a number of variants, depending on clinical presentation and electrophysiological findings [2]. The classic variants are acute demyelinating inflammatory polyneuropathy (AIDP) und acute motor axonal neuropathy (AMAN). These are characterised by rapidly-progressing, ascending symmetrical weakness, with attenuation or loss of muscle proprioceptive reflexes. Amongst paediatric patients in the peak phase of the disease, 75% can no longer walk unaided, 30% are tetraparetic, 35–50% show cranial nerve involvement, and 15–20% have respiratory failure and/or autonomic dysfunction. Furthermore, up to 70% suffer from neuropathic pain, which can be severe and occasionally occur as the first symptom. Localised forms of GBS include Miller Fisher Syndrome (MFS) (cranial nerve affection and ataxia, areflexia, serum anti-GQ1b antibody detection in >90% cases) and the pharyngeal-cervical-brachial variant (predominantly bulbar and neck weakness, serum IgG antibodies against GT1a frequently detected), both of which are extremely rare in childhood [3]. Chronic inflammatory demyelinating polyneuropathy (CIDP) with both a protracted onset (progression > 8 weeks, or > 4 weeks in children) and chronic-progressive or relapsing-remitting impairment needs to be distinguished from GBS, due to differences in the course of disease and therapeutic consequences. The incidence of CIDP in children is around 3–5% of that of GBS [4].

Immunomodulatory therapy with plasmapheresis (PE) or intravenous immunoglobulins (IVIG) has been proven effective in GBS [5,6], namely by accelerating the improvement of weakness. Improvement follows a plateau phase that ranges from days to weeks and runs an extremely variable course, regardless of whether a specific therapy has been applied or not. Although a large group of children does undergo rapid recovery, a small group remains in whom the course of disease is much longer: the median time taken to reach a symptom-free state is 66 days; 10th-90th percentile, 22–181 days; maximum 790 days [7].

The overall long-term prognosis for children with GBS is more favourable than that in adults, whereby the majority of children largely regain motor function. However, even after years, it is not uncommon for a detailed examination to uncover moderately-to slightly-pronounced neurological and neuropsychiatric deficits such as fatigue and paraesthesia, as well as poor co-ordination and concentration [8,9]. Limited information exists about the factors that could serve as predictors for recovery. In a study cohort of 215 children, univariate analysis revealed that cranial nerve impairment, the need for ventilatory assistance, tetraplegia, and

inexcitable nerves all had a significantly-adverse association with the recovery of walking capacity; however, the best predicting factor was muscle strength at day 10 after disease onset (multivariate regression analysis) [10]. The AMAN variant has a more acute and severe course than AIDP, with a higher rate of ventilated patients and delayed recovery. Nonetheless, it has been repeatedly shown that the long-term prognosis for both variants is equally favourable in children [11,12].

The aim of this guideline is to inform all involved parties (i.e., medical specialists, therapeutic professionals and the affected persons) about current status of scientific research into GBS, and to provide practical recommendations for diagnostic procedures and the treatment of GBS in childhood and adolescence. The extended version of the guideline (in German) containing detailed methodology, evidence tables and a full list of references can be found alongside a lay version at the Association of the Scientific Medical Societies (Arbeitsgemeinschaft Wissenschaftlich Medizinischer Fachgesellschaften, AWMF) website (https://www.awmf.org/leitlinien/detail/ll/022-008.html).

2. Methodology

This guideline has been developed by a group of delegates from relevant specialist societies and organisations in Germany; it is the result of an initiative by the German-Speaking Society of Neuropediatrics (GNP), and is supported by the Association of Scientific Medical Societies. The development of an evidence- and consensus-based S3-guideline aimed especially at this age group seemed appropriate, since: (i) GBS occurs more rarely in childhood and adolescence than in adulthood, (ii) disease progression can differ from that in adults, (iii) examination and treatment methods are more difficult to apply, and (iv) long-term recovery is generally better compared to that in adults.

The methodology used for the literature search and analysis as well as the group discussions amongst guideline participants, were carried out in accordance both with international standards and AWMF recommendations for S3-guidelines (https://www.awmf.org/leitlinien/awmf-regelwerk.html). A systematic literature search was performed and each publication was classified in terms of its level of evidence (LoE) according to criteria set down by the Scottish Intercollegiate Guidelines Network (SIGN). For the formal recommendations 1 through 29. a written, 3-step Delphi process was used to establish consensus amongst the guideline group members. The grades of recommendation and the strength of agreement within the guideline group were classified as described in Tables 1 and 2, respectively. Details of this process can be found in supplement 1. Further topics, that we thought to be not yet suitable for this formal process, were consented by informal discussions between the authors. At the end a final consensus process was carried out with board members of the participating professional organisations.

Table 2
Classification of consensus strength according to the AWMF.

Strong consensus	Agreement amongst >95% of participants
Consensus	Agreement amongst >75–95% of participants
Majority consensus	Agreement amongst >50–75% of participants
No consensus	Agreement amongst <50% of participants

3. Diagnostic recommendations

A number of internationally-accepted schemes and guidelines exist for the diagnosis and classification of GBS [13]. In particular, the one developed by the Brighton Collaboration meets a high standard of evidence and also addresses the special features of childhood GBS [14]. The latter essentially served as the basis for the recommendations, and was supplemented with information from several current publications.

3.1. Diagnostic strategy

Recommendation 1: We recommend basing the diagnosis of GBS on an appropriate anamnesis, a relevant constellation of clinical findings, and the exclusion of other relevant potential causes. To ensure the highest level of diagnostic certainty, additional evidence is required in the form of increased protein levels in the CSF, along with an at-the-most mildly-increased cell count, and electrophysiological signs of neuropathy.

- Strong recommendation (⇑⇑) derived from evidence-based and internationally-approved case definitions and guidelines (SIGN 1-).
- Strength of consensus: Strong

Comment: The diagnosis of GBS cannot be established by a single clinical parameter or test result. Instead, it is based on the typical (albeit non-specific) combination of clinical and paraclinical findings, with simultaneous exclusion of relevant differential diagnoses. The Brighton Collaboration GBS Working Group defined a set of diagnostic criteria derived from a systematic literature review (Table 3) [14]. This publication also provides detailed information on the definition of individual findings as well as distinct advice on how to approach GBS diagnosis in children. The validity of these criteria was retrospectively tested and largely confirmed in a cohort of 494 adult patients from prospective Dutch treatment studies [15]. Roodbol et al. validated the criteria for children and adolescents via a retrospective analysis of 67 patients from Sophia Children's Hospital, Erasmus MC, Rotterdam [16].

3.2. Cerebrospinal fluid (CSF) analysis

Recommendation 2: We recommend a diagnostic procedure

Table 1
Guideline levels of recommendation according to the AWMF manual.

Level of Recommendation	Description	Syntax	Symbol
A	Strong Recommendation: considerable benefit generally substantiated by high-quality evidence; benefit also demonstrated or expected in terms of applicability and viability of evidence	“we recommend” OR “is recommended"/"we recommend against " OR “is not recommended"	⇑⇑/⇓⇓
B	Moderate Recommendation: considerable benefit substantiated by non-first-class evidence, or by evidence with only limited viability, or by well-documented evidence for a moderate benefit or limited applicability	“we suggest” OR “is suggested"/"we suggest against” OR “is not suggested"	⇑/⇓
0	Open Recommendation: No proof of/insufficient evidence for a net benefit; or benefit unclear because of non-viable evidence or a lack of applicability.	may be considered/no specific recommendation"	⇔

Table 3
Diagnostic criteria for GBS according to Ref. [14].

- Level 1 of diagnostic certainty:
  - Bilateral and flaccid paralysis of the extremities
  - and diminished or absent tendon reflexes of the paretic extremities
  - and monophasic disease profile and 12 h to 28-day period between symptom onset and peak and subsequent clinical plateau phase
  - and electrophysiological findings indicative of GBS
  - and cyto-albuminological dissociation
  - and lack of alternative diagnosis for paresis
- Level 2 of diagnostic certainty:
  - All of the above-mentioned clinical criteria present
  - and electrophysiological findings indicative of GBS
  - or cyto-albuminological dissociation
- Level 3 of diagnostic certainty:
  - All of the above-mentioned clinical criteria present
  - Electrophysiological and CSF findings lacking/negative

that includes a lumbar puncture with subsequent CSF protein analysis and a cell count.

- Strong recommendation (⇑⇑) derived from evidence-based and internationally-approved case definitions and guidelines (SIGN 1-).
- Strength of consensus: Consensus

Recommendation 3: For diagnostic certainty in the event of an initially-normal CSF finding, a lumbar puncture may be repeated 7–10 days after the first symptoms appear - that is, if it is deemed necessary due to unclear anamnestic, clinical or electrophysiological results. However, we only suggest repeating this follow-up lumbar puncture in cases where the other findings remain inconclusive, rather than simply because of initial normal CSF protein levels.

- Open recommendation (⇔), since this is an invasive procedure that can cause discomfort and be stressful for children and often has no therapeutic consequences (SIGN 4).
- Strength of consensus: Strong

Comment: The typical CSF finding for this disorder is an increased protein level with a normal cell count (known as cyto-albuminological dissociation). Nevertheless, it should be noted that protein concentration is often normal during the first week, and only increases with disease progression [15]. After 7–10 days, however, it generally reaches a level above that of the reference value, which notably differs in children according to age [17]. It is also important to note that CSF protein levels can be elevated in other disorders that are similar to GBS. Therefore, a normal CSF protein reading does not rule out GBS, while an elevated protein level is not solely sufficient to confirm diagnosis.

The CSF cell count is usually normal, although occasionally it can be mildly elevated to <50/mm^3, rarely more [18]. In such cases, HIV, neuroborreliosis or malignant meningitis should be considered as possible causes [2,19]. Due to the fact that the GBS-related increase in protein is dependent on time, and the standard CSF value for protein depends on age, the cell count can potentially be more valuable as a differential diagnostic factor than protein level.

3.3. Electrophysiological classification

Recommendation 4: An electrophysiological examination is recommended for confirming GBS diagnosis, and is necessary for obtaining the highest level of diagnostic certainty and distinguishing between variants. If this diagnostic tool is not available, we suggest either consulting a specialised neurologist or referring the patient to an appropriate clinical centre.

- Strong recommendation (⇑⇑) derived from evidence-based and internationally-approved case definitions and guidelines (SIGN 1-).
- Strength of consensus: Strong

Recommendation 5: For confirmation of diagnosis in the event of an initially-normal electrophysiological finding, the procedure may be repeated 1–2 weeks later if it is deemed necessary because of other unclear data. However, if a diagnosis of GBS has been confirmed by other parameters and the course of disease is favourable, an unremarkable electrophysiological examination in the first week of illness does not have to be repeated if there is no particular clinical reason for it.

- Open recommendation (⇔), since this is an invasive procedure that can be a burden for children and often has no therapeutic consequences (SIGN 4).
- Strength of consensus: Strong

Comment: A typical electrodiagnostic finding is required in order to reach the highest level of diagnostic certainty described by Sejvar et al. [14] Such examinations can be painful and are often difficult to perform in children. Moreover, the necessary expertise is often lacking in paediatric hospitals. Nonetheless, nerve conduction studies and, to a lesser extent, EMG, are required for distinguishing between GBS variants. Notably, due to the latent appearance of pathological spontaneous activity it only makes sense to perform an EMG 2–3 weeks after onset.

Although electrophysiological criteria for the diagnosis of GBS and its variants have been repeatedly defined, they are not always consistently applied and cannot be considered definitive [20,21]. The pragmatic criteria displayed in Table 4 are based on recommendations described by Sejvar et al. [14], whereby age-specific reference values and skin temperature should be taken into account, especially in very young children. The earliest signs that may already be evident within the first 4 days are changes in F-waves (77%) and distal latency (55%) [22].

3.4. Ultrasound examination of the peripheral nerves

Peripheral nerve ultrasound is a relatively new method that has only been described in isolated cases in children. It can reveal signs of swelling in proximal nerve segments early on in GBS patients, and the fact that it is a pain-free procedure makes it particularly attractive for use in children, especially in cases of diagnostic uncertainty [23–25]. Similar to the electrophysiological tests described above, ultrasound examination of the peripheral, proximal and cranial nerves requires considerable experience, meaning that the prevalence of this method is still limited in clinical practice and a general guideline recommendation would therefore be premature.

3.5. Differential diagnoses

Table 5 shows a selection of alternative diagnoses that must be ruled out during the diagnostic process for GBS. This is carried out mostly through clinical examination, although further diagnostic techniques may be used in exceptional cases [14].

3.6. Infectiological diagnostics

Recommendation 6: Microbiological and serological diagnostics may be carried out in children and adolescents with

Table 4
Electrophysiological criteria for the diagnosis of GBS and its most important variants according to Ref. [14].

- Electrophysiological criteria for AIDP.

At least 1 of the following findings derived from the measurement of at least 2 nerves, or at least 2 measurements on 1 nerve when all others are inexcitable and the amplitude of the distal compound muscle action potential (dCMAP) is >10% below the lower limit of normal (LLN):

1) motNCV <90% LLN (85% if dCMAP < 50% LLN).
2) Distal Motor Latency >110% of the upper limit of normal (ULN) (>120% in dCMAP < 100% LLN).
3) Amplitude ratio of pCMAP/dCMAP <0.5 und dCMAP >20% LLN.
4) F-wave latency >120% ULN.

- Electrophysiological criteria for AMAN.

None of the criteria for AIDP applies here except for 1 sign of demyelination at 1 nerve, if dCMAP <10% LLN. Normal amplitude of sensory nerve action potentials.

- Electrophysiological criteria for AMSAN.

None of the criteria for AIDP applies here except for 1 sign of demyelination at 1 nerve, if dCMAP <10% LLN. Amplitude of sensory nerve action potentials <10% LLN.

- Electrophysiological criteria for nerve inexcitability

dCMAP absent in all nerves, or dCMAP <10% LLN can be detected in 1 nerve.

AIDP = acute inflammatory demyelinating polyneuropathy, AMAN = acute motor axonal neuropathy, AMSAN = acute motor-sensory axonal neuropathy, motNCV = motor nerve conduction velocity, LLN = lower limit of normal, ULN = upper limit of normal, pCMAP = proximal compound motor action potential, dCMAP = distal CMAP.

spontaneously-occurring or post-infectious GBS.

- Open recommendation (⇔) with limited data available and a lack of therapeutic effects (SIGN 2- to 3).
- Strength of consensus: Strong

Comment: Infectiological diagnostics in GBS are interesting from both theoretical and epidemiological perspectives. Detection of *C. jejuni* is suggestive of AMAN (rare in children from Western Europe). Borreliosis or *Mycoplasma pneumoniae* infections are each treated individually, although it is unknown if this treatment influences the disease course. The establishment of an etiological link with an immunological basis theoretically requires a time interval of 1–6 weeks between the disease suspected to be the cause and the onset of neurological symptoms of GBS (Sejvar et al., 2011b). A comprehensive prospective case-control study in adult patients was able to identify a likely causal association with the following infectious agents: *Campylobacter jejuni*, *CMV, EBV* und *Mycoplasma pneumoniae* [26]. In childhood GBS, a preceding infection is identified as the potential causative agent in 60–70% of cases, hence occurring more frequently than in adults. The most common causes are upper airway infections and gastroenteritis. Also in children with GBS *Mycoplasma pneumoniae* could play a special role [27]. In the individual patient, however, it is not possible to distinguish between a solely temporal versus a causal link [28].

Recommendation 7: If GBS occurs within 1–6 weeks of vaccination, thorough microbiological and serological diagnostics are recommended for investigating a potential link with the vaccinating antigen, as well as with alternative causal agents.

- Strong recommendation (⇑⇑) derived from evidence-based and internationally-approved case definitions and guidelines (SIGN 2-).
- Strength of consensus: Strong

Comment: Etiological clarification does not hold any therapeutic value in this situation. However, the results arising from microbiological and serological diagnostic tests can have substantial legal implications at the social and health care levels, and in some cases can even pose a liability risk. Indeed, the risk of developing GBS is mentioned as a potential complication in the package leaflets of a number of vaccines, and the German “Act on the Prevention and Control of Human Infectious Diseases“ (IfSG) intends to ease the burden of proof (‘simple probability’) in these cases (§61). However, the available data show that most of the underlying reports deal exclusively with single cases and small groups of patients in whom the alternative causes of GBS appear to have been excluded. Nevertheless, well-conducted case-control studies have been able to show that most vaccines have a very unlikely causal link to GBS. The only exception comes from a swine flu vaccine that was used in an American immunisation campaign in 1976–77 and led to a significant increase in the number of GBS cases. This effect was not observed again in later immunisation campaigns, even after vaccination during the recent swine flu pandemic in 2009–10 [29]. Furthermore, an accumulation of GBS cases was observed 30–40 years ago following immunisation with a rabies vaccine that was grown on mammalian brain tissue. This, however, has not been observed in association with modern rabies vaccines [30].

Table 5
The most important differential diagnoses of GBS.

Intracranial
- Meningeosis neoplastica/leucaemica
- Brain stem encephalitis

Peripheral Nerves
- Axonal sub-acute recurrent neuropathy, with elevated CSF lactate levels in patients with a PDHclα-mutation
- Metabolic disorders such as hypermagnesemia or hypophosphatemia
- Tick paralysis
- Heavy metal toxicity such as arsenic, gold and thallium
- Medication-induced neuropathy (e.g. vincristine, platinum compounds, nitrofurantoin, paclitaxel)
- Porphyria
- Critical illness neuropathy
- Vasculitis
- Diphtheria

Spinal cord
- Infarction, myelitis, compression

Anterior horn motor neurons
- Polio and other enteroviruses that can trigger poliomyelitis, including West Nile Virus

Nerve roots
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Cauda equina compression

Neuromuscular end-plate
- Myasthenia gravis
- Organophosphate poisoning
- Botulism

Muscle
- Critical illness myopathy
- Polymyositis
- Dermatomyositis
- Hypo-/hyperkalemia
- Periodic paralysis

3.7. Antibodies against gangliosides and paranodal proteins

Recommendation 8: Specific anti-ganglioside antibodies may be tested for in children and adolescents with GBS. This should be performed with a valid INCAT-ELISA test [31].

- Open recommendation (⇔) derived from evidence-based and internationally-approved case definitions and guidelines (SIGN 2 + to 2-).
- Strength of consensus: Consensus

Comment: The post-infectious occurrence of GBS gives rise to the 'molecular mimicry' hypothesis for the etiopathogenesis of GBS and its variants; this is exemplified by the appearance of AMAN after *C. jejuni* infection and its association with increased levels of antibodies against various ganglioside compounds. Glycolipids detected on the surface of *C. jejuni* have been shown to strongly resemble the human gangliosides found on the cell membrane of peripheral neurons. Generation of antibodies against these *C. jejuni* glycolipids leads to a cross-reaction with the gangliosides, which in turn causes axonal damage [32]. Although these specific antibodies cannot be detected in all patients, they are found with high frequency in certain subtypes of GBS. For example, anti-GQ1b IgG is found in more than 90% of MFS patients. AMAN is frequently associated with increased levels of serum IgG antibodies against GM1, GM1b, GD1a und GalNAc-GD1a [33].

Antibodies against neurofascins and other paranodal proteins have only recently been recognised as causative factors in therapy refractory cases of chronic neuropathy [34,35]. Individual cases und small case series show frequent resistance against IVIG, but a positive reaction to corticosteroids, plasmapheresis or rituximab [34]. Ascertainment of these antibodies can also be considered in GBS children with an unfavourable, chronic course of disease, although a guideline recommendation that rates these findings as a prognostic and therapeutic factor does not yet seem suitable at this point.

3.8. Magnetic resonance imaging

Recommendation 9: In cases where the available findings are ambiguous, and particularly if there is evidence of pathology at either the spinal level (e.g., bladder dysfunction at the onset of disease, definable motor or sensory lesion) or central level (encephalopathy, pyramidal signs), we recommend native or (where applicable) contrast-enhanced magnetic resonance imaging (MRI) of the brain and spinal cord.

The use of contrast-enhanced MRI should be critically considered, and decisions about the indication for its application and the choice of contrast-medium are reserved for the acting paediatric radiologist or radiologist. This takes into account publications that have described the deposition of certain gadolinium preparations in body regions including the CNS also in children - although this has so far not yet been described in GBS patients [36]. Only macrocyclic gadolinium preparations should be used in a standard dosage of 0.1 mmol/kg body weight.

- Strong recommendation (⇑⇑) based on serious differential diagnoses which, in some circumstances, can require acute therapeutic actions which differ from that used for GBS (e.g. spinal bleeding or abscess, myelitis, ADEM, tumours) (SIGN 2 + to 2-).
- Strength of consensus: Consensus

Comment: Although a spinal MRI is primarily carried out to exclude space-occupying lesions or any other pathology, a contrast-enhanced MRI procedure could also support the diagnosis of GBS. A number of publications has reported pathological uptake of contrast agent, particularly by the ventral nerve roots and cranial nerves, hence suggesting that a contrast-enhanced MRI could serve as a diagnostic criterium for GBS in the face of persistently-unremarkable CSF and nerve conduction findings. In a retrospective study by Yikilmaz et al. 38 of 40 patients with childhood GBS showed contrast enhancement of the nerve roots; Mulkey et al. reported 22 of 24 patients with spinal nerve root enhancement in an initial MRI [37–39]. However, increased uptake of contrast agent is also possible in other inflammatory conditions (serous meningitis, neuroborreliosis) and neurometabolic disorders (Krabbe disease). Since prospective examinations have not yet been carried out, the sensitivity and specificity of contrast-enhanced MRI remains unclear in children and adolescents with GBS.

3.9. Assessment of dysphagia and dysarthria in childhood GBS

There are currently no scientific studies pertaining to the relevance of dysphagia and dysarthria in children with GBS. A recent study in adults by Ogna et al. identified the quality of swallowing, tongue strength, and the coordination of swallowing and breathing as predictors for requiring ventilatory assistance [40]. A similar conclusion may also be drawn for children with GBS, whereby supplementing blood-gas monitoring with the evaluation of speech and swallowing can be effective in optimising treatment. The potential occurrence of cranial nerve impairment, especially involving the facial nerve (often bilateral), but also the glossopharyngeal and vagus nerves, warrants repeated thorough examination.

3.10. Assessment tools for evaluating impairment during the course of disease

Recommendation 10: The application of valid, reliable and change-sensitive assessment tools, even during routine care, is suggested for properly documenting the course of disease in GBS. Such tools facilitate therapeutic decisions by enabling an objective description of the clinical course, as well as early recognition of complications, course fluctuations and progression.

- Moderate recommendation (⇑) derived from evidence-based and internationally-approved case definitions and guidelines (SIGN 1-).
- Strength of consensus: Strong

Comment: The use of valid assessment tools is mandatory for scientific investigations. The available clinical scales are easy to apply and serve to describe 'Impairment' (MRC) and 'Activity and Participation' (GBS Score, Rankin) during the onset, peak and recovery phases of GBS (Table 6) [14]. They have been used in numerous treatment studies for GBS and other immunoneuropathies, and are deemed to be valid and reliable in adults [41]. These clinical scales are also recommended for and used in children, although they have not been formally validated for this age group. Theoretically speaking, all these scales have the disadvantage of lacking metric/linear qualities, and instead only possess an ordinal data quality, something which can complicate statistical interpretation. This issue and its solution are being tackled by applying modern, advanced methods in data analysis and assessment development, such as the Rasch Model [42,43].

4. Treatment recommendations

The literature search on treatment uncovered recent systematic reviews and Systematic Cochrane Reviews (CSR) addressing different therapeutic options; insofar as these reviews are based on

Table 6
Recommended functional assessment tools for monitoring the course of disease in GBS.

Medical Research Council (MRC) Scale for Manual Muscle Testing
5 – patient can maintain position against maximal resistance and through the entire physiological range of motion of the joint
4 – patient can maintain position against moderate resistance, and moves actively through the entire physiological range of motion of the joint
3 – patient cannot maintain position against resistance, but can move the extremity against gravity through the full range of motion
2 – patient can move the extremity through part of the physiological range of motion if gravity is eliminated
1 – muscle contraction can be detected by palpation if gravity is eliminated
0 – no contractions identifiable
GBS disability scale (Hughes und Cornblath) [18]
0 – healthy
1 – minor symptoms or signs of neuropathy, but capable of manual work and running
2 – can walk without the aid of a stick for 5 m across an open space, but is not capable of manual work or running
3 – can walk with a stick, orthosis or support (5 m across an open space)
4 – bedridden or wheelchair-bound
5 – ventilation assistance required (for any part of the day or night)
6 – dead
Modified Rankin Scale (MRS)
0 - no symptoms
1 - no significant impairment, despite some symptoms; able to carry out all usual activities
2 - slight impairment; not able to carry out all previous activities but can tend to own matters without the need for assistance
3 - moderate impairment; requires some help but able to walk without assistance
4 - moderately-severe impairment; unable to walk unassisted and cannot tend to bodily needs without assistance.
5 - severe impairment; bedridden, incontinent, requires constant nursing care and attention
6 - dead

randomised-controlled studies, their level of evidence (LoE) is medium to high (SIGN 1- to 1+). This, however, mostly pertains to statements about treatment in adult GBS patients and only relates to very few controlled studies in children. Relevant childhood studies were therefore sought beyond these CSRs, but it turned out that all had a weak to very-weak LoE (SIGN 3 to 2-).

4.1. Antibiotic therapy

Recommendation 11: Antibiotic therapy may be carried out for the treatment of a potential underlying disease in well-justified individual cases.

- Open recommendation (⇔) based on expert opinion (SIGN 4).
- Strength of consensus: Strong

Comment: A causal treatment approach is not possible. Even when a treatable underlying pathogen (*campylobacter, mycoplasma*, *borrelia*, *herpes virus* etc.) is identified, it is unclear whether an antibiotic/anti-viral treatment can positively influence the immunological disease process through antigen elimination.

4.2. Supportive therapy

The supportive and symptomatic treatment of disease manifestation in GBS and its potential complications is of utmost importance not only during the acute phase of the disease, but especially in severe cases; this, however, is mostly based on publications with a weak LoE, even in adults [44]. Age-specific supportive therapy data with more than a very weak LoE are not available in children (SIGN 2–4).

Recommendation 12: Medicinal and (optional) physical thrombosis prophylaxis is recommended for bedridden adolescents from the onset of puberty.

- Strong recommendation (⇑⇑) based both on expert recommendation and the clinical importance of the measure, despite the weak LoE from adult studies (SIGN 3 to 4).
- Strength of consensus: Strong

Comment: In immobile patients with long periods of bed confinement, deep leg-vein thrombosis and possible lung emboli may otherwise need to be reckoned with.

Recommendation 13: We recommend carrying out systematic monitoring of breathing and cardiovascular function with the appropriate measures in children and adolescents, both during the acute phase of GBS and following discharge from the intensive care unit (ICU).

- Strong recommendation (⇑⇑) based on expert opinion and the vital importance of the measure, despite the weak LoE in numerous case series (SIGN 3 to 4).
- Strength of consensus: Strong

Recommendation 14: We recommend commencing mechanical ventilation in children and adolescents with GBS upon the first signs of respiratory exhaustion and before clinical decompensation occurs. Intubation is additionally recommended in cases of dysphagia that are accompanied by aspiration of saliva (difficult secretion management) or poor airway clearance (absent or insufficient cough).

- Strong recommendation (⇑⇑) based on expert opinion and the vital importance of the measure, despite the weak LoE in numerous case series (SIGN 3 to 4).
- Strength of consensus: Strong

Comment: According to the published case series on GBS in childhood, 15–25% of patients were dependent on mechanical ventilation. Respiratory failure in children particularly needs to be reckoned with when the disease progresses quickly and the upper extremities and cranial nerves are affected [45]. Moreover, following discharge from the ICU, the possibility of secondary deterioration in the ensuing weeks should be kept in mind.

Recommendation 15: A tracheostomy fitted with an adequate cannula (depending on swallowing and respiratory capacities) is suggested when no improvement in respiratory function and/or secretion management is foreseeable after 1–2 weeks of respiratory treatment.

- Moderate recommendation (⇑) based on expert recommendation, as well as on the importance of the measure for quality of life, despite the weak LoE (SIGN 4).
- Strength of consensus: Strong

Comment: Despite the extent of surgical intervention, a tracheostomy facilitates breathing and allows sedative levels to be reduced. Furthermore, the correct choice of cannula can restore the patient's ability to communicate [44,46].

Recommendation 16: Due to the possible occurrence of autonomic dysregulation with hypertension and tachyarrhythmia, regular monitoring of blood pressure and heart rate by appropriate means is recommended, both during the acute phase of the disease and following discharge from the ICU.

- Strong recommendation (⇑⇑) based on expert opinion and the vital importance of the measure, despite the weak LoE in numerous case series (SIGN 4).
- Strength of consensus: Strong

Comment: Autonomic neuropathy with autonomic dysregulation and impaired heart rate variability has been described in ~50% of children with GBS [47]. Hypertensive crises (cardiac failure!) and tachyarrhythmia can also become life-threatening. In this context, central nervous system complications in the form of posterior reversible encephalopathy syndrome (PRES) have occasionally been described in adults as well as in an adolescent patient [48].

Recommendation 17: In addition to adequate doses of peripherally-acting analgesics, we recommend treating paraesthesia and pain with anticonvulsants such as carbamazepine or gabapentine/pregabaline, and potentially with antidepressants.

- Strong recommendation (⇑⇑), given that this measure holds great importance for the patient's quality of life, based on a few good-quality randomised-controlled trials (LoE 1+).
- Strength of consensus: Strong

Comment: Neuropathic pain also constitutes a common symptom in children with GBS (in up to 70% of patients), and can sometimes present as the earliest symptom [45,49]. Opioids should be administered with caution due to their side-effects on the bladder and intestine. In cases of anticonvulsant and antidepressant use, particular attention should be given to their potential anticholinergic effect, which can have implications for cardiac conduction.

Recommendation 18: Physiotherapy (positioning, respiratory therapy, passive movements) is suggested for supplementing treatment in the acute phase.

- Moderate recommendation (⇑) based on both expert opinion and the fact that the measure holds importance for the functional development of the patient; the LoE is nonetheless very weak (limited case series) (SIGN 3 to 4).
- Strength of consensus: Strong

Comment: These measures are expected to avoid complications such as muscular atrophy and contractures resulting from immobility. However, painful manipulations have to be avoided!

Recommendation 19: In cases of severe impairment, quadriplegia, and ventilation dependency, we recommended adequate psychological support and (if necessary) sedation for the patient, along with an ongoing counselling service for the family.

- Strong recommendation (⇑⇑) based on the fact that this measure holds great importance for the patient's quality of life, despite the weak LoE derived from case series and expert recommendations (SIGN 3 to 4).
- Strength of consensus: Strong

Comment: There are only isolated case descriptions available for the psychological burden experienced by children during the acute phase of GBS [50]. However, the high number of diverse emotional and psychological problems, which can even persist in the long-term, underscore the importance of this often clinically-neglected issue [9].

Recommendation 20: In the first year following GBS, we suggest avoiding all vaccinations according to individual benefit-risk-assessment. Thereafter, the indication for any vaccination comprising of the same agents that were applied 1–6 weeks prior to the appearance of GBS needs to be carefully considered.

- Moderate recommendation to forego vaccination (⇓) based on expert opinion and ambiguous data (SIGN 4).
- Strength of consensus: Consensus

Comment: In the rare group of patients with recurring GBS, both vaccinating agents and infections can trigger GBS in a non-specific fashion. In such cases it is necessary to proceed with particular caution, namely by weighing up the risk of contracting the wild-type infection versus the risk of retriggering of GBS [30,51].

4.3. Immune treatment

4.3.1. High-dose intravenous 7S-Immunoglobulin therapy

Recommendation 21: Treatment with intravenous 7S-Immunoglobulin (IVIG) is recommended in children and adolescents with severe GBS (i.e., loss of ability to walk unaided).

- Strong recommendation (⇑⇑) based on adult-derived data with high-quality and high-consistency evidence, and a lower LoE in children (SIGN 1++ for adults, 1- to 2- for children).
- Strength of consensus: Strong

Recommendation 22: Treatment with IVIG is also suggested for patients in whom considerable ongoing deterioration is expected, due to symptom onset only occurring a short time earlier and/or because of persistent progression.

- Moderate recommendation (⇑) with a weak LoE in childhood GBS (SIGN 1 + for adults, 2- for children).
- Strength of consensus: Strong

Comment: Since the proof of concept for IVIG historically followed that of plasmapheresis (PE), the effect of IVIG has been compared to PE rather than to a placebo.

The authors of the current Cochrane Review summarised five adequate studies with 536 severely-affected patients, most of whom were adults. There was no difference between the effects of IVIG vs. PE on recovery, as measured by the likelihood of a 1-point improvement on the GBS scale after four weeks (moderate LoE). The combination of PE followed by IVIG did not yield any significant additional benefits, although an effect in individual patients cannot be ruled out. A combination with immunoabsorption showed no additional effect. The incidence of side-effects did not differ significantly between PE vs. IVIG therapy, although there was a higher rate of therapy discontinuation in the PE group. The Cochrane Review authors concluded that more studies are required to investigate (i) the use of IVIG in patients with mild GBS only, (ii) the initiation of therapy after more than 14 days of symptom onset,

and (iii) optimal dose ranges [5].

The simplicity with which IVIG therapy can be applied makes it appear particularly suited to children as well. Although there are only very few controlled studies available for this age group, a large amount of open data also exist that suggest a similar level of IVIG efficacy to that observed in adults (see the full German version of this Guideline for more details). In light of the available data, the Cochrane Review authors argue that additional placebo-controlled studies in children can no longer be carried out for ethical reasons [5].

In the absence of systematic dose-ranging study data, IVIG is usually administered in children as it is in adults with acute GBS, namely with a single cycle of 2 g/kg body weight distributed over 4–5 consecutive days. Reducing the period of IVIG administration to 2 g/kg in 2 days did not show any improved effects but was associated with a higher frequency of relapses [52].

Singh-Grewal et al. prospectively documented the side-effects observed in a group of 58 children who had collectively undergone 345 IVIG treatment cycles for varying indications. The most common side-effects were headache (12.8% of infusions), fatigue (5.2%), stomach-ache (2.3%) and myalgia (2.3%). Acute side-effects such as skin rash, fever, bronchospasm and thoracic pain occurred more rarely (0.3–0.6%) [53].

4.3.2. Plasmapheresis, plasma exchange

Recommendation 23: When contraindications for IVIG exist in children and adolescents with severe GBS, we suggest applying immunomodulatory therapy with PE; this is also suggested as an option when IVIG therapy turns out to be ineffective.

- Moderate recommendation (⇑), despite a very good LoE in adult studies; the LoE for children is very weak (SIGN 1++ for adults, 2–3 for children).
- Strength of consensus: Consensus

Comment: The use of PE has regressed with the availability of an alternative, more manageable, less burdensome treatment with IVIG; however, when contraindications or IVIG intolerance exist, a transfer to an established paediatric centre for the purpose of plasmapheresis should be considered. On the other hand, application of PE within 1–2 weeks of the preceding IVIG therapy is not indicated.

Plasmapheresis was the first therapeutic approach for which an effectiveness with a high LoE was demonstrated in adults with severe GBS [54]. The authors of the current CSR identified six controlled studies with a moderate-to-high LoE (randomisation vs. symptomatic treatment). When compared to the control group, the PE group experienced a significant benefit in terms of onset of improvement, duration of mechanical ventilation, improvement by one point on the GBS scale after four weeks, the recovered ability to walk unaided, the likelihood of remaining free from severe residual symptoms, and the restoration of normal muscle strength after one year [6]. One study with only mildly-affected patients (i.e. still able to walk at the point of randomisation) demonstrated a more rapid onset of improvement after two PE treatment cycles compared to no PE therapy. In moderately-severe GBS (i.e., patient no longer able to stand without assistance at the point of study randomisation), four PE cycles were more effective than two, while in severely-affected patients (ventilation-dependent at the point of randomisation), six cycles were no more effective than four [55,56]. The best effect of PE is seen when therapy is started within seven days of symptom onset, although an effect can still be detected if applied up to 30 days post-onset. The given dosages for PE mostly comprise 4–5 cycles with an exchange volume of 200–250 ml/kg body weight over 7–14 days. A procedure with continuous flow is more effective than that with intermittent flow, and albumin is a more favourable exchange fluid than FFP [6].

Although one of the studies covered by the Cochrane Review did include children from the age of 10, they were not evaluated separately. The few studies in children investigating the potential differences between PE and IVIG, or their respective effects against historical control data, yielded similar results to those reported for adults.

It was recently reported that a therapy regimen in which 0.4 g/kg IVIG was directly infused at the conclusion of each PE cycle was associated with particularly favourable effects. This open-label study included nine children with severe GBS and respitarory insufficiency. The artificial ventilation could be terminated after a mean of 7 days (range 5–14), they left the hospital after 18 (10–30) days and all were able to walk unaided on day 28 after admission [57]. However, these data are strongly subject to bias and thus have to be confirmed in a controlled study.

4.3.3. Corticosteroids

Recommendation 24: Corticosteroids (CSTs) are not recommended for children and adolescents during the acute phase of GBS.

- Strong recommendation **against** the use of CSTs under these circumstances (⇓⇓) due to a good LoE for this in adults, and despite very weak evidence in children; also based on the predicted side-effects (SIGN 1 + for adults, 3 for children).
- Strength of consensus: Strong

Recommendation 25: If disease activity continues to progress or recur over a period that exceeds 4–8 weeks, we suggest considering either CSTs or another type of immunomodulatory therapy, given the likelihood of a CIDP diagnosis.

- Moderate recommendation (⇑) based on uncontrolled case series (SIGN 3).
- Strength of consensus: Strong

Comment: Corticosteroids are not effective during acute GBS, despite it being an immune-mediated illness. A current CSR comprising a meta-analysis of six quasi-randomised studies found that corticosteroids alone did not hasten recovery from acute GBS (moderate-high LoE) [58]. This pertains to a GBS with the typical acute disease course criteria. A lack of treatment response to CSTs is also expected in GBS patients with a long-persisting, but non-progressive plateau phase. However, when disease progression persists beyond four weeks in children or eight weeks in adults, or when relapses occur later than eight weeks after onset, this leads to a diagnosis of CIDP, where corticosteroids have been shown to be effective in 70–80% of patients of all age groups [4]. Furthermore, a trial with high-dose corticosteroids could be considered in the extremely rare cases of Bickerstaff encephalitis or myelitis combined with GBS, although there are no convincing data on treatment for this condition [59,60].

4.3.4. Difficult-to-treat cases

Recommendation 26: In difficult-to-treat cases, IVIG or PE therapy may be repeated after a few weeks. A distinction should be made between cases with a protracted monophasic disease course versus those with therapy-related fluctuations or a transition into CIDP.

- Open recommendation (⇔) which currently lacks evidence from studies that go beyond individual observations (SIGN 4).
- Strength of consensus: Strong

Comment: Despite the proven therapeutic effect of IVIg and PE, the recovery phase varies considerably amongst patients, and can be very prolonged in some cases. Around 25–30% of patients are viewed as non-responders. Clinical parameters and the increase in serum immunoglobulin concentration 2 weeks after the IVIG application have been identified as potential prognostic markers [61,62]. A placebo-controlled study is currently in progress to determine whether applying a second course of IVIG one week after the first course is able to positively influence the course of disease in adults with poor prognostic criteria [63].

Insufficient recovery, continued progression, or relapse can also be observed in childhood GBS patients in three different settings, for each of which different therapeutic consequences ensue [64]:

1. An initially progressive disease course with a subsequent plateau phase without recovery is classified as severe GBS, for which the optimal treatment approach remains unclear [64]. However, in children a satisfactory recovery can still be expected even after a prolonged plateau-phase of up to 90 days [45].
2. A secondary decline following an initial improvement is most likely to be a treatment-related fluctuation, which can occur once or twice within eight weeks of beginning treatment with IVIG or plasmapheresis [64,65]. Since the initial signs of improvement are suggestive of a treatment effect on the patient, it is reasonable to apply a second or third course of the same therapy.
3. When disease progression persists for more than one month in children or two months in adults, or when secondary progression occurs more than twice following an initial improvement, or more than eight weeks after therapy onset, the presence of CIDP should be considered and treated accordingly [64–66]. This situation is an indication for treatment with IVIG, corticosteroids or plasmapheresis. Here, usually a maintenance treatment is necessary which is most easily performed with IVIG 1 g/kg b.w. in one to two days, to be repeated every 3–5 weeks [67].

4.3.5. Other substances and treatment approaches

Recommendation 27: We suggest against the use of immunosuppressive treatment approaches as an alternative to immunomodulation with plasmapheresis and IVIG.

- Moderate recommendation **against** using immunosuppressives (⇓); lack of proof for efficacy in studies with an admittedly very-weak LoE (SIGN 3 to 4).
- Strength of consensus: Consensus

Comment: Small scale pilot studies with Interferon β-1A, BDNF (Brain-derived neurotrophic factor), MMF (Mycofenolate-mofetil), eculizumab and the Chinese herbal medicine tripterygium polyglycoside have investigated alternative immunological therapies to PE and IVIG; they have been partly included in a recent Cochrane Review [68–70]. Although no proven effects were found, potential effects cannot be completely ruled out due to low statistical power of all these studies. A decision for an individual trial with such usually toxic compounds should always take into account the relatively good long-term prognosis in children with GBS, even after a very long plateau phase.

However, in all cases with an unusually-prolonged disease course, the possible presence of neuropathy caused by **antibodies against paranodal proteins** should be investigated in addition to CIDP using the appropriate diagnostic tools. In the presence of raised levels of anti-neurofascin- or other antibodies, treatment with rituximab can be useful, although this is currently based on just a few observations [34,35].

4.4. Rehabilitation

Recommendation 28: We recommend an interprofessional rehabilitation program for children and adolescents suffering from severe GBS with prolonged recovery. The aim of this is to allow the child maximal and satisfactory levels of independence and participation in everyday life, as well as the best chance of restoring functional capacity, not only throughout the rehabilitation phase but also within the child's own social environment.

- Strong recommendation (⇑⇑), despite the moderate evidence quality for its effectiveness in adults with GBS, and a current lack of evidence in children (SIGN 2 + for adults, 4 for children); also based on its assumed importance for functional capacity, participation and mental stability.
- Strength of consensus: Strong

Recommendation 29: We suggest basing the decision about whether rehabilitation should take place in an outpatient versus a hospital setting on (i) the severity of symptoms and impairment, (ii) the resources available to the patient and its family, and (iii) local access to adequate therapy.

- Moderate recommendation (⇑) based on expert opinion (SIGN 4).
- Strength of consensus: Strong

Comment: A recent controlled study provided data on rehabilitation in adult GBS patients [71], but such information remains elusive in children and adolescents. However, based on our experience, we recommend a similar approach to that described for adults; that is, an interprofessional rehabilitation program consisting of occupational therapy, physiotherapy and language/speech therapy, each of which centres on the patient's individual situation. Therapy goals should be tailored to the child's needs and capabilities. The child's family and surroundings are included as resources. The deployment of appropriate technical aids can also contribute to successful rehabilitation [72–75].

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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