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Alternative Therapies to Immunoglobulin for Guillain–Barré Syndrome

Rapid Review

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Abbreviations

CI	confidence interval
CrI	credible interval
CIDP	chronic Inflammatory demyelinating polyneuropathy
GBS	Guillain-Barré syndrome
IVIg	Intravenous Immunoglobulin
PE	plasma exchange
MD	mean difference
OR	odds ratio

Key Messages

- Plasma exchange may be more effective than placebo in reducing disability scale scores and improving the likelihood of disability improvement in patients with Guillain-Barré syndrome.
- Plasma exchange showed similar effectiveness as IV immunoglobulin on disability outcomes in treating Guillain-Barré syndrome.
- Limited evidence from a health technology assessment subsection suggests that plasma exchange may have a similar safety profile as IV immunoglobulin.
- An evidence-based guideline suggests that plasma exchange can be used as 1 of the immune therapies (IV immunoglobulin alternatives) for children with Guillain-Barré syndrome who have contraindications for IV immunoglobulin or when IV immunoglobulin is ineffective. However, most supporting evidence was from adults.
- We did not find any study reporting on the rate of recovery, duration of hospitalization, or cost-effectiveness of plasma exchange for treating Guillain-Barré syndrome that met the inclusion criteria for this report.

Context and Policy Issues

Guillain-Barré syndrome (GBS) is an acute, immune-mediated disease characterized by acquired weakness in limbs, truncal, facial, swallowing, and breathing muscles.[1] GBS has various clinical forms, including acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, and Miller-Fisher syndrome.[1,2] All peripheral myelinated nerves, including motor, sensory, and cranial sympathetic nerves, are possible sites of involvement.[1] GBS is a rare disease and can affect all age groups, including infants.[1-3] The overall annual incidence of GBS is 1 to 2 cases per 100,000 in adults and 0.34 to 1.34 cases per 100,000 in individuals aged 18 years or less, with lower incidence in children.[1,4] The risk of GBS increases with age after the first decade of life by approximately 20% for every 10 years of age.[1,2] Males are more often affected than females by 1.5 times.[2] Approximately 80% of patients can walk independently, and over 50% of patients are symptom-free by 1 year.[5] However, 5% to 10% of patients reported delayed or incomplete recovery and children usually have a better prognosis than adults.[4,5] The mortality rate increases with age as well, with less than 1% in children younger than 15 years to 8.6% in those older than 65 years.[2]

GBS presents as sudden onset of progressive and symmetric muscle weakness accompanied by abnormal deep tendon reflexes, sensory symptoms, dysautonomia, and respiratory symptoms.[1,2] The nadir of weakness or physical function is usually reached after 24 hours and more than 90% of patients reached the nadir by 4 weeks after syndrome onset with the mean time to nadir being 12 days.[1,2] Sensory symptoms may precede weakness and include mild paresthesias, numbness and pain, which are common complaints in GBS patients.[1,2] In children, pain and gait difficulty are predominant initial symptoms of GBS.[2,3] Dysautonomia can manifest as tachycardia, bradycardia, facial flushing, paroxysmal hypertension, orthostatic hypotension, urinary retention, anhidrosis, or diaphoresis.[2] Typical respiratory symptoms include dyspnea on exertion,

shortness of breath, difficulty swallowing, and slurred speech.[2] The initial clinical symptoms usually become apparent and progress over a period of 2 weeks.[1,2]

The cause of GBS is not fully understood, but research indicates that around two-thirds of GBS patients report experiencing a triggering antecedent event before onset.[1,3] These triggering events are often infections (up to two-thirds of cases), including gastroenteritis caused by Campylobacter (C.) jejuni (the most common pathogen identified in about 25% of cases), respiratory tract infections caused by influenza or COVID virus.[1,3] Other triggers of GBS include some vaccinations, cytomegalovirus, HIV, other infections, surgery, trauma, systematic diseases, and certain medication.[1-3] These events may initiate autoimmune responses against peripheral nerve antigens that cause GBS. The triggering mechanisms for GBS are still under investigation, but autoantibodies or T-cells involved in molecular mimicry stimulated by triggering events may play an important role in pathological changes of GBS.[1-3] Common pathological changes of GBS are demyelination and axonal loss.[1,3] In North America or Europe, acute inflammatory demyelinating polyneuropathies are the predominate underlying pathological process, while axonal loss changes are more common in Asia and Central America.[1,2]

Patients with GBS often require admission to an inpatient setting, with up to 30% needing mechanical ventilation and an intensive care, however, most have a favourable long-term recovery.[5,6] For those with impending respiratory failure, severe or rapidly progressive weakness, or autonomic instability, intensive care unit admission is necessary.[5] Supportive care and immunomodulatory therapy are important in managing GBS.[2] Immunomodulatory therapy includes IV immunoglobulin (IVIg), plasma exchange (PE, also called plasmapheresis), corticosteroids, and other pharmacological treatments.[2,4,5] Previous systematic reviews show evidence of moderate certainty supporting IVIg or PE as 2 effective disease-modifying treatments.[7,8] IVIg inhibits macrophage activation and prevents antibody binding and complement activation, but is contraindicated in patients with congestive heart failure and renal function deficiency.[6] PE removes hyperreactive antibodies and pro-inflammatory cytokines but is contraindicated in patients with myocardial infarction (within 6 months) or septic shock.[6]

Although PE and IVIg had different mechanisms of action, they may be similarly effective in clinical outcomes overall.[2,4,5] The choice between the 2 depends on their availability, cost, patient values and preference, and their contraindications.[5] However, a previous evidence summary has reported the effectiveness of IVIg and PE are controversial in pediatric patients with or without mechanical ventilation[9] and some safety concerns in PE for patients with GBS.[4-6] Moreover, the availability of immunoglobulin has decreased due to the COVID-19 pandemic and increasing demand.[10] There is currently no comprehensive health technology report available that compares the effectiveness and safety of PE as an alternative to IVIg compared with IVIg and placebo. Therefore, this report aims to review the clinical effectiveness and safety of alternative therapy to IVIg, specifically PE, compared to IVIg alone or placebo for GBS. We also provide a summary of relevant health technology assessments.

Research Questions

1. What is the clinical effectiveness of alternative treatments to IV immunoglobulin (IVIg) compared to IVIg or placebo for Guillain-Barré syndrome?
2. What is the safety of alternative treatments to IVIg compared to IVIg or placebo for Guillain-Barré syndrome?
3. What are the evidence-based guidelines regarding the use of alternate treatments to IVIg for Guillain-Barré syndrome?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concept was Guillain-Barré syndrome. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons and guidelines. The search was completed on March 24, 2023, and limited to English-language documents published since January 1, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1. We also excluded duplicate publications and citations identified by the search. If related research work was published both as a preprint and in a peer-reviewed journal, we excluded the preprint and only included the peer-reviewed publication. Publications were published before 2018 or non-English publications were also excluded. Expert opinions or guidelines with unclear methods or ambiguous recommendations were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A Measurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[11] for systematic reviews and the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[12] for systematic

Table 1: Selection Criteria

Criteria	Description
Population	Children and adults with Guillain-Barré syndrome
Intervention	Plasma exchange
Comparator	Q1 to Q2: IV immunoglobulin, placebo Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., improvement in disability, rate of recovery, duration of hospitalization) Q2: Safety (e.g., adverse events, severe adverse events) Q3: Recommendations regarding best practices (e.g., which alternative to use, dose and timing of treatment, indications)
Study designs	Health technology assessments, systematic reviews, evidence-based guidelines

review and network meta-analyses, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[13] for guidelines. We also used AMSTAR 2 to critically appraise included health technology assessment report. Summary scores were not calculated for the included studies. Instead, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 319 citations were identified in the literature search. After reviewing the titles and abstracts, 300 citations were excluded and 19 potentially relevant reports from the electronic search were retrieved for full-text review. From the grey literature search, 16 potentially relevant publications were retrieved for full-text review. Of these potentially relevant articles, 32 publications were excluded for various reasons, and 3 publications met the inclusion criteria and were included in this report. These publications included 1 systematic review, 1 health technology assessment, and 1 evidence-based guideline. Appendix 1 presents the PRISMA[14] flow chart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One systematic review,[15] 1 health technology assessment,[16] and 1 evidence-based guideline[17] were included in the current report. The systematic review covered a wide range of interventions for GBS,[15] but only the comparisons of PE versus placebo and PE versus IVIg were relevant to the current report. The health technology assessment focused on summarizing the effectiveness and safety of IVIg for patients with chronic inflammatory demyelinating polyneuropathy (CIPD),[16] only a subsection of the report regarding the safety of IVIg and plasma exchange in patients with GBS was relevant to the current report. We only described the characteristics and results of this subsection in this health technology assessment report. Additional details about the characteristics of included publications are provided in Appendix 2.

Study Design

A systematic review published in 2021 was included in this report, which covers individual studies in the period from January 1, 1980 to January 1, 2019.[15] The review included 28 primary studies, consisting of 27 randomized controlled trial (RCTs) and 1 nonrandomized clinical study, and conduced Bayesian network meta-analyses (NMAs). However, the prior distributions used in this Bayesian NMA were unclear. The NMA reported 3 network comparators, including placebo, PE, and IVIg. The relevant comparisons for the current report were PE versus IVIg, and PE versus placebo. The subsection of 1 included health technology assessment conducted pairwise meta-analysis specifically on the safety of IVIg and plasma exchange in patients with GBS.[16]

One evidence-based clinical practice guideline for GBS in childhood and adolescence was included in this report, which was published in 2020.[17] The guideline was developed by a group of delegates from relevant specialist societies and organizations in Germany with most authors being specialists in pediatric or neurology departments. One of the authors of the guideline had personal experience with GBS as the mother of a GBS patient in Germany. The level of evidence was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) grading system, however, without detailed descriptions of ratings for evidence. The grades of recommendation included strong recommendation, moderate recommendation, and open recommendation, with corresponding wording as "recommend," "suggest," or "may be considered or no specific recommendation," respectively. The guideline authors used a written and 3-step Delphi process to achieve consensus for recommendation.

Country of Origin

The included systematic review and NMA was from China,[15] the health technology assessment was from Australia,[16] and the evidence-based guideline was meant to apply in Germany and was developed by specialists from Germany, Australia, Switzerland, and the Netherlands and a mother of a GBS patient partner from Germany.[17] The primary studies of the included systematic review were conducted in Asia (India, China, Japan), Europe (Netherlands, Belgium, Germany, UK, Switzerland, France, Sweden), Egypt, Australia, and only 1 study with 50 participants (published in 1996) was conducted in Canada.[15]

Patient Population

The systematic review included both children and adults diagnosed with GBS, regardless of disease severity, based on internationally accepted diagnostic criteria.[15] These criteria consisted of acute polyradiculoneuropathy causing progressive weakness of 2 or more limbs, with an onset phase of fewer than 4 weeks, reduced or absent tendon reflexes, and no alternative causes.

The health technology assessment focused on the effectiveness and safety of IVIg for patients with chronic inflammatory demyelinating polyneuropathy (CIDP).[16] However, a relevant subsection was found within the report that discussed the potential harms of IVIg and plasma exchange in patients with GBS. Only the information that was relevant to patients with GBS was included in our report.

The clinical practice guideline provided recommendations for the management of GBS in childhood and adolescence.[17] The guideline was intended to be used by all parties involved in the care of patients with GBS in this age group, including specialists, therapeutic professionals, and the affected persons.

Interventions and Comparators

One systematic review compared the effectiveness of 15 therapies for GBS,[15] including PE (4 to 5 times), half-course of PE (2 times of PE), IVIg with 3 different dosages (0.4 g/kg/d to 0.5 g/kg/d for 4 to 6 days, 0.4g/kg/d for 3 days, and 1g/kg/d for 2 days), methylprednisolone, prednisolone, immunoadsorption plasmapheresis, interferon beta-1a, brain-derived neurotrophic factor, cerebrospinal fluid filtration, tripterygium wilfordii polyglycoside, PE plus IVIg, immunoadsorption followed by IVIg, and IVIg plus eculizumab. The comparisons of PE versus IVIg and PE versus placebo were relevant to this report. The subsection of the 1 included health technology assessment did not report the details of IVIg and PE for patients with GBS.[16]

Outcomes

The systematic review evaluated the effectiveness of 15 therapies for GBS on 2 effectiveness outcomes: disability grade change and disability improvement (measured by ≥ 1 grade of disability scale).[15] Several versions of the disability scales were used. The disability scales used in individual studies were not reported in detail, including their psychometric properties, range, and interpretation scores such as minimal important difference. However, these scales were composed of approximately 7 categories ranging from 0 to 6: 0 = "healthy," 1 = "minor symptoms or signs of neuropathy but capable of manual work," 2 = "able to walk without the support of a stick but incapable of manual labour," 3 = "able to walk with a stick, appliance, or support," 4 = "confined to bed or chair bound," 5 = "requiring assisted ventilation," 6 = "dead." These categories reflect varying levels of physical function levels, from minor symptoms or signs of neuropathy to requiring assisted ventilation or dead.

The health technology assessment included a subsection on adverse events associated with IVIg and PE in patients with GBS, but the publication did not provide clear definitions or details of adverse events.[16] The included guideline considered the therapeutic effects of IVIg and PE, as well as their potential side effects.[17] In making their recommendations, the guideline development panel also took into account the epidemiological characteristics and prognosis of GBS in children and the challenges involved in implementing interventions for this condition.[17]

Summary of Critical Appraisal

Systematic Review With NMA

In the included systematic review,[15] the objective was clearly described, multiple databases and reference lists of enrolled articles were searched, MeSH terms of the search and study selection flow charts were provided. The review authors declared no conflicts of interest and presented a list of included articles. This systematic review was funded by academic institutions in China, which may have little influence on potential publication bias.[15] In the systematic review, article selection and data extraction were done independently by 2 reviewers,[15] which probably reduced the likelihood of error. However, this review did not provide lists of

excluded articles, report performing a grey literature search, and assess the sources of funding in individual studies, which may have led to some studies being or potential publication bias being overlooked. Although the systematic reviews reported the risk of bias of included individual studies graphs in the result section, it was unclear how the quality assessment was conducted. The review authors did not assess the potential impact of study risk of bias on the interpretation of results, and as a result, some comparisons may have been driven by individual studies with a high risk of bias.

The systematic review included Bayesian NMAs that preserve within-study randomization (no naive comparisons) and the population of interest was patients with GBS, including both adults and children.[15] This NMA includes 15 interventions, and no critical interventions were missing. The interventions of interest (IVIg, PE, placebo) from a connected network of trials. The NMA presented a variety of results, such as network plots, point estimates, 95% credible intervals, consistency analysis, and ranking probability graphs. However, safety outcomes, which are critical for decision-making, were not included in the analysis. Furthermore, a non-randomized trial was included, which may have induced bias in the NMA.

The NMA did not report individual study results, nor did it examine the subgroup effects of significant patient characteristics, such as age or disease severity, on treatment effects on clinical outcomes.[15] The authors also did not assess the systematic differences in treatment effect modifiers across different treatment comparisons in the network. Therefore, the transitivity assumptions of indirect comparisons were not fully tested. In addition, the authors used fixed-effect models to synthesis for all comparisons, including some meta-analysis with moderate heterogeneity (I^2 > 50%), which would probability result in narrow credible intervals (CrI) and favour interventions compared to random-effect models. The conclusions of the NMA were based solely on statistical tests and did not consider the certainty of evidence. Interventions with top rankings may have low certainty evidence.

Health Technology Assessment

The health technology assessment included in the report searched multiple databases and the authors declared no conflicts of interest, which may reduce the potential for publication or selection bias.[16] However, the report was not intended to include patients with GBS, but rather focused on CIDP. The safety data from 3 individual primary studies on GBS were used as a supplement for assessing the harms of PE or IVIg for CIDP.

In this report, the full search strategy, grey literature search, study selection process, and data extraction were unclear.[16] The details of included studies (e.g., study design, risk of bias, sources of funding), and methods for the statistical combination of results were not adequately described.[16] The details of included studies such as study design, risk of bias, and sources of funding were not provided.[16] These limitations increase the possibility of missing important relevant articles or errors in data extraction. The authors did not assess the quality of individual studies,[16] which raises concerns that the results may be driven by studies with a high risk of bias. The search probably did not comprehensively consider GBS-related terms or keywords, so the safety data may be incomplete. Due to unclear reporting details of characteristics of GBS patients, the study population may not be representative of GBS generally.

Evidence-Based Guideline

In this report, we only use the short English version of the evidence-based clinical practice guideline,[17] and the extended German version was not assessed. The guideline included clear descriptions of objectives, scope, population, target users, guideline developers, and recommendation statements.[17] The guideline presented the recommendations clearly,[17] but it did not provide clear guidance on their applicability. The guideline was the results of an initiative by the German-Speaking Society of Neuropediatrics and was supported by the association of several scientific medical societies, and the authors declared no conflicts of interest.[17]

The guideline employed comprehensive literature search, recommendations and consensus development methods using Delphi techniques, evidence assessment using SIGN methods, and provided strength of the recommendation.[17] However, the details of these methods, the interpretation of evidence assessment, and the links between evidence and recommendations were unclear. The level of evidence supporting these recommendations in children is lower compared to that in adults. The guideline mostly cites Cochrane reviews (before 2018) as their evidence base, which predominantly includes studies conducted in adults.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

The systematic review included in this report conducted a NMA that compared disability related outcomes for PE and IVIg, and PE and placebo.[15] The health technology assessment subsection reported the adverse events associated with IVIg and PE in patients with GBS.[16] The included guideline provided multiple recommendations regarding PE and IVIg for children with GBS.[17]

Clinical Effectiveness of PE Versus Placebo on Disability

Disability Grade Change

The systematic review reported that patients who received PE (full- or half-course) had statistically significantly lower disability scale grades (indicating better function) compared to those who received placebo.[15] The directions of both direct and indirect estimates were consistent when comparing full-course PE versus placebo. The network estimate comparing half-course PE versus placebo was derived fully from the direct comparison.

Disability Improvement

The pooled estimates of full-course PE versus placebo on this outcome were totally from direct evidence.[15] The odds of disability improvement (defined as an improvement of 1 or more grades on disability scales) were 2.7 times higher in those receiving full-course PE compared to those receiving placebo.[15] There was no comparison available for half-course PE versus placebo on disability improvement outcomes.

Clinical Effectiveness and Safety of PE Versus IVIg

Disability: Grades Change and Improvement

The systematic review reported that no statistically significant difference in disability grade changes between patients who received PE (full- or half-course) compared to those who received IVIg.[15] The odds

of disability improvement (defined as an improvement of 1 or more grades on disability scales) were also similar between full-course PE and IVIg, and these estimates were based on network analysis.[15] However, it is unclear whether these estimates were derived from direct or indirect comparisons between full-course PE and IVIg. There was no comparison available for half-course PE versus IVIg on disability improvement outcome.

Adverse Events

The included health technology assessment included a subsection reporting adverse events for IVIg and PE among patients with GBS.[16] However, the specific details of PE (unclear full- or half-course) and adverse events were not clearly stated. The assessment was based on data from 3 primary individual studies, and the pooled results indicated no significant difference in the odds of adverse outcomes between patients with GBS receiving PE and those receiving IVIg.

Cost-Effectiveness of PE and IVIg

No cost-effectiveness evidence regarding PE and IVIg for patients with GBS was identified; therefore, no summary can be provided.

Evidence-Based Guidelines Regarding the Use of PE and IVIg

The German clinical practice guidelines offered recommendations for immune treatments for children with GBS, with a short version published in English.[17] The guideline panel members have considered PE and IVIg to have similar effectiveness and side effects, with a higher rate of therapy discontinuation in the PE group, the disease progression differing between adults and children, and long-term recovery generally better in children and adolescents compared to adults.[17] For children and adolescents with severe GBS (i.e., loss of ability to walk unaided), the guideline strongly recommends IV "7S"-IVIg. IVIg is suggested (moderate recommendations) for patients with expected considerable ongoing deterioration, while PE is suggested (moderate recommendations) as an alternative when IVIg is contraindicated or ineffective. There is an open recommendation that IVIg or PE may be repeated after a few weeks for difficult-to-treat cases.

PE is suggested as the second-line immune treatment after IVIg for severe cases of GBS or patients with expected considerable ongoing deterioration. The guideline prefers IVIg over PE for children and adolescents with GBS who require immune therapies.[17] The systematic review with NMA and the health technology assessment captured in our report were not included in the guideline.

The clinical practice guideline did not provide information on the dose and timing of interventions used in their recommendations, but this information was mentioned in the comments section.[17] For IVIg, it was typically administered as a single cycle of 2 g/kg body weight over 4 to 5 consecutive days in children and reducing the period to 2 days has been associated with a higher frequency of relapse. PE usually required an exchange volume of 200 mL/kg to 250 mL/kg body weight for 4 to 5 cycles over 7 to 14 days. PE with continuous flow or using albumin as the exchange fluid is more favourable than intermittent flow or fresh frozen plasma.

Appendix 4 presents the main study findings.

Limitations

The systematic review with NMA included a substantial number of clinical trials (28 clinical trials), but most included primary studies in the systematic review had high risk of bias in the blinding of outcome assessment domain.[15] This may have resulted in detection bias, as the outcome measures were closely related to outcome accessors' judgment. As a result, the evidence for the effectiveness of PE versus IVIg may not be completely reliable. Additionally, the evidence for adverse events was limited (only from 3 clinical studies with unclear risk of bias),[16] and it is possible that the safety issues of PE and IVIg were not fully captured by the report. However, the included guideline suggests that adverse outcomes for PE versus IVIg were similar in patients with GBS although patients receiving PE had a higher rate of therapy discontinuation than those receiving IVIg.[17] We did not find any studies reporting on rate of recovery, duration of hospitalization, cost-effectiveness of PE or IVIg among patients with GBS that met the inclusion criteria of this report.

The included guideline suggests that clinicians consider disease severity and expected disease progression when selecting immune therapies such as PE or IVIg.[17] However, the available body of evidence did not allow us to comment on the subgroup effect of PE, such as the pediatric population or patients with different disease durations or severities. It is also unclear whether the relative effects of PE differ from those of IVIg across these subgroups. Additionally, there are some consensus statements available for treatment options for GBS,[18] we did not find any guideline recommendations regarding use of PE or IVIg for adults with GBS.

The primary studies in the included systematic reviews were conducted in Asia, Europe, and only 1 study with 50 participants (published in 1996) was conducted in Canada.[15] The clinical practice guideline was from Germany, and the guideline authors from Europe.[17] Therefore, the generalizability of these findings to settings in Canada is uncertain.

Conclusions and Implications for Decision- or Policy-Making

One systematic review with NMA was identified to address the clinical effectiveness of PE for patients with GBS compared to IVIg or placebo.[15] However, the NMA had several limitations, including several discrepancies in the results section, the inclusion of data from 1 nonrandomized observational study, and without test transitivity assumptions. Despite these limitations, the evidence suggested that PE statistically significantly reduced disability score (indicating better function) and increased the odds of likelihood for disability (physical function) improvement compared to placebo. Despite previous evidence summary suggesting that PE may be better than IVIg for ventilated pediatric patients in terms of functional outcome,[9] the current report suggests that the effectiveness of PE was similar to IVIg on disability outcomes. The risk of adverse events of PE may be similar to IVIg as well, but adverse events were probably incompletely captured by the current report, which was limited with only 3 clinical studies of unclear risk of bias.[16]

An evidence-based practice guideline from Germany suggested that PE could be used for children with GBS who have contraindications for IVIg or when IVIg is ineffective.[17] However, the evidence base for these recommendations were from Cochrane systematic reviews (before 2018), which included mostly studies

conducted in adults, and the level of evidence for children was lower than that in adults. The links between these recommendations and the evidence bases were unclear. We did not find any recommendations regarding the use of PE and IVIg in adults with GBS.

PE therapies are typically more expensive and require longer hospital stays or more resources than IVIg, such as a special team, equipment, or exchange fluids.[6] Although these issues may be helpful for decision- or policy-making, no evidence regarding the cost-effectiveness of PE or IVIg for patients with GBS was identified that met the inclusion criteria for this report.

In addition to considering the effectiveness, safety and cost of PE and IVIg, there are several other factors that may influence the decision-making process between the 2 immune treatment options. For example, contraindication for each treatment should be considered, such as septic shock or myocardial infarction within 6 months for PE, and renal function deficiency or congestive heart failure for IVIg.[6] Additionally, the availability of each treatment option should be considered. Moreover, patients' experiences and perceptions of GBS may also play a role in the decision-making process.[19]

Due to the limitations of the body of evidence, such as the limitations of the NMA, incomplete safety outcome data, and lack of blinding in included individual primary studies, these findings should be interpreted with caution. In addition, the generalizability of the evidence to settings in Canada was unclear. Therefore, cost-effectiveness studies, systematic reviews with safety outcomes and more RCTs with robust methodology, such as blinding the outcome assessors, are required to better inform decision- or policy-making.

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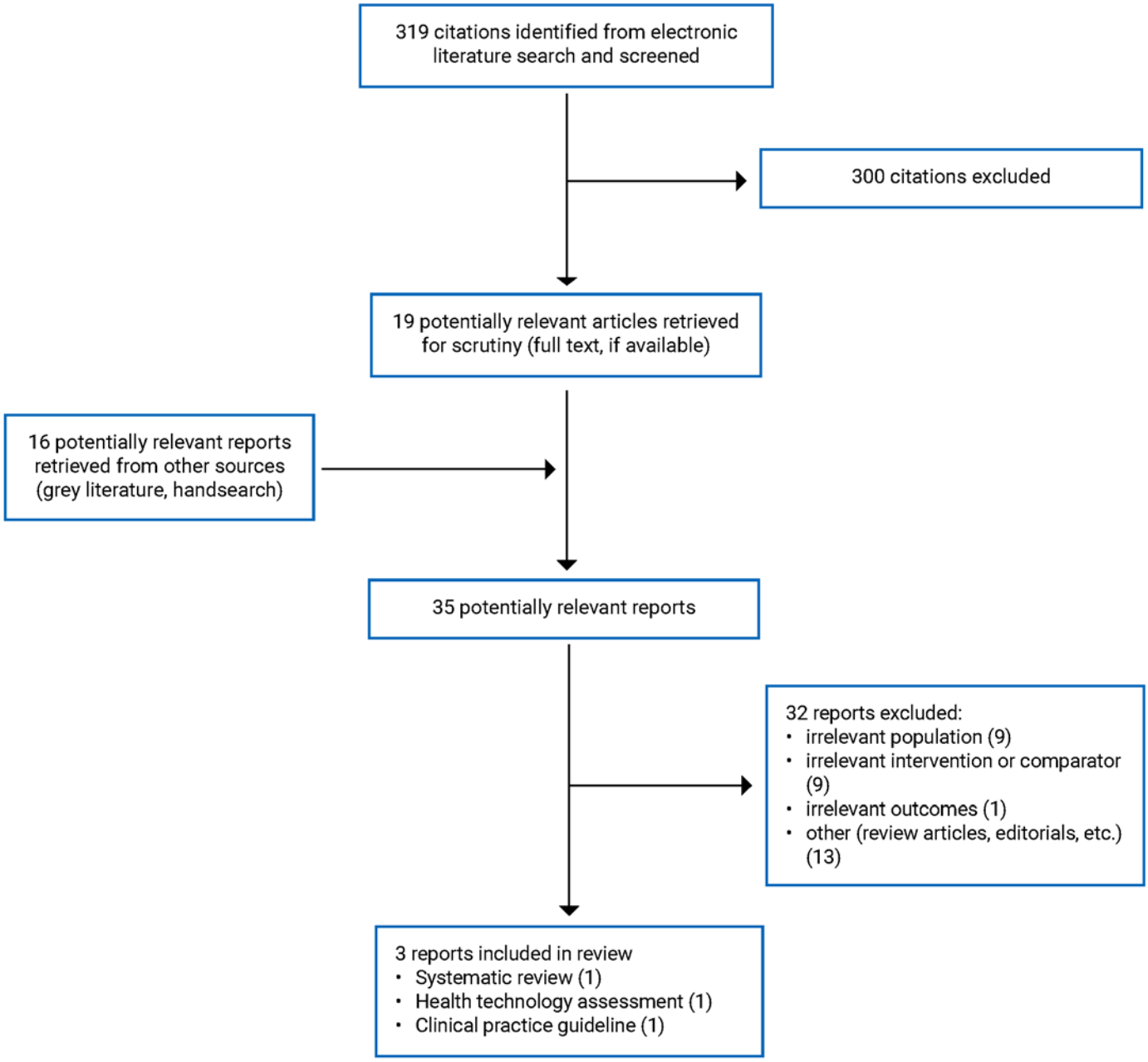
19. Laparidou D, Curtis F, Akanuwe J, Jackson J, Hodgson TL, Siriwardena AN. Patients' experiences and perceptions of Guillain-Barre syndrome: A systematic review and meta-synthesis of qualitative research. *PLoS ONE [Electronic Resource].* 2021;16(2):e0245826. PubMed

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Lin et al. (2021)[15] China **Funding source:** National Natural Science Foundation of China and the authors declared no conflict of interest.	**Study design**: systematic review and network meta-analysis was registered on PROSPERO: CRD: 42019119178. **Number of included studies**: 28 (RCT: 27; observation study: 1). **Search**: January 1, 1980 to January 1, 2019	Children or adults with GBS of all degrees of severity N = 2,474 **Sex**: NR **Age**: NR **Disease duration or severity**: NR	**Intervention:** 15 therapies: full-course PE, half-course of PE IVIg, MTP, prednisolone, immunoadsorption plasmapheresis, IFNb-1a, BDNF, CSF filtration, TWP, PE+IVIg), immunoadsorption followed by IVIg, IVIg + eculizumab **Dosage**: IVIg: 0.4 to 0.5 g/kg/d for 4 to 6 days; 1 g/kg/d for 2 days; 0.4 g/kg/d for 3 days. **Comparator**: placebo or supportive care **Details:** NR	**Outcomes:** Disability grade change Disability improvement (measured by ≥ 1 grade of disability scale) Time frame for outcomes assessment: after 4 weeks **Follow-up:** NR

GBS = Guillain-Barré syndrome; NA = not applicable; NR = not reported. RCT = randomized controlled trial; TCZ = tocilizumab; PE = plasma exchange; IVIg = IV immunoglobulin, MTP = methylprednisolone; IFNb-1a = interferon beta-1a; BDNF = brain-derived neurotrophic factor; CSF = cerebrospinal fluid; TWP = tripterygium wilfordii polyglycoside.

Table 3: Characteristics of Included Health Technology assessment

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Mittal et al. (2021)[16] Australia **Funding source:** NR, the authors declared no conflict of interest.	**Study design:** Assessment report regarding IVIg for CIDP (B.7 extended assessment of harms relevant to the current report) **Number of included studies relevant to the current report: 3**	Patients with CIDP (patients with GBS in the B.7 section relevant to the current report) **Sex**: NR **Age**: NR **Disease duration or severity**: NR	**Intervention:** PE (unclear, full-, or half-course) **Details:** NR **Comparator**: IVIg **Dosage**: NR	**Outcomes:** AEs **Follow-up**: NR

CIDP = chronic inflammatory demyelinating polyneuropathy; GBS = Guillain-Barré syndrome; NA = not applicable; NR = not reported. RCT = Randomized Controlled Trial; TCZ = Tocilizumab; PE = plasma exchange; IVIg = IV immunoglobulin, AE = adverse event.

Table 4: Characteristics of Included Guideline

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
[a]Korinthenberg et al. (2020)[17]						
Intended users: All involved parties (i.e., medical specialists, therapeutic professionals and the affected persons) **Target population**: patients with GBS in childhood and adolescence	GBS diagnostic procedures and treatment. Interventions include antibiotic therapy, supportive therapy, immune treatment (IVIg, PE, corticosteroids and other approaches), and rehabilitation.	Effects (e.g., Improvement on the GBS scale) and adverse events Special considerations: (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.	A systematic search of the literature was performed. Methods for evidence synthesis were unclear in the English report. Detailed methodology probably located in the extended version in German.	The level of evidence of each publication was classified according to criteria from Scottish Intercollegiate Guidelines Network (no details were provided in the English version).	The guideline was developed by a group of delegates from relevant specialist societies and organizations in Germany. For the formal Recommendations, a written, 3-step Delphi process was used to establish consensus. Level of recommendation: A: strong recommendation; B: moderate recommendation; C: open recommendation. Strength of Agreement: strong consensus (> 95% agreement); consensus (> 75% to 95% agreement); majority consensus (> 50% to 75% agreement); o consensus (,50% agreement). For other topics other than recommendations:	This guideline is the result of an initiative by the German-Speaking Society of Neuropediatric, and is supported by the Association of Scientific Medical Societies.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
					informal discussions between the authors were conducted first and then a final consensus process was performed with participating members and professional organizations.	

GBS = Guillain-Barré syndrome; IVIg = IV immunoglobulin; PE = plasma exchange.

[a]This guideline's characteristics are based on the English (short) version. However, an extended version of the guideline is also available in German.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of Systematic Review and NMAs and HTA Using AMSTAR 2[11] and the ISPOR Questionnaire[12]

Strengths	Limitations
Lin et al. (2021)[15]	
The purpose of the study was clearly described. The protocol of this review was prospectively registered in the PROSPERO. Multiple databases were searched (Web of Science, PubMed, Embase, and the Cochrane library). MeSH and related entry terms were provided. The reference list of enrolled articles was reviewed manually. A flow chart of study selection was provided. The study selection and data extraction processes were conducted by 2 reviewers independently. The review authors conducted quality assessments for eligible studies (unclear methods but implied using the Cochrane's RoB tool) and presented the risk of bias graph. Publication bias was assessed using funnel plots. The review authors reported no conflicts of interest. The population is relevant to the current report and no critical interventions missing. The context applicable to the report population. The researchers attempt to identify and include all relevant trials. The intervention of interest (IVIg, PE, placebo) from a connected network of trials. The statistical methods used that preserve within-study randomization (no naive comparisons). Consistency analysis and ranking probabilities were conducted. Both direct and indirect evidence were included in the NMA. The network plot was presented in Figure 3. The results of direct comparisons reported separately from indirect comparison and network meta-analysis for some comparisons. The pointed estimates and 95% credible intervals were reported. The ranking probability graphs were provided.	The exclusion criteria were not clearly described. The details of included studies were not adequately described. The full search strategy was not available. A grey literature search was not reported. The study selection process and data extraction were unclear. The list of excluded studies was not provided. The review authors did not report the sources of funding for eligible studies. The safety outcomes are missing. This network included a nonrandomized trial. The authors did not assess the systematic differences in treatment effect modifiers across the different treatment comparisons in the network. Rationale for using fixed-effect models was inadequate (only considered the low I^2) and the authors used the fixed-effect models to synthesis for all comparisons that includes some meta-analysis with moderate heterogeneity (I^2 > 50%). The individual study results and the details of outcome measures were not reported were not reported. The effect of important patient characteristics (e.g., age or disease severity) on treatment effects were not reported. The review authors did not assess the potential impact of risk of bias in individual studies or publication bias on result interpretations and conclusions. Several discrepancies were identified across reported figures (2 to 8): Figure 2 B showed a closed loop in PE, IVIg and PE+IVIg, but the indirect estimate for IVIg vs. PE is missing in Figure 8 "I" panel; the title for Figure 7 (for outcome 2, should be for outcome 1) and Figure 8 (for outcome 1, should be for outcome 2) probably refer to wrong outcome measures. The conclusions were driven by the statistical tests (ranking probability) and did not consider the certainty of evidence.
Mittal et al. (2021)[16]	
Multiple databases were searched (PubMed, Embase, clinical trials.gov). The report authors declared no conflicts of interest.	The target population did not intend to include patients with GBS. Instead, safety data relevant to GBS was used as a complement for patients with CIDP, when satisfactory data for

Strengths	Limitations
	CIDP patients was not available. The inclusion and exclusion criteria were unclear. The full search strategy was not available. A grey literature search was not reported. The study selection process and data extraction were unclear. A flow chart of study selection was unavailable. The list of excluded studies was not provided. The details of included studies (e.g., study design, risk of bias, sources of funding) were not adequately described. The methods for the statistical combination of results us unclear. The review authors did not assess publication bias and the quality of included individual studies.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; CIDP = chronic inflammatory demyelinating polyneuropathy; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NA = not applicable; NMA = network meta-analysis; NR = not reported; RoB = risk of bias; RCT = randomized controlled trial.

Table 6: Strengths and Limitations of Guideline Using AGREE II[13]

Item	[a]Korinthenberg et al. (2020)[17]
Domain 1: Scope and purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Not explicit but implied yes.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Not explicit but implied yes.
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	No
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	To some extent but lacked details.

Item	[a]Korinthenberg et al. (2020)[17]
12. There is an explicit link between the recommendations and the supporting evidence.	Unclear
13. The guideline has been externally reviewed by experts before its publication.	Unclear
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial independence	
22. The views of the funding body have not influenced the content of the guideline.	Not explicit but implied yes.
23. Competing interests of guideline development group members have been recorded and addressed.	The authors have no conflicts of interest to declare.

AGREE II = Appraisal of Guidelines for Research and Evaluation II; NA = not applicable; NR = not reported.

[a]The critical appraisals for the guideline were based on the English (short) version. However, an extended version of the guideline is also available in German.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 7: Summary of Findings by Outcome — Disability Outcomes

Author (year) and study design	Comparisons	Results and effect size			
		Statistics	Direct estimates	Indirect estimates	Network estimates
Disability grade change (lower scores indicate better physical function)					
Lin et al. (2023)[15] Systematic review and NMA with 28 articles	Full-course PE vs. Placebo	Pooled MD (95% CrI)	−0.77 (−1.2 to −0.28)	−1.4 (−2.7 to −0.10)	−0.83 (−1.3 to −0.38)
	Half-course PE vs. Placebo	Pooled MD (95% CrI)	−1.1 (−1.8 to −0.35)	NA	−1.1 (−1.8 to −0.35)
	Full-course PE vs. IVIg (0.4 to 0.5 g/kg/d for 4 to 6 days)[a]	Pooled MD (95% CrI)	NR	NR	0.078 (−0.26 to 0.41)
	Half-course PE vs. IVIg (0.4 to 0.5 g/kg/d for 4 to 6 days)	Pooled MD (95% CrI)	NR	NR	−0.19 (−1.1 to 0.72)
	IVIg (1 g/kg/d for 2 days) vs. Full-course PE	Pooled MD (95% CrI)	NR	NR	−0.053 (−0.83 to 0.73)
	IVIg (0.4 g/kg/d for 3 days) vs. Full-course PE	Pooled MD (95% CrI)	NR	NR	0.43 (−0.59 to 1.4)
Disability improvement (measured by ≥ 1 grade of disability scale)					
Lin et al. (2023)[15] Systematic review and NMA with 28 articles	Full-course PE vs. Placebo	Pooled OR (95% CrI)	2.7 (1.7 to 4.5)	NA	2.7 (1.7 to 4.8)
	Full-course PE vs. IVIg (0.4 to 0.5 g/kg/d for 4 to 6 days)[a]	Pooled OR (95% CrI)	NR	NR	0.74 (0.44 to 1.2)

CrI = credible interval; IVIg = IV immunoglobulin; MD = mean difference; NA = not applicable; NR = not reported; PE = plasma exchange.

[a]The systematic review also reported the comparison of IVIg (0.4 to 0.5 g/kg/d for 4 to 6 days) vs. PE.

Table 8: Summary of Findings by Outcome — Adverse Events

Author (year) and study design	Results				
	Comparisons	Statistics	Effect size	I^2 (%)	Notes
Mittal et al. (2021)[16] Systematic review with 3 relevant articles	IVIg vs. PE (unclear, full-, or half-course)	Pooled OR (95% CI)	0.76 (0.38 to 1.49)	NR	P value = 0.43

CI = confidence interval; IVIg = IV immunoglobulin; NR = not reported; OR = odds ratio; PE = plasma exchange.

Table 9: Summary of Recommendations in Included Guideline

Recommendations or statements	Supporting evidence	Strength of recommendation
Korinthenberg et al. (2020)[17]		
Treatment with intravenous 7S-Immunoglobulin (IVIG) is recommended in children and adolescents with severe GBS (i.e., loss of ability to walk unaided)" p12	Adults: high-quality and high consistency with SIGN: 1++ Children: lower LoE with SIGN 1- to 2-	Strong recommendation Strength of consensus: strong
"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" p12	Adults: SIGN: 1+ Children: weak LoE with SIGN 2-	Moderate recommendation Strength of consensus: strong
"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." P13	Adults: SIGN: 1++ Children: very weak LoE with SIGN 2 to 3	Moderate recommendation Strength of consensus: Consensus
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. P13	Lacks evidence from studies that go beyond individual observations: SIGN 4	Open recommendation Strength of consensus: Strong

CIDP = chronic inflammatory demyelinating polyneuropathy; IVIg = IV immunoglobulin; LoE = level of evidence; SIGN = Scottish Intercollegiate Guidelines Network; PE = plasma exchange.

[a]These recommendations were based on the English (short) version. However, an extended version of the guideline is also available in German.

Appendix 5: References of Potential Interest

Previous CADTH Reports

Sutton D, Visintini S. Off-label use of intravenous immunoglobulin for neurological conditions: a review of clinical effectiveness. *(CADTH rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/label-use-intravenous-immunoglobulin-neurological-conditions-clinical-effectiveness. Accessed 2023 Mar 31.

Systematic Reviews

Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;2014(9). PubMed

Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2017;2017(2). PubMed

Doets AY, Hughes RA, Brassington R, Hadden RD, Pritchard J. Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barre syndrome. *Cochrane Database Syst Rev*. 2020;1:CD008630. PubMed

Goudarzi S, Esmaeeli S, Valencia JD, Lu ME, Hales RR, Fehnel CR, et al. Treatment options for COVID-19-related Guillain-Barre syndrome: a systematic review of literature. *Neurologist*. 2021;26(5):196-224. PubMed

Guideline

Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain–Barré syndrome in ten steps. *Nature Reviews Neurology*. 2019;15(11):671-83. PubMed

Additional References

Morales-Ruiz V, Juarez-Vaquera VH, Rosetti-Sciutto M, Sanchez-Munoz F, Adalid-Peralta L. Efficacy of intravenous immunoglobulin in autoimmune neurological diseases. Literature systematic review and meta-analysis. *Autoimmun Rev*. 2022;21(3):103019. PubMed

Sulli S, Scala L, Berardi A, Conte A, Baione V, Belvisi D, et al. The efficacy of rehabilitation in people with Guillain-Barre syndrome: a systematic review of randomized controlled trials. *Expert Rev Neurother*. 2021;21(4):455-61. PubMed

Laparidou D, Curtis F, Akanuwe J, Jackson J, Hodgson TL, Siriwardena AN. Patients' experiences and perceptions of Guillain-Barre syndrome: A systematic review and meta-synthesis of qualitative research. *PLoS ONE* [Electronic Resource]. 2021;16(2):e0245826. PubMed

Guo F, Zhang YB. Clinical features and prognosis of patients with Guillain-Barre and acute transverse myelitis overlap syndrome. *Clin Neurol Neurosurg*. 2019;181:127-32. PubMed