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Immunoglobulin unresponsive Guillain-Barré syndrome: rinse or repeat? A systematic review

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ABSTRACT

Introduction Severe Guillain-Barré syndrome (GBS) patients may not show improvement after a single course of intravenous immunoglobulin (IVIg) therapy. Current treatment options include either a second course of IVIg or therapeutic plasma exchange (TPE). This systematic review aims to evaluate the current literature on the use of a second course of IVIg or TPE in patients who fail to show clinical improvement after the first IVIg course.

Methods We searched PubMed, Embase and Medline databases up until 26 October 2023. Studies that evaluated adult patients with confirmed GBS who have failed one full course of IVIg and subsequently received either repeat IVIg or TPE were included. Risk of bias was performed using study-specific checklists. A narrative synthesis of results is presented.

Results A total of 37 articles were identified (1 randomised controlled trial (RCT), 3 observational and 33 case reports/series), consisting of 422 patients in total. 12 studies evaluated repeat IVIg and 24 studies evaluated TPE after IVIg. There was no superiority of a repeat course of IVIg or TPE in all clinical outcome measures.

Conclusions The evidence suggests with a low degree of certainty that there is no beneficial effect of further IVIg in unresponsive GBS. The quality of evidence regarding TPE after IVIg is insufficient to suggest any efficacy due to a lack of RCTs. We recommend standardised case reporting with consideration for a multinational case registry and RCTs to determine the efficacy of TPE after initial IVIg unresponsiveness.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intravenous immunoglobulin (IVIg) treatment can prove ineffective in some severe cases of Guillain-Barré syndrome (GBS), creating a dilemma in clinical decision-making; should you repeat IVIg, or switch to therapeutic plasma exchange (TPE)?

WHAT THIS STUDY ADDS

⇒ This is the first systematic review of IVIg unresponsive GBS. 12 studies evaluated repeating IVIg (including one randomised controlled trial) showing no clinical benefit and potential for harm. 22 studies evaluating TPE following IVIg showed no efficacy in two observational studies and variable efficacy within case reports/series. The overall quality of evidence was poor and the reporting variability between studies prevented a meta-analysis from being performed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We recommend standardised case reporting for GBS patients failing to respond to IVIg and further research regarding TPE following IVIg efficacy and safety.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an autoimmune-mediated acute peripheral polyneuropathy. Although rare, it represents the most common cause of acute flaccid paralysis worldwide. Classically, patients present 1–2 weeks following an immunological stimulus with acute onset bilateral ascending paralysis and reduced deep tendon reflexes.[1 2]

A significant proportion (32%–40%) of severely affected patients fail to show improvement following a single course of intravenous immunoglobulins (IVIg).[1 3] Management options in this refractory group are either giving a second course of IVIg or changing to therapeutic plasma exchange (TPE). However, there is currently only low-quality, indirect evidence to support decision-making here. Achieving an answer for this patient cohort is essential for patients, their families and from a health economic perspective (given the dependency on costly intensive care unit (ICU) services for organ support).[4]

This objective of this systematic review is to comprehensively evaluate the current published evidence regarding GBS management following a lack of response to first course of IVIg, to assess if we should consider a second course of IVIg or initiate TPE within an appropriate time frame.

METHODOLOGY

This review is reported according to Preferred Reporting Items for Systematic

Table 1 Eligibility criteria for systematic review. GBS criteria are defined by NINDS[5 6]

PI-O	Inclusion criteria	Exclusion criteria
Population	GBS confirmed cases using established clinical criteria (NINDS). Adult (>18 years) No response or inadequate response after IVIg treatment is defined as no clinical improvement within 4 weeks	Responders to initial treatment Pregnancy Treatment-related fluctuations (defined as temporary improvement following initial treatment). Paediatric (<18 years) TPE/alternative treatment as the initial therapy
Intervention	Repeat full course IVIg (0.4 g/kg/day for 5 days) Change to and completion of full course of TPE	Change to alternative treatments including medications used in currently active clinical trials
Outcomes	Primary outcome: Disability assessment using various scoring methods (Hughes Functional Grading Scale, MRC sum score, etc) Secondary outcomes Mortality ICU admission/intubation Hospital/ICU length of stay	

GBS, Guillain-Barré syndrome; ICU, intensive care unit; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; NINDS, National Institute of Neurological Disorders and Stroke; TPE, therapeutic plasma exchange.

Reviews and Meta-Analysis 2020 standards. A protocol was created and published into the PROSPERO database (CRD42020200389) and updated accordingly.

Patient and public involvement

No patient or public involvement was sought for the purposes of this systematic review.

Eligibility criteria

A comprehensive list of eligibility criteria can be found in table 1.

Information sources and search strategy

A broad search strategy was used across relevant databases, including PubMed, Embase, Web of Science, Medline, Trip and Cochrane on 20 July 2020. We updated the search again on 26 October 2023. The search strategy is detailed in box 1. No limitation on study design was applied, although conference abstracts and editorials were excluded. Given that there has not been a systematic review on this topic already, there was no date limitation. Only articles published in English were included. Article reference screening was also performed to ensure a comprehensive capture of the literature.

Box 1 Example search strategy in PubMed

(((((((PEX OR "plasma exchange" OR plasmapheresis OR immunotherapy OR IVIg OR "intravenous immunoglobulin*")) OR ("Immunotherapy"[Mesh])) OR ("Plasmapheresis"[Mesh])) OR ("Plasma Exchange"[Mesh])) OR ("Immunoglobulins, Intravenous"[Mesh])) AND (((("guillain-barre syndrome" OR GBS OR "guillain barre syndrome")) OR ("Guillain-Barre Syndrome"[Mesh]))) AND ((resistan* OR futil* or deteriorat* OR repeat* OR switch OR unrespons* OR ineffectiv* OR "second dose" OR follow* OR combin* OR fail* OR "poor prognosis")).

Screening and selection

Responses were collated and ordered using EndNote V.X9 (Clarivate) where duplicates were deleted before title and abstract screening was performed by two authors (TR and AG) using Rayyan (Qatar Computing Research Institute, Doha, Qatar). Full-text screening was performed in duplicate by two authors (TR and AG). Disagreements at all stages were discussed with an additional author (NG).

Data collection

Data extraction was performed in full by a single author (TR) and duplicated by two other authors (CT/JW) independently from TR to confirm reporting accuracy. Data were extracted directly into a Microsoft Excel 2019 spreadsheet. All discrepancies were discussed and adjusted.

Data items and summary measures

A full list of data extracted from each article has been published in the study protocol. The primary outcome was treatment effectiveness, defined as an improvement in chosen disability assessment following second-line therapy at any time point using any disability scoring system. Predominantly, we referred to Hughes Functional Grading Scale (HFGS), and where possible and reliable, we converted the reported functional outcomes to the HFGS system. Where this is not reported, the Modified ERASMUS GBS outcome score, Medical Research Council (MRC) power scoring system was used. Secondary outcomes were mortality, ICU admission/requirement of invasive mechanical ventilation (IMV) and hospital/ICU length of stay. Baseline patient characteristics alongside timing of therapy were extracted to determine whether any associations exist between population/interventions and outcomes.

Effect measures

The effect measure uses mean difference in score and risk/OR (adjusted where possible). For case report/series, the disability grade assessment before and after second-line treatment described in the report was extracted.

Study risk of bias assessment

Risk of bias was performed in full by TR, with a random 40% of studies having duplicate assessment (by CT/JW) to ensure reporting accuracy. Disagreements were discussed with an additional author (AG). For randomised controlled trials (RCTs), the Cochrane Risk of Bias V.2.0 tool was used [7]for observational trials, the Newcastle-Ottawa Scale was used, [8] and case reports/series were evaluated using the methodology proposed by Murad *et al*.[9]

Synthesis methods

Given the large proportion of case reports/series included within this review with a high degree of reporting bias and heterogeneity, a narrative synthesis of the literature is applicable to this review.

RESULTS

Study selection

A total of 37 studies were included in this synthesis after database searching on two separate occasions revealed 5456 studies (figure 1).

Study characteristics

The characteristics of the included studies are summarised in table 2. Among the 37 studies, there were 1 RCT, 3 observational studies and 33 case reports/series. In total,

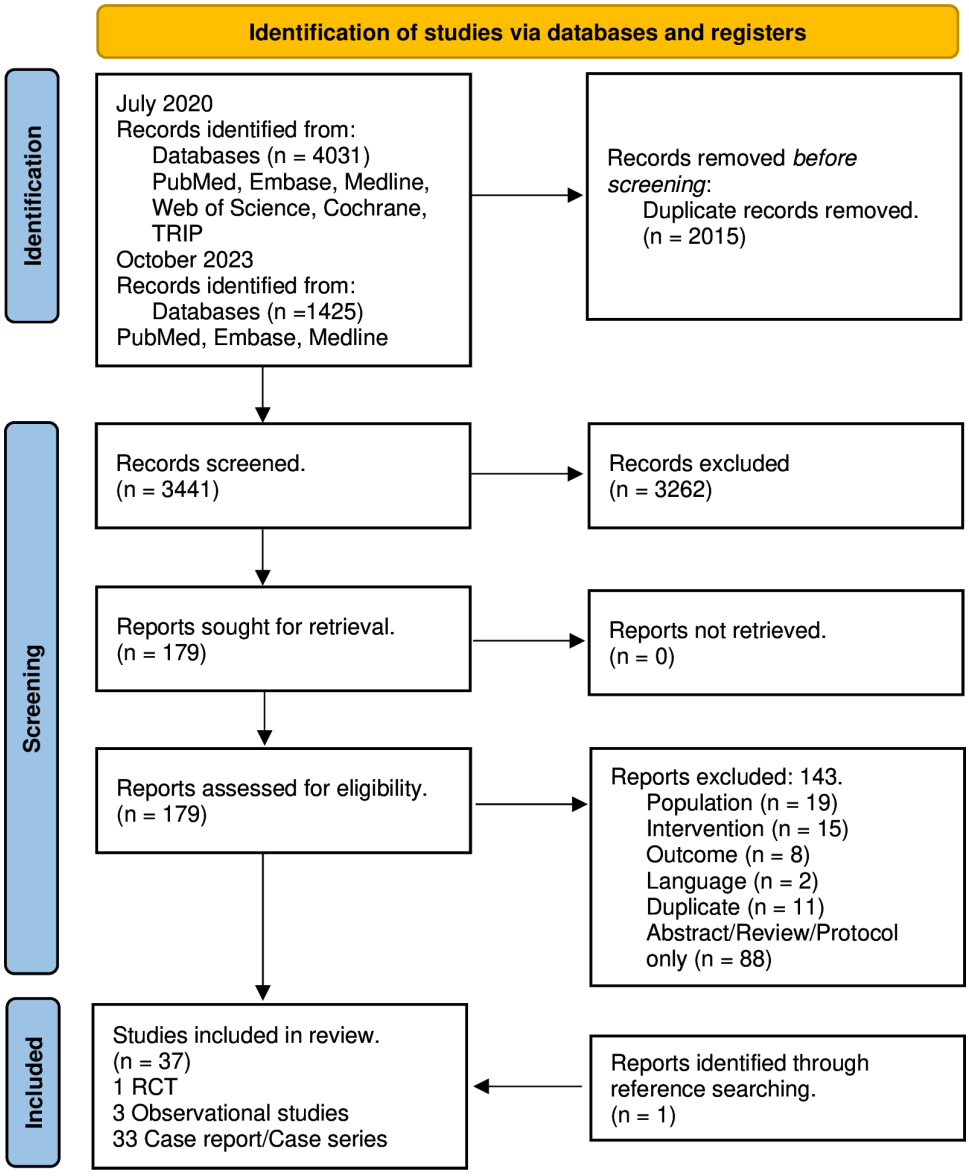

Figure 1 PRISMA flow diagram for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomised controlled trial.

Table 2 Study characteristics

Study	Design	No of patients	IVIg or TPE	Outcomes
Walgaard *et al*[10]	RCT	93 (49 controls)	IVIg	Disability assessment, mortality, IMV requirement, hospital/ICU length of stay
Faustino *et al*[11]	Observational	26 (18 controls)	Both	Disability assessment, ICU admission
Oczko-Walker *et al*[12]	Observational	18	TPE	Disability assessment, hospital length of stay
Verboon *et al*[13]	Observational	237 (199 controls)	IVIg	Disability assessment, mortality, IMV requirement, ICU length of stay
Al-Hashel *et al*[14]	Case report	1	TPE	Disability assessment, mortality
Aratani *et al*[15]	Case report	1	TPE	Disability assessment
Berciano *et al*[16]	Case report	1	IVIg	Disability assessment, mortality
Buzzigoli *et al*[17]	Case report	1	TPE	Disability assessment
Castro and Ropper[18]	Case series	5	TPE	Disability assessment
Chen[19]	Case report	1	TPE	Disability assessment, mortality
Chen *et al*[20]	Case report	1	TPE	Disability assessment
Coomes *et al*[21]	Case report	1	TPE	Disability assessment
Dada and Kaplan[22]	Case series	3	TPE	Disability assessment
Farcas *et al*[23]	Case series	4	IVIg	Disability assessment
Furiya *et al*[24]	Case report	1	TPE	Disability assessment
Kelebek Girgin *et al*[25]	Case report	1	Both	Disability assessment, mortality
Godoy and Rabinstein[26]	Case series	3	TPE	Disability assessment
Hilts *et al*[27]	Case report	1	TPE	Disability assessment
Kara *et al*[28]	Case Report	1	IVIg	Disability assessment
Lopes *et al*[29]	Case report	1	IVIg	Disability assessment
Nithyashree *et al*[30]	Case series	5	IVIg	Disability assessment
Puma *et al*[31]	Case report	1	IVIg	Disability assessment
Rajdev *et al*[32]	Case report	1	TPE	Disability assessment
Ralapanawa *et al*[33]	Case report	1	TPE	Disability assessment
Ravikumar *et al*[34]	Case report	1	TPE	Disability assessment
Re *et al*[35]	Case Report	1	Both	Disability assessment
Şahïn *et al*[36]	Case report	1	TPE	Disability assessment
Salvalaggio *et al*[37]	Case report	1	TPE	Disability assessment, mortality
Shalman *et al*[38]	Case report	1	IVIg	Disability assessment
Stoll and Rakocevic[39]	Case report	1	TPE	Disability assessment
Szczeklik *et al*[40]	Case report	1	TPE	Disability assessment
Tard *et al*[41]	Case report	1	TPE	Disability assessment
Tatarelli *et al*[42]	Case report	1	TPE	Disability assessment
Thöne *et al*[43]	Case report	1	TPE	Disability assessment
Tzachanis *et al*[44]	Case report	1	TPE	Disability assessment
Wu *et al*[45]	Case report	1	TPE	Disability assessment, mortality
Yoshida *et al*[46]	Case report	1	IVIg	Disability assessment

ICU, intensive care unit; IMV, invasive mechanical ventilation; IVIg, intravenous immunoglobulin; RCT, randomised controlled trial; TPE, therapeutic plasma exchange.

there are 422 patients, with 261 patients receiving either placebo or control, defined as a single course of IVIg.

Repeat IVIg for all outcomes included 12 studies, 1 RCT, 2 observational and 9 case reports/series. In total, there were 374 patients, including 261 control participants.

In the TPE group, 24 studies were included for all outcomes, including 2 observational trials and 22 case reports/series.

One observational study evaluated both repeat IVIg and change to TPE within their results and has, therefore, been presented in both outcome tables. Two case reports outline two patients who received IVIg without an adequate response, followed by both a repeat course of IVIg and TPE.

Risk of bias

The risk of bias assessment for the RCT is shown in table 3. Some concerns were raised about randomisation bias within the context of our review questions. Patients were randomised following IVIg commencement before treatment unresponsiveness was established. Patients were included in the study if they were predicted to

Table 3 Risk of bias assessment for RCT[7]

Study	Randomisation	Deviations from intervention	Missing data	Outcome measurement	Selection of result	Overall bias
Walgaard *et al*[10]	Some concerns	Low	Low	Low	Low	Low

RCT, randomised controlled trial.

have a poor prognosis (based on modified Erasmus GBS outcome score of more than or equal to 6). This would allow patients with treatment-related fluctuations (TRF) to be included, however, the exact number of patients with TRF was clearly reported. Very few participants were lost to follow-up (6/99).

Within the observational studies (table 4), Verboon *et al* had moderate to high risk of bias due to comparability. The patient groups were not comparable in this study because patients who responded to first course of IVIg were compared with those who did not respond. The two groups' outcomes are likely to be different regardless of having a second course of IVIg.[13]

Similarly, Faustino *et al* had a high risk of bias due to similar comparability bias and significant baseline differences between treatment groups.[11] Oczko-Walker *et al* were also found to have a high risk of bias, due to the lack of presentation of baseline characteristic data for the IVIg followed by TPE group. Furthermore, we found a lack of stratification for the main outcomes reported in the methodology.[12]

For case reports/series, there was an overall high risk of bias with only 4 of 33 reports detailing selection criteria for patients (table 5).[18 23 26 30] All studies used criteria concordant for a diagnosis of GBS. It was not possible to assess dose-response effect or a challenge rechallenge phenomenon due to the selection of the studies requiring patients to have a loading dose of IVIg and either a repeat loading dose of IVIg or TPE course. Only 7 of 33 reports have outcome data sufficient for a quantitative synthesis,[18 23 26 29–31 34] and 3 studies were deemed a severe risk of bias due to non-specific outcome measures.[19 22 38]

Disability assessment

IVIg repeat

Of the included reports, disability was assessed by all 12 studies, including 1 RCT, 2 observational studies and 9 case reports/series (table 6). In total, 374 patients were assessed including 261 patients receiving placebo or single IVIg therapy.

Walgaard *et al*, in an RCT, demonstrated no difference in HFGS at all measured time points up to 26 weeks between a single IVIg course and a repeat IVIg course. Furthermore, a second IVIg course failed to increase the HFGS by more than one point for the same time periods compared with placebo.[10]

Two observational studies measured disability outcomes. Verboon *et al* demonstrated no significant difference in HFGS at 4 or 26 weeks between the control and repeat IVIg group.[13] Repeat IVIg was stratified by timing of second treatment course to either early (within 2 weeks), or late (two to 4 weeks). Significantly more patients improved their disability score at 26 weeks in the control group vs late IVIg repeat (p=0.001). Significantly fewer patients were able to walk at 6 months in the late repeat IVIg group versus the early and control groups (18% vs 69% and 64%, respectively, p=0.01). The other observational trial found no difference in HFGS between single and repeat IVIg group.[11] The overall reporting to time to second IVIg course was variable and incomplete (see online supplemental material 1 for a more detailed description).

In case reports/series, there was variable improvement in disability assessment in eight studies, with six reports demonstrating neurological improvement within 3 months of repeat IVIg,[23 26 28 30 31 38] and two reports showing improvement within 6 months of repeat IVIg.[29 46]

Switch to TPE

Two observational trials and 22 case reports/series reviewed patients who had received TPE following the first course of IVIg (table 7). In total, 72 patients were assessed including 22 patients receiving placebo or single IVIg therapy.

Faustino *et al* demonstrated no significant improvement in HFGS in these patients compared with controls.[11] Oczko-Walker *et al* showed a statistically significant deterioration in HFGS from admission to discharge. However, from nadir (prior to commencing TPE) to discharge, there was a non-significant trend towards recovery.[12]

Within the 22 case reports, 6 studies showed improvements in muscle strength and HFGS or equivalent within 1 month of TPE initiation,[17 18 32–34 41] a further three reports demonstrated improvement by 3 months of TPE

Table 4 Risk of bias assessment for observational studies[8]

Study	Selection	Comparability	Outcome	Overall
Faustino *et al*[11]	1	0	1	Poor
Oczko-Walker *et al*[12]	1	1	2	Poor
Verboon *et al*[13]	2	1	2	Moderate–poor

Table 5 Risk of bias assessment for case report/series

Study	Selection	Ascertainment		Causality		Sufficient reporting
		Exposure	Outcome	Alternative ruled out	Adequate follow-up	
Al-Hashel *et al*[14]	N	Y	Y	N	Y	N
Aratani *et al*[15]	N	Y	N	N	N	N
Berciano *et al*[16]	N	Y	Y	Y	Y	N
Buzzigoli *et al*[17]	N	Y	N	Y	N	N
Castro and Ropper[18]	Y	Y	Y	Y	N	Y
Chen[19]	N	Y	N	N	N	N
Chen *et al*[20]	N	Y	Y	Y	Y	N
Coomes *et al*[21]	N	Y	N	Y	N	N
Dada and Kaplan[22]	N	Y	N	N	N	N
Farcas *et al*[23]	Y	Y	Y	Y	Y	Y
Furiya *et al*[24]	N	Y	N	Y	Y	N
Kelebek Girgin *et al*[25]	N	Y	Y	N	Y	N
Godoy and Rabinstein[26]	Y	Y	Y	Y	Y	Y
Hilts *et al*[27]	N	Y	Y	Y	Y	N
Kara *et al*[28]	N	Y	Y	Y	N	N
Lopes *et al*[29]	N	Y	Y	Y	N	Y
Nithyashree *et al*[30]	Y	Y	Y	Y	Y	Y
Puma *et al*[31]	N	Y	Y	Y	Y	Y
Rajdev *et al*[32]	N	Y	Y	Y	N	N
Ralapanawa *et al*[33]	N	Y	Y	Y	Y	N
Ravikumar *et al*[34]	N	Y	Y	Y	Y	Y
Re *et al*[35]	N	Y	N	Y	Y	N
Şahïin *et al*[36]	N	Y	N	Y	Y	N
Salvalaggio *et al*[37]	N	Y	Y	N	Y	N
Shalman *et al*[38]	N	Y	N	N	N	N
Stoll and Rakocevic[39]	N	Y	N	Y	Y	N
Szczeklik *et al*[40]	N	Y	Y	Y	Y	N
Tard *et al*[41]	N	Y	N	Y	Y	N
Tatarelli *et al*[42]	N	Y	N	N	N	N
Thöne *et al*[43]	N	Y	Y	Y	Y	N
Tzachanis *et al*[44]	N	Y	N	Y	Y	N
Wu *et al*[45]	N	Y	Y	Y	Y	N
Yoshida *et al*[46]	N	Y	Y	Y	Y	N

initiation,[24 40 43] one report within 6 months of TPE initiation[31] and six reports showing improvement beyond 6 months.[15 20 21 27 39 44] Two reports with improvement in unspecified timing.[22 42]

Both observational trials and case reports/series were not consistent in reporting time to TPE following the first course of IVIg. Out of 24 studies, 8 had documented time to TPE,[17 18 24 33 34 39 43 45] with only 2 studies giving TPE beyond 2 weeks of first IVIg course[24 39] (see online supplemental material 2).

Both IVIg and TPE

Among the included studies, only two case reports describe patients receiving a second course of IVIg and TPE.[25 35] Kelebek Girgin *et al* described a patient with axonal GBS secondary to HIV infection who was started on IVIg initially with HFGS score of 1 but continued to deteriorate. After the second IVIg course, the patient's HFGS score was 5. TPE started with no improvement in disability assessment, and the patient died on day 35 secondary to sepsis.[25] The other report describes a patient

Table 6 Summary of results for repeat IVIg

Study	Study type	No of pts	Age, sex	Disability at nadir	Key result
Walgaard *et al*[10]	RCT	Repeat IVIg: 49	Median: 66.0 (IQR 59.5–74.0), 63%, M	MRC sum score: 23 (6–38). Disability score: 3: 2%, 4: 57%, 5: 41%, TRF 6%	aOR (95% CI) HFGS at 4 weeks: 1.4 (95% CI 0.6 to 3.3) 8 weeks: 1.5 (95% CI 0.7 to 3.3) 12 weeks: 2.1 (95% CI 0.9 to 4.6) 26 weeks: 1.0 (95% CI 0.5 to 2.2). HFGS improving by ≥1 at 4 weeks: 1.8 (95% CI 0.6 to 5.3) 8 weeks: 1.0 (95% CI 0.4 to 2.5) 12 weeks: 1.7 (95% CI 0.5 to 5.4) 26 weeks: 0.4 (95% CI 0.1 to 2.6)
		Placebo: 44	Median: 59 (IQR 42.5–70.0), 77%, M	MRC Sum score: 26 (12–35). Disability score: 3: 2%, 4: 52%, 5: 45%, TRF: 11%	
Verboon *et al*[13]	O	20 Early IVIg (within 2 weeks)	Median: 65 (IQR: 54–70), 60%, M	HFGS 5: 80% HFGS 4: 20% HFGS 3: 0% HFGS 2: 0%	Early IVIg vs control: aOR for lower HFGS compared with a single IVIg course at: 4 weeks: 0.7 (95% CI 0.16 to 3.04) 26 weeks: 0.89 (95% CI 0.22 to 3.53) Late IVIg vs control: aOR for lower HFGS compared with control at 4 weeks: 0.66 (95% CI 0.18 to 2.5). 26 weeks: 0.4 (95% CI 0.1 to 1.62), Improving >1 in HFGS compared with control at 4 weeks: 0% vs 31%, p=0.00226 weeks: 36% vs 88%, p=0.001. Early IVIg vs late IVIg: walking at 26 weeks: control: 64%, early: 69%, late: 18%, (early/control vs late p=0.01)
		18 Late IVIg (2–4 weeks)	Median: 59 (IQR 53–71), 67%, M	HFGS 5: 67%HFGS 4: 33%HFGS 3: 0%HFGS 2: 0%	
		199	Median: 59 (IQR 43–70), 55%, M	HFGS 5: 42% HFGS 4: 54% HFGS 3: 4% HFGS 2: 1%	
Faustino et al[11]	O	26 (4 patients received second IVIg)	Repeat IVIg: Median 71.5 (IQR: 35–88), 37.5%, M	Mean HFGS: 4	Compared to one cycle of IVIg (n=18): aOR for improvement in Hughes scale: 0.21, 95% CI 0.19–2.22, p = 0.19.
Berciano *et al*[16]	CR	1	83, M	HFGS: 5	Day 30 of admission: remained HFGS: 5 and subsequently died
Farcas et al[23]	CS	4	Age range: 22– 62, 75% M	Disability grade scale [47] adapted to HFGS. Mean: HFGS: 5	Days post second IVIg. Pt 1: HFGS: 2 by 30 days Pt 2: HFGS: 3 by 15 days Pt 3: HFGS: 2 by 17 days Pt 4: HFGS: 3 by 15 days
Godoy and Rabinstein[26]	CS	3	Age range: 21–54, 66%, M	HFGS: 5	Days post second IVIg: Pt 1: HFGS: 4 at 5 days (45 days from admission) Pt 2: HFGS: 4 at 3 (38 days from admission) Pt 3: HFGS: 4 at 7 days (59 days from admission) 6 months: All patients HDGS 3.
Kara et al[28]	CR	1	43, M	HFGS:5 MRC 0-1/5	Day 12: able to open mouth and protect airway, trapezius MRC 4+/5.
Lopes et al[29]	CR	1	52, M	Quadriplegia MRC 2-4/5	Day 18: halted neurological deterioration. 4 months: Near complete resolution of symptoms

Continued

Table 6 Continued

Study	Study type	No of pts	Age, sex	Disability at nadir	Key result
Nithyashree *et al*[30]	CS	3	Mean: 60 (range: 52–74), 67%, M	HFGS: 5	Day 164: 1 patient: HFGS 46 months: 2 patients: HFGS 51 year: 1 patient: HFGS 3
		2	Mean: 50 (range: 39–62), 100%, M	HFGS: 5	Mean 33 days: HFGS: 43 months: both patients HFGS: 3 6 months: both patients HFGS: 0
Puma *et al*[31]	CR	1	61, M	HFGS: 5	Day 27: Improved neurology Day 57: MRC 2-3/5 day 240: MRC 3-4/5
Shalman *et al*[38]	CR	1	21, M	HFGS: 5	Day 21: movement of fingers and HFGS: 4 a 'few days' later
Yoshida *et al*[46]	CR	1	50, M	HFGS: 5	Day 130: Hughes grade 3 Eventually grade 2 but unspecified timing

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; aOR, adjusted OR; CR, case report; CS, case series; HFGS, Hughes functional GBS scale; IVIg, intravenous immunoglobulin; M, male; MFS, Miller Fisher syndrome; MRC, medical research council; N/A, not applicable; NR, not reported; O, observational study; RCT, randomised controlled trial.

with GBS and lymphoma with nadir MRC 1–2/5. TPE was initiated on days 30–33, followed by a further IVIg course on days 34–38, leading to a marked improvement in respiratory function and eventual discharge after 3 months with intensive rehabilitation.[35]

Secondary outcomes

Mortality

In the repeat IVIg cohort, one RCT, one observational study and a single case report describe mortality. Walgaard *et al* describe the death of four patients (8%) within the second IVIg group, and no patients within the control arm.[10] One patient's cause of death was deemed to be a serious adverse event of the IVIg intervention (acute coronary syndrome). Two of the remaining three patients died due to withdrawal of care, and the final patient died of cardiac arrest after discharge. Verboon *et al* reported 6% GBS-related mortality in the control group, vs 0% in the repeat IVIg arm, however, the difference was not statistically significant (p=0.44). One case report of repeat IVIg highlights a patient with axonal GBS patient who showed a lack of response to treatment and mortality within 30 days.[16]

Mortality for the TPE switch group is reported in four case reports.[14 19 37 45] The mean age was 52 years, all cases were male. Three died within 2 months[14 37 45] and one unclear timing.[19] Without a formal cause of death for each patient, it is impossible to subgroup mortality in this review.

ICU admission/requirement of IMV

In the repeat IVIg cohort, ICU admission/IMV requirement was reported in 1 RCT, 2 observational studies,[11 13] and 8 case reports including 16 patients.[16 23 26 28 30 31 38 46]

Walgaard *et al* noted no statistically significant difference in ICU admission/requirement of invasive ventilation in the RCT between repeat IVIg and placebo (30 patients (61%) vs 25 patients (57%) respectively, aOR 1.3 (95% CI 0.5 to 3.3)).[10]

Verboon *et al* noted 28 of the 38 (74%) repeat IVIg patients required IMV, stratified to 16 patients in the early IVIg (80%) and 12 patients in the late IVIg group (67%). The control group had only 88 patients (44%) IMV requirement meaning significantly less mechanical ventilation than in the early repeat IVIg group (p=0.003).[13] Faustino *et al* reported no difference between ICU admission rate between repeat IVIg and control (OR 0.67, 95% CI 0.57 to 7.85, p=0.75) or IMV requirement rate (OR 5.67, 95% CI 0.27 to 117.45, p=0.26).[11] In the 8 case reports/series, 17 patients were admitted to ICU and started on IMV, with only 1 case describing a patient not requiring IMV in this cohort.[29]

In the TPE following IVIg group, only 1 observational trial[11] and 15 case reports/series (including 19 patients)[14 15 17–20 24 32 34 37 40–43 45] describe ICU admission or requirement of IMV. Faustino *et al* noted no difference in ICU admission (OR 6.0, 95% CI 0.51 to 70.67, p=0.15), however, there was a weak statistically significant trend towards IMV requirement (OR 17.0 (95% CI 1.02 to 283.01) p=0.05).[11] In case reports/series, seven reports of TPE following IVIg did not result in ICU admission or IMV.[21 22 27 33 36 39 44]

In one of two cases where both second course of IVIg and TPE were used required ICU admission and IMV.[25]

Length of stay (ICU/hospital)

In the repeat IVIg cohort, one RCT and one observational trial evaluate length of stay. Walgaard *et al* noted very similar ICU length of stay in the IVIg repeat group at a median of 23 days (IQR: 8–55) vs 25 days (IQR: 4–77) for placebo. Hospital length of stay was median 39 days (IQR: 21–67) in the repeat IVIg arm vs 30 days (IQR: 21–73) in the placebo group. Duration of IMV was

Table 7 Summary of results for switch to TPE

Study	Study type	No of pts	Age, sex	Disability at nadir	Key result
Faustino *et al*[11]	O	26 (4 received TPE)	71.5 (35–88), 37.5%, M	Mean HFGS: 4 (IQR: 1–5)	Compared with one cycle of IVIg (n=18) aOR for improvement in HFGS: 10.60, (95% CI 0.97 to 1115.90), p=0.53
Oczko-Walker *et al*[12]	O	18	NR	Mean HFGS: 4.7	At discharge: Non-significant improvement in HFGS compared with before TPE (p=0.154). HFGS significantly deteriorated compared with admission (p=0.0438) No association between time to initiate TPE after IVIg failure and outcome (p=0.1929)
Al-Hashal *et al*[14]	CR	1	31, M	HFGS: 5	Day 25: No improvement and death
Aratani *et al*[15]	CR	1	43, F	HFGS: 5	2.5 years: Complete resolution of symptoms
Buzzigoli *et al*[17]	CR	1	78, F	HFGS: 5	Day 8: HFGS: 3
Castro and Ropper[18]	CS	5	Mean: 60 (range: 24–64.5), 80%, M	HFGS: 5 in all patients	1 week: Improvement in 2/5 patients. HFGS 4 in one, the other remains HFGS 5 with improved MRC power (unspecified)
Chen[19]	CR	1	57, M	HFGS: 5	Unclear timing: No improvement and death
Chen *et al*[20]	CR	1	58, M	HFGS: 5	15 months: HFGS 4. 5 years: MRC 2-3/5, impaired sensation
Coomes *et al*[21]	CR	1	45, M	HFGS: 5	Several months: HFGS 4
Dada and Kaplan[22]	CS	3	NR	HFGS: 4 in all patients	Unclear time frame: 1/3 patients: no response. 1/3 patients: improved to HFGS: 3. 1/3 patients: improved to HFGS: 2.
Furiya *et al*[24]	CR	1	72, F	HFGS: 5	Day 34: Movement of all limbs 7 months: HFGS 3 18 months: HFGS 2
Hilts *et al*[27]	CR	1	58, M	HFGS: 4 Quadriplegia, upper-limb MRC: 3/5 and lower-limb MRC: 1/5	Day 309: HFGS 3
Rajdev *et al*[32]	CR	1	36, M	HFGS: 5	Day 19: HFGS 4 Day 23: MRC 4-5/5 in distal muscle groups bilaterally
Ralapanawa *et al*[33]	CR	1	55, M	HFGS: 5	10–15 days after TPE: improved muscle strength distally and peripherally 3 months: Proximal muscle power MRC: 5/5. 4 months: impaired distal muscle strength
Ravikumar *et al*[34]	CR	1	60, M	HFGS: 5	Day 11: ventilator triggering Day 14: neck movement Day 19: open and close mouth Day 27: obey commands. Day 32: ICU discharge Hughes scale 5 6 months: Hughes scale 5, mild proximal muscle strength.
Şahïn *et al*[36]	CR	1	19, M	Quadriplegia (MRC 1/5)	6 months: 'Nearly normal' neurology.
Salvalaggio *et al*[37]	CR	1	60, M	HFGS: 5	Day 20: No improvement and death
Stoll and Rakocevic[39]	CR	1	23, F	Quadriplegia (unspecified)	8 months: HFGS: 3
Szczeklik *et al*[40]	CR	1	25, M	HFGS: 5	6 weeks: HFGS: 3 5 months: Full motor recovery
Tard *et al*[41]	CR	1	76, M	HFGS: 5	Within 1 month: MRC 2/5 proximally 2 months: improved muscle strength 4 months: continued improvement
Tatarelli *et al*[42]	CR	1	47, M	HFGS: 5	Unclear timing: 'almost complete recovery of neurological function'
Thöne *et al*[43]	CR	1	58, F	HFGS Miller Fisher syndrome: 5	Day 40: HFGS: 4 Day 44: MRC 2-3/5 6 weeks: MRC 3-4/5
Tzachanis *et al*[44]	CR	1	79, M	Cranial nerve III and VII palsy, altered consciousness, quadriplegia (unspecified)	1 year: Complete resolution of symptoms

Continued

Table 7 Continued

Study	Study type	No of pts	Age, sex	Disability at nadir	Key result
Wu *et al*[45]	CR	1	61, M	HFGS: 5	Day 48: No improvement and death

AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; aOR, adjusted OR; CR, case report; CS, case series; HFGS, Hughes functional GBS scale; M, male; MFS, Miller Fisher syndrome; MRC, Medical Research Council; N/A, not applicable; NR, not reported; O, observational study; TPE, therapeutic plasma exchange.

longer in the placebo arm (26 days (IQR: 12–58) vs 43 days (IQR: 9–80)). No statistical analysis was possible in these outcomes due to non-normal distributions of the results.[10]

Verboon *et al* noted longer ICU length of stay in the late repeat IVIg treatment arm (median 64 days, IQR: 33–144), compared with both the control (30 days, IQR 13–55) and early repeat IVIg (31 days, IQR 18–82). Furthermore, patients in the late repeat IVIg cohort had longer IMV duration (76 days, IQR: 33–239) vs controls (27 days, IQR: 15–61) and early repeat IVIg (55 days, IQR 26–220).[13]

One observational trial evaluated TPE after IVIg noted length of stay, indicating significantly higher hospital length of stay in patients receiving IVIg and TPE vs IVIg alone (26.39 days vs 8.36 days, p=0.00008).[12]

DISCUSSION

This is the first systematic review to identify all the current literature on GBS patients who fail to respond or show any clinical improvement (including ongoing decline) to IVIg and explore the efficacy of a second course of IVIg or switching to TPE.

There is only one RCT which has evaluated the use of additional IVIg,[10] with the remaining being case reports and observational studies. Currently, there is no evidence to support the use of repeat IVIg in GBS patients who have not shown an improvement following first IVIg course for disability, mortality, requirement for mechanical ventilation, or ICU admission.

Although not fully understood, IVIg is thought to exert its GBS disease mitigating effects through blockade of macrophage-induced damage to Schwann cell membranes, regulation of complement cascade and cytokine activity and immunomodulation of B-cells.[48 49] The lack of response in some patients may be explained by interindividual differences in IVIg pharmacokinetics, where there is a significant variation in the half-life between individuals of between 18 and 33 days.[50] Despite some evidence that patients with a lower serum increase in IgG following IVIg administration had a more prolonged recovery compared with those with a greater serum IgG rise,[51] Walgaard *et al* demonstrated that this was not associated with improvement in outcomes.[10]

Although it was beyond the scope of this systematic review to evaluate treatment safety, Walgaard *et al*, noted a significant increase in IVIg-related serious adverse events including venous thromboembolic events in the repeat IVIg group.[10] Furthermore, a recent national shortage for IVIg in the UK following the COVID-19 pandemic has put a significant strain on the National Health Service. Therefore, the use of repeated IVIg is not to be used lightly and should go through a formal specialist committee.

The evidence quality determining the efficacy of TPE after IVIg unresponsiveness is sparse in comparison to the repeat IVIg studies, with only 2 observational trials and 22 case reports/series. With the evidence that is currently available, TPE following IVIg unresponsiveness is a possible therapeutic option with reports of some success, however, there is no strong evidence to confirm this.

Given that around 60%–70% of the substances from the intravascular compartment are removed during a full plasma exchange course,[52] concern that TPE following IVIg administration may effectively 'rinse' any circulating IVIg, negating its potential efficacy is not unfounded. The lack of reporting for TPE timing following IVIg in two-thirds of included studies makes it difficult to determine how much of an effect the IVIg would have had. Despite this, 19 of 26 patients in case reports had improvements in disability parameters, and there was a non-significant improvement in disability assessment from pre-TPE to post-TPE in 18 patients in an observational study.[12]

In the last few years, antibodies targeting node and para-node of myelinated nerves have been increasingly identified in some GBS cohorts.[53] GBS patients who produce IgG1-3 antibodies against para-nodal proteins exert pathogenic effects via mechanisms associated with complement. As a result, the effects of IVIg, which in part provides therapeutic benefit through complement modulation, are more effective.[54] IgG4 antibodies, however, exert pathogenic effects via non-complement pathways, resulting in a minimally effective or transient response to treatment. As a result, in patients unresponsive to IVIg, it could be prudent to perform anti-para-nodal antibody testing and subgroup analysis where the use of TPE or anti-CD20 drugs may provide a more efficacious option.[53 55]

The strengths of this systematic review are that this is the first and only comprehensive evaluation of treatment options for severely affected GBS patients. IVIg is often used as a first-line treatment for GBS, predominantly because of its convenience and availability. These patients are often managed in the intensive care setting with the need for mechanical ventilation for prolonged periods with associated significant patient morbidity and financial and health economic burden.

This systematic review establishes the need for further evidence, and it answers this question from a pragmatic position, aiming to facilitate clinical decision-making for neurology and intensive care colleagues.

The main limitation of this study is the inability to draw conclusions for ongoing clinical practice due to the extremely high risk of bias of the included studies. With a great reliance on case reports/series for this review, reporting heterogeneity and risk of publication and selection bias is very high.

Our most significant finding is that high-quality studies investigating the appropriate next treatment for this group are lacking and recommend further research. Although Walgaard *et al* have provided the most reliable analysis to answer part of our clinical question, the small number of patients included in the study reflects the nature of the incidence of GBS. Consequently, large observational data sets may be useful in assessing therapy response and outcomes.

Disease registries may be helpful to streamline standardised reporting. Moreover, RCTs are needed to evaluate the efficacy of TPE following first course IVIg at a reasonable time point. Finally, we recommend standardisation of GBS reporting with IVIg treatment unresponsiveness, by focusing on GBS subtype, timing of initial IVIg treatment, initiation of second-line treatment and neurological assessment throughout the clinical course for at least 6 months. This will allow for compilation of cases and the possibility of making better inferences about efficacy while a higher-quality study is performed.

CONCLUSION

Currently, there is no evidence to support the use of a second course of IVIg in GBS patients for improving disability, mortality or ICU admission in patients, and the practice does pose a potentially significant risk to patients through adverse events. However, the degree of certainty is low. Furthermore, the quality of evidence for TPE after IVIg is very low and at present there is insufficient high-quality evidence to either demonstrate benefit or no harm. We recommend standardised case reporting with consideration for a multinational case registry and RCTs to determine the efficacy of TPE or a further course of IVIg after initial IVIg unresponsiveness.

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