

Gamunex[®] in Guillain-Barré Syndrome: A Postmarketing, Retrospective, Observational Study

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ABSTRACT: Background: The objective of this retrospective study was to evaluate the effectiveness and safety of Gamunex[®] (immune globulin [human] 10%; hereinafter “Gamunex”) when administered intravenously in the initial treatment of Guillain-Barré syndrome (GBS). The study was conducted as a postapproval commitment for Health Canada. **Methods:** A medical chart review for hospitalized patients diagnosed with GBS and treated with Gamunex (Gamunex 10% and IGIvnx[®] 10%; $N = 109$; $n = 69$ evaluable) was conducted at seven Canadian study centers in reverse chronological order. The primary endpoint for assessing effectiveness was the proportion of patients with treatment success compared with a prospectively defined historical effectiveness threshold for plasma exchange (PE) treatment (55.05%). Treatment success was assessed as ≥ 1 point improvement from baseline on the GBS Disability Scale or abbreviated GBS Disability Scale. Cases were not evaluable if treatment success, relapse, or treatment failure could not be determined by the available chart data. **Results:** Applying a conservative estimate with all nonevaluable patients ($n = 40$) classified as treatment failures, Gamunex treatment success was estimated at 57.8% (63 of 109 patients), which exceeded the predefined historical PE effectiveness threshold. In the evaluable population of this study, Gamunex treatment was successful in 91.3% of patients (63/69). Some 23 (21.1%) of 109 Gamunex-treated patients experienced ≥ 1 adverse event; the profile and frequency were consistent with the adverse events reported for Gamunex in the product’s labeling and with the natural clinical course of GBS. **Conclusions:** The effectiveness of Gamunex for treatment of GBS was comparable to PE therapy. Gamunex was observed to have an acceptable safety profile in this study population.

RÉSUMÉ: Le Gamunex[®] dans le traitement du syndrome de Guillain-Barré: étude observationnelle, rétrospective, post-commercialisation. **Contexte:** Le but de cette étude rétrospective était d’évaluer l’efficacité et la sécurité du Gamunex[®] (immunoglobuline humaine à 10%, nom commercial Gamunex) administré par voie intraveineuse dans le traitement initial du syndrome de Guillain-Barré (SGB). Cette étude a été réalisée pour Santé Canada dans le cadre d’un engagement post-commercialisation. **Méthodologie:** Nous avons effectué une revue des dossiers des patients hospitalisés chez qui un diagnostic de SGB avait été posé et qui ont été traités par le Gamunex (Gamunex 10% et IGIvnx[®] 10%; $N = 109$; $n = 69$ dossiers évaluables) dans 7 centres de recherche canadiens, par ordre chronologique inverse. Le critère d’évaluation principal de l’efficacité du traitement était la proportion de patients dont le traitement avait été un succès par rapport à un seuil d’efficacité historique défini prospectivement pour la plasmaphérèse (PP) (55.05%). Le succès du traitement a été défini comme étant une amélioration de 1 point ou plus par rapport aux valeurs initiales à l’échelle d’invalidité GBS ou à l’échelle d’invalidité GBS abrégée. Les cas n’étaient pas considérés comme étant évaluables si le succès du traitement, la rechute ou l’échec du traitement ne pouvaient pas être déterminés selon les données disponibles au dossier. **Résultats:** Selon un estimé conservateur, les patients non évaluables ($n = 40$) étant classifiés comme présentant un échec thérapeutique, le succès du traitement par le Gamunex a été estimé à 57,8% (63/109 patients), ce qui excède le seuil d’efficacité PP historique prédéfini. Dans la population de patients évaluables de cette étude, le traitement par le Gamunex a été efficace chez 91,3% des patients (63/69 patients). Vingt-trois (21,1%) des 109 patients traités par le Gamunex ont présenté 1 effet indésirable ou plus; le profil et la fréquence de ces effets indésirables concordaient avec ceux rapportés pour le Gamunex dans l’étiquetage du produit et avec l’évolution clinique naturelle du SGB. **Conclusions:** Dans cette étude, l’efficacité du Gamunex dans le traitement du SGB était comparable à celle du traitement par PP. Le profil de sécurité du Gamunex était acceptable dans la population étudiée.

Keywords: Guillain-Barré syndrome, immune system, Gamunex, immunoglobulin, plasma exchange

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INTRODUCTION

Guillain-Barré syndrome (GBS) is a rare but potentially life-threatening disease with an incidence of 1.11 per 100,000 person-years.¹ Prior infections of various types, be it flu or other infections, have been associated with the development of GBS,²⁻⁷ and the clinical disease course and severity of GBS appear to be dependent on the type of preceding infection.⁸⁻¹¹

Effective treatments for GBS involve immunotherapy with intravenous (IV) immunoglobulins (IVIg) and/or plasma

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exchange (PE).¹²⁻¹⁴ For the past decade, the use of IVIg has largely replaced PE as the treatment of choice for GBS due to its treatment effect being similar to that of PE, its convenience in administration, and its good safety profile.

The objective of this retrospective study was to evaluate the effectiveness and safety of Gamunex when administered as the initial treatment of GBS. Our study was a postapproval commitment to Health Canada following licensure of the GBS indication for Gamunex[®] 10% and IGIVnex[®] 10% (hereinafter referred to as “Gamunex”).

METHODS

Study Design

This study was designed as a retrospective observational study (Figure 1) in which data from patient hospital charts at seven study centers in Canada were collected and reported. Chart review ranged from 2014 to when Gamunex became available in Canada in 2003. The study was designed to collect chart review parameters from 80 consecutive charts of IV Gamunex-treated patients, with at least 20 charts from pediatric patients (<18 years of age) and 20 charts from patients requiring mechanical ventilation within 7 days of admission. The charts were chosen in reverse chronological order at the site level but not across all sites. Of note, the charts for pediatric patients came from two of the seven centers. Some 20 charts of PE-treated patients from this period were to serve as a concurrent control group. Information regarding the demographic characteristics and severity of GBS in both the Gamunex- and PE-treated cohorts were collected.

The study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and was approved by the research ethics board of each participating Canadian center.

Inclusion and Exclusion Criteria

Patients were included if they had a documented diagnosis of acute GBS or any variant and had received Gamunex alone or PE alone as therapy within the first 7 days of diagnosis.

Patients were excluded if they had received another IVIg product or PE within 3 months prior to the current GBS admission, had received a second specific GBS therapy <7 days after initiation of their first specific GBS therapy, were enrolled in a GBS interventional clinical trial, or had a change in diagnosis (e.g., chronic inflammatory demyelinating polyneuropathy) at any point during medical care.

Effectiveness Variables

The primary effectiveness endpoint was the proportion of patients with treatment success at either 4 weeks after admission or at hospital discharge, whichever occurred first, compared with the historical success rate for PE treatment as reported in the 2012 Cochrane Review of IVIg versus PE in GBS¹⁵ and in the 2012 Cochrane Review of PE versus supportive care in GBS.¹⁴ The historical success rate for PE treatment observed in 11 controlled clinical trials¹⁶⁻²⁶ was 56.70%. To account for heterogeneity across studies, a metaanalysis indicated that the estimated overall success rate of PE was 61.17% (95% confidence interval = 49.54% to 72.80%). For the primary effectiveness endpoint in the study, the success rate for Gamunex treatment was set at >55.05% (i.e., 90% of the overall success rate [61.17%] in the published historical PE group).

The denominator for calculating success rate was the number of patients with assessable results of treatment success based on the GBS Disability Scale,²⁷ the abbreviated GBS Disability Scale, or a change in mechanical ventilation status.

The secondary endpoint was the proportion of treatment success in adult Gamunex-treated patients compared to the proportion of treatment success in concurrent PE-treated patients. Other endpoints included the proportion of patients who relapsed and the proportion of patients who were treatment failures. If treatment success, relapse, or treatment failure could not be determined by the available chart data, the case was excluded from the effectiveness-evaluable population. Nevertheless, available safety, demographic, IVIg utilization, and resource utilization data were collected and reported.

Safety Variables

All adverse events (AEs) while receiving Gamunex alone or PE alone and up to 72 hours after the final Gamunex dose or the final PE session were recorded. Any AE occurring more than 72 hours after the final dose where the clinical notes in the patient chart indicated a relationship to the Gamunex or PE treatment were also documented. Adverse events collected from the patient medical charts were classified as adverse reactions (ARs) (defined as any AE occurring during treatment or within 72 hours of the last treatment and any AE occurring more than 72 hours after the last treatment if the medical chart indicated a causal relationship to treatment as unlikely related, possibly related, or related).

Statistical Analysis

Statistical analyses and data presentations were generated using SAS software (v. 9.2 or higher). All statistical inferences were tested two-sided with an α level of 0.05. All data were presented by treatment group (Gamunex or PE). Missing data were identified on the patient chart review form as “not available” or “n/a,” and missing data were not imputed. Treatment success through 56 days was assessed as follows: (1) at least a one-point improvement from baseline on the GBS Disability Scale, (2) at least a one-point improvement from baseline on the abbreviated GBS Disability Scale, or (3) a change in mechanical ventilation status from ventilated at baseline to ventilator-independent around the clock. Relapse was defined as a patient who had deteriorated after an initial improvement and required additional treatment for GBS. Patients who did not meet the aforementioned criteria were classified as failures, as were those who were discharged from the hospital but subsequently readmitted for worsening GBS after initial admission for the identified GBS episode.

RESULTS

A total of 123 hospitalized patients diagnosed with GBS (109 Gamunex-treated and 14 PE-treated) were assessed via retrospective medical chart review (Figure 1). Data from 69 Gamunex-treated cases met the effectiveness-evaluable criteria (52 adults and 17 pediatric patients). Of those 69 patients, 13 (8 adults and 5 children) received mechanical ventilation. Only 4 PE-treated cases were identified from the original time period (2003–2014), and, after extending the date range to 1994, 14 PE-treated cases were identified, of which 13 were evaluable. A total of 3 of the 13 adults in the PE-treated group received mechanical ventilation.

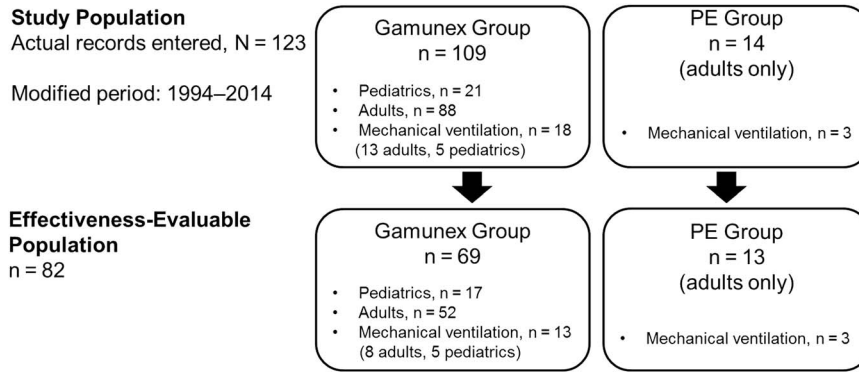


Figure 1: Study diagram.

The baseline demographic data are summarized in Table 1. Possible antecedent infection in the 4 weeks prior to the onset of GBS was indicated as a comorbid condition in 79 (72.5%) of the 109 Gamunex-treated patients and in 12 (85.7%) of the 14 adult PE-treated patients. Classic GBS was diagnosed in 72 (66.1%) of the 109 Gamunex-treated patients and in 8 (57.1%) of the 14 PE-treated patients. A total of 21 (17.1%) of the 123 patients in the study received mechanical ventilation and, therefore, were categorized as having severe GBS. Notably, once the diagnosis of GBS was established, Gamunex or PE treatment was generally initiated without delay.

Standard dosages and regimens were generally utilized. Overall, the mean total Gamunex dose was 1.94 g/kg (median of 2.00 g/kg) administered over a mean of 3.9 days (median of 5 days). In terms of PE, procedural details were available for 10 patients for whom the majority (n = 8) received either 4 or 5–6 PEs. Following completion of acute hospital care for GBS, approximately half of both the Gamunex- and PE-treated patients were discharged to home, and about a third were discharged to a rehabilitation facility.

Effectiveness Data

A total of 40 (36.7%) of the 109 Gamunex-treated patients had insufficient data to be evaluated. Taking a conservative approach, if all 40 cases were classified as treatment failures, the success rate

of Gamunex was at least 57.8% (63 of 109), which exceeded the prospectively defined effectiveness threshold (Table 2). In the effectiveness-evaluable population, Gamunex treatment was successful in 63 (91.3%) of 69 cases. Of the 14 patients treated with PE, 13 were evaluable, and treatment was successful in 84.6% (11 of 13). Table 3 shows the results for the other endpoints. No cases of GBS relapse were identified in this chart review. Among the 6 Gamunex failure cases, 3 patients (2 adults and 1 pediatric patient) required a second treatment. No PE-treated patients received a second treatment.

Safety Data

All ARs are shown in Table 4. All recorded AEs met the criteria of an AR, with the exception of two events in the PE group (renal tubular necrosis and anemia) that did not have an onset date recorded, but these events were still reported as ARs. The overall AR rate was similar between treatment groups. Twenty-three (21.1%) of 109 Gamunex-treated patients and 3 (21.4%) of 14 PE-treated patients experienced at least 1 AR.

Seven serious adverse events (SAEs) occurred among 7 patients (6 Gamunex-treated, 1 PE-treated), of which 2 (both Gamunex-treated) were considered possibly treatment-related. Some 6 Gamunex-treated patients experienced 1 SAE each: pneumonia, pneumothorax, respiratory failure, convulsion, hemolytic anemia, and aseptic meningitis. Two of these—hemolytic anemia and aseptic

Table 1: Patient hospitalization and baseline demographics

	Gamunex			PE
	Adult	Pediatric	Subtotal	
Hospitalized, n (%)	88 (100.0)	21 (100.0)	109 (100.0)	14 (100.0)
Sex				
Female, n (%)	36 (40.9)	2 (9.5)	38 (34.9)	5 (35.7)
Male, n (%)	52 (59.1)	19 (90.5)	71 (65.1)	9 (64.3)
Age, years				
Mean (SD)	52.2 (18.6)	7.7 (5.0)	43.7 (24.4)	48.2 (17.6)
Median (range)	54 (19–88)	6 (2–16)	48 (2–88)	46 (22–77)
Weight, kg				
Patients with documented weight, n	67	21	88	7
Mean (SD)	77.12 (19.4)	34.82 (23.3)	67.03 (27.2)	96.01 (17.5)
Median (range)	75 (39.5–130)	24.3 (11.4–78.6)	71.1 (11.4–130)	101.6 (70–121)

PE = plasma exchange; SD = standard deviation.

Table 2: Primary effectiveness results comparing treatment outcomes of Gamunex-treated patients with historical metaanalysis data of PE-treated patients

Outcome	Historical PE metaanalysis Reported data N = 582 n (%)	Gamunex	
		All N = 109 n (%)	Evaluable N = 69 n (%)
Success	333 (56.7)	63 (57.8) ^a	63 (91.3)
Failure	n/a	6 (5.5)	6 (8.6)
Nonevaluable ^b	n/a	40 (36.7)	n/a

PE = plasma exchange.

Treatment outcomes were assessed based on the Guillain-Barré syndrome (GBS) disability scale. If the GBS Disability Scale was missing, the abbreviated GBS Disability Scale was used.

^aA success rate of 55.05% among Gamunex-treated patients (90% of the historical PE success rate of 56.7%) was considered adequate effectiveness.

^bCases were nonevaluable if treatment success, relapse, or treatment failure could not be determined by the available chart data.

meningitis in a toddler with concurrent blood culture positive for *Acinetobacter*—were considered possibly related to treatment. One PE-treated patient experienced one SAE: respiratory failure.

Two patients died during the study (one Gamunex- and one PE-treated), both because of respiratory failure.

INTERPRETATION

Despite the limitations inherent in retrospective data extraction from medical charts, the effectiveness of Gamunex demonstrated in this retrospective study was comparable to historical data. Even using a conservative estimate, with all nonevaluable patients ($n = 40$) classified as treatment failures, Gamunex treatment success was estimated at 57.8% (63 of 109) of patients, exceeding the predefined historical PE effectiveness threshold. When assessing the primary effectiveness endpoint with the evaluable population, the proportion of evaluable Gamunex-treated patients was comparable to the historical effectiveness rate for PE treatment in GBS, with the overall success rate of Gamunex being 91.3% (63 of 69). Secondary endpoints also showed the effectiveness of Gamunex, indicating that this therapy is successful in GBS. Furthermore, the safety profile of Gamunex treatment reported in this study and the AR frequencies were consistent with those reported on Gamunex product labels as well as with the natural clinical course of GBS.

The patients in our retrospective study were demographically similar to GBS patients worldwide. In a recent review,²⁸ GBS was reported as more common in males, and the proportion of variant

Table 3: Treatment outcomes by subgroup of Gamunex-treated patients (effectiveness-evaluable population)

Subgroup	Patients, n	Treatment success, n (%) ^a
All patients	69	63 (91.3)
Age group		
Adults	52	50 (96.2)
18–64 years	39	37 (94.9)
≥65 years	13	13 (100.0)
Pediatrics (<17 years)	17	13 (76.5)
Total dose (g/kg)		
No dose recorded	14	13 (92.9)
<1.0	1	1 (100.0)
1.0	0	0 (–)
>1.0 to <2.0	13	13 (100.0)
2.0	20	18 (90.0)
>2.0	21	18 (85.7)
Disease severity		
Mild or moderate	57	53 (93.0)
Severe	12	10 (83.3)
Classic versus variant GBS		
Classic GBS	49	46 (93.9)
Variant GBS	20	17 (85.0)
Full scale versus abbreviated scale		
Full GBS scale	66	60 (90.9)
Abbreviated GBS scale	3	3 (100.0)

GBS = Guillain-Barré syndrome.

^aIf the GBS Disability Scale was missing, an abbreviated GBS Disability Scale was used. Subjects without treatment outcome assessments are not included in this table. If the total dose was not specified in the patient chart, it was calculated by adding the individual daily doses (where provided) or multiplying the daily dose by the number of doses.

Table 4: Frequency of adverse events by patient

	Gamunex			PE
	Adult n = 88 n (%)	Pediatric n = 21 n (%)	Subtotal n = 109 n (%)	n = 14 n (%)
Any adverse events	14 (15.9)	9 (42.9)	23 (21.1)	3 (21.4)
Vomiting	4 (4.5)	0	4 (3.7)	0
Headache	3 (3.4)	1 (4.8)	4 (3.7)	0
Nausea	3 (3.4)	0	3 (2.8)	0
Rash	0	3 (14.3)	3 (2.8)	0
Hemolytic anemia	1 (1.1)	1 (4.8)	2 (1.8)	0
Back pain	2 (2.3)	0	2 (1.8)	0
Urticaria	2 (2.3)	0	2 (1.8)	0
Respiratory failure	1 (1.1)	0	1 (0.9)	1 (7.1)
Renal tubular necrosis	0	0	0	1 (7.1)
Anemia	0	0	0	1 (7.1)
Staphylococcal infection	0	0	0	1 (7.1)
Ear pain	1 (1.1)	0	1 (0.9)	0
Inappropriate antidiuretic hormone secretion	0	1 (4.8)	1 (0.9)	0
Eye pain	1 (1.1)	0	1 (0.9)	0
Abdominal pain	1 (1.1)	0	1 (0.9)	0
Constipation	1 (1.1)	0	1 (0.9)	0
Asthenia	1 (1.1)	0	1 (0.9)	0
Chest discomfort	1 (1.1)	0	1 (0.9)	0
Infusion site discomfort	1 (1.1)	0	1 (0.9)	0
Infusion site extravasation	1 (1.1)	0	1 (0.9)	0
Infusion site pain	0	1 (4.8)	1 (0.9)	0
Anaphylactoid reaction	0	1 (4.8)	1 (0.9)	0
Meningitis aseptic	0	1 (4.8)	1 (0.9)	0
Pneumonia	1 (1.1)	0	1 (0.9)	0
Muscle spasms	1 (1.1)	0	1 (0.9)	0
Convulsion	0	1 (4.8)	1 (0.9)	0
Dizziness	1 (1.1)	0	1 (0.9)	0
Hypoesthesia	0	1 (4.8)	1 (0.9)	0
Syncope	1 (1.1)	0	1 (0.9)	0
Insomnia	1 (1.1)	0	1 (0.9)	0
Pneumothorax disorder	1 (1.1)	0	1 (0.9)	0
Erythema	0	1 (4.8)	1 (0.9)	0
Pruritus	1 (1.1)	0	1 (0.9)	0
Rash macular	0	1 (4.8)	1 (0.9)	0
Hot flush	1 (1.1)	0	1 (0.9)	0

PE = plasma exchange.

GBS in the current study is comparable to the worldwide experience. A preceding infection in the 4 weeks prior to the onset of GBS was indicated as a comorbid condition in 72.5% of Gamunex- and 85.7% of PE-treated patients, which is consistent with the GBS literature where an antecedent upper respiratory or gastrointestinal infection can be found in up to 90% of affected individuals.²⁹⁻³¹

The choice of GBS treatment is dependent on patient-related factors, socioeconomic considerations, and norms based in part on regional government-based health coverage policies. While PE may appear less costly than IVIg,^{32,33} the administration of PE requires specialized equipment (often not available in many hospitals), trained personnel, and access to two veins with high flow volumes that may require insertion of a central venous line. PE

can also be more difficult to administer in young children due to large volume shifts affecting autonomic cardiovascular stability. IVIg has a response rate that is comparable to that of PE in GBS and requires only one peripheral vein to administer. IVIg does not require any special equipment or training, and it has greater availability than PE in Canada.

LIMITATIONS

Comparison of outcomes from current charts with historical published results was impeded by differing standards of care during each time period, different inclusion/exclusion criteria, and different treatment effect assessment scales. While using concurrent PE cases as a control cohort mitigates some of these factors, clinician selection of Gamunex or PE may not be random. Because of the infrequency of use of PE in GBS in recent years, such patients had to be drawn from a time period prior to the availability of Gamunex in Canada (2003), which may introduce a bias due to a period effect. In addition, the subgroup analyses of Gamunex effectiveness are limited by the small numbers of patients in several of the subgroups.

CONCLUSIONS

The results from this study show that the success of Gamunex treatment for the treatment of GBS exceeds the predefined historical PE effectiveness threshold at 57.8% (63 of 109 patients) in a conservative estimate, which included all 40 nonevaluable patients classified as treatment failures, and at 91.3% (63 of 69 patients) in the evaluable population. Moreover, the effectiveness of Gamunex (91.3%) was shown to be comparable to PE (84.6%). The risk ratio of Gamunex versus PE was 1.08 (in favor of Gamunex), which was identical to the observed risk ratio from the Cochrane metaanalysis¹⁵ comparing IVIg to PE, further supporting the effectiveness of IVIg in GBS. The success rates of Gamunex were not notably different among subgroups of patients distinguished by age, total Gamunex dose received, or GBS severity and type. The safety profile of Gamunex in this study was comparable to that reported for Gamunex in the approved product labeling and was consistent with events experienced in the natural clinical course of GBS.

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DISCLOSURES

KC, KH, and EM are employees of Grifols, a manufacturer of Gamunex. VB has consulted for Grifols, CSL Behring, BioNevia, Lilly, Pfizer, Dainippon, Sumitomo, and Eisai, and has received research grant support from all of these. ZAS has received unrestricted educational grants and research funding from CSL Behring and Grifols.

STATEMENT OF AUTHORSHIP

Each author was a significant contributor to the writing, critical review, and editing of the manuscript from outline through to the final version. All authors approved the final manuscript. ZAS and VB were investigators who participated in the study and have been involved in clinical interpretation of the findings. KC, KH, and EM are Grifols employees and were instrumental in the study design, conduct, analysis, and interpretation of study results as the program director and study manager, medical monitor, and clinical development head, respectively.

REFERENCES

1. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36(2):123-33.
2. Webb AJ, Brain SA, Wood R, Rinaldi S, Turner MR. Seasonal variation in Guillain-Barré syndrome: a systematic review, meta-analysis and Oxfordshire cohort study. *J Neurol Neurosurg Psychiatry*. 2015;86(11):1196-201.
3. Islam Z, Jacobs BC, Islam MB, Mohammad QD, Diorditsa S, Endtz HP. High incidence of Guillain-Barré syndrome in children, Bangladesh. *Emerg Infect Dis*. 2011;17(7):1317-8.
4. van Koningsveld R, Rico R, Gerstenbluth I, et al. Gastroenteritis-associated Guillain-Barré syndrome on the Caribbean island Curaçao. *Neurology*. 2001;56(11):1467-72.
5. McKhann GM, Cornblath DR, Ho T, et al. Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. *Lancet*. 1991;338(8767):593-7.
6. Smith DW, Mackenzie J. Zika virus and Guillain-Barré syndrome: another viral cause to add to the list. *Lancet*. 2016;387(10027):1486-8.
7. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet*. 2016;387(10027):1531-9.
8. Geleijns K, Roos A, Houwing-Duistermaat JJ, et al. Mannose-binding lectin contributes to the severity of Guillain-Barré syndrome. *J Immunol*. 2006;177(6):4211-7.
9. Hadden RD, Karch H, Hartung HP, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. *Neurology*. 2001;56(6):758-65.
10. Ang CW, Laman JD, Willison HJ, et al. Structure of *Campylobacter jejuni* lipopolysaccharides determines antiganglioside specificity and clinical features of Guillain-Barré and Miller-Fisher patients. *Infect Immun*. 2002;70(3):1202-8.
11. Kuijff ML, Samsom JN, van Rijs W, et al. TLR4-mediated sensing of *Campylobacter jejuni* by dendritic cells is determined by sialylation. *J Immunol*. 2010;185(1):748-55.
12. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA. Immunotherapy for Guillain-Barré syndrome: a systematic review. *Brain*. 2007;130(Pt 9):2245-57.
13. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;9:CD002063.
14. Raphael JC, Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2012;7:CD001798.
15. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2012;7:CD002063.
16. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet*. 1997;349(9047):225-30.
17. van der Meche FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome: Dutch Guillain-Barré Study Group. *N Engl J Med*. 1992;326(17):1123-9.

18. Diener HC, Haupt WF, Kloss TM, et al. A preliminary, randomized, multicenter study comparing intravenous immunoglobulin, plasma exchange, and immune adsorption in Guillain-Barré syndrome. *Eur Neurol.* 2001;46(2):107-9.
19. Greenwood RJ, Newsom-Davis J, Hughes RA, et al. Controlled trial of plasma exchange in acute inflammatory polyradiculoneuropathy. *Lancet.* 1984;1(8382):877-9.
20. The Guillain-Barré Syndrome Study Group. Plasmapheresis and acute Guillain-Barré syndrome. *Neurology.* 1985;35(8):1096-104.
21. Osterman PO, Fagius J, Lundemo G, et al. Beneficial effects of plasma exchange in acute inflammatory polyradiculoneuropathy. *Lancet.* 1984;2(8415):1296-9.
22. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. *Ann Neurol.* 1987;22(6):753-61.
23. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. *Ann Neurol.* 1997;41(3):298-306.
24. Bril V, Ilse WK, Pearce R, Dhanani A, Sutton D, Kong K. Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barré syndrome. *Neurology.* 1996;46(1):100-3.
25. Nomura K, Hamaguchi K, Hosokawa T, et al. A randomized controlled trial comparing intravenous immunoglobulin and plasmapheresis in Guillain-Barré syndrome. *Neurol Therapeut.* 2001;18(1):69-81.
26. El-Bayoumi MA, El-Refaey AM, Abdelkader AM, El-Assmy MM, Alwakeel AA, El-Tahan HM. Comparison of intravenous immunoglobulin and plasma exchange in treatment of mechanically ventilated children with Guillain-Barré syndrome: a randomized study. *Crit Care.* 2011;15(4):R164.
27. Hughes RA, Newsom-Davis JM, Perkin GD, Pierce JM. Controlled trial: prednisolone in acute polyneuropathy. *Lancet.* 1978;2(8093):750-3.
28. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nat Rev Neurol.* 2014;10(8):469-82.
29. Koga M, Yuki N, Hirata K. Antecedent symptoms in Guillain-Barré syndrome: an important indicator for clinical and serological subgroups. *Acta Neurol Scand.* 2001;103(5):278-87.
30. Jacobs BC, Rothbarth PH, van der Meche FG, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. *Neurology.* 1998;51(4):1110-5.
31. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. *Lancet.* 2016;388(10045):717-27.
32. Winters JL, Brown D, Hazard E, Chainani A, Andrzejewski C Jr. Cost-minimization analysis of the direct costs of TPE and IVIg in the treatment of Guillain-Barré syndrome. *BMC Health Serv Res.* 2011;11:101.
33. Baranwal AK, Ravi RN, Singh R. Exchange transfusion: a low-cost alternative for severe childhood Guillain-Barré syndrome. *J Child Neurol.* 2006;21(11):960-5.