health
Department:
Health
REPUBLIC OF SOUTH AFRICA

National Essential Drug List
Tertiary/Quaternary Medication Review Process
Component: Medications for use in Neurology

1. Executive Summary

Date: August 2018
Medicine (INN): Intravenous immunoglobulin
Medicine (ATC): J06BA02
Indication (ICD10 code): Guillain-Barré syndrome (GBS) (G61.0)
Patient population: Moderate to severe GBS
Incidence: Annual incidence 1-3/100 000 population
Level of Care: Tertiary
Prescriber Level: Specialist consultation
Current standard of Care: Supportive
Efficacy estimates: (preferably NNT): NNT to recover ability to walk with assistance in 4 weeks = 7 (95% CI 1.19 to 2.15) [1]
NNT to avoid ventilation = 5 [2]
(extrapolated from plasma exchange data, no IVIG vs placebo studies)
Reviewer name(s): Dr Anand Moodley

2. Name of author(s)/motivator(s): Dr Moodley

3. Author affiliation and conflict of interest details: no conflicts declared

4. Introduction/ Background

Guillain-Barre syndrome is an acute parainfectious auto-immune disorder affecting the peripheral nerves and nerve roots. It is synonymous with acute inflammatory demyelinating polyradiculopathy (AIDP). GBS is thought to result from an immune response to a preceding infection (URTI or gastro-enteritis) that cross-reacts with peripheral nerve components because of molecular mimicry. The immune response can be directed towards the myelin or the axon of peripheral nerve, resulting in demyelinating and axonal forms of GBS.

Rapidly progressive generalized weakness is the hallmark, and 17-30% of cases develop severe respiratory weakness requiring ventilator support. Patients with dyspnea on exertion, shortness of breath, difficulty swallowing or slurred speech are managed in ICU. Patients are intubated when vital capacity falls to 15ml/kg.[3]

The diagnosis is made by a combination of clinical features, electrophysiological abnormalities and CSF findings. Clinically, patients present with rapidly progressive and symmetrical quadriparesis over 2 to 4 weeks, with or without bilateral facial weakness, bulbar weakness and respiratory muscle weakness. Electrophysiological findings of demyelination are detected usually after the first week of illness and an albumino-cytological dissociation on CSF examination, within the first 2 weeks of illness.[4]

Variants of GBS include Miller Fisher Syndrome (ataxia, areflexia and external ophthalmoplegia), pure sensory GBS, paraplegic GBS, pure dysautonomia, pharyngeal-cervical-brachial GBS and pure axonal GBS (AMAN – acute motor axonal neuropathy and AMSAN- acute motor and sensory axonal neuropathy). The latter 2 are more common in HIV infection.

Treatment consists of intravenous immunoglobulin (IVIG) or plasma exchange (PE), and the majority of patients recover well. However, despite advances in intensive care, the mortality rate is still between 4-15%, and with up to 20% of those surviving being permanently disabled.[Error! Bookmark not defined.] The incidence of GBS is between 1.2 and 1.9 per 100 000 (US data).[5] South African epidemiological data are unavailable. In a study by Franclo Henning et al. at the University of Stellenbosch, based on a seroprevalence of HIV infection of 5.8% in 2014, they calculated that GBS is 18.74, 95% CI [7.69, 40.60] times higher in HIV-positive than in HIV–negative individuals.[Error! Bookmark not defined.]

Disease modifying agents:

The main modalities of therapy for Guillain-Barré syndrome (GBS) are plasma exchange (PE) (also called plasmapheresis) and administration of intravenous immune globulin (IVIG). These treatments hasten recovery from GBS. Patients recover sooner when treated early. The beneficial effects of plasma exchange and IVIG are believed to be equivalent.

Plasma Exchange (PE) however, although equivalent in efficacy to IVIG, it is associated with more complications such as hypotension, sepsis, problems with intravenous access. PE is also not readiligy available in the public sector, and is far more costly than IVIG.

Aside from plasma exchange and IVIG, no other pharmacologic agents have been found to be effective for GBS. In particular, glucocorticoids are not beneficial. In a systematic review and meta-analysis of six trials with 587 participants, glucocorticoid-treated patients with GBS showed no significant difference in disability grade compared with patients who were not treated with glucocorticoids. Furthermore, in four small trials, patients treated with oral glucocorticoids had significantly less improvement than patients who were not treated with oral glucocorticoids.

5. Purpose/Objective i.e. PICO question

-P *(patient/population): Adults and children with* moderate to severe GBS
-I *(intervention):* Intravenous immunoglobulin
-C *(comparator):* Placebo or supportive care; Plasma Exchange
-O *(outcome):* Walking recovery
Avoidance of mechanical ventilation

NEMLC recommendation: it was recommended that avoidance of mechanical ventilation would be an important outcome to consider for these patients.

6. **Methods:**
   a. **Data sources:** Pubmed, Google scholar, Cochrane Library
   b. **Search Strategy:** (May 2018)
   (("Immunoglobulins, Intravenous"[Mesh]) OR "Plasma Exchange"[Mesh]) AND "Guillain-Barre Syndrome"[Mesh]
   Randomised Controlled Trials – 15 results
      - 5 included – applicable to question
      - 10 non-included – did not pertain to the question

Results	Included/excluded	Reasons
• Two cost-analyses	Excluded	Not applicable for initial efficacy/safety decision
• One Kinetic study	Excluded	Not applicable
• One study, combination IVIG and apheresis	Excluded	Not applicable
• One study looked at CSF infiltration	Excluded	Not applicable
• One study looked at interferon beta	Excluded	Not applicable
• One study evaluated addition of methylprednisolone	Excluded	Not applicable
• One study – follow up questionnaire on function	Excluded	Not applicable
• One study evaluating pain response	Excluded	Not applicable
• One study evaluating the IgG Fc N glycosylation portion	Excluded	Not applicable
• One study evaluating duration of IVIG	Excluded	Evaluating patients with contraindications to PE
• One study evaluating IVIG and PE compared to immune absorption	Included	
• One study evaluating therapeutic effect of PE and IVIG	Excluded	Not randomised
• Two studies in children, one comparing IVIG to PE, IVIG vs no treatment.	Included	IVIG compared to PE and no treatment

Meta-analysis - 13 results:
2 Cochrane reviews which had a number of iterations,(most recent update used – no RCTs post this date) evaluating plasma exchange versus placebo, or plasma exchange versus IVIG were identified.
Others excluded – either earlier versions of the Cochrane, different question, or very poor quality.

For the outcome of avoidance of mechanical ventilation: The best available evidence was a 1987 controlled study[2], as recommended by expert opinion. Note: Study was not identified in literature search.

   c. **Excluded studies**
   Excluded studies identified related to pain management in GBS, and other treatment modalities.

   d. **Evidence synthesis**

Only one small sub-group in a randomised controlled trial (RCTs) compared IVIG to no treatment. Trials have compared IVIG with plasma exchange.

Randomised controlled trials

Author, date	***Type of study***	**n**	**Population**	**Comparator**	**Primary outcome**	**Effect sizes**	**Comments**
El Bayoumi, et.al. 2011	*Prospective randomized study*	20 – IVIG 20 - PE	Children with GBS requiring mechanical ventilation	PE	Duration of mechanical ventilation Secondary outcome measures were length of PICU stay and ability to walk unaided within four weeks of PICU discharge.	PE group had shorter duration of mechanical ventilation (median 11 days, IQR 11 to 13) compared to IVIG (median 13 days, IQR 11.3 to 14.5), p = 0.037 PICU stay P = 0.094 Walk unaided within 4 weeks after discharge P =0.606	Study findings only pertain to a subset of patients
Korinthe berg R, et. al. 2005	*Randomised multicenter study of GBS*	Group 1: 21 Group 2: 51	Children with GBS: 2 Groups: • Children able to walk unaided (vs no treatment) • Children unable to walk	Group 1: IVIG 1g/kg over 2 days vs. No Treatment Group 2: IVIG 1gkg over 2 days vs. 4g/kg over 5 days	Group 1: Degree of disability at nadir Group 2: Number of days needed to regain the ability to walk unaided	Group 1: No significant difference between those receiving treatment and those with no treatment, however recovery occurred faster in early treatment group. Group 2: No difference between 2 days vs 5 days.	Small study, underpower ed.
Diener HC, et.al. 2001	*Phase III randomized controlled trial*	76	Patients with acute severe or moderate idiopathic demyelinating polyradiculoneuro pathy	IVIG or PE or immune absorption	At least a one grade improvement in functional score by day 28	IVIG - 16/20 patients PE – 15/21 patients Immune absorption -7/14 No significant differences in 3 groups	Recruitment stopped early due to change in referral policy and IVIG starting to be used as standard of care. Small sample

Meta - Analysis

Author, date	*Type of study*	n	Population	Comparator	Primary outcome	Effect sizes	Comments
Cochrane Review – Plasma exchange for GBS[1, 5] *(2012, update 2017)*	Systematic review and Meta-analysis of randomised and quasi-randomised trials	6 Trials 649 patients	Patients with GBS	Supportive Care	Time after randomisation to recover walking with aid	Plasma exchange significantly increased the proportion of patients who recovered the ability to walk with assistance RR = 1.60, 95% CI 1.19 to 2.15). <u>Secondary outcomes:</u> • Five trials (623 participants), the RR of being improved by one or more grades after four weeks was 1.64 (95% CI 1.37 to 1.96) in favour of PE. • Those treated with PE had significantly better time to recover walking without aid (three trials with 349 participants, RR 1.72 (95% CI 1.06 to 2.79)) and requirement for artificial ventilation (five trials with 623 participants, RR 0.53 (95% CI 0.39 to 0.74)). • Significantly more participants had relapses by the end of follow-up in the plasma exchange than the control group (6 trials with 649 participants, RR 2.89 (95% CI 1.05 to 7.93)). • At one year, full muscle strength recovery was significantly greater with plasma exchange than without (five trials with 404 participants, RR 1.24 (95% CI 1.07 to 1.45)). • Severe motor sequelae was significantly less (six trials with 649 patients, RR 0.65 (95% CI 0.44 to 0.96)) • No significant difference in deaths (six trials with 649 participants, RR 0.86 (95% CI 0.45 to 1.65)) or participants with adverse events (three trials with 556 participants), except fewer arrhythmias in plasma exchange treated participants (RR 0.75 (95% CI 0.56 to 1.00)).	Included trials were of moderate quality. Bias assessed as moderate overall – high risk of bias assessed for lack of blinding.
Cochrane Review – IVIG for GBS[6] *(2014)*	Systematic review and Meta-analysis of randomised and quasi-randomised trials	12 Trials 1159 patients	Adults and children with GBS	Supportive care OR plasma exchange	Hasten recovery and reducing long-term morbidity	• Seven-grade disability scale after four weeks was not significantly different: MD of 0.02 of a grade more improvement in the IVIG than the PE group; 95% CI 0.25 to 0.20 (5 trials). • Number improved by 1 or more disability grades after 4 weeks, PE 56.2% vs IVIG 60.7%: RR 1.08, (0.94 to 1.23) • Dead or disabled after 12 months, PE 16.7% vs IVIG 16.3%: RR 0.98 (0.55 to 1.72) [1 study only] • Relapse or treatment related fluctuation, PE 6% vs IVIG 5.3%: RR 0.89 (0.42 to 1.89). • Patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to PE (RR 0.14, 95% CI 0.05-0.36).	Adverse events were not significantly more frequent with either treatment

Cochrane Review - PLASMA EXCHANGE[1, 5] (2012 and 2017 update)

Moderate-quality evidence demonstrated that plasma exchange was showed significantly more improvement than supportive care alone.

Cochrane Review - INTRAVENOUS IMMUNOGLOBULIN [6] (2014)

"The Plasma Exchange Cochrane review has shown that PE hastens recovery compared with supportive treatment alone. There are no adequate comparisons of IVIG with placebo in adults, but this review provides moderate quality evidence that, in severe disease, IVIG started within two weeks from onset hastens recovery as much as PE."

Author, date	***Type of study***	**n**	**Population**	**Intervention**	**Outcomes**	**Effect sizes**	**Comments**
French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome, 1987[2]	Multicenter, randomised, controlled trial	220	Patients with GBS	Plasma exchange vs control (supportive therapy)	• Required assisted ventilation	• 42.6% of control group versus 21.4% of plasma exchange group requiring ventilation. NNT = 5	Patients with respiratory failure were put onto mechanical ventilation, however, no detail was provided on how this decision was made.
					• Decreased in time to ventilator weaning.	• 31 median days in control group versus 18 days in plasma exchange group.	
					• Time to onset of motor recovery	• 13 median days in control group versus 6 days in plasma exchange group.	
					• Time to walk with assistance	• 44 median days in control group versus 30 days in plasma exchange group.	
					• Time to walk without assistance	• 111 median days in control group versus 70 days in plasma exchange group.	

French Cooperative Group on Plasma exchange study [2] (1987)

This is an older study with evidence quality limitations. Additionally it was investigating plasma exchange, and thus this data is used to extrapolate IVIG results.

IVIG DOSING AND SIDE EFFECTS: Intravenous immune globulin is given for five days at 0.4 gram/kg per day. Administering the desired dose of 2g/kg over a shorter time frame is not recommended due to the potential for fluid overload, autonomic problems and renal impairment. High-dose IVIG has also been associated with headaches, haemolysis, dermatological adverse effects, flu-like symptoms, thrombotic events and rarely aseptic meningitis.[7] Treating for 2 days does not shorten the in-patient stay as one cannot discharge a patient with GBS after 2 days even if the patient received IVIG during those days. The risk for deterioration and requirement for ventilation still exists. Furthermore, intensive physiotherapy, rehabilitation, prevention of pressure sores, urinary and respiratory infections and DVTs must be looked for and appropriately managed. Side effects include aseptic meningitis, rash, acute renal failure (mostly related to sucrose containing products), and (rarely) hyperviscosity leading to stroke. IgA deficiency can lead to anaphylaxis.

Outcome measures:

The primary outcome measure for studies in the plasma exchange vs supportive care and plasma exchange vs IVIG was change in disability grade 4 weeks after randomisation. The disability grade used in most studies was the Modified Rankin Scale (addendum I). Ability to walk was a common outcome measure across studies. Secondary outcomes included requirement for artificial ventilation, relapses, discontinuation of treatment and death. Following previous presentation at NEMLC, it was recommended that avoidance of mechanical ventilation would be an important outcome to consider, in terms of cost, availably of resources and adverse outcomes associated with mechanical ventilation.

e. Evidence quality: Moderate quality, high risk of bias in area of blinding.

GUILLAIN-BARRE SYNDROME IN CHILDREN [8]

- Reports of the use of IVIG in children with GBS are limited, and no large randomized controlled trials exist. Nevertheless, data from the available small open-label randomized trials in children suggest that IVIG shortens the time to recovery compared with supportive care alone. Similarly, most observational studies show that IVIG hastens recovery in children. While these trials and studies in children have not proven that IVIG leads to improvement in overall prognosis, their results are consistent with the larger randomized trials showing a beneficial effect of IVIG treatment for GBS in adults.
- Experience with plasma exchange in children with GBS is limited. Based on the Cochrane review of 2012, results of plasma exchange treatment in paediatric patients appear to be similar to those in adults, with a shortened course and reduced incidence of respiratory failure. The main benefit seems to be a decrease in the interval from maximum weakness to recovery of independent walking. However the meta-analysis consisted of a small number of children who were all ≥10 years of age.
- Plasma exchange requires special equipment and trained personnel and can be performed only at centres with expertise in the treatment of children. Furthermore, younger children most often require placement of a central venous catheter. Potential complications of central venous catheters include infection, pain, nerve damage, thrombosis, perforation, dissecting hematomas, air embolism, or arteriovenous fistulae.

IVIG is preferred to plasma exchange in children because of the relative safety and ease of administration, although it has not been shown to have better results.

DOSING: The total dose of IVIG for the treatment of GBS in children is 2 g/kg, given as 1 g/kg for two days or 400 mg/kg for five days. This dose is empiric and is based upon treatment of patients with immune deficiency disorders.

Cost

Dose/ kg/day	Average weight patient	Total dose	Rounded dose	Price IVIG	Cost/day	No. days	Cost/course
0.4g	70kg	28g	24g	R440/g	R12,320	5	**R61,600.00**

NNT to prevent ventilation = 5, thus cost to prevent ventilation: R308, 000 (treat 5 patients).

Prevention of ICU stay costs and considerations

Cost per ICU bed/day*	Average ICU stay**	Total cost of stay
R9,260	14	R129,640

*UPFS Fee Schedule- April 2018

**Estimated average stay

The estimated cost for an ICU admission is R129 640, and although this does not offset the cost to prevent ventilation by treating with IVIG (R308 000), there are other benefits of keeping patients out of ICU such as a lack of availability of ICU beds, and risks of ventilator/hospital acquired infections. These all support trying to avoid ICU admission with the use of IVIG treatment. ICU treatment is not an alternative to IVIG. Plasma exchange is the alternative, which unfortunately is expensive, unavailable, invasive and associated with its own complications.

Cost comparison to Plasma exchange

IVIG		Comment/source
Dose of 0.4g/kg/day	24g	70kg patient
Total dose of IVIG to complete 5 day course	140g	IVIG regimen: IV admin on 5 consecutive days
Cost per IVIG vial	R 440.00	Cost per gram - SEP Dec 2018
Cost of IVIG course	R 61,600.00	
Cost per course of treatment	**R 61,600.00**	

PE		Comment
Cost per PE	R 14,993.46	Public sector SANBS rate 2019/2010
Total PE Cost	R 89,960.76	ASFA 2013 guidelines suggest 5-6 procedures over 10-14 days
Cost of central line insertion	R 1,003.00	USPF 2019 Lists it as a Minor Theatre Procedure – Cat D
Cost of saline per course of treatment	R 137.28	
Cost for albusol 20%	R 27,739.30	6.24 vials (R740.90/vial) SEP Dec 2018
Cost per course of treatment	**R 118,837.34**	

Summary:
The updated Cochrane review of 2017 has shown that PE hastens recovery compared with supportive treatment alone. There are no adequate comparisons of IVIG against placebo in adults, but the Cochrane review of 2014 showed that IVIG started within two weeks from onset of symptoms, accelerates recovery as much as PE. Adverse effects were not significantly different between IVIG and PE. In children, according to low quality evidence, IVIG probably hastens recovery compared with supportive care alone.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	Plasma exchange is superior to supportive care for moderate to severe GBS in time to recover walking 'Cochrane reviews of 2012 and 2017'. The Cochrane review of 2014 shows equivalent outcomes between IVIG and Plasma Exchange.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ] List the members of the group. Plasma Exchange List specific exclusion from the group: Glucocorticoids	Rationale for therapeutic alternatives included: Plasma Exchange is the alternative. It's equivalent in efficacy to IVIG but has more complications: hypotension, sepsis, problems with intravenous access, availability and cost. Rationale for exclusion from the group: No benefit with glucocorticoids. References: Hughes, R et al. Immunotherapy for Guillain-Barre¤ syndrome. A systematic review. Brain (2007), 130, 2245-2257

<table>
<tr><td>VALUES & PREFERENCES /</td><td>Is there important uncertainty or variability about how much people value the options?
Minor ☐ Major ☐ Uncertain ☐

Is the option acceptable to key stakeholders?
Yes ☒ No ☐ Uncertain ☐</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive ☐ Less intensive ☒ Uncertain ☐</td><td>Cost of medicine:<table><tr><th>Medicine</th><th>Cost (ZAR) per course</th></tr><tr><td>IVIG</td><td>R61, 600.00</td></tr><tr><td>PE</td><td>R123, 483.43</td></tr></table>Additional resources:
Hospital costs were not included as they were considered to be equivalent</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes ☐ No ☒ Uncertain ☐</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes ☒ No ☐ Uncertain ☐</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	☒

Recommendation

Based on available evidence and comparison to plasma exchange, intravenous immunoglobulin is recommended at a dose of 0.4g/kg for 5 days in patients with moderate to severe GBS, within the first 2 weeks of onset of moderate to severe weakness. However if the clinical presentation is such that the disease is considered to be mild (Rankin scale 1-2), has reached a plateau or is reversing, IVIG is not recommended.

Rationale: Standard of Care, more affordable and practical as compared to PE

Level of Evidence: LoE II

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
	X	

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

MODIFIED RANKIN SCORE

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

REFERENCES

[1] Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD001798.

[2] 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: 753-761.

[3] Mohamed I Ali, Evans R Ferna´ndez-Pe´rez, Shanthan Pendem, Daniel R Brown, Eelco FM Wijdicks, and Ognjen Gajic. Mechanical Ventilation in Patients With Guillain-Barre´ Syndrome. Respir Care 2006;51(12):1403–1407.

[4] Van den Berg B, Walgaard C, Drenthen J, et al. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 2014; 10:469.

[5] Raphaël JC, Chevret S, Hughes RA, Annane D Plasma exchange for Guillain-Barré syndrome. The Cochrane Database Syst Rev. 2012.

[6] Hughes RAC, Swan AV and Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. The Cochrane Library 2014, issue 9.

[7] Gou Y, et.al. Adverse effects of immunoglobulin therapy. Frontiers in Immunology. 2018, 9 (1299).

[8] Monique M Ryan, Guillain-Barré syndrome in children: Treatment and prognosis . Aug 2016