National Essential Medicine List
TertiaryLevel Medication Review Process
Intravenous Immunoglobulins

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: April 2019
Medicine (INN): Intravenous Immunoglobulin
Medicine (ATC): J06BA
Indication (ICD10 code): Various conditions under *D80, D81, D82, D83*
Patient population: Primary Antibody Immunodeficiency with recurrent infections
Prevalence of condition: 1:25000 to 1:100000
Level of Care: Tertiary
Prescriber Level: Specialist
Current standard of Care: Intravenous Immunoglobulin
Efficacy estimates: (preferably NNT): Prevention of pneumonia NNT = 2[1] *(small chart review)*

2. **Name of author(s)/motivator(s)**

Tertiary Expert Review Committee

Author affiliation and conflict of interest details

No conflicts of interest related or relevant to this review.

3. **Introduction/ Background**

Humoral immunodeficiency is defined by impaired antibody production leading to decreased levels of immunoglobulins (IgM, IgG, IgA, IgE), or hypogammaglobulinaemia. This can lead to susceptibility to a wide range of infections including. Hypogammaglobulinaemia can be due to a primary genetic (congenital) defect, or secondary to other conditions or drugs. Drugs causing hypogammaglobulinaemia include certain anticonvulsants, antirheumatic drugs, biological agents such as rituximab, glucocorticoids and other immunosupressants such as calcineurin inhibitors. Protein losing states such as nephrotic syndrome, and malignancies such as myeloma and chronic lymphocytic leukemia is also associated with hypogammaglobulinaemia.

Primary humoral immunodeficiences encompass a large number of genetic disorders, caused by molecular defects intrinsic to B cells or a failure of interactions between B and T cells. Cellular immunity is largely intact. Examples of specific diseases include X-linked agamaglobulinemia (XLA), autosomal agammaglobulinemias, hyperimmunoglobulin M syndromes, and common variable immunodeficiency (CVID). CVID is the most commonly encountered entity.
Diseases where both B and T cell function is abnormal is defined as combined immunodeficiencies, and include severe combined immunodeficiency (SCID) and syndromes such as Nijmegen breakage syndrome, Ataxia-telangiectasia and Wiskott-Aldrich syndrome, to name a few.

Diagnosis of the primary humoral immunodeficiencies involves demonstrating persistently low immunoglobulin levels (as a class, or specific subclasses) in the absence of secondary causes. Other

important investigations include B, and T-cell subset evaluation, and demonstrating impaired vaccine responses to polysaccharide and protein vaccines.

The most common clinical manifestation is recurrent, often severe, upper and lower respiratory tract infections with encapsulated bacteria. Chronic infectious diarrhea, such as giardiasis, is also common. Viral infections also occur with greater frequency and severity. Additional infectious diseases may be associated with particular syndromes. Other clinical manifestations include a range of autoimmune phenomena, failure to thrive, nodular lymphoid hyperplasia of the gut, and hepatosplenomegaly. An increased risk of lymphoproliferative neoplasms is also well documented. Although CVID is diagnosed before the age of 10 years in 30% of cases, it's often first diagnosed in adolescents and young adults. Many of the other syndromes is diagnosed in infancy or early childhood, and a diagnosis of CVID should be made with caution in a patient younger than 4 years old.

A cohort study of 473 patients diagnosed over a period of 4 decades showed that 6% of patients fulfilling the diagnostic criteria for CVID never report any infections.[12]

CVID is estimated to affect as many as 1 in 25000 individuals (Vary between 1:10000 to 1:100000 depending on report). SCID has an approximate incidence of 1 in 60000 live births. Other syndromes such as XLA is much rarer (approximately 1 in 380000 live births).

The South African Primary Immunodeficiency Register (PID Registry) currently has data for 356 patients. Just more than half of these are antibody deficiencies requiring immunoglobulin replacement. As not all provinces, and academic centres contribute to the registry, this is most likely an underestimation of the number of patients in South-Africa.

Pooled human immunoglobulin replacement therapy lead to a significant reduction in the frequency and severity of infections. It can be given intravenously or subcutaneously. Immune globulin replacement therapy reduces the number of infections and decreases antibiotic use and hospitalizations. Immunoglobulin replacement therapy may also reduce progression to chronic lung disease and bronchiectasis. There is significant variation in dose and schedule of replacement therapy.

Pooled human immunoglobulin is listed on the WHO essential medicines list for the treatment of primary immunodeficiencies.[9]

4. **Purpose/Objective i.e. PICO question** [comparison to current standard of care for a specific indication]: automated

-P *(patient/population): Primary antibody immunodeficiency*
-I *(intervention): Immunoglobulin replacement therapy*
-C *(comparator): Placebo*
-O *(outcome): Reduced infections*

5. **Methods:**
   - **Data sources** *Pubmed, Google Scholar, Cochrane Database and article reference.*
   - **Data sources:** Pubmed, Google scholar, Cochrane Library
   - **Search Strategy:**
     (("Agammaglobulinemia"[Mesh]) AND "Immunoglobulins, Intravenous"[Mesh]) AND "Infection"[Mesh]
     Limits: meta-analysis, randomized controlled trials, systematic reviews, humans.
     3 studies: all inappropriate , 1 in secondary immunodeficiency and 2 on leukemia.

     (("Immunoglobulins"[Mesh]) AND "Immunologic Deficiency Syndromes"[Mesh]) NOT "HIV Infections"[Mesh]) AND "Infection"[Mesh]
     Limits: meta-analysis, randomized controlled trials, systematic reviews, humans
     13 results: all inappropriate, related to organ transplant, leukaemia, dose, route, secondary deficiency and sepsis.

     A general search for concensus guidelines and general reviews was done. References were searched for applicable studies.
     Two small reviews were identified, evaluating the use of IVIG in patients with primary immunodeficiency. It must however be noted that these studies were small, and not of good quality.

     Additionally a meta-anlaysis and a retrospective chart review evaluating different immunoglobulin trough levels were included.

   - **Excluded studies**
     Studies involving secondary immune deficiency were excluded.

Evidence synthesis – Immunoglobulin replacement therapy has been in clinical use since the early 1980's, and is often considered the standard of care for reducing infection rates and severity. As such there is limited evidence, particulary randomized controlled studies evaluating the efficacy of immunoglobulins in this indication.

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Bernatowska, et. al. [2]		8	Children with primary immunodeficiency syndromes	Plasma	Clinical improvement	Low dose IVIG therapy: significantly ($p < 0.01$) fewer days with clinical illness than those receiving plasma treatment	High IVIG doses lead to further significant clinical improvement.
Busse et.al[1]	Chart review	50	Patients with common variable immunodeficiency	No treatment	Incidence of pneumonia	42 (84%) had pneumonia at least once before receiving IVIG therapy. After treatment of gamma globulin, patients experiencing pneumonia decreased to 11 (22%).	
De Gracia et al[8]	Prospective non randomised	24	Adult patients consecutively diagnosed with CVID	Pretreatment versus during treatment	Pulnomary function, HRCT score, Infections	In patients with chronic pulmonary disease (CPD) FEV1 improved from 54±13 (% predicted) to 61±13. FEV1 remained stable in patients without CPD	45% (11) had CPD at onset of treatment. Significant reduction in serious and mild infections was also shown.
Brent et al[10]	Registry review	801	Adults with Idiopathic hypogammaglobulinaemia and CVID in UKPID registry	N/A		Patients with bronchiectasis had significant delay from onset of symptoms to initiation of immune globulin replacement 7 (range 2-23) years versus 5 (range 1-14). P0.01	
Kainulainen et al[11]	Single centre cohort study	22	18 with CVID 4 with X-linked agammaglobulinemia. 14 patients prospectively followed for 3 years to assess progression of pulmonary disease	N/A	Pulmonary progression in 14 prospectively evaluated patients	36% (5/14) patients progressed despite immunoglobulin replacement	Study has been critized for lower trough Ig levels attained (5g/L)

Evidence synthesis: dosing

Retrospective evidence links higher trough levels with better outcomes.

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Gathman, 2014[3]	Retro-spective analysis	2212 patients	European Society for Immuno-deficiencies database (28 medical centres contributing)	Different Immune-globulin dose/trough levels	Incidence of infection, Time in hospital	Statistically significant (p.<0.001) reductions in the incidence of severe infections were found for higher trough IgG levels. (see figure included below) Statistically significant reduction in "days in hospital" was found with trough cutoff of 4g/L (p=0.004), and 7g/L (p=0.02). The greatest difference in outcomes where noted with the cut-off trough IgG value of 4g/L.	Median IVIG treatment interval was 30 days. There was significant variation in average monthly IG dose. The median dose for all centres was 460mg/kg/month, ranging from 129 to 750mg/kg/month.

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Orange, 2010[4]	Meta-analysis	17 Studies, 676 patients, 2127 patient years	6 studies in United States, 3 multi-national, 3 in single European countries, 3 in Middle East, 1 in Canada 1 in Argentina	Different immuno-globulin trough leveles	Pneumonia incidence	Pneumonia incidence decreased by 27% for each 100mg/kg increase in dose. Pneumonia incidence was 5 fold higher with trough level of 5g/L compared to 10g/L.	All included studies involved fewer that 100 patients each with a median of 34

Strict evidence-based data on starting doses, infusion intervals and titration schedules for immuno-globulin replacement do not exist. Most consensus guidelines recommend starting in doses between 300 and 600 mg/kg every 3–4 weeks intravenously (or the equivalent given in divided doses once or twice a week subcutaneously) to achieve trough IgG serum levels around 6–8 g/l.[5, 6]

Randomized data is lacking, but evidence is accumulating that higher trough levels is associated with better outcomes. The aim of therapy is preventing bacterial infections, and each patient has a unique threshold level of IgG to prevent breakthrough bacterial infections. To this end, patients need monitoring for breakthrough infections.

Although published data does show a link between trough immunoglobulin levels and infection rate, Lucas et al published the Oxford experience over 22 years and showed that dosing based on clinical outcomes is effective. Their local practice is to start at 400mg/kg/month and adjust based on breakthrough infections. It is proposed that initiation at a lower dose of 300mg/kg be recommended, and titrated in the event of a serious infection (requiring hospital admission and intravenous antibiotics) or more than 3 moderate infections per year (requiring oral antibiotics)[5]. A serious infection necessitating hospital admission and intravenous antibiotics, or three moderate infections per year requiring oral antibiotics warrants an increase in dose of around 100 to 150mg/kg/month.[7]

a. **Evidence quality:** Immunoglobulin replacement therapy has been in use since early 1980'sand has become the standard of care in the primary immunodeficiency setting. There is therefore a scarcity of randomized data, evaluating the effect of immunoglobulin therapy in preventing/decreasing/minimizing infections.

6. Alternative agents:

Immunoglobulin replacement therapy can be administered either intravenously (IVIG), or subcutaneously (SCIG). The standard is IV, however SC could be considered where IV is not possible. For consideration, cost of SC product is two to three times that of IVIG.

Immunoglobulin replacement is first line therapy for agammaglubulinaemia and CVID. Prophylactic antibiotics may have a role as additional therapy to prevent infections occurring despite adequate immunoglobulin replacement therapy[13]. Chronic antibiotic use is associated with the emergence of resistant pathogens in the patient and community, and cannot be recommended as the sole treatment option for patients with severe antibody deficiency syndromes.

7. Costs

The majority of the immunoglobulin product are IV, however there is currently one IM/SC product registered in South Africa.

IV Immunoglobulin	IM/SC Immunoglobulin
R444 to R666 per gram	R1719.68 per gram

IVIG is recommended as the most cost effective immunoglobulin. Additionally IM administration predisposes patients to necrosis and abcess formation.

Estimated cost per patient

	Cost per gram	Dose (g/kg)	Patient weight (kg)	Dose per patient/month	Cost per dose/month	Cost per patient per year
Adult (70kg)	R444.00	0.3	70	21	R9,323.92	R111,887.08
Child (30kg)	R444.00	0.3	30	9	R3,995.97	R47,951.66

Consideration: Pneumonia hospital admission (bed and antibiotic therapy), ranges from R9838.60 (general ward) to R46 978.60 (ICU), . [based on estimate of 5 day admission – UPFS rates, and piperacillin tazobactam 4.5g 8 hourly for 5 days]

Budget impact

Estimates and assumptions:

- From survey of Tertiary Centres managing these patient, it is estimated that there are approximately 10-15 patients per province. An estimate of 120 patients was used.
- Estimated 50/50 split: adults/children

	Cost per patient per year	number of patients	Budget impact
Adult (70kg)	R111,887.08	60	R6,713,224.95
Child (30kg)	R47,951.66	60	R2,877,099.55
		Total Budget impact	**R9,590,324.50**

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:	Immunoglobulin replacement therapy is the only available option to adress the underlying antibody deficiency in these conditions. No randomised contolled trials exist, but retrospective data has shown it to be effective in reducinginfections/hospitilisation /antibiotic use.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: x Harms outweigh benefits: Benefits = harms or Uncertain:	

<table>
<tr><td>VALES & PREFERENCES / ACCEPTABILITY</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 [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [x] Uncertain [ ]</td><td>Cost of medicines/ month:<table><tr><th>Medicine</th><th>Cost</th></tr><tr><td>IVIG</td><td>R444 to R666/gram</td></tr><tr><td>SCIG/IMIG</td><td>R1719.68/gram</td></tr></table>Cost per patient/year<table><tr><th></th><th>Cost/year</th></tr><tr><td>Adult (70kg)</td><td>R111, 887.08</td></tr><tr><td>Child (30kg)</td><td>R47,051.66</td></tr></table></td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

	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
Type of recommendation	☐	☐	☐	☐	**X**

Recommendation	Intravenous Immunoglobulin should be available on the Essential Medicines List for replacement therapy in primary antibody deficiency syndromes for patients with recurrent infections. It is recommended that dosing be started at 300mg/kg increased by 100mg/kg/mo in the event of a serious infection (requiring hospital admission and intravenous antibiotics) or more than 3 moderate infections per year (requiring oral antibiotics)[5].
Review Indicators	New data on dosing Availability of cheaper subcutaneous formulations

References:

[1]Busse PJ, et. al. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. Journal of Allergy Clinical Immunol. 2002, 109(6):1001-4.

[2] Bernatowska E, et. al. Results of a prospective controlled two-dose crossover study with intravenous immunoglobulin and comparison (retrospective) with plasma treatment. Clinical Immunology and Immunopathology. 1987, 43(2):153-162.

[3] Gathmann B, Mahlaoui N, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin immunol 2014;134:116-26.

[4] Orange JS, Grossman WJ, et al. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin Immunol 2010;137,21-30.

[5] Albin S, Cunningham-Rundles C. An update on the use of immunoglobulin for the treatment of immunodeficiency disorders. Immunotherapy (2014) 6(10), 1113-1126.

[6] Bonilla FA, Barlan I, et al. International Concensus Document (ICON): Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2016; 4(1):38-59.

[7] Lucas M, Lee M, et al. Infection outcomes in patients with common variable immunodeficiency disorders: Relationship to immunoglobulin terapy over 22 years. J Allergy Clin Immunol 2010;125:1354-60.

[8] de Gracia J, Vendrell M, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. International Immunopharmacology 2004;4:745-753

[9] https://www.who.int/medicines/publications/essentialmedicines/en/

[10] Brent J, Gusman D, et al. Clinical and laboratory correlates of lung disease and cancer in adults with idiopathic hypogammaglobulinaemia. Clinical and Experimental Immunology 2016;184:73-82

[11] Kainulainen L, Varpula M et al. Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 1999;104(5):1031-1036

[12] Resnick ES, Moshier EL, et al. Morbidity and mortality of common variable immune deficiency of 4 decades. Blood 2012;119:1650-1657

[13] Aguilar C, Malphettes M et al. Prevention of Infections During Primary Immunodeficiency. Clinical Infectious Diseases Sept 28 2014:1-9

Annexure A

The following items are available in South Africa (Single Exit Price Database extract, May 2018):

Applicant Name	Medicine Proprietary Name	ROUTE	Strength	Unit	Dosage Form	Pack Size	SEP	Unit Price	Grams/ product	Cost per gram
Mirren (Pty) Ltd	Beriglobin P 2 ml	SC or IM	160	mg/ml	INJ	2	550.30	275.15	0.32	R1,719.68
Mirren (Pty) Ltd	Beriglobin P 5 ml	SC or IM	160	mg/ml	INJ	5	1,375.83	275.17	0.8	R1,719.78

National Bioproducts Institute (NPC)	Polygam® 1 g	IV	1	g	POI	50	666.00	13.32	1	R666.00
National Bioproducts Institute (NPC)	Polygam® 3 g	IV	3	g	POI	100	1,331.99	13.32	3	R444.00
National Bioproducts Institute (NPC)	Polygam® 6 g	IV	6	g	POI	200	2,663.98	13.32	6	R444.00
National Bioproducts Institute (NPC)	Polygam® 12 g	IV	12	g	POI	400	5,327.96	13.32	12	R444.00
Octapharma SA (Pty) Ltd	Octagam ® 50 ml	IV	50	mg/ml	INF	50	1,416.55	28.33	2.5	R566.62
Octapharma SA (Pty) Ltd	Octagam ® 100 ml	IV	50	mg/ml	INF	100	2,833.09	28.33	5	R566.62
Octapharma SA (Pty) Ltd	Octagam ® 200 ml	IV	50	mg/ml	INF	200	5,666.19	28.33	10	R566.62
Pharmaplan (Pty) Ltd	Intraglobin F 200 Ml	IV	50	mg/ml	SOL	200	6,030.84	30.15	10	R603.08
Pharmaplan (Pty) Ltd	Intraglobin F 50 Ml	IV	50	mg/ml	SOL	50	1,507.72	30.15	2.5	R603.09
Pharmaplan (Pty) Ltd	Intraglobin F 10 Ml	IV	50	mg/ml	SOL	10	301.57	30.16	0.5	R603.13
Pharmaplan (Pty) Ltd	Intraglobin F 100 Ml	IV	50	mg/ml	SOL	100	3,015.41	30.15	5	R603.08
Pharmaplan (Pty) Ltd	Intraglobin F 20 Ml	IV	50	mg/ml	SOL	20	603.10	30.15	1	R603.10