2014

MPH Dissertation

A review of the use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

This dissertation is submitted in partial fulfilment of the MPH (Hospital Management) at the University of KwaZulu-Natal

Shenaaz Raiman
University of KwaZulu-Natal
11/26/2014

A review of the use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

Submitted to:

NELSON R. MANDELA SCHOOL OF MEDICINE
UNIVERSITY OF KWAZULU-NATAL DURBAN
SOUTH AFRICA

In partial fulfilment of the academic requirements for the degree
Master of Public Health, in the Discipline of Public Health Medicine
School of Nursing and Public Health, College of Health Sciences
University of KwaZulu-Natal

The dissertation contributes 50% to the MPH qualification

BY
SHENAAZ RAIMAN, 9703187

SUPERVISOR:
DR. STEPHEN KNIGHT

CO-INVESTIGATOR:
DR. TYSON B. WELZEL

2014, Cape Town

Reference Number: BE071/12. College of Health Sciences, Biomedical Research Ethics Committee

26 November 2014

ABSTRACT

Introduction

Polyvalent intravenous immunoglobulin (IVIG) is registered for a limited number of specific indications in South Africa but is increasingly being used for unregistered or off-label uses. No national evidence-based guidelines are available to guide clinicians with IVIG prescribing and against which use could be monitored. This results in IVIG being used in a range of clinical situations with questionable indications.

Objectives and methods

This study aimed to ascertain the registered and unregistered uses and cost of IVIG at a tertiary paediatric hospital in South Africa. A cross sectional descriptive study design was employed through a patient folder review, supplemented by data from the pharmacy electronic dispensing database, as well as the National Health Laboratory Service database. This study was conducted on all patients aged 0 to 18 years who were issued IVIG during a 39 month period from 2009 to 2012 within this facility.

Results and discussion

During the study period, 185 patients received at least one dose of IVIG and a total 916 issues (3642g) were dispensed. Use fell into the Medicines Control Council registered indications in 76 (44%) patients involving 416 (48%) issues. Only 87 (53%) of the patients were tested for HIV and in these the HIV sero-prevalence was 19%. The cost per patient amounted to ZAR15 937 in South African Rand. The highest IVIG issue-values were for Guillain-Barré syndrome (ZAR301 586), primary immunodeficiencies (ZAR340 953) and ‘other transplants’ (ZAR546 708). The annual cost for IVIG/1000 admissions adjusted for inflation was ZAR24 294, ZAR24 847and ZAR60 251 for 2009/2010, 2010/2011 and 2011/2012 financial years respectively. IVIG accounted for between 1.6%, 1.7% and 4.6% of the pharmacy expenditure per year in the study period.

Conclusion

More than half of all IVIG issued at this paediatric hospital was used off-label. Considering the pressures on supply and the pharmaceutical costs, manifesting as an increasing share of the pharmacy budget, a more standardised, protocol-driven approach to the prescription of IVIG is called for. It is recommended that further reviews are conducted to determine the evidence-base for the use of IVIG in the current off-label conditions.

DECLARATION

I, **Shenaaz Raiman**, declare that:

I. The research reported in this dissertation, except where otherwise indicated, is my original research.

II. This dissertation has not been submitted for any degree or examination at any other university.

III. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

IV. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a) their words have been re-written but the general information attributed to them has been referenced;

b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.

V. Where I have reproduced a journal publication of which I am an author, I have indicated in detail which part of the publication was actually written by me alone and not by other authors, editors or others.

VI. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the References sections.

Signature and Name:

Discipline of Public Health Medicine, School of Nursing and Public Health,
College of Health Sciences, University of KwaZulu-Natal, South Africa
November 26, 2014

ACKNOWLEDGEMENTS

I would like to thank the following people for their support and assistance is this study:

Dr Tyson B. Welzel, Division of Emergency Medicine, University of Cape Town, my co-investigator for his support through my studies and without whom this study could have never happened.

Dr Stephen Knight, Discipline of Public Health Medicine, University of KwaZulu-Natal, my supervisor, for his advice and input at all stages of the project.

Prof. Brian Eley, Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital, and the Department of Paediatrics and Child Health, University of Cape Town for presenting me with the concept and idea to pursue an exploratory subject at the hospital.

Theresa Blockman, for her assistance and provision of the pharmacy data.

Tessa Strauss and Naiema Salie, who are noted for their prompt and kind assistance and explanation of the hospital data through the Information Management Unit.

Dr. Chris Scott and Trisha Chetty, for assisting with information.

Last, but certainly not least, my husband, Shoaib Ahmed Vayej, for his patience, love, support and numerous weekends spent taking care of our son, Muhammad Yusuf, whilst I toiled over my research.

Finally, I dedicate my work to my parents, for making sacrifices and giving me the skills to enrich my knowledge, and to my Creator, Allah, whose pleasure I strive for in every way in all that I do.

PUBLICATIONS OR PRESENTATIONS

1. Approval and acceptance for an oral presentation at the 10th Public Health Association of South Africa (PHASA) Conference 2nd Student Symposium. Due to work constraints, this offer had to be declined.

2. Acceptance for an oral presentation at the South African Academy of Hospital Pharmacists (SAAHIP) in Drakensburg in March 2015.

3. Article to be submitted to the South African Journal of Child Health for publication.

ACRONYMS AND ABBREVIATIONS

ALT	Alanine Transaminase
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
EMA	European Medicines Agency
FDA	Food and Drug Administration/Association
GBS	Guillain-Barré syndrome
HBsAg	Hepatitis B surface antigens
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IMIG	Intramuscular immunoglobulin
ITP	Idiopathic thrombocytopaenic purpura
IVIG	Polyvalent human intravenous immunoglobulin
MGH	Massachusetts General Hospital
NBI	National Bioproducts Institute
NHI	National Health Insurance
PCR	Polymerase Chain Reaction
PIDD	Primary immune deficiency disease
PTC	Pharmacy and Therapeutics Committee
RCWMCH	Red Cross War Memorial Children's Hospital

SCIG	Sub-cutaneous immunoglobulin
UAE	United Arab Emirates
USA	United States of America
WHO	World Health Organisation

TABLE OF CONTENTS

TABLES

* In the article, tables and figures are only referred to by a primary number. However, for featuring within this chapter, it has been converted to numbers denoting the chapter.

FIGURES

CHAPTER I:
INTRODUCTION

1.1 INTRODUCTION

Polyvalent human intravenous immunoglobulin (IVIG) is a polyclonal immunoglobulin collected from large pools of donated human plasma for intravenous use in South Africa. It provides antibodies for immunity for general diseases affecting the population from which it is derived. Consequently, the manufacturing, extraction and provision of this therapeutic product can be quite costly but can also lend itself to a wide and vague multitude of therapeutic modalities. The aim of this research study was to determine the actual indication for usage of IVIG at a paediatric hospital in the Western Cape, South Africa and to correlate this usage to registered and unregistered uses. In doing so, the researcher hoped to determine a baseline for further investigation into paediatric use and indications within the South African context.

1.1.1 What needs to be known?

To date, there have been no articles published from South Africa that describe the pattern and spectrum of usage of intravenous immunoglobulin in adults or in children.

Red Cross War Memorial Children's Hospital (RCWMCH) has shown an apparent trend of increased use of IVIG over the last few years. In order to gain an understanding of the indications of use of IVIG at the hospital, a retrospective audit on the dosages and indications for use was completed.

1.2 RESEARCH QUESTION

What were the indications and actual usage of polyvalent human intravenous immunoglobulin (IVIG) at a paediatric tertiary referral hospital in South Africa from January 2009 until March 2012?

1.2.1 Why is the problem important?

Polyvalent Intravenous Human Immunoglobulin is available in South Africa as Polygam® produced by the National Bioproducts Institute (NBI),[1] which until 2010 was the sole supplier of IVIG in South Africa. Recently, externally produced products have entered the local market, but are still relatively expensive.

In South Africa, high concentrations of IVIG are derived from pooled human plasma, sourced from non–remunerated blood donors. Demand has increased for a number of possible reasons, such as the following: a) there is a generally longer duration of use; b) the spectrum of usage has increased; or c) the number of patients for the traditional indications has increased. All in all, the demand on the suppliers has increased substantially (Appendix A).

In 2010 the National Bioproducts Institute (NBI), the then sole South African supplier of IVIG, embarked on a major refurbishment process of its factory to cope with the increasing demand. The IVIG usage per 1000 population in South Africa is increasing (Table 1.1). In addition, most of the plasma harvested from blood donors in the country goes towards producing IVIG, to the point of redirecting plasma from other immunoglobulin preparations to meet demand. As an added measure, exports to the rest of sub-Saharan Africa have been limited or stopped. It is foreseen that demand will continue to outstrip supply.[†]

Table 1.1: Grams IVIG used in South Africa per 1000 population

Year	2001	2006	2011
Grams IVIG per 1000 population	2.06	4.01	5.74

Source: Personal communication: Trisha Chetty, Head: Information of NBI, Sept 2011)

At national, provincial or hospital level, there is no standard policy guiding use and duration of IVIG therapy in this country that is known, other than for its registered uses. Anecdotal evidence suggests that the unregistered IVIG uses might outweigh its registered use. It is also not known whether clinical outcomes are measured routinely both for registered and unregistered use or whether the administration of IVIG has its defined and desired response.

RCWMCH is a specialist paediatric state hospital in sub-Saharan Africa, with a catchment area that stretches beyond the provincial and national borders due to its specialist referrals. These specialist tertiary and quaternary areas include oncology, haematology, neurology, renal, and dermatology. RCWMCH has 290 beds with a busy outpatient service. The hospital reported having 23 210 admissions in the 2009/2010 financial year, 22 380 in 2010/2011 and 22 551 admissions in the

[†] *Personal communication: Trisha Chetty, Head: Information of NBI, Sept 2011)*

2011/2012 financial year. Privately funded patients also have access to these highly specialised services and differ in the proportions accessing various clinical services.

Polyclonal IVIG is very expensive and has remained one of the top 50 cost drivers in the pharmacy budget for a number of years at RCWMCH. This evidence is obtainable through the electronic dispensing record called JAC at the pharmacy department for 2009-2014 (a monthly report lists the statistics for the top 100 drugs usage in the hospital). The high usage and increasing trend in using IVIG is mirrored in other tertiary referral centres in the Western Cape, which might result in successively larger percentages of the pharmacy budget being attributed to the purchase of IVIG.

Whilst theoretically polyclonal IVIG is restricted in its use by the Provincial Code List within most state facilities, it is usually not known exactly for which indications polyclonal IVIG is used.

It is not clear whether the increased use of IVIG is due to there being a greater therapeutic need for IVIG. If this is the case, alternate suppliers of the immunoglobulin would need to be sought in order to keep up with demand, as the current sole supplier is unable to increase production of IVIG according to this need.

Alternatively, the increased demand may have resulted from inappropriate use of IVIG, despite there being suitable alternatives, or from the quasi experimental use of IVIG as a newer therapeutic solution for certain medical conditions. It is estimated that approximately 60 to 70% of IVIG use in adults complies with United States Food and Drug Administration (FDA)/approved indications.[2] A third of IVIG usage worldwide is purported to be attributed to indications for which there is scarce or no scientific evidence.[3] Within the paediatric context, the long-term risks associated with the injudicious use of IVIG in general are unknown, while the actual proportion of hypersensitivity reactions and other associated side effects from treatment at RCWMCH has also remained undocumented.

Without all this information, pharmacy and management would be unable to formulate an evidence-based policy for IVIG use at the hospital.

1.2.2 How will the study solve the problem?

Understanding the usage patterns and spectrum of use of IVIG at RCWMCH was integral to determining the frequency of its off-label (unregistered use). An analysis of the past indications, evidence for use and dosages used could assist in determining rationale for future use and duration of

evidence for use and dosages used could assist in determining rationale for future use and duration of use in a broader context. In addition, a pattern of disease profiles that warrants the use of IVIG (outside the registered use) in the paediatric setting could be established. The study was aimed at comparing the registered use with off-label use at RCWMCH.

Finally, this study aimed at calculating the average annual per patient cost of IVIG, which could allow for future cost projections. Forecasting and the creation of a specific budget for the indications could allow for better control and management of IVIG. Ultimately, the aim was to fuel further studies in this field within South Africa and to enrich the knowledge base within the context of low and middle-income countries and the populations they service. This could assist in the development of an evidence-based guideline for the use of IVIG provincially and nationally in the South African context.

1.3 PURPOSE OF THE RESEARCH

The purpose of this research was to assess the use and indications for use of polyvalent human intravenous immunoglobulin at Red Cross War Memorial Children's Hospital, a tertiary paediatric hospital in South Africa, for the period January 2009 to March 2012, to provide baseline data that would guide the development of evidence-informed guidelines for its future use.

1.3.1 Specific objectives of the research

The specific objectives of the study were to do the following:

1. Describe the total annual usage of IVIG;
2. Describe the demographic profile of children who have received intravenous immunoglobulin therapy;
3. List the main indications for usage as recorded in patient folders and/or by relevant clinicians' judgement;
4. Correlate the indications for intravenous immunoglobulin therapy to registered and off-label use recommendations during this time period;
5. Determine the expenditure on immunoglobulin therapy and relate this to the total drug expenditure during each financial year;
6. Calculate the annual cost and cost per patient for forecasting pharmacy budgets; and

7. Identify the unregistered indications for IVIG for which treatment protocols need to be developed.

1.3.2 Assumptions underlying the study

This study was conducted with the assumption that despite the large amount of IVIG used at RCWMCH, 80% of the time it was used for registered indications during the time period January 2009 until 31 March 2012.

1.3.3 *OPERATIONAL DEFINITIONS USED IN THE STUDY*

The only indications that might differ from the standard definitions include the following:

- Registered indication: An indication for IVIG registered with the Medicines Control Council of South Africa and as listed in IVIG the package insert
- Off-label: Medication that is being used for an unlicensed or unregistered indication as per package insert approved by the Medicines Control Council of South Africa or other relevant registering body in context
- Issue: A dose of IVIG dispensed in any of its varied strengths and recorded against a patient name in the pharmacy dispensing database
- Admission: Patients admitted to RCWMCH with the length of stay >1 day
- Patient day equivalent (PDE): Patient days + 1/3 outpatient / service group / casualty headcount.
- Average length of stay (ALOS): Patient days/separations (discharges/day patients/deaths/ external transfers out)
- Cost per patient: Total expenditure / PDE
- Haemovigilance: An organized system of surveillance throughout the transfusion chain intended to evaluate information in order to prevent the appearance or recurrence of adverse reactions related to the use of blood products.

CHAPTER II:
LITERATURE REVIEW

2.1 INTRODUCTION

Polyvalent human intravenous immunoglobulin (IVIG) has been used to treat several groups of conditions including primary immunodeficiencies, secondary immunodeficiencies, autoimmune diseases and neurological disorders. Several countries including the United States, United Kingdom, Canada and Australia have published evidence-based guidelines for the administration of immunoglobulin therapy. [4],[5],[6],[7] In South Africa, IVIG is registered for a narrow spectrum of indications.[8] However, beyond these registered indications, no evidence-based guideline exists that could guide the clinician through the multitude of off-label or unlicensed indications. Individual clinical judgement determines consideration and use at the RCWMCH but such subjectivity can lead to varied, expensive and occasionally indefensible practice.

A brief history of the mechanism of action, origin, history, manufacture and global picture is essential for greater understanding of the need for IVIG. This chapter discusses the literature that was reviewed in an attempt to gain insight into the various aspects contributing to IVIG production, its use and indications within the global and South African context. An extensive review was also conducted to identify other similar studies that have been conducted within South Africa or beyond and the results were tabulated and compared in a summarised review.

2.1.1 What is intravenous immunoglobulin (IVIG)?

Polyclonal human IVIG is a plasma protein replacement therapy containing large concentrations of varying subclasses of IgG (Immunoglobulin G) antibodies as well as minute quantities of IgA (Immunoglobulin A) and IgE (Immunoglobulin E) found naturally in human plasma. It is obtained from pooling the plasma of no less than 1000 non-remunerated blood donors per batch and then subjecting the plasma to a stringent fractionation and pasteurisation process to obtain the final useable product.[9] These IgG molecules reflect the collective acquired immunity of the donor pool from which it is derived.

Approximately 25 commercial products are available globally. These are however not considered generic to one another, due to the variances in source, manufacturing processes and ultimately

product.[10] The therapeutic efficacy is not the same for each unit of IVIG used. There are varying concentrations of immunoglobulin and IgG subclasses and hence antibody titre, as well as differing infusion rates and side effects. In addition, the various IgG formulations are thought to include small amounts of soluble CD_4 cells, cytokines, soluble cytokine inhibitors, major histocompatibility complex and stabilising agents that exhibit their own independent effect as determined from the donor plasma pool.[11]

Consequently, whilst all these products are therapeutically effective, the concentration and uses may differ in minor ways in the country in which they are registered. [12]

The mechanism of action of polyclonal IVIG is multifaceted, lending itself as a therapeutic medium to a wide array of disease states, as is evident in Table 2.1 and Appendix A.

Table 2.1: Mechanism of action of polyclonal IVIG

- Modulation of complement activation;
- Saturation of idiotypic antibodies;
- Suppression of Fc receptors on macrophages and activation of dendritic cells to mediate anti-inflammatory effects helping to reduce the severity of the autoimmune disease or inflammatory states; and
- Suppression of a multitude of inflammatory mediators including chemokines, cytokines and metalloproteinases.[13],[14]

Source: Adapted from Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med. Sep 6 2001;345(10):747-55.

For this reason, IVIG has an important role in the treatment of auto-immune and immune deficiency states by conferring a passive immunity, while also acting as an immunomodulator. These various mechanisms may be important in the different therapeutic uses of IVIG, including (1) replacement therapy for primary and secondary immunodeficiencies, i.e. antibody deficiencies; (2) specific passive immunotherapy; and (3) management of specific inflammatory and/or immunologic disorders. The complete mechanism of action of IVIG, however, is not fully understood and further research is on-going with evidence for greater therapeutic outcomes with use in other infectious disease states as well as other autoimmune conditions coming to the fore.[15]

IVIGs have shown to be beneficial in a number of primary immune deficiency disorders, including B-cell and T-cell disorders, and combined T-cell and B-cell immune deficiencies (Table 2.2). Patients with primary immune deficiency disorders are usually at increased risk for respiratory infections, particularly with *Pneumococcus* sp. and *Haemophilus influenza;* for gastrointestinal infections, particularly with *Campylobacter* sp., rotavirus, or *Giardia* sp. and for infections of the urinary tract. [16], [17], [18]

Table 2.2: Primary immune deficiency disorders known to respond to intravenous immunoglobulin replacement therapy

Class	Disorders	Immune defect
T-lymphocyte disorders	DiGeorge syndrome (complete thymic aplasia)	Lymphopaenia; T helper cell deficiency resulting in poor antibody production
	Hyper IgM syndrome	Deficiency of IgG, increased IgM; defect in expression of CD40 ligand on T cells
B-lymphocyte disorders	X-linked agammaglobulinaemia	Hypogammaglobulinaemia
	Common variable immunodeficiency	Hypogammaglobulinaemia
Combined T- and B-lymphocyte disorders	Wiskott-Aldrich syndrome	Low IgM; poor antibody production
	Ataxia telangiectasia	Low IgA; poor antibody production
	Severe combined immunodeficiency	Agammaglobulinaemia with severe T-cell defects

Source: Adapted from Ballow M. Intravenous Immunoglobulins: Clinical Experience and Viral Safety. J Am Pharm Assoc. 2002;42(3). Accessed online from http://www.medscape.com/viewarticle/436640_2 on 12 March 2014.[19]

Secondary immune deficiencies are sometimes associated with B-cell malignancies, leading to severe and recurrent bacterial infections. These infections are particularly serious when serum IgG levels decrease to < 6.4 g/l. [20], [21] IVIG has shown to be beneficial for these patients at high risk for secondary and complicated infections.

2.1.2 History of IVIG

The initial use of immunoglobulins occurred unbeknownst to the users in the 1800s, in form of animal sera. Clinicians used animal sera to treat smallpox, rabies and diphtheria without patient knowledge or consent. Success was variable and treatment failure, serum sickness and/or death were common. The first specific use of antibodies themselves was in the 1930s, when they were derived from human placental material to treat measles. [22]

However, it was not until the 1940s when Sr. Edwin Cohn was given the task by the National Research Council of the United States of America (USA) to create a readily available blood product, albumin, for the treatment of shock. Cohn developed a large scale fractionation process for the separation of plasma proteins by treatment with cold ethanol, salt, pH, temperature and centrifugation. The Cohn-Oncley cold alcohol fractionation process is still in use today for the production of immunoglobulins. [23]

Immunoglobulins derived from human plasma were first used in 1952 and given intra-muscularly to treat auto-immune conditions, including hypogammaglobulinaemia. [21] However, due to large volumes required and slow absorption from the injection site, the treatment proved very painful and not sustainable. Experiments with intravenous immunoglobulin in the 1960s yielded large scale systemic reactions and adverse events due to complement activation of the protein aggregates, prekallikrein activator and contamination by impurities. In 1982, anion exchange chromatography was successfully used for the purification of IVIG and resulted in a more stable and unmodified IgG component, as well as inclusion of IgG subclasses. [20]

In 1981, intravenous IgG was used to treat idiopathic thrombocytopaenic purpura (ITP) for the first time, with success. [24] The following year, the World Health Organisation (WHO) implemented a minimum standard for the manufacture of IVIG products. The main criteria for production include the following:

- The production batch should be prepared from a pool of at least 1000 donors.
- The batch should contain at least 90% intact IgG and as little IgA and IgM as possible.
- IgG subclasses should be present in a distribution similar to natural plasma (WHO reference plasma: IgG1 [60%]; IgG2 [29.4%]; IgG3 [6.5%]; IgG4 [4.1%]).

- The level of antibody against at least two bacterial species and two viruses should be ascertained; additionally, the IVIG should have at least 0.1 i.u. of anti-Hepatitis B surface antigens (HBsAg) and a radioimmunoassay titre of 1 to 1000 per ml of anti-Hepatitis A (HAV) virus.
- The preparation should be free of fragments and aggregates, as well as prekallikrein activator, kinins, plasmin, accumulating preservatives, and other damaging contaminants.
- The immunoglobulin should be modified biochemically as little as possible
- The immunoglobulin should retain opsonizing and complement-fixing activities and other natural biologic characteristics. [25]

Since 2006 technological developments in the manufacture of immunoglobulin have resulted in the preparation of a sub-cutaneous immunoglobulin (SCIG). The SCIG dosage form assists patients needing chronic therapy such as patients with primary immunodeficiency disease (PIDD) and patients unable to make immunoglobulin requiring replacement therapy, by preventing serious bacterial infections. The advantages of this dosage form over IVIG and intramuscular immunoglobulin (IMIG) include the following:

- Minimisation of adverse effects associated with IVIG;
- Less painful than IVIG or IMIG;
- Is therapeutically equivalent to IVIG;
- Transfusion time is greatly reduced and obliterates the need for vascular access;
- Can be self-administered at home, thereby decreasing the need for a hospital admission for administration as with IVIG;
- Fewer side effects experienced, like fevers, myalgias, headache, chills and
- More cost effective in long-term therapy.

However, most low to middle-income countries are confined to usually one manufactured product of IVIG and have not seen SCIG enter the market as yet. In addition, sub-cutaneous products showed greater localised site reactions and should not be considered in non-compliant patients.[26]

- **Manufacturing, donors and safety issues**

Subsequently, various manufacturing steps and techniques have been added to prevent viral transmission and re-aggregation of its proteins. Whilst bacteria and protozoa may contaminate blood products, potentially blood-borne viruses are the major infectious risk in the product. Bacteria and protozoa are unlikely to survive the cold ethanol precipitation procedure used to produce immunoglobulin. However, a small risk of viral infection from human plasma preparations can never be entirely ruled out. IVIG produced in 1993 and 1994 was subsequently responsible for over 125 cases of Hepatitis C infection (HCV).[27] Whilst this was the only known and documented outbreak, an effort to increase the quality and safety of plasma derived products is one of the key components of IVIG manufacture. Many health authorities, including the WHO, have issued guidelines outlining the requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. These guidelines refer extensively to the following factors:

- **Quality of plasma collected**

The careful selection of donors is essential. A careful medical examination and viral testing are preliminary requirements in plasma donation centres. In addition, anonymous questionnaires for eliminating high risk donors are administered. The locations of donor facilities are carefully considered. Collection from donors in countries where there is a high prevalence of blood borne diseases is now avoided and data from collection centres in the early 1990s showed low annual prevalence for HIV, Hepatitis B virus (HBV) and HCV. [28] In addition there have been higher trends of blood borne diseases or HCV antibodies in remunerated donors compared to non-remunerated (volunteer) donors in certain localities in the USA.[9]

The WHO guidelines encourage volunteer or unpaid donation of blood and plasma. The frequency of donation is controlled by quarantine of plasma of new or first time donors for a few months until subsequent testing has eliminated any contaminated or infectious plasma. The danger of frequent plasma donation by the same donor is that plasma could be donated whilst a blood borne disease is in its window period and thus it is necessary to create a database of screened and regular volunteer blood or plasma donors. As a result of some of these factors, the diligent but necessary screening of donors can reduce the plasma pool base subsequently.

- **Stringent screening process of donated plasma for infectious agents**

Introductory screening tests for blood or plasma donors include individual tests for HBsAg, Anti-HCV, Anti-HIV-1 and -2, syphilis serology and Alanine Transaminase (ALT). Table 2.3 below shows some of the viruses that can be eliminated by scrupulous donor and plasma screening. Due to possible inconsistencies in specificity and selectivity of antibody assays, several immunoglobulin manufacturers are now investigating polymerase chain reaction (PCR) based assays for plasma testing. The PCR-based assays work by detecting viral genomic material through nucleic acid amplification and can therefore detect viruses that may have otherwise escaped antibody detection tests. For example, Aventis in the USA developed a PCR-based assay that detects viral nucleic acids from HCV, HBV, and HIV-1. The company uses it to test small plasma pools in new drug mechanism experiments. This test is capable of detecting virus loads of $\geq 1.2 \times 10^3$ genome equivalents (GE)/ml of HBV, $\geq 8.4 \times 10^3$ GE/ml of HCV, and $\geq 4.9 \times 10^3$ GE/ml of HIV-1 with 95% confidence. The assay is well suited for plasma pool testing, and the data demonstrates that it is sensitive and reproducible. [29], [30]

Recently, the European Committee for Proprietary Medicinal Products recommended screening of immunoglobulin preparations for HCV Ribonucleic Acid using PCR-based tests.[18]

Table 2.3: Ease of transmission via immunoglobulin therapy

Eliminated by careful donor screening/testing:
Hepatitis B virus
HIV 1 & 2
Known to be relevant:
Hepatitis C virus
Unknown:
sporadic Creutzfeldt–Jakob diseases (spCJD)
variant Creutzfeldt–Jakob disease (vCJD)
Protection by high titres of neutralising antibodies:
Parvovirus B19
Hepatitis A virus
Not clinically relevant but transmitted:
Hepatitis G virus
Transfusion transmitted virus

Source: Adapted from Helen M. Chapel for the IUIS Committee on Primary Immunodeficiency Disease[10]

- **Accreditation of manufacturing facilities and donor blood centres**

The production of plasma products has been regulated by good manufacturing principles and mandatory repeated inspections since the late 1980s in the USA. Any change in the immunoglobulin production process requires repeated inspections by regulators. Accreditation and regulation have led to some companies closing due to insufficient funding. This resulted in a gross shortage of immunoglobulin in the late 1990s that was felt globally. [9]

- **Additional viral elimination steps in manufacture**

The dominant manufacturing method in the production of immunoglobulin remains the Cohn's Alcohol Fractionation process (Also known as Cohn-Oncley cold alcohol fractionation process (Figure 2.1). This process uses the various solubilities of plasma proteins through heat, pH and ethanol concentration to partition out the fractions through centrifugation. This process is utilised to manufacture not only immunoglobulins but also Factor VIII, fibrinogen and the initial goal for this process, albumin.

The Cohn-Oncley's process is also capable of inactivating and reducing viruses like HIV-1, HIV-2, Pseudorabies virus, HBV and Simian virus as an adjunct to the fractioning methods. However, lipid coated viruses and enveloped viruses like Parvovirus B19 and Hepatitis C virus are not effectively inactivated. Hence, the WHO guidelines require that additional steps be used for further inactivation of enveloped viruses and elimination of the immunoglobulin precipitate. The methods used are varied and include solvent/detergent processes, dry heat, pasteurisation, heat-treatment of freeze dried products, incubation at low pH, enzyme treatment (pepsin), nanofiltration, chromatography and caprylate precipitation.[31]

Excipients like sucrose may be added to the plasma pool to prevent aggregation of the immunoglobulins at higher temperatures. The aggregation of globulins has been associated with adverse effects like fevers, chills, tremors and pain. Excipients add stability to preparations but cause changes in pH, osmolality, dextrose content, etc. Interestingly, different methods in conjunction with the Cohn-Oncley cold alcohol fractionation process result in different outputs and yield of intact immunoglobulin monomers.

Consequently, depending on the donor pool, method of manufacture, excipients utilised, anti-viral steps employed, each product of IVIG is not the generic equivalent of any other. In the USA, the varied

registrations of IVIG products allow different products to be used selectively, according to each patient's disease profile and needs. [32]

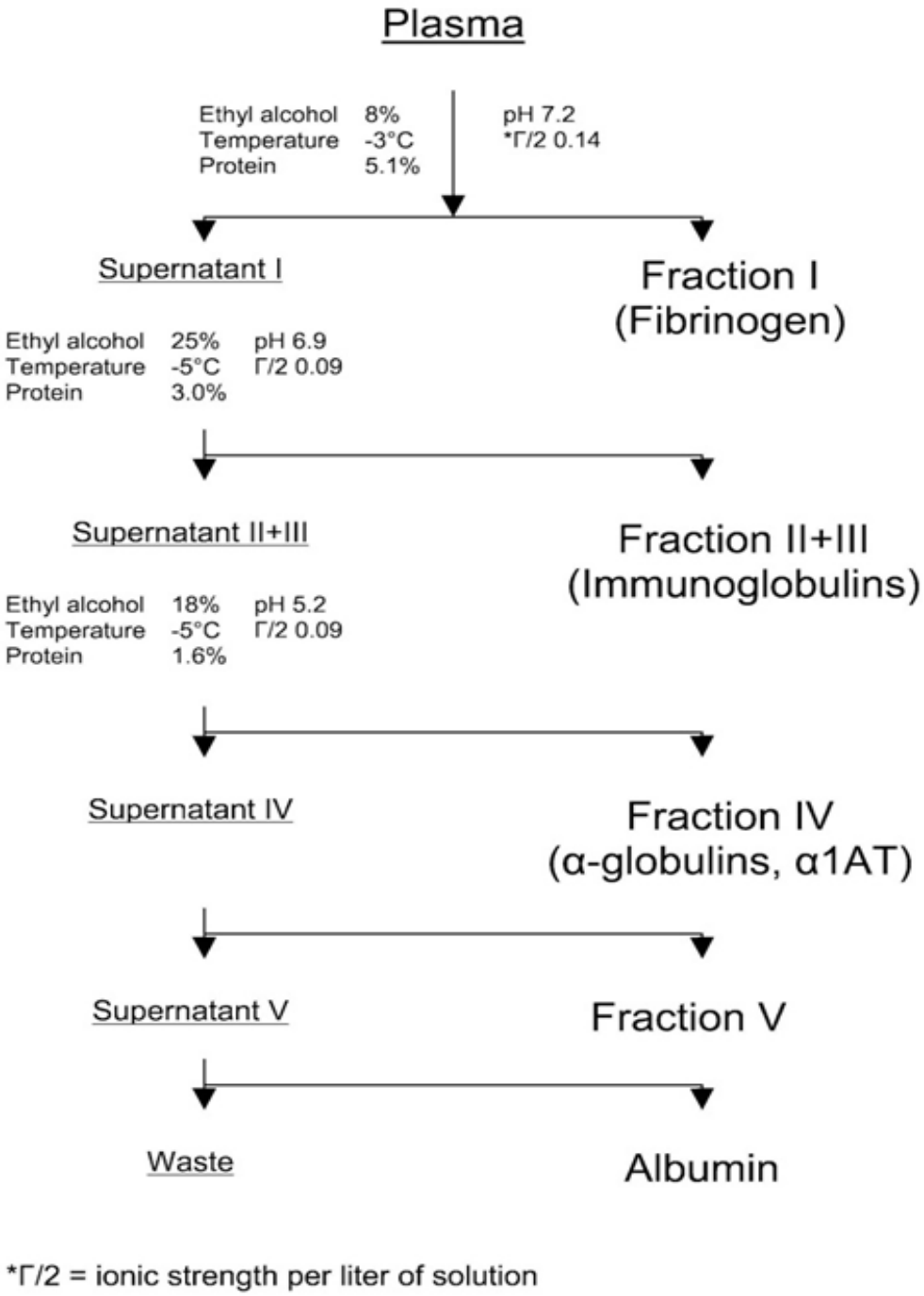


Figure 2.1: Cohn-Oncley cold alcohol fractionation process

Source: Adapted from Buchacher, A; Iberer, G. Purification of immunoglobulin G from human plasma: aspects of yield and virus safety. Biotechnology J. 2006. 1, 148-163.[33]

2.1.3 Side effects and adverse effects

IVIG has been a relatively safe product, due to the strict controls placed upon its manufacture and subsequent viral screening. There has been no known or documented transmission of HIV via an IVIG infusion. Adverse effects have been associated with infusion issues rather than the product itself. As some products contain sucrose (for disaggregation), these risk renal failure, particularly in diabetic patients, septic patients, the elderly, and patients with any pre-existing renal insufficiency.[5],[19]

As highlighted above, different products exist internationally that allow for individual selection of a particular IVIG solution to match the patient's profile. In the South African context, where there is one major national supplier, this matching cannot take place. Hence, when the benefit of administration outweighs the risk, due diligence must be given to monitoring and investigation for any adverse effects after infusion.

Mild side effects of IVIG include: headache, nausea, abdominal pain, myalgias and arthralgias; urticaria and other rash conditions; chest discomfort and tachycardia; low grade fever and chills; and flushing. These can be treated by slowing down the infusion rate or pausing the infusion temporarily until symptoms resolve. Utilising an alternative product, if available, may also be worth considering. In some cases mild steroids, antihistamines and analgesics may also be considered to resolve some of these minor side effects. [5], [19]

Major side effects include aseptic meningitis syndrome, acute renal failure, thrombo-embolism, myocardial infarction and anaphylaxis. Aseptic meningitis syndrome has been associated with IVIG use in patients with a history of migraine prior to infusion. Adequate hydration, slower infusion rates and treatment with analgesia and migraine medication can help to prevent this complication. If discontinued, the symptoms and resulting effects are reversible. The elderly, in whom cerebral or cardiac ischaemia may co-exist, the overweight and/or severely hypovolaemic patients are more prone to thromboembolism.[5]

Finally, IVIG must be given with caution to patients who have pre-existing antibodies to IgA or who have IgA deficiencies. This is due to the small amount of IgA that can be present in polyclonal IVIG products, resulting in sensitisation and anaphylaxis to the antibodies of IgA or other IgA particulate matter that might be present. Reactions to IgA in IgA deficient patients usually happens 30 to 60

minutes post IVIG administration. Levels of IgA should be determined particularly in primary immunodeficiency states like hypogammaglobinaemia or agammaglobulinaemia.[19]

Rare but potentially serious side effects include serum sickness, haemolytic anaemia, leukopaenia or neutropaenia and pulmonary oedema.

Stringent regulations in donor screening, manufacturing processes, regulation and accreditation have put a strong focus on quality and safety. Particularly in low and middle-income countries, there is a need to afford more stringent monitoring and evaluation post administration to determine adverse events. Haemovigilance strategies need to be adopted pre- and post-administration.[19]

2.1.4 Global demand

IVIG has been the major driver in the plasma products industry due to an increasing usage thereof for a multitude of clinical indications. Many of these indications are new and have only been considered in the past few years. Currently major IVIG users are in high-income countries: North America and Europe have approximately 20% of the world's population but use approximately 75% of all IVIG produced globally. Unmet needs in low-income countries, as well as emerging markets, are likely to increasingly fuel the need for IVIG in years to come.[34]

In 2009 the global demand for plasma-derived products was estimated to be US$11.8 billion. Of this, 46% was attributed to the cost of IVIG (US$5.4 billion), albumin 10% and Factor VIII 9%. It is estimated that immunoglobulins are likely to exceed US$9.0 billion by 2018 (notwithstanding registration for new indications in high-income countries).

The following are some of the reasons for an increasing demand:

- Increase in global population;
- Rise in global per capita GDP and rise in health expenditure;
- Increased ageing population;
- Increasing awareness of the benefits of immunoglobulins clinically;
- Proposed registrations of new indications for use;
- Increase in diagnosed bleeding disorders and identification of primary immune deficiencies and

- Greater off-label use of IVIG.[35], [33]

Worldwide supply and demand of plasma and plasma-derived medicine

There was an average annual increase of approximately 12% in the use of IVIG from 1984 to 2008. Thereafter the global growth rate in IVIG use is about 7% annually due to more stringent and good manufacturing principles being enforced that negatively affected supply. Consolidation of industries led to enhanced product safety and efficiency. Some high-income countries like Australia are currently seeing a growth of about 10%. In low to middle-income countries, data does not currently exist on annual usage. [36]

Approximately 82 tons of IVIG were consumed worldwide in 2008 and 120 tons were estimated to have been used in 2012. Use is estimated to rise to about 132 tons globally by 2015 (Table 2.4). The shortage of plasma-derived medicines and in particular IVIG has had the most impact in low and middle-income countries. High costs for production, long production times (6-8 months) as well as shortages in plasma from available donors contribute to this shortage. In addition, both the on- and off-label uses are generally for rare indications for which health budgets in developing countries are unable to allocate sufficient resources.[37]

Table 2.4: Global IVIG demand from 2006 to 2015 (Metric tons)

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
IVIG is approved for Alzheimer's disease treatment in 2012										
Metric tons	68	75	82	88	94	100	107	120	135	151
Annual growth rate		10.%	9%	7.%	7.%	7.%	7.%	12.%	12.%	12.%
IVIG is not approved for Alzheimer's disease treatment in 2012										
Metric tons	68	75	82	88	94	100	107	115	123	132
Annual growth rate		10%	9%	7%	7%	7%	7%	7%	7%	7%

Source: Adapted from Robert P. Global Plasma Demand in 2015. [39]

IVIG usage is currently highest in the USA, followed by Sweden, Austria and France. In addition developing markets like China and Japan are likely to fuel the demand for IVIG further. One important additional consideration that is likely to increase demand excessively is that clinical trials for the use of IVIG in Alzheimer's have been underway since 2009. Interim results are showing promise with

definite results expected within the next few months. Consequently, there is a pending FDA registration for such use. In the USA it is estimated that at least 2.4 million people are afflicted with Alzheimer's. Almost every country imports plasma with the exception of the USA which is able to sustain its supply through a remunerated plasma donor process. [38], [39]

In 2007, approximately 26 million litres of plasma was fractionated globally. Of this about 9 million litres were recovered plasma from blood donation and about 18 million litres were sourced by plasmapheresis through plasma donation. Only 72.5 metric tons of IVIG were produced yielding 2.8 gram per litre.[41] Yield outputs vary depending on the manufacturing process used, the viral elimination methods employed, the quality of blood donation and plasmapheresis, maintenance of cold chain procedures, regulation and accreditation of good manufacturing practices by the production plants. Often producers have to outweigh risks of high output with safety of product. For example, some viral elimination methods utilise heat which also destroys the IgG monomers at these temperatures rendering the product yield safe but low. As of 2012, 1 litre of plasma yielded approximately 3.3 grams of IVIG. Of the 78 fractionating plants that existed in the world in 2010, the majority were located in Europe and China. [33], [34], [35], [36]

Specific issues in middle and low-income countries on supply and demand include: the availability and affordability of blood and blood products; poor regulation and guidance on blood products; the potential risk of transfusion transmitted diseases; lack of reporting systems; and wastage of plasma due to ineffective mechanisms for safe screening and manufacturing.

The World Health Organisation has listed IVIG as an essential medicine for children, particularly for the indication of primary immunodeficiency where it is lifesaving.[40] The *Achilles Project* was developed by the WHO to assure the safety and availability of blood products in developing countries. Members of the World Health Assembly were encouraged to implement a set of guidelines on the collection of blood products, screening manufacturing, fractionation, viral removal and other blood product associated criteria to ensure safety and quality of the blood products. The key role was to encourage developing countries to create their own fractionation plants (government funded) and to establish a safe and sound donor volunteer programme for plasmapheresis. To this end, the WHO made available numerous guidelines on these processes, assisted with accreditation of facilities and the training of quality and safety inspectors, offered standardised regimens and encouraged the harmonisation of regulations relating to the production of IVIG.[41]

The production of a sufficient quantity of qualified and safe plasma is the solution to global shortages. The WHO sees the creation of independent fractionation plants as the only way of sustaining the need for plasma-derived products. In low and middle-income countries in particular, there is an inherent need to recover all plasma available in the country and initiate a source plasmapheresis programme. Current trends show an inability to cope with current demands globally, let alone the newer indications coming to the fore in years to come. It is highly unlikely that costs for productions are going to decrease. As it stands, IVIG in South Africa is currently unaffordable for many chronic conditions such as chronic inflammatory demyelinating polyneuropathy (CIDP), primary immunodeficiencies both in private as well as in public budgets. As a result, IVIG should be restricted in its use to life threatening and registered indications until a greater capacity is developed for increasing yields and recovery of IVIG.[33], [35], [37], [39]

2.1.5 The South African context

In South Africa the sole supplier of polyclonal IVIG is the National Bioproducts Institute. Established as a non-profit organisation in 2004, it is involved in the production of blood transfusion products nationally. Due to increasing demands for IVIG and other blood products, NBI in 2010 embarked on a major refurbishment process to their production plant. Currently three other Immunoglobulin G (IgG) products are registered: intramuscular IgG products like Intragam®, and Beriglobin® unsuitable for higher doses, and since 2012, intravenous Octagam®. Intraglobin F® was briefly available via special application from the MCC (section 21 approval). Red Cross War Memorial Children's Hospital had to make use of this in 2011 when Polygam® was unavailable in the quantities required. NBI is reliant on a volunteer blood donor programme through the South African National Blood Transfusion Services and Western Province Blood Transfusion Service as well as other international suppliers. The plasma is screened for hepatitis B surface antigen, HIV-p24 antigen, and antibodies to syphilis, HIV-1, HIV-2 and hepatitis C (Appendix B). Parallel importation as well as the need for alternative suppliers of IVIG could result in greater competition; products with more specific indications; could sustain supply, as well as assist in more viable pricing.

South Africa currently has a dual public and privately funded healthcare system. Approximately 84% of all South Africans, generally lower income and unemployed citizens, make use of the public health medical service whilst higher income groups access their own private medical care.[42]

A provincial code list is developed by clinical and pharmaceutical heads of state facilities containing drugs on national tender that meet these public health priorities. This code list of drugs is regularly updated and revised to meet the current demands based on the scientific evidence presented in motivations by local clinicians.

The public system is geared towards prioritising key health issues to meet the need of the majority of the public, but cannot fully address individual and rare disease conditions adequately at all times. The public health system in South Africa is organised in different levels of care, namely primary, secondary, district and tertiary level of care where a referral system exists for appropriate service of care at each level. Drugs are restricted for use by the level of health service offered. In the Western Cape, usage of IVIG is restricted to central and tertiary level healthcare facilities for paediatrics and specialist usage only. Patients who need IVIG would have to be referred to these institutes. Occasionally, secondary level hospitals have reluctantly issued IVIG as it erodes the budget of these facilities greatly and requires them to purchase IVIG outside the coding restrictions.

Polyclonal IVIG is expensive, costing between ZAR362 (2009) and ZAR469 (2014) per gram IVIG at state level and approximately 20% more in private health facilities. In some private facilities IVIG is approximately ZAR659 per gram (2014) but this is determined by individual facilities and varies with different private institutions based on the single exit pricing system.[‡] The above costing excludes any additional expenses incurred by the infusion itself, bed occupancy within a ward and any supportive therapy. Rather than being restricted by a provincial code list, usage in private is determined by what the funder is willing to cover and pay for. Different medical funders offer varying levels of cover and have established norms for their own usage (Appendix C).

With clinical research continuously expanding the potential applications of IVIG, the concern for increasing demand and inadequate supply is valid. The broad mechanism of action allows IVIG as a therapeutically viable choice and often last resort in many disease and infectious conditions. Whilst attempts have been made to document the unregistered use in various institutes internationally, no such audit has been documented within South Africa.

[‡] Incidentally, it is interesting to note that the gold price per gram ranged from around ZAR250 (2009) and ZAR420 in this time period of the study. Currently the gold price per gram is ZAR432.(November 2014)

The South African government has embarked on a project of rolling out a national healthcare plan that allows for broader quality access to healthcare for all. The plan is for this social healthcare net called the National Health Insurance (NHI) to be rolled out over a period of 14 years, starting with a pilot project from 2012 to 2017 in five health districts. Essentially it involves amalgamating the public and private systems from a human resource, equipment and facility point of view. One of the areas that will need harmonisation is that of a national system of rational drug use.[32], [33], [43]

IVIG is registered internationally and nationally for only a few specific indications (see Table 2.5). At the same time, the majority of IVIG use can be attributed to the off-label use with approximately 150 varied indications documented, as tabulated by Leong *et al*.[44] (Appendix D). IVIG has had a huge impact clinically, especially in the treatment of some rare disorders in the fields of neurology, haematology, immunology, nephrology, rheumatology and infectious diseases. The broad spectrum of activity as replacement or booster therapy in humans does not preclude its use as adjunct therapy to a myriad of disease conditions.[45]

Table 2.5: Registered/Labelled uses of intravenous immunoglobulin (2014)

MCC (South Africa)[7]	**FDA (USA)[46]**	**EMA (Europe)[47]**
<u>Replacement therapy in:</u> • Primary antibody deficiency syndromes	Primary immunodeficiencies	<u>Replacement therapy in:</u> • Primary immunodeficiency syndromes with impaired antibody production.
Myeloma or chronic lymphocytic leukaemia with severe hypogammaglobulinaemia and recurrent infections	Chronic lymphocytic leukaemia	Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed.
		Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma (MM) patients who have failed to respond to pneumococcal immunisation.

Table 2.5: Registered/Labelled uses of intravenous immunoglobulin (2014) cont.

MCC (South Africa)[7]	FDA (USA)[48]	EMA (Europe)[49]
		Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
<u>For immunomodulation in:</u> • Idiopathic Thrombocytopenic Purpura (ITP) in children and adults. • Kawasaki disease. • Guillain-Barré syndrome (GBS)	• Idiopathic thrombocytopenic purpura • Kawasaki disease	<u>Immunomodulatory effect in:</u> • Primary immune thrombocytopenia* (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count. • GBS • Kawasaki disease
Allogeneic bone marrow transplantation	Allogeneic bone marrow transplant	
Children with congenital AIDS and recurrent infections	Paediatric HIV	Children and adolescents with congenital AIDS and recurrent bacterial infections.
	Chronic inflammatory demyelinating polyneuropathy (CIDP). Only the Gamunex® brand manufactured by Talecris® is approved for CIDP in 2008; under the USA Orphan Drug law provisions	
	Kidney transplant with a high antibody recipient or with an ABO incompatible donor	

Source: Polygam® . South African Electronic Package Inserts. Polygam. Last accessed on 10 August 2014, available online from: http://home.intekom.com/pharm/nbi/polygam.html;
U.S Food and Drug Administration (FDA)-Last accessed 18 October2014, available online from: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm;
European Medicines agency(EMA)Last Accessed 18 October 2014, available online from:http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp-&mid=WC0b01ac0580032ec8.

Internationally, at least 25 different brands of IVIG exist, all not being the generic equivalent of the other. Supply of every product varies greatly from country to country. Registration of each product is associated with licensed use for specific indications. Tolerability to different generics is a concern in countries where various products exist and choices can be made as to which product is most suitable for the individual patient. In South Africa and other developing countries this is not so readily available. The current competitors to NBI for example have products that are not financially viable as yet and can be procured only at a higher cost. However, these products could offer other benefits like decreased reconstitution volumes in fluid restricted patients.

2.1.6 Literature review

A literature review was conducted to determine if any similar studies have been done in the audit or use of IVIG nationally or internationally. The PUBMED, Cochrane and Google Scholar databases were scrutinised using the advanced search builder. Articles were excluded based on the following criteria:

- In any language other than English;
- Articles older than 1995 as information was outdated;
- Articles pertaining to specific indications including Sepsis, Kawasaki disease, ITP, GBS and so on;
- Articles relevant to animal studies in the field of veterinary science;
- Articles based on internet databases requiring voluntary input by IVIG users and
- Article pertaining only to costs of IVIG.

Search terms used in builder:

1. Search (((intravenous immunoglobulin) OR intravenous immune globulin) OR ivig) AND use OR indication;
2. Search (((((intravenous immunoglobulin) OR intravenous immune globulin) OR ivig) AND use)) AND hospital;
3. Search 1+2 AND off-label;
4. Search 1+2+3 AND p?ediatric*;
5. Search 1+2 AND Guideline* OR protocol* and
6. 1+2+3+4+5

An initial search was conducted using the terms ‘intravenous immunoglobulin’, OR ‘intravenous immune globulin’, OR ‘IVIG’, AND ‘use’. The articles (n=123) in PUBMED were scanned and abstracts read for relevancy. Search terms were then built as described above. Articles discussing general, unlabelled use, adverse effects, new uses, subcutaneous use and articles demonstrating a need for a protocol/guideline were selected. Search strings were developed based on the MeSH search as described in Figure 2.2 below. The main articles of interest relevant to this study were selected based on IVIG use/utilisation/surveillance in a ward, hospital, multihospital or nationwide setting. This yielded 15 articles of which two were only available in abstract form. An advanced Google search was then conducted to determine any missing gaps in collation of relevant articles. The same search terms were used and a further 10 articles were found, three of which were available only in abstract format. Finally, a Cochrane database search using the same terms was conducted yielding zero results relevant to the topic above, articles and systemic reviews found referred to specific conditions and uses.

References were checked in the 25 articles found for further resources of interest to the study and a further three articles were found.

Several searches as described above were conducted for particular subjects of interest to the study. For example, the paucity of paediatric data made it necessary to exclude the word paediatric and conduct searches based on adult information or where no mention was listed. Search strings were subsequently built up to refine each search.

- Search criteria: Search string 1 PUBMED
- Search string 2 Google Scholar
- Search string 3 Cochrane Database.

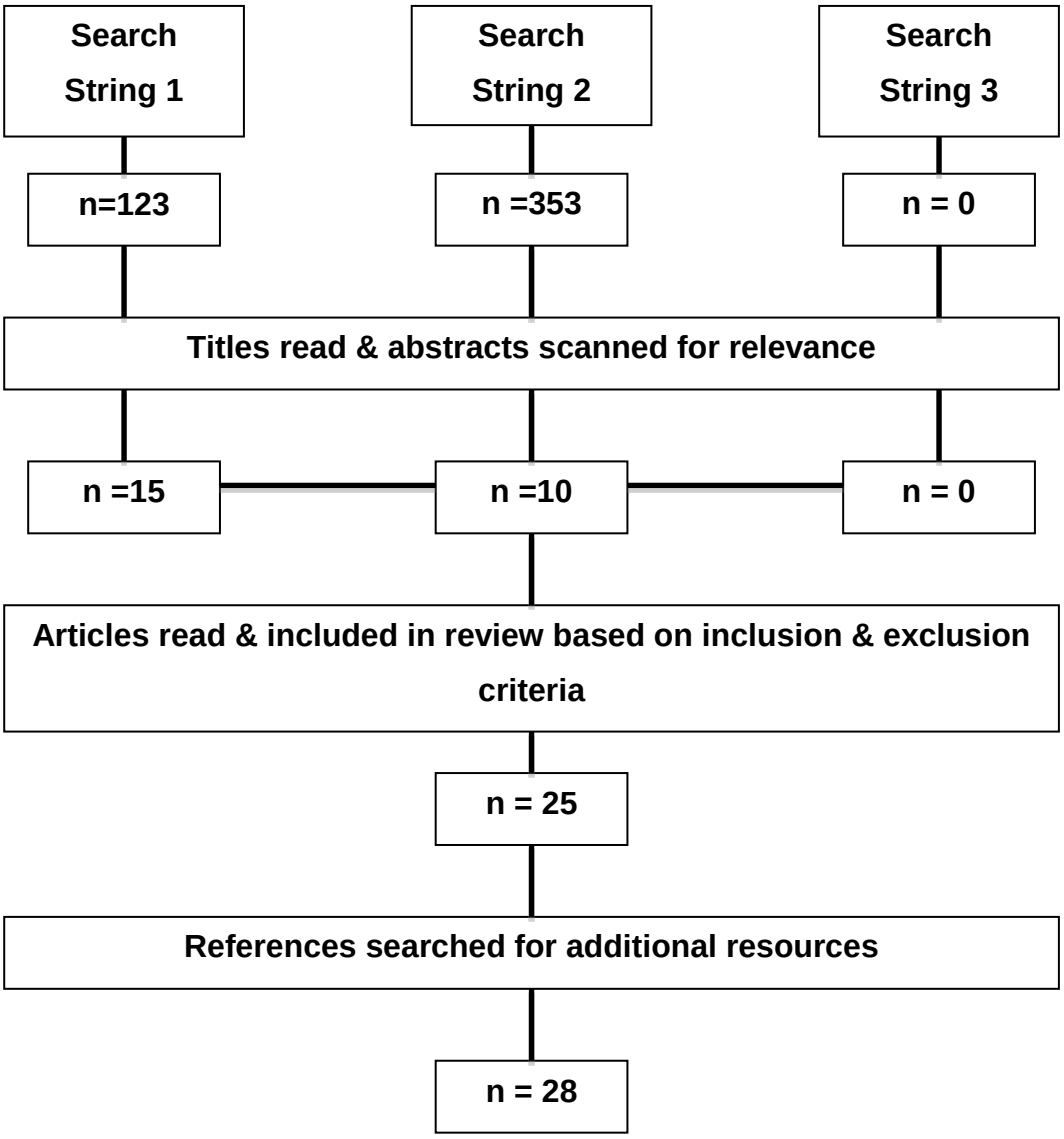


Figure 2.2: Literature review search results

Twenty eight articles were found pertaining to IVIG use, utilisation and surveillance in a hospital setting, multihospital setting or countrywide (Figure 2.2). Many other articles appeared to be applicable, but upon reading some of them it became clear that they lacked pertinent details or did not fit the inclusion aspects considered. Articles were rejected for not being applicable to the search criteria, only reporting ancillary issues or being specific to a single clinical indication.[50] Tables 2.6-2.8 were developed and created from the articles found on IVIG use at the end of this chapter. These summarise and categorise the literature found into Table 2.6: Paediatric-related articles on IVIG

use/utilisation; Table 2.7: Adult Hospital/s and regional IVIG use/utilisation; and Table 2.8: Nationwide/Countrywide use/utilisation of IVIG. What follows are some pertinent articles relating to the use of IVIG in paediatrics.

One of the first articles published on IVIG use in a hospital setting was by Frayha *et al.* [51] in 1997. A series of drug use evaluations were conducted in King Faisal Specialist Hospital, Saudi Arabia during a two-month period, pre- and post-guideline implementation and training on IVIG use. As an exploratory and rudimentary descriptive study, off-label use could only really be compared to other studies from its pre-guideline implementation data (36% labelled use of IVIG). However, a very small sample size makes this study significantly weaker than others, yet it serves as a basis for future audits in various other countries. A key finding of this study suggests the need for a guideline/protocol to control the use of IVIG and the effectiveness of instituting a policy for monitoring therapeutic indication.

Other studies similar to these that looked into the effectiveness of guideline implementation include the first known paediatric only audit on IVIG use in a large children's hospital in Houston Texas in 1998 by Gurwitch *et al.* [52] Off-label use was estimated to be 66% of the 164 paediatric patients surveyed pre-guideline implementation and subsequently 7.5% after the introduction of the guideline, highlighting the imperative need for guidelines in a paediatric hospital setting. It is comparable from a pre-guideline perspective to the other older study in Detroit by Gajewski *et al.* [53] which looked at four hospitals, one of which had 34 beds for paediatric patients. Similarly, this prospective study showed an off-label use of 66% in the paediatric population, though the Gajewski study suffers from a small paediatric sample size (N=107). The main indications for use reported by the Gurwitch study at the paediatric facility included primary immunodeficiency disorders, Kawasaki disease, ITP, GBS, bone marrow transplantation, Cytomegalovirus disease and Paediatric HIV.

Darabi *et al.* [54] later conducted a retrospective study in Massachusetts General Hospital (2006) looking at the indications for use among 194 adult patients issued IVIG over a one-year period. Therapeutic indications for IVIG were mainly off-label (57%) by FDA classification, similar to the Texas Paediatric Study. The main indications for off-label use included chronic neuropathy including chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, as were many of the other indications reported. It is important to note that at the time the FDA had only approved six indications for use, Guillain-Barré syndrome being an off-label use under the FDA registration process in the USA. A possible limitation in assessment of indication as reported in the study could include the

fact that all requests for IVIG had to be pre-approved by the blood transfusion service physician before being issued for use. A hospital guideline was already in place, which could have controlled the data collected further and not shown the number of initial requests for IVIG.

However, many of the uses seen at Massachusetts General Hospital matched that of the guidelines developed by the University Hospital Consortium in 1998 on acceptable use of IVIG which differed from the strict FDA registration. Very few randomised controlled trials were and are still currently available to rationalise this major off-label use although the Cochrane Database is now addressing some of the more common off-label uses. Currently, the FDA predicts that approximately 50 to 70% of IVIG use can be attributed to off-label use. This suggests an urgent need for specific trials and registration for use. [55]

The use of IVIG in Canada was highest in the period 1998-2006, showing a 115% increase per capita and making them the world's largest users of IVIG during that time.[56] Efforts to control use have included many evidence-based guidelines, and protocols in sub-specialties including neurology, haematology, and infectious diseases. The National Advisory Committee on Blood and Blood Products and the Canadian Blood Services have developed and maintained at least 15 different evidence-based guidelines on specific indications and use.[57] Registries and databases have been created nationwide to monitor and survey the IVIG use continuously. To this end, many studies have resulted from this focus group, four of which pertain to IVIG indications and usage in various facilities in Canada (Tables 2.7 and 2.8).

In 2003, Hanna *et al*. [58] conducted a retrospective review in ten teaching and community hospitals, two of which were paediatric facilities, representing 890 patients. Their results indicated a 38% off-label use in the paediatric populations as opposed to 53% in adults. This might suggest that off-label use could be more widespread in adult populations but is limited by a selection bias in that only two paediatric hospitals featured in the study compared to eight adult hospitals.

The other paediatric study of note by Dashti-Khavidaki *et al.* [59] included a sample of 43 paediatric patients of which 42% received IVIG for off-label indications in an academic children's hospital in Tehran, Iran. As reported in the study and of interest, patients in the registered use group experienced significantly greater clinical improvement than those in the off-label or unregistered group. This study also reported 45% adverse drug reactions, which is far higher than the other studies reporting on adverse drug reactions, namely Gajewski (12%)[51] and Chen (11%)[6] respectively. They attributed it

to potential differences in sensitivities to IVIG formulations or nursing negligence. However, it could also be attributed to a more focused and detailed reporting of adverse events in such a setting.

Of direct interest and relevance to this study are two of the latest articles published in 2013 relating to IVIG use in paediatrics. The first study in Cairo[60] describes the use of IVIG in an ICU setting of a paediatric tertiary hospital between 2008 and 2011. The study resonates with this research study, being the only other study conducting research in a resource limited setting of a low to middle-income country in Africa. Interestingly, the results indicate conformance with FDA and Level 1a evidence (using the American Heart Association framework on levels of evidence) for 62% of the study patients. The sample size was limited to 45 patients who received IVIG in an ICU setting, restricting any inferences to greater compliance in this setting from being made. In direct contradiction, Wu's study demonstrated interesting outcomes, possibly unique to the environment in Asia. This study is noted for the largest sample size (N=1302) in a paediatric study over a 10-year period from 2000-2009, recently published on data from Singapore[61]. Key findings from this study showed 75% compliance with FDA approved indications for IVIG use, a much larger proportion of patients with Kawasaki disease compared to other studies, where non- approved FDA indications like neonatal sepsis and secondary immunodeficiency had negative outcomes resulting in mortality of the patients despite IVIG usage. Finally, this study demonstrated the need for more studies to investigate the role of IVIG use for these indications and the necessity for local guidelines to monitor the prescription of IVIG. Two other studies in paediatrics conducted in the United Arab Emirates (UAE) and Italy with relatively small sample sizes (N=74 and N=67 respectively), indicate a 61% and 26% off-label use with weak evidence. Tables 2.6, 2.7 and 2.8 were created by the researcher to summarise all relevant articles relating to IVIG use that have been published to date. However some clear distinctions are seen between all the available literature relating to IVIG use and indications that must be noted:

- Differences in definitions of appropriate use, recommended use and inappropriate or off-label use across hospitals, boards, regions and countries make extrapolation and comparison difficult to quantify. This is particularly relevant as greater knowledge and more technological systems for data collection come to the fore.
- Variances in sample size or inadequate sample sizes. As many of these studies serve as exploratory studies in their respective country, initial sample sizes were very small and the methodology not described in great detail. Subsequent larger sample sizes in studies tended to

focus on either adult and paediatric data, or national databases across various hospitals, states or countrywide and relied on existing databases for collection of data.

- Nine articles mention paediatrics specifically in their summation. However, it cannot be ruled out entirely that paediatrics was not a component of larger multihospital and state-wide studies. As such, these greater sample sizes could give a more representative view of IVIG use in that location but no inferences can be made on paediatric usage.
- Sources of information. Some articles pose significant limitations depending on the method of data collection. These include national databases, folder reviews, clinical case notes, and expert opinion.
- Type of study. Prospective versus retrospective studies often yield very different results. In general, a prospective review is a stronger study.
- Guidelines approved for use. One of the greatest limitations to comparisons between similar articles listed in the table is the immense variation in guidelines used in these articles. Whilst some studies use the audit to make recommendations towards a need for a guideline, a few articles relate directly to the effectiveness of available guidelines. In addition, some articles use national guidelines (where available), while others rely on clinical associations like haematology, neurology etc. Added to this, some articles use FDA or European Medicines Agency (EMA) registration approvals and in-hospital policies where available. Clinical expertise and panels are also prevalent in distinguishing recommended and non-recommended indications. All this leads to a very subjective and variable record of results that is relevant for the specific locations only. Interestingly, the study by Feasby *et al.* demonstrated how ineffective guidelines were in containing the off-label and non-recommended use of IVIG in the British Columbian hospitals.
- Approved and registered indications. Finally, it is quite apparent that the different registrations for particular indications make a significant difference in results. Guillain-Barré syndrome for example is not approved for use by the FDA and consequent interpretation of off-label use is influenced greatly by this fact. In Europe, where Guillain-Barré syndrome was approved for use under the EMA, studies conducted there exhibit a generally smaller percentage of off-label use, one reason of which could be attributed to this registration. Some countries like Australia and Canada where established guidelines exist also include a set of recommended indications that

whilst not strictly registered for use, have sufficient evidence showing efficacious and appropriate use. This naturally influences the off-label results further.

- Levels of evidence. In some studies, labelled/off-label uses were not the only criteria considered as appropriate. Levels of evidence are defined in different studies by different bodies/organisations. These levels are utilised to categorise the literature available for a therapeutic indication by the strength of the studies available (evidence-based medicine) but do not all conform to each other, making direct comparisons between levels difficult.

Nevertheless, by far the majority of studies display an apparent need for consensus guidelines, approved definitions and indications with standardised level of grading. Off-label or unregistered use varied in the paediatric studies from 25% to 66%, and it is unknown what the paediatric population in the South African setting would reflect. To date, whilst many studies have been conducted in high-income country settings, none exist in South Africa and the picture may be very different for a number of reasons. First and foremost, resource limitations and an increased focus by national health budgets on highly prevalent diseases may influence the unregistered uses and indications for use. In addition, the burden of disease may be different taking into consideration factors like HIV, TB and other infectious diseases that this cohort may be exposed to.

To date no publication exists expounding on the use and development of a national guideline or protocol governing use of IVIG within South Africa. The provincial pharmaceutical and therapeutics committee of the Western Cape is interested in collating the information presented from this study from a paediatric perspective. An adult review on usage will also be undertaken and the indications then evaluated for clinical and evidence-based efficacy towards the formulation of a guideline or protocol.

With clinical research continuously expanding the potential applications of IVIG, this concern is valid. The broad mechanism of action allows IVIG as a therapeutically viable choice and often last resort in many disease and infectious states. Whilst attempts have been made to document the unregistered uses in various institutes internationally, and develop a guideline from which to control usage, no such audit has been documented within South Africa. This information could be used to formulate evidence-based guidelines and policies regarding the unregistered use of IVIG within the paediatric and South African context.

Table 2.6: Summary of articles published on IVIG use in paediatrics

Article	City, Country	Study Type	Year Published	Period of study	Total Sample Size	Total Number of hospitals	Paediatric sample size	Registered Board	Guideline/ Guidance for classification	Percentage Labelled Use (by number of Patients)Recommended Use and non-recommended use where otherwise stated	Percentage Off-labelled Use	Adverse Drug Reactions
Gajewski *et al.* [50]	Detroit, U.S.A	Retrospective Audit	1994	6 months	107	4	34 patients	FDA	FDA categorisation/ available literature/ national guideline for categorisation	11% in the adult hospital and 35% in the paediatric hospital	89% in the adult hospital and 65% in the paediatric hospital	11.30%
Gurwitch *et al* .[51]	Texas, USA	Prospective	1998	12 months-1996-1997	164	1	164	FDA	Hospital IVIG Taskforce Guideline	Pre guideline: 44% and Post guideline: 93%	Pre Guideline 66%; Post guideline7.5%	Unknown
Hanna *et al* .[56]	Canada	Retrospective	2003	1997-1999 (adults) and 1998-1998 (paediatrics)	1014 adults and 890 paediatric patients	10	890	FDA	Assessed against the Canadian consensus guidelines for IVIG use in 1997	47% and 62%	53% adults and 38% paediatric (appropriate use by guideline) 6% no scientific evidence	Unknown
Dashti-Khavidaki *et al* .[57]	Tehran, Iran	Prospective	2008	6 months-	43	1	43	FDA	Unknown	58.00%	16.7% with scientific evidence and 25% without evidence	45.80%
Ruiz-Antorán *et al.* [3]	Spain	Prospective	2010	3 months-2004/2005	554	13	554	EMA(Spanish Medicine Agency)	EMA	60%	16% with scientific evidence and 24% withut scientific evidence	Unknown
Dawoud *et al.* [62]	United Arab Emirates	Retrospective	2012	2010-2011	60 adults,74 paediatric patients	1	74	FDA	Reuters classification	46% appropriate use in adults,39% appropriate use in paediatrics	54% inappropriate use in adults and 61% inapproprite use in paediatrics	
Galal N.M[58]	Cairo, Egypt	Retrospective	2013	2008-2011	45	1	45	FDA	FDA categorisation/Evidence Category	62% with Evidence 1a/1b	38% level 2/3 (weak) evidence	recorded by adverse event eg. Fever, headache,
Wu *et al* .[59]	Singapore	Retrospective	2013	2000-2009	1302	2	1302	FDA	FDA classification	75%	25%	6.50%
De Meo *et al* .[63]	Italy	Retrospecitive	2013	2011-2012	67	1	67	EMA(Regional guideline)	Regional Guideline	74%	26%	Unknown

Table 2.7: Summary of articles published on IVIG use in adults

Article	City, Country	Study Type	Year Published	Period of study	Sample Size	Total Number of hospitals	Paediatric hospital/activity representation	Registered Board	Guideline/ Guidance	Percentage Labelled Use (by number of Patients)Recommended Use and non-recommended use where otherwise stated	Percentage Off-labelled Use (with Scientific Evidence and without sc evidence)	Adverse Drug Reactions
Frayha *et al.* [49]	Riyadh, Saudi Arabia	Retrospective Audit: Follow up Drug Use evaulation;pre and post guideline	1993	10 months-1994	131 (total Drug Use Evaluations DUE's)	1	0	FDA	PTC- Hospital guideline categorisation	Pre Guideline: 36% ; post guideline: 82%	Pre guideline: 61% Final DUE post guideline:18%	Unknown
Lee *et al.* [73]	Auckland, New Zealand	Retrospective	1998	1996	135	4	Unknown	Unknown	Autralasian Society of Blood Transfusion	Unknown	Unknown	13 cases: 10%
Chen *et al* .[6]	USA	Prospective	2000	Unknown	251	12	Unknown	FDA	Consensus guidelines for categorisation	43%	52%: 38% and 14%	11%
Vinent *et al* .[86]	Barcelona, Spain	Prospective-Retrospective	2001	1998-2000	62	1	0	EMA/ UHC	University HealthSystem Consortium Guideline for Off label Use Recommendations/categorisation	70%	19% and 11%	17 times= 27%
Pendergrast *et al* .[75]	Toronto, Canada	Retrospective	2005	1995-2000	429	4	0	FDA	FDA,American and Canadian Consensus conference	>80% (by publsihed recommendations)	<20%	Unknown
Perayre Badia *et al* .[74]	Barcelona, Spain	Prospective	2006	5 years- 2000-2004	405	1	0	Spanish Medicines agency/ EMA	University hospital Consortium Expert Panel for Off Label Use	5.00%	24.2% and 8.4%	Unknown
Darabi *et al* .[52]	Massachusetts, USA	Retrospective Audit	2006	2004	194	1	0	FDA	Pre-approved by a Blood Transfusion Service Physician prior to issue	*43.4%	*56.6%: authors claim it adheres mostly to University hospital consortium guideline due to pre-approval process.	Unknown
Lin *et al.* [76]	Sydney, Australia	Prospective	2006	2003-2004 (6 months)	165	2	0	Australian Health ministers Advisory Council Indications for IVIG	AHMAC (Australian Health ministers Advisory Council 2000 guideline)	74.50%	25.50%	Unknown
Alangari *et al.* [78]	Saudi Arabia	Retrospective	2008	3 years: 2003-2005	305	1	0	FDA	Unknown	35.70%	9.5%: First line off label indication, 31.8% for alternative off-label recommendation and 24.4%: ina ppropriate use	Unknown
Sarti *et al.* [79]	Florence, Italy(neurological and neuromuscular disorders only)	Retrospective	2009	2003-2006	235	1	0	EMA/FDA	No mention of categorisation in study	60.40%	25.6% and 14%	Unknown
Frauger *et al.* [2]	Marseille, France	Prospective	2010	6 months-2005/2006	435	3	1	EMA	CEDIT guideline(Committee for the Evaulation of Innovative Technologies)	70%	9% & and 18%	Unknown
Foster *et al.* [82]	Canada	Retrospective	2010	5 years: 1999-2004	145	5 ICUS	0	FDA/Candian Registration	Categorised by National Advisory Committee on Blood and Blood Products and Canadian Blood Services	18.6% (appropriate)	74.5% potentially indicated and 6.9%, not indicated/inapropriate	199 adverse events but causality not established: confounding
Farber *et al.* [84]	Belgium	Retrospective	2011	1 year: 2009	136	1	0	EMA	Unknown			
Manna *et al* [83]	Sasakatoon Health Region, Canada	Retrospective	2013	2011-2012	2011:227, 2012:216	1	Unknown	Canadian FDA	Canadian Regultions/guideline	2011:64%, 2012:79%	2011:36%, 2012: 21%	0
Moralejo *et al* [85]	Spain	Retrospective	2014	2012	77	1	Unknown	British clinical guideline	British clinical guideline for hospital use: 2nd Ed. 2011: colour classification	Strong evidence: 44%; Reasonable evidence 34%	Weak evidence 22%	Unknown

Table 2.8: Summary of articles published on IVIG use regionally or countrywide

Article	City, Country	Study Type	Year Published	Period of study	Sample Size	Total Number of hospitals	Paediatric hospital/ activity	Registered Board	Guideline/ Guidance	Percentage Labelled Use (by number of Patients) Recommended Use and non-recommended use where otherwise stated	Percentage Off-labelled Use (with Scientific Evidence and without sc evidence)	Adverse Drug Reactions
Hutchinson *et al.* [81]	New Zealand (only prospective use considered)	Retrospective/ Prospective	2006	1 year 6 months: 2004- 2005	Prospective Audit:457	Regional use in 8 participating District Health boards	Unknown	Australian Health ministers Advisory Council Indications for IVIG	Australian health ministers Advisory council guideline and Auckland district Health board guidelines	Varied across regions	Varied across regions	Unknown
Constantine *et al*. [5]	Atlantic Provinces, Canada	Retrospective	2007	2 years	unknown	Provincial database registry	Unknown	FDA	Regional guideline, national guidelines/ expert opinion/optimization tools	37.1%	62.9% off label. Post guideline strategy: 4.2 % decrease in off label	Unknown
Simeons, S. [80]	Belgium	Retrospective	2011	2007	9629	47 hospitals: All hospitals in Belgium from IMS Health hospital database	Unknown	EMA	Unknown	Estimate 50-60%	Estimate 40-50%	Unknown
Feasby *et al.* [77]	British Columbia, Canada	Retrospective	2012	2001-2003	2256	Electronic database of all facilities using IVIG in British Columbia	Unknown	Clinical expert panel recommendations	Clinical expert panel recommendations and adherence to IVIG Management Program	54.1%	17.4% uncertain benefit and 28.% inappropriate	Unknown

CHAPTER III:

ARTICLE FOR SUBMISSION TO JOURNAL

The following article will be submitted to the South African Journal of Child Health. Appendix K describes the requirements for an article submission to this journal.[62] Below is a brief summary of the *Submission Preparation Checklist* as required by the journal. This dictated some of the overall format and style choices in the document as a whole and are therefore specifically emphasised here.

As part of the submission process, authors are required to check their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named author's consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).Journal articles listed in the references are not in italics.
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable).
10. Any conflict of interest (or competing interests) is indicated by the author(s).

Use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

[1]Raiman S., [1]Knight SE, [2]Welzel TB

[1] University of KwaZulu-Natal

[2] University of Cape Town

Ms. Shenaaz Raiman

B.Pharm.
School of Nursing and Public Health, College of Health Sciences
University of KwaZulu-Natal
Email: fieryminx@gmail.com

Dr. Stephen E. Knight

MBChB (Wits), FCPHM(SA)
School of Nursing and Public Health, College of Health Sciences
University of KwaZulu-Natal
knights@ukzn.ac.za

Dr. Tyson B. Welzel

MBChB (UCT), DipPEC(SA), HDip Int Med(SA) EMDM (Novara), MMedSc(ClinEpi)
Division of Emergency Medicine
University of Cape Town
tyson.welzel@uct.ac.za

Summary:

Background

Polyvalent intravenous immunoglobulin (IVIG) is registered for a limited number of specific indications in South Africa but is increasingly being used for un-registered or off label uses. No guideline exists nationally to monitor and control IVIG prescription. This results in its use in many clinical situations with varying levels of evidence.

Objectives and Methods

This study aimed to ascertain the registered and unregistered use and cost of IVIG at a tertiary paediatric hospital in South Africa.

A cross sectional descriptive study design was employed with a patient folder review, supplemented by data from the electronic pharmacy dispensing database, as well as the National Health Laboratory Service database, was conducted on all patients (0 to 18 years) who were issued IVIG as out- or inpatients during a 39 month period from 2009 to 2012.

Results

During the study period, 185 patients received at least one dose of IVIG and a total 916 issues (3641.5g) were dispensed. In 76 (44%) patients (involving 414 issues, 48%), the Medicines Control Council registered indications for its use were followed. Only 87 (53%) of the patients were tested for HIV and in these the HIV sero-prevalence was 19%. IVIG accounted for between 1.6%, 1.7% and 4.6% of the pharmacy expenditure per year in the study period.

Conclusion

More than half of all IVIG issued at this paediatric hospital was used off-label. Considering the pressures on supply and the pharmaceutical costs, a more standardized, protocol-driven approach to the prescription of IVIG is called for.

Introduction

Polyvalent Human Intravenous Immunoglobulin (IVIG) has been used to treat several groups of conditions including primary immunodeficiencies, secondary immunodeficiencies, autoimmune diseases, some neurological disorders and an ever widening array of other disease conditions for which there are varying levels of epidemiological evidence for its treatment efficacy.[1] Many studies on IVIG focus on its potential benefit in a range of different conditions, the ever increasing associated costs and the limited supply due the stringent criteria by which the product is manufactured. Several countries including the United States of America, United Kingdom, Canada and Australia have published evidence-informed guidelines for the administration and control of intravenous immunoglobulin therapy. [2,3,4]

In South Africa, IVIG is registered for a narrow spectrum of clinical indications by the Medicines Control Council (MCC) (Table 3.1). However, there is little or no clinical guidance on the multiple potential additional applications of IVIG use, leading to its subjective and indiscriminate usage locally.

Table 1: Comparison of registered/labelled indications for IVIG in the USA, Europe and South Africa

MCC (South Africa)*	FDA (USA)†	EMA (Europe)‡
Replacement therapy in: primary antibody deficiency syndromes	Primary immunodeficiencies	Replacement therapy in primary immunodeficiency syndromes with impaired antibody production.
Myeloma or chronic lymphocytic leukaemia with severe hypogammaglobulinaemia and recurrent infections	Chronic lymphocytic leukaemia	Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed.
		Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma (MM) patients who have failed to respond to pneumococcal immunisation.
		Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
For immunomodulation in: • Idiopathic Thrombocytopenic Purpura (ITP) in children and adults. • Kawasaki disease. • Guillain-Barré Syndrome.	• Idiopathic thrombocytopenic purpurae • Kawasaki disease	Immunomodulatory effect in: • Primary immune thrombocytopenia (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count • Guillain Barré Syndrome (GBS) • Kawasaki disease
Allogeneic bone marrow transplantation.	Allogeneic bone marrow transplant	
Children with congenital AIDS and recurrent infections	Paediatric HIV	Children and adolescents with congenital AIDS and recurrent bacterial infections.
	Chronic inflammatory demyelinating polyneuropathy (CIDP).	
	Kidney transplant with a high antibody recipient or with an ABO incompatible donor	

In South Africa, IVIG is procured primarily through the National Bioproducts Institute (NBI), the commercial unit of the South African Blood Transfusion Services. It is obtained from pooling the plasma of multiple non-remunerated blood donors, [5] where these IgG molecules

*Source: * Polygam® . South African Electronic Package Inserts. Polygam. Last accessed on 10 August 2014, available online from: http://home.intekom.com/pharm/nbi/polygam.html*

†*U.S Food and Drug Administration (FDA)-Last accessed 18 October2014, available online from: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm*

‡ *European Medicines agency(EMA)Last Accessed 18 October 2014, available online from:http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8*

reflect the collective acquired immunity of the donor pool from which it is derived. Hence, like blood and other blood derived products, it is regarded as a scarce commodity, as its supply is restricted by the availability of safe and excess donor serum. In addition, IVIG is expensive: gram for gram it is currently more expensive than gold.[§] Commercially there are over 25 licensed IVIG products available worldwide but the therapeutic efficacy of each unit varies depending on the concentrations of constituent immunoglobulins, the excipients added, the manufacturing process and the osmolality, pH and dextrose content of the final product. Consequently different preparations of IVIG are not strictly generics of each other.

This study describes the use (registered or non-registered) and cost of IVIG in the paediatric practice of a public sector hospital in South Africa.

RCWMCH in Cape Town is the paediatric academic referral hospital in the Western Cape. About 250 000 in- and outpatients are seen per year, with patients being referred from other parts of the country, as well as specialist referrals from the rest of Africa.[6]

Methods

This health systems research used an observational, cross-sectional descriptive study design. The study sample was made up of all paediatric patients (0 to 18 years) who were issued polyclonal IVIG both as in- and outpatients during a 39 month period from 2009 to 2012. Any child receiving intramuscular immunoglobulin was excluded in the study.

Data was collected from the pharmacy's electronic dispensing database, supplemented by a folder review of all patients who had IVIG dispensed. Four attempts were made to obtain patient folders if they were not found initially. All extracted data was recorded on a customised data-collection sheet by a trained fieldworker. An 'issue' was defined as a dose of IVIG dispensed in any of its varied strengths and recorded against a patient name in the dispensing database of the pharmacy. Patient level data was anonymised. The study received bioethics approval (BE0071/12) from the University of KwaZulu-Natal, as well as hospital permission.

---

§ Incidentally, it is interesting to note that the gold price per gram ranged from around ZAR 250. (2009) to ZAR 420. in this time period of the study. Currently the gold price per gram is ZAR 416. Referenced from: Gold rate 24. Last accessed 2 November 2014. Available online from: http://www.goldrate24.com/gold-prices/africa/south_africa/

Diagnoses leading to the prescription of IVIG were obtained from the patient folders and the primary indications were verified by the responsible clinical department. Patients were categorised as being given IVIG for registered use if diagnosed with one of the seven MCC registered indications. All other indications were categorised as unregistered (off-label) use.

Additional data such as results of liver function tests, blood counts, Immunoglobulin G (IGG) trough testing and HIV status were obtained from the National Health Laboratory Services (NHLS) data-base at the hospital. Where relevant, data was described with a 95% confidence interval utilising a p=0.5 error margin.

Financial data was obtained from 2 separate sources: 1) patient level data was collected from the dispensing system in the pharmacy; 2) Financial data was extracted from the hospital information system. Hence the financial trends for IVIG use could be reported from 2009 to 2014. The patient review which was from 2009 to 2012. Annual expenditure on IVIG was adjusted to 2014 values using the South-African consumer price index and hence represents real values in order to make the data stationary.

Results

A total of 185 patients received IVIG in the study period, of which 100 (54%) were males. There were 45 (24%) issues to infants, 73 (39%) to children one to five years of age and 67 (36%) to those between five and 18 years of age. The median and mean ages of paediatric patients who received IVIG were 3.4 and 5.0 years respectively. A total of 916 issues of IVIG were made to 185 patients during the study period. Patient data on duration of therapy for 185 patients included 135 (73%) patients who were given a once off dose, 36 (20%) received IVIG therapy on two successive days and 13 (7%) of patients received three to nine successive doses of IVIG. One patient was issued 14 successive days of IVIG therapy. Two patients following liver transplant received 50 and 54 doses of IVIG respectively. Most (154, 90%) of the patients received IVIG for the first time in the study period.

Only 28 (15%) of 185 patients, were tested for IGG trough levels of which seven had primary immunodeficiency and five had cancer. Only eight of 171 (4%) patients had a record of having had adverse events due to administration of IVIG. Liver function tests used to assess the effect of IVIG on liver enzymes were reported in 57 (31%) of the patients.

Only 87 (47%) patients had their HIV status recorded of which 17 were HIV infected giving an HIV sero-prevalence of 19.5% (95% Confidence Interval (CI): 11.2% to 27.9%). The rest were either not HIV tested or no results were found.

Table 2: Paediatric patient demographics who were given IVIG at RCWMH in the study period

	Age < 1 year	Age 1 to < 5 years	Age ≥ 5 years	Totals
Number of patients (%)	45 (24%)	73 (40%)	67 (36%)	185
Number of issues	132	468	316	916
Males n (%)	25 (56%)	37 (51%)	38 (57%)	100 (54%)
Mean weight (kg)	6.3kg (n=41)	12.8kg (n=67)	28.9kg (n=61)	17.0kg (n=169)
Mean dose prescribed (g)	8.7	20.2	29.1	21.6
Mean concentration (g/kg)	0.86	0.81	0.77	0.81
HIV tested† (%)	27 (31%)	36 (41%)	24 (28%)	87 (47%)
HIV +ve n (%)	8 (30%)	3 (8%)	6 (30%)	17 (19%)
Registered Use * n (%)	16/41 (39%)	43/68 (63%)	17/62 (27%)	76/171 (44%)

*Diagnosis available on 171 /185 patients †PCR and/or Rapid testing

Table 3: Clinical categories of patients in study by age group and issues of IVIG

Clinical Categories	Age < 1	Age 1 -<5	Age ≥ 5	Patients n (%)**	Issues n (%)
Primary Immunodeficiency ‡	3	4	2	9 (5%)	215 (25%)
Guillain-Barré syndrome ‡	1	22	8	31 (18%)	98 (11%)
Kawasaki's Disease ‡	6	11	2	19 (11%)	46 (5%)
Chronic Lymphocytic Leukaemia ‡	0	2	1	3 (2%)	19 (2%)
Paediatric HIV ‡	4	1	1	6 (4%)	16 (2%)
Idiopathic Thrombocytopenic Purpura ‡	2	3	2	7 (4%)	12 (1%)
Allogeneic bone marrow transplant ‡	0	0	1	1 (1%)	8 (1%)
Sub-total of MCC Indications	16	43	17	76 (44%)	414 (47%)
Other transplantation	1	9	8	18 (11%)	189 (22%)
Other oncology	0	4	2	6 (4%)	73 (8%)
other autoimmune disorder	1	2	6	9 (5%)	63 (7%)
Other infections	11	4	7	22 (13%)	50 (6%)
Kidney transplant	0	2	6	8 (5%)	28 (3%)
other neurological conditions	1	1	8	10 (6%)	21 (2%)
Uncertain	6	2	6	14 (8%)	21 (2%)
Thrombocytopaenia	5	0	0	5 (3%)	8 (1%)
other haematology	0	1	2	3 (2%)	5 (1%)
Sub-total off-label use	25	25	45	95 (56%)	458 (53%)
Total	**41(24%)**	**68 (40%)**	**62 (36%)**	**171(100%)**	**872(100%)**

‡ MCC registered indications

The clinical indications for having received IVIG were identified from the folders in 171 (92%) of the 185 paediatric patients in the study sample, which accounted for 872 IVIG issues (Table 3).Only 76 (44%) of the patients issued IVIG had diagnoses that were for registered indications as per MCC (Table 2). This accounted for 414 (47%) of the 872 total IVIG issues during the study period. This varied according to age group: registered use was highest (57%) in patients in the one to five year category and lowest (21%) in patients less than one year of age. A further 14 patients with 21 issues had indications for which IVIG could not be verified by the relevant clinicians and had to be labelled 'uncertain'. The total grams administered in the study period were 3641.5g and the mean dose prescribed for a registered indication was 22.6g compared to 19.7g for unregistered indications.

Table 4: Categorisation of unregistered diagnoses in this study (n= 94) by patient numbers

	Category	Named conditions
1	Other Infections	sepsis (17), encephalitis(5)
2	Other Autoimmune disorders	systemic lupus erythematosis (3), dermatomyositis (4), systemic juvenile idiopathic arthritis (1), Evan's syndrome (1)
3	Other Haematology	haemophagocytic lymphohistiocytosis (2), chronic anaemia secondary to parvovirus (1)
4	Other Neurological conditions	peripheral neuropathy (1), transverse myelitis (1), acute demyelinating encephalomyelitis (1), radiculomyelitis (1), acute inflammatory demyelinating polyneuropathy (1), Sydenham's chorea (1), neurodegeneration (2), opsoclonus-myoclonus-ataxia syndrome (1), myoclonus(1)
5	Other Oncology	acute lymphocytic leukaemia (4), juvenile myelomonocytic leukaemia (2)
6	Other Transplants	liver transplants (16), stem cell (1), solid organ (1)
7	Thrombocytopaenia	acute thrombocytopaenia (4)
8	Kidney Transplant	acute renal rejection (5), antibody mediated rejection (2), Takayasu arteritis failed transplant (1), prevention of rejection (1)
9.	Uncertain	generalised muscle weakness (1) large ventricular septal defect (1) type 1 truncus arteriosus (1) bronchopneumonia (1) tracheostomy for glial heterotopia (1) asymptomatic anaemia (1) lobular panniculitis(1) profound anaemia: recurrent episodes(1) BCG disease(1) acyanotic heart disease(1) Hirschsprung's disease(1) lymphadenopathy(1) cramps in legs(1) pulmonary haemosiderosis(1)

Costing

The total cost of all IVIG in the study period was ZAR 2.9 million, of which ZAR 1.7 million was spent for unregistered indications. The cost per patient amounted to ZAR15 937. The highest IVIG issue-values were for Guillain-Barré Syndrome (GBS) (ZAR 301 586), primary immunodeficiencies (ZAR 340 953) and 'other transplants' (ZAR 546 708). The mean issue value per patient in this subset (unregistered) was ZAR 3 732 as opposed to the registered use of ZAR 2 653 in 2014 values.

IVIG comprised 1.6% of the total annual pharmacy expenditure in 2009/2010, 1.7% in 2010/2011 and 4.6% in 2011/2012 financial years respectively and accounted for ZAR 24 294, ZAR 24 847 and ZAR 60 251 per 1000 admissions in those respective financial years. Figure 1 demonstrates the mean monthly and annual IVIG expenditure by financial year. The general trend shows an increase in real expenditure on IVIG, both in real terms and as a share of RCWMCH pharmacy budget, except for the 2013/14 financial year.

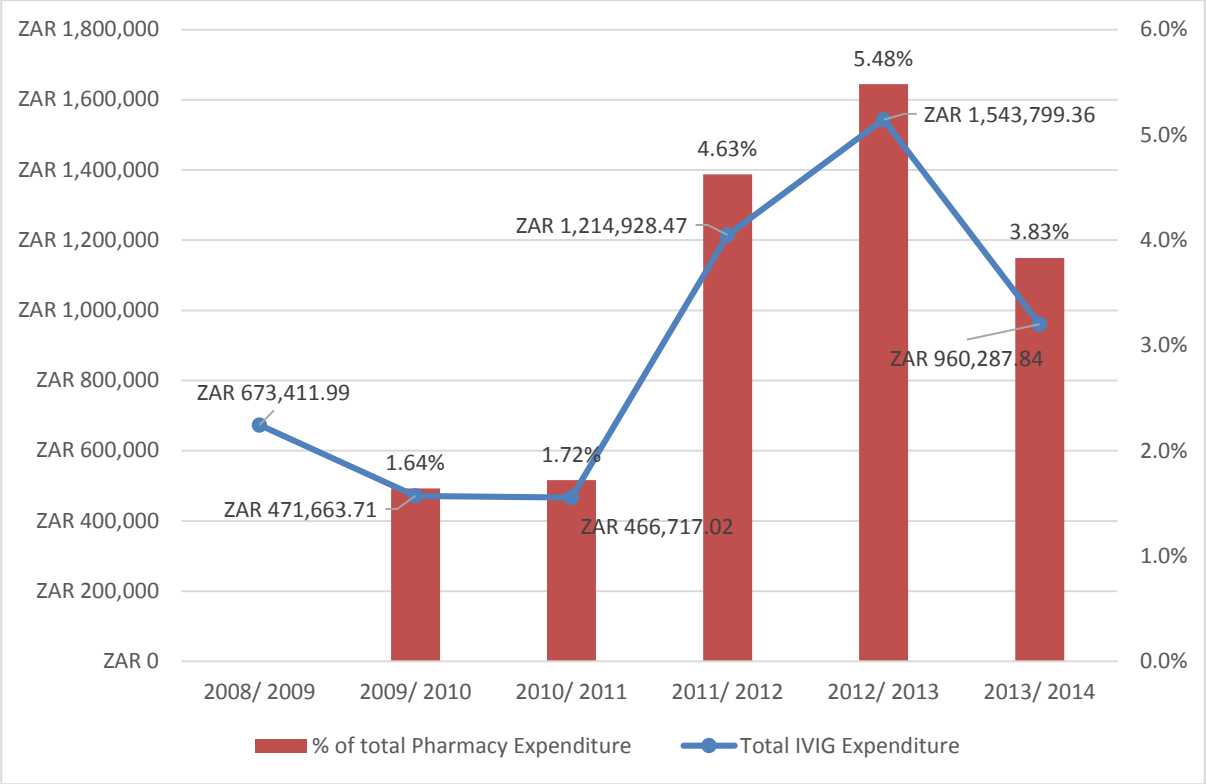


Figure 1: Expenditure on IVIG against Percentage of Pharmacy expenditure adjusted for inflation in financial years

Discussion

Intravenous immunoglobulin use has been reported in 28 studies in a wide range of settings both in adults and children in an attempt to rationalise usage or formulate guidelines for controlling it. To date, no study on IVIG usage and its indications has been reported in South Africa. When considering registered and unregistered uses, there was a disparity between the number of patients (185) prescribed IVIG and the number of issues per patient. In addition, some patients were prescribed a disproportionate number of issues.

There are currently differences in registered indications between the United States Food and Drug Administration (FDA), European Medicines Agency (EMA) and MCC (Table 1). The major difference is that in the US, IVIG is not registered for use in GBS as plasmapheresis is considered the therapeutic modality of choice and has a better cost-benefit ration than IVIG use.[7]

In 2013, a study of 45 patients in Cairo, Egypt [8], described the pattern and usage of IVIG in a paediatric intensive care facility. In this resource-limited setting, (24, 62%) of IVIG use was for non-registered indications but where there was 'a high level of evidence'. Neonatal sepsis was categorised as having a high level of evidence and was the main indication for IVIG use. Recent studies suggest that neonatal use in sepsis may only be beneficial prophylactically where resources permit usage. [9] The use of IVIG for sepsis in our study (17, 10%) was considered as 'unregistered' by the MCC, however only four (2%) of our patients, could be classified as neonates.

Other paediatric studies on IVIG use in the US (Texas),[10] Iran (Tehran),[11] Spain,[12] UAE[13] and Asia (Singapore)[14], represent a large range of clinical care and socio-economic background, showed a variety of unregistered/off label use, in 25% to 66% of instances. Some reports quantify registered uses of IVIG, whereas other studies describe the evidence-base for IVIG use. Comparing the evidence is further hindered by the different policies followed by registration bodies, the definition of appropriate use, various guidelines utilised as well as different classifications of evidence used. Most of the reported studies used the FDA classification to determine on/off label usage, thus excluding GBS. The exception was a Spanish study which used the EMA guidelines in it classification of off-label use. Interestingly, the Asia study showed greater compliance to FDA approved indications, compared to the other studies. Most use in this study was for patients diagnosed with

Kawasaki's Disease (794, 60%) receiving IVIG, which reflects the higher burden of this disease in Asia. [14]

Our results show more off-label / unregistered IVIG use both by patient numbers and by IVIG issues compared to other paediatric studies reported. Only the UAE study (N=74) reported 61% off label use by FDA criteria, but was limited by a small sample size.

Obtaining a primary diagnosis was a challenge in patients with multiple co-morbidities, as the data was retrospectively extracted from the patient medical records. Legibility of the notes was low and detailed diagnosis and treatments were often absent. The dose of IVIG prescribed was mostly evidence-based for specific indications but the length of therapy given varied greatly. ICD10 codes were not recorded by clinicians. The consultants responsible for the original care of the patients were asked to verify probable reasons for using

Most IVIG for unregistered use was prescribed for 'other transplants' (189 issues to 18 patients), predominantly for liver transplants and mostly daily IVIG was prescribed for a minimum of one week (Table 3,4). IGG trough testing was one of the variables considered in the study as a marker for determining the effectiveness of therapy and the need for further IVIG. Only two patients with liver transplant were screened for IGG trough testing and none during the course of IVIG therapy. The use of IVIG post liver transplantation though becoming more common, is not yet standard level of care.[15] A more uniform basis for IVIG use will need to be explored thoroughly in further trials.

Nine patients with 215 issues were classified as having a primary immunodeficiency and all were assessed with IGG trough testing and IGG levels taken for outcome post IVIG treatment. Monthly doses of IVIG were issued in line with dosing practises. A further six patients had paediatric HIV with associated infections. It is important to note that data in this study showed that only 47% (87 / 185) had evidence of HIV PCR or Rapid testing, judging both by the NHLS database and clinical notes. This is perturbing considering that children with congenital HIV and recurrent infections are a registered indication for IVIG therapy. In addition, South Africa is in the midst of a national drive to increase detection and treatment of HIV. This would suggest that insufficient testing for HIV (Rapid and/or PCR) was either offered or recorded in this paediatric facility.

A further 14 (8%) patients had uncertain indications for being prescribed IVIG or may be considered as in the case of the Cairo study used because no other therapeutic option was

available, lack of a suitable alternative or needing an urgent response (Table 4). The disease ranges in these patients were varied, no trends other than stat doses could be found and 6 of these patients were issued IVIG whilst in the intensive care unit. IVIG could have been administered as 'last chance medicine' in acutely ill patients in a last ditch effort to improve outcome. Apart from the registered clinical categories, the unregistered ones listed as diagnoses needed to be evaluated for evidence and a clinical recommendation made for use in various conditions approved by the Provincial Pharmaceutics and Therapeutics committee. There are varying levels of evidence available for potential use of IVIG. Within a resource constrained setting the thorough evaluation of the evidence-base and a clinical guide to use should be the natural next step.

As compared to most other studies in paediatric IVIG use, which were limited by short review times, small sample sizes and /or restricted to specialised care, this study covered 39 months of continued usage within a whole hospital. It is important to note that this study was limited to describing clinical use by MCC registration status. The analysis of the evidence-base for each unregistered indication was beyond the scope of the study. Expenditure on IVIG by year appears to be increasing with a slight decline in the 2013-2014 financial years possibly due to very few transplants taking place that year. Now that it is evident that the majority of use is unregistered and seeing that IVIG is a costly therapeutic option, it becomes imperative to establish the evidence-base for use when designing a guideline/ protocol for the paediatric use of IVIG.

Limitations to study

There were two significant sets of information bias arising from (a) the use of the pharmacy dispensing database system (b) the interpretation of the diagnoses by the investigator. In the former, all pharmacists will at some time or other have issued IVIG via the pharmacy dispensing system, so that the electronic record reflects the average accuracies/ inaccuracies of all the staff over the past three years. In the latter, the investigator will have had to interpret a number of usually clinician-specific diagnoses and allocate them to a diagnostic category. Most clinical notes do not list all diagnoses, let alone the primary diagnosis, so that it may not have been clear which indication IVIG was prescribed for in the first instance. Due to this, it was not possible to apply International Classification of Diseases (ICD) 10 diagnostic labels in all cases. The ability to retrieve all the folders and verify the electronic database was also not possible in all cases.

Conclusion and Recommendations

The majority of IVIG used in this paediatric referral hospital in South Africa was for unregistered indications in the study period. Ascertaining the diagnosis and indications for IVIG use retrospectively from patient records was a challenge because of the poor quality of recorded patient data. A multihospital study where the indications and issues for IVIG are prospectively recorded will reduce information bias and make the findings more generalizable. In addition, the list of indications for use presented here would need to be categorised and validated for evidence and a clinical guideline developed to manage the use within this resource limited setting. It would be recommended that a guideline restricting use in unproven indications should be developed in light of product shortages nationally, increasing expenditure on the medicines budget, as well as rationalising medicine use internally.

The authors have no conflicts of interest to declare.

References

[1] Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol 2005;142:1-11. [http://dx.doi.org/10.1111/j.1365-2249.2005.02834.x] [PMID:16178850, PMCID:PMC1809480]

[2] National Blood Authority Australia. IVIG Criteria for Use. 2nd ed. Lyneham: National Blood Authority, 2012. http://www.nba.gov.au/PDF/IVIg.pdf (accessed 10 November 2014).

[3] Constantine MM, Thomas W, Whitman L, *et al.* Intravenous immunoglobulin utilization in the Canadian Atlantic provinces: a report of the Atlantic Collaborative Intravenous Immune Globulin Utilization Working Group. Transfusion 2007;47:2072-2080. [http://dx.doi.org/10.1111/j.1537-2995.2007.01400.x] [PMID:17958537]

[4] Chen C, Danekas LH, Ratko TA, *et al.* A multicenter drug use surveillance of intravenous immunoglobulin utilization in US academic health centers. Ann Pharmacother 2000;34:295-299. [http://dx.doi.org/10.1345/aph.19252] [PMID:10917372]

[5] Sisti AM, Vitali MS, Manfredi MJ, Zarzur JA. Preparation of lyophilized and liquid intravenous immunoglobulin G: development and scale-up. Vox Sang. 2001;80:216-224. [http://dx.doi.org/10.1046/j.1423-0410.2001.00041.x] [PMID:11438029]

[6] Red Cross War Memorial Children's Hospital Overview: Western Cape Government. Secondary,tertiary and Emergency Care. Department of Health. Available online from: http://www.westerncape.gov.za/your_gov/149 (accessed 5 November 2014)

[7] 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. [http://dx.doi.org/10.1186/1472-6963-11-101] [PMID:21575219, PMCID:PMC312158]

[8] Galal, NM. Pattern of intravenous immunoglobulins (IVIG) use in a pediatric intensive care facility in a resource limited setting. African Health Sciences 2013;13(2):261 – 265. Available online at [http://dx.doi.org/10.4314/ahs.v13i2.9][PMID:24235922, PMCID:PMC3824471]

9 Oba Y, Iwata K. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. 2011;365(13):1201-11

[10] Gurwitch KD, Goldwire MA, Baker CJ. Intravenous immune globulin shortage: experience at a large children's hospital. Pediatrics. 1998;102(3 Pt 1):645-7. [PMID:9738190]

[11] Dashti-Khavidaki S, Khalili H, Farshadi F, Aghamohammadi A, Movahedi M, Hajibabaei M. Inpatient paediatric use of intravenous immunoglobulin at an academic medical centre. Singapore Med J. 2008;49(2):147-9. [PMID:18301844]

[12] Ruiz-Antoran B, Agusti Escasany A, Vallano Ferraz A, *et al*. Use of non-specific intravenous human immunoglobulins in Spanish hospitals; need for a hospital protocol. Eur J Clin Pharmacol. 2010;66(6):633-41. [http://dx.doi.org/10.1007/s00228-010-0800-y] [PMID:20204337]

[13] Dawoud T, Tatari H, Gebran N. A utilisation review of intravenous immunoglobulin in a tertiary care hospital in United Arab Emirates. European Journal of Hospital Pharmacy 2012;19:286–288. [http//dx.doi.org/10.1136/ejhpharm-2012-000070]

[14] Wu J, Lee AJ, Goh AE, *et al.* Use of intravenous immunoglobulin in an Asian paediatric population over a 10-year period. J Paediatr Child Health. 2013;49(8):629-34. [http//dx.doi.org/10.1111/jpc.12262.Epub 2013 Jun 11]

[15] Bucuvalas JC, Anand R. Studies of Pediatric Liver Transplantation Research G Treatment with immunoglobulin improves outcome for pediatric liver transplant recipients. Liver Transpl 2009;15:1564–1569. [PMID:24788560, PMCID:PMC4005731]

This page has intentionally been left blank

CHAPTER IV:
ADDITIONAL RESULTS, DISCUSSION, LIMITATIONS, CONCLUSION AND RECOMMENDATIONS

4.1 ADDITIONAL RESULTS

The article presented in Chapter III was limited to a 3 000 word count. Even though the article answered the aims and objectives outlined in the protocol, Chapter IV presents some of the most pertinent additional information obtained in this medical folder review.

4.1.1 Annual issues of IVIG and grams dispensed

A total of 185 patients received 3641.5g of IVIG in the study period. Of these issues, 172 (92%) were to in-patients admitted to the facility. As this was a paediatric hospital, dosing is based on g/kg and small amounts can be attributed to the small patient weights as opposed to those used in adults. The usual dose for IVIG as per Polygam® package insert dosing guideline[8] is indicated below and serves merely as a guide to clinicians prescribing IVIG:

Replacement therapy in immunodeficiency:

- Primary immunodeficiency: Starting dose: 0,4-0,8 g/kg, thereafter: 0,2-0,8 g/kg every two to four weeks to obtain IgG trough levels of at least 4-6 g/L
- Secondary immunodeficiency: 0,2-0,4 g/kg every three to four weeks to obtain IgG through levels of at least 4-6 g/L
- Children with AIDS: 0,2-0,4 g/kg every three to four weeks.

Immunomodulation:

- Idiopathic Thrombocytopenic Purpura: 0,8–1 g/kg on day one, may be repeated once within three days or 0,4 g/kg/day for two to five days. May be repeated if relapse occurs
- Kawasaki disease: 2 g/kg as a single dose in conjunction with aspirin or 1,6–2 g/kg in divided doses for two to five days in conjunction with aspirin
- Guillain-Barré syndrome: 0,4 g/kg/day for three to seven days.

Allogeneic bone marrow transplantation:

- Treatment of infections and prophylaxis of graft versus host disease:
  Starting dose: 0,5 g/kg every week starting seven days before transplantation and up to three months after transplantation.

Table 4.1: Annual issues of IVIG and grams dispensed during the study period

IVIG Pack sizes	2009 issues	2009 grams	2010 issues	2010 grams	2011 issues	2011 grams	2012[§] issues	2012 grams	Total issued
1g	83	83g	66	66g	52	52g	24	24g	
3g	116	348g	79	237g	88	264g	37	111g	
6g	104	624g	76	456g	56	336g	38	228g	
2.5g	0	0g	1	2.5g	36	90g	0	0g	
12g	0	0g	3	36g	36	432g	21	252g	
Total	303	1055g	225	797.5g	268	1174g	120	615g	3641.5g

[**] Data for the first three months issues in 2012

[††] Data for the first three months grams usage in 2012

From Chapter III it is interesting to note that 468 doses (over half of the total issues in the study period) were issued to the age group category 1 to <5 years of age. This age group had a mean weight of 12.8kg. The sharp increase in IVIG usage from 2010 to 2011, as demonstrated in Figure 2.1 of the article, is mirrored by weights dispensed (see Table 4.1): Usage rises sharply from 797.5g in 2010 to 1174g in 2011. The trend appears to continue into the next financial year 2012/2013. Intraglobin F had to be used when National Bioproducts Institute experienced major shortages and was unable to meet the hospital's demands. This necessitated motivating for and purchasing a product 'unregistered in

South Africa' via a Section 21 process involving the MCC. As Intraglobin F is only available as a 2.5g vial, that can account for variation of the eventual dispensed versus used doses. In most instances prescribers use grams closest to the nearest pack size due to the range in dosing available for most indications.

4.1.2 Costing

Table 4.2: Total and mean monthly IVIG expenditure adjusted for inflation to 2014 values

	Nominal IVIG expenditure (ZAR)	Average inflation	Real IVIG expenditure (2014 ZAR)	Total pharmacy expenditure	% of total pharmacy expenditure
2009/ 2010	471 663.71	7.26%	576 709.00	28 727 119.59	1.64%
2010/ 2011	466 717.02	4.10%	548 185.04	27 124 414.98	1.72%
2011/ 2012	1 214 928.47	5.01%	1 358 919.06	26 264 778.71	4.63%
2012/ 2013	1 543 799.36	5.75%	1 632 876.58	28 166 689.00	5.48%
2013/ 2014	960 287.84	5.77%	960 287.84	25 062 314.00	3.83%

Table 4.2 demonstrates the mean monthly and annual IVIG expenditure by financial year. This expenditure is shown in both nominal and real 2014 terms. The real values are the nominal values inflated by the applicable South African consumer price index, allowing for direct comparison. The figures reflect an increase in real expenditure on IVIG, both in absolute terms, as well as the increasing share of the RCWMCH pharmacy budget. Only the 2013/14 financial year shows a drop to pre-2012 values. Factors influencing this last decrease could have been the reduced number of transplants performed in that financial year, as transplants accounted for an ever-increasing share of the increase.

Cost per patient in this research study sample for the study period amounted to ZAR15 937 for IVIG and excludes administration, admission and other associated medication and hospital costs. In contradiction, the mean hospital cost per patient for RCWMCH in 2009/2010 was: ZAR2 617; 2010/2011: ZAR3 090 and 2011/2012: ZAR3 763 respectively and thus considerably lower than the cost per patient in this research study sample.

Table 4.3: RCWMCH statistics on patient numbers by financial years

Financial year	Number of in-patients	Number of admissions	Patient day expenditure (pde) ZAR	Average length of stay (days)
2009/ 2010	88 949	23 210	153.25	4.8
2010/ 2011	87 871	22 380	148.81	4.9
2011/ 2012	83 295	22 551	139.76	4.6
2012/ 2013	79 061	20 509	133.56	4.8
2013/ 2014	79 964	22 131	135.60	4.5

Overall there were fewer in-patients and admissions at RCWMCH from 2009 to 2014 (Table 4.3). Patient day expenditure and average length of stay are on the wane too. With the opening of Khayelitsha District Hospital (April 2012) and Mitchell's Plain Hospital (Oct/Nov 2013), primary and secondary level paediatric patients started accessing the services in their districts, thereby resulting in lower admission rates and decreased number of inpatients at RCWMCH, as exhibited. In the past these patients would have gone to RCWMCH. In spite of this, IVIG comprised 1.6% of the total annual pharmacy expenditure in 2009/2010, 1.7% in 2010/2011 and 4.6% in 2011/2012 financial years respectively and accounted for ZAR24 294, ZAR24 847 and ZAR60 251 per 1 000 admissions in those respective financial years, showing a steady increase.

Table 4.4: Clinical categories by number of issues, mean issue value and cost (ZAR) in nominal values

Clinical categories	Mean issue value (ZAR)	Issues (n)	Totals (ZAR)
Other transplantation	2 893	189	546 708
Primary immunodeficiency	1 586	215	340 953
Guillain-Barré syndrome	3 077	98	301 586
Other autoimmune disorders	4 679	63	294 749
Other infections	3 892	50	194 621
Kawasaki disease	3 172	46	145 898
Kidney transplant	4 166	28	116 651
Other oncology	1 442	73	105 272
Other neurological conditions	4 666	21	97 996
Idiopathic Thrombocytopaenia Purpura	3 905	12	46 854
Uncertain	1 792	21	37 626
Paediatric HIV	1 947	16	31 156
Chronic Lymphocytic Leukaemia	1 322	19	25 126
Allogenic bone marrow transplant	2 298	8	18 381
Other haematology	1 710	5	8 548
Thrombocytopaenia	993	8	7 944
All Grps	2 661	872	2 320 071

Table 4.4 describes the comprehensive list of clinical categories by cost, issues and mean issue value from most costly clinical category to least costly. The article in Chapter III separates these categories by age, patient number and issues by registered and unregistered use. Only the top three most costly indications are described in the article due to word limitations so the comprehensive list above allows a

clearer picture of the cost drivers of IVIG in the study period by including the mean cost value per clinical category.

4.2 ADDITIONAL DISCUSSION

[For sense of flow and continuity, the unabridged version of the discussion follows.]

Approximately 28 studies have looked at IVIG use within different contexts and applications: either within a sub-specialty or at facility level; across single facilities or countrywide use; both in adults and paediatrics. These studies attempt to rationalise usage or formulate guidelines for controlling use. Tables 2.6 to 2.8 (Chapter II) summarise all the pertinent literature. The paediatric study of this research study looked at all IVIG issues within a paediatric facility as a whole and was not limited to a specific clinical setting such as intensive care or oncology. In specialised units, prescribing patterns tend to be affected by the specific conditions seen and can be determined by the failure to achieve a desirable response with other agents, lack of a suitable alternative and/or the need for an urgent response.

When considering registered and unregistered uses, the results varied by number of issues as opposed to the number of patients in the study sample. Different studies have utilised various methodologies for describing use. This study attempted to incorporate three different ways of describing this use:

- Number of issues: Here the number of issues based on the data recorded in the pharmacy dispensing system is reported on. This method allows all the records in the pharmacy displaying dispensing records of IVIG to be collated, so it is more comprehensive. However, it is limited by the ability to find the folders of these patients in the records department. Furthermore, the prescription charts in the folders verified administration of the IVIG. The implication of counting the number of issues is that quantities and strengths of IVIG are not incorporated into these values and issues represent whole vials rather than final dosage administered.
- Gram dispensed/used: This data could not be automatically retrieved from the dispensing system in the pharmacy as only amounts rounded off to the nearest pack size would have been recorded and not the actual dose given. However, to prevent wastage and for convenient dosing, most prescribers would use the nearest pack size in their dosing estimations seeing as there is a range in doses one could use for specific indications. This was verified by viewing the prescription records in each patient folder where obtainable.

- Patient numbers receiving IVIG: When determining the use of IVIG by indication and consequent registered/unregistered use, it is imperative to describe IVIG use by patient numbers. These results give one an indication of the use by the study sample population. Most of the IVIG study methodologies use this system. However, this number can be misleading, as it does not show the quantity of use/issues/grams utilised stratified by specific indication.

This study did all three and as such had differing values by grams, issues and patient numbers. Reporting by issues could be verified by grams prescribed in the prescription and wastage of IVIG could be determined. Interesting concepts arose from this delineation, e.g. primary immunodeficiency was determined as being one of the more costly indications yet only nine patients were seen with this diagnosis in the study period. This could be ascribed to the extended duration of therapy required for this subset of patients. Consequently two trends of IVIG use were distinct: acute versus chronic use. Ultimately all three methods displayed an increase in usage and a higher amount of unregistered use.

4.2.1 Paediatric studies on IVIG (Table 2.6)

A recent study by Galal[60] described the pattern and usage of IVIG in an intensive care paediatric facility in Cairo, Egypt. Sixty-two percent (n=45) of all IVIG use in this resource-limited setting was categorised as having level 1a/1b evidence, equivalent to MCC registered use, with 46% (n=21) of the cases classifiable as unregistered. This is less to that shown in this research study, in which 56% of the issues were for unregistered use by patient numbers. One major difference between the Egypt study and this research study was that neonatal sepsis was analysed as having Class 1a evidence. All clinical indications for IVIG in sepsis (n=17) were defined by this research study as belonging to the unregistered category (MCC) of which four patients could be classified as neonates. A recent systematic review and meta-analysis that quoted a low risk of bias of the included studies suggests that there is no reduction in mortality in patients with sepsis (RR 0.97; 95% CI 0.81–1.1).[63] IVIG use in neonatal sepsis could be considered only as a replacement to improve outcomes prior to sepsis as quoted by this study.[63]

Other paediatric studies on IVIG use in the USA (Texas)[50], Iran (Tehran)[57], Spain[3], UAE[64], Italy[65] and Asia (Singapore)[61] (see Table 2.6) representing a large variation in clinical care and socio-economic background, show a range of unregistered/off-label use, varying from 25% to 66%. No overarching trends are evident. However, a clear distinction is made in trying to elucidate studies that quantify registered uses versus studies that seek to delineate the evidence-base of such use.

Comparisons are further hindered by variations in the registration bodies, the definition of appropriate use, various guidelines utilised as well as different classifications of evidence used as described in the in-depth literature review. In addition, most of these studies used the FDA classification to determine on/off -label usage, thus excluding GBS. The only exception is the Spanish study[3] which used the EMA registration in it classification of off-label use. Interestingly, the Asia study[61] showed greater compliance to FDA approved indications, contrary to the other studies with the key feature being a remarkably high prevalence of patients diagnosed with Kawasaki disease (794, 60%) receiving IVIG. This has been rationalised as representing the higher burden of this disease within the Asian population.[61]

4.2.2 Top three cost drivers of IVIG at RCWMCH in study period

Most IVIG for unregistered use was prescribed for 'other transplants' (189 issues to18 patients), this subset being made up predominantly by liver transplants, with all patients being issued daily doses of IVIG for a minimum of one week. Alternate day dosing was also evident in one patient for up to seven days. Two other patients had recorded use beyond this time. IGG trough testing was one of the variables considered in the study as a marker for determining the effectiveness and need for further IVIG and determined through laboratory results. Two of these liver transplant patient were screened with IGG trough testing pre-therapy and none during the course of IVIG therapy. The prescribing patterns by individual clinicians suggest that, based on the evidence available, the use of IVIG post liver transplantation though becoming more common, is not yet standardised.[66] A more standardised basis for use will need to be explored thoroughly in further trials.

Nine patients with 215 issues were classified as having a primary immunodeficiency and all were assessed with IGG trough testing and IGG levels taken for outcome post IVIG treatment. Monthly doses of IVIG were issued in line with dosing practises. A further six patients had paediatric HIV with associated infections. It is important to note that data in this study showed that only 47% (87/185) had evidence of HIV PCR or rapid testing, judging both by the NHLS database and clinical notes. This is perturbing when considering that children with congenital HIV and recurrent infections are a registered indication for IVIG therapy. In addition, South Africa is in the midst of a national drive to increase detection and treatment of HIV. This would suggest that insufficient testing for HIV (rapid and/or PCR) was either offered or recorded in this paediatric facility, the latter being a realistic assumption if looking at the quality of the medical notes.

It is important to note the differences in IVIG registration between FDA, EMA and MCC. The FDA labelled use differs from the MCC in one important therapeutic indication for IVIG: GBS is not considered a registered use in the USA. Plasmapharesis is considered a viable treatment modality of choice and has a better cost benefit ratio compared to IVIG use in the USA.[67] GBS was the third most expensive indication but had the most number of patients diagnosed with this condition (n=33). Consequently, the mean issue value was ZAR3 077. The cost per patient in this subset was much less for GBS than for other indications, implying that treating many patients with GBS is more cost effective than IVIG therapy for other indications.

Interestingly mean issue value was highest for other autoimmune disorders and other neurological disorders. Indications for use in patients (n) include the following:

Other autoimmune disorders	systemic lupus erythematosis (3), dermatomyositis (4), systemic juvenile idiopathic arthritis (1), Evan's syndrome(1)
Other neurological conditions	peripheral neuropathy (1), transverse myelitis (1), acute demyelinating encephalomyelitis (1), radiculomyelitis (1), acute inflammatory demyelinating polyneuropathy (1), Sydenham's chorea (1), neurodegeneration (2), opsoclonus-myoclonus-ataxia syndrome (1), myoclonus(1)

This indicates that very specific conditions under autoimmune and neurological conditions can be major cost drivers due to extended duration of therapy. As these conditions are rare diseases with a few patients affected each year, evidence-based guidelines may be difficult to develop. At the same time, it is exactly in these conditions where the need for scientific justification of use may be highest.

The results in this research study demonstrate a significantly greater trend towards off-label/unregistered use both by patient numbers and by IVIG issues compared to most paediatric studies cited. This is echoed by the UAE study (n=74) which showed 61% off-label use by FDA but was limited by a smaller paediatric sample size and did not provide all clinical paediatric services within its facility. The current research study has the advantage of demonstrating use in all clinical areas since all paediatric services are offered by RCWMCH. In addition, it highlights the scenario of IVIG use in paediatrics in a low to middle-income setting as described.

Outcome measures, side effects and adverse effects were inadequately described in the doctor's notes in this study. Only eight patients in the doctor's notes had records of having an adverse effect after

administration of IVIG. This accounted for 4% of the study sample but could not be validated by a concurrent Adverse Drug Event Report submission. Similarly, the NHLS database had to be perused subsequently to determine if LFTs and IGG testing had been requested for patients in the sample. Trough IGG should be initiated prior to commencement with IVIG to determine the baseline of IGG in replacement therapies. Failure to do this hinders the ability to definitively establish the efficacy of IVIG as therapy. In addition, IGG levels should continue post IVIG administration for chronic therapy. Very rarely was this good practice met, with only 28 (15%) of 185 patients being tested for IGG trough levels and seven of them had primary immunodeficiency and five had cancer. As IVIG is metabolised by the liver, LFTs are good indicators of distribution of IVIG and its effects on the liver. Liver function tests used to assess the effect of IVIG on liver enzymes were reported in 57 (31%) of the patients

4.2.3 IVIG expenditure

Expenditure on IVIG by financial year appears to be increasing year on year as demonstrated in Figure 2.1 and Table 4.2. The increase in usage is evident over the five years with 2013/2014 being an anomaly. As transplants are accounting for an ever-increasing proportion, the lower number of transplants in that particular time period could account for that transient dip. The percentage of IVIG purchased against the pharmacy expenditure doubled from 2010/2011 to 2011/2012 financial years respectively. As use is based entirely on demand and not limited to clinical or formulary restrictions, factors like number of in-patients and total admissions in the hospital would need to be considered to assess whether the increases shown in this study are a result of the increased patient numbers seen at the hospital or are as a result of increased use in patients. Table 4.3 indicates that the number of in-patients decreased at the period when pharmacy expenditure on IVIG doubled. Over the five-year period admissions decreased by approximately 1000 admissions and the in-patient numbers decreased by 9000 patients. One could thus conclude that since 92% of all IVIG use was for in-patients, the prescribing of IVIG in the 2011/2012 year was not due to overall increases in patient numbers. As IVIG is available without restriction in the tertiary facilities in the Western Cape, use is open and subjective. The provincial code list/formulary does not specify the indications for which it may be used, thereby allowing the use to be solely determined by prescriber demands.

The cost per patient in the current study sample was considerably more than that of the average cost per patient. This excludes any other associated costs and was calculated only from the cost of IVIG, demonstrating the huge expense IVIG contributes to the overall cost per patient for this group.

4.2.4 Additional limitations to study

This study, although worthwhile and explorative, also exposed a unique environment not previously covered by other existing literature. However, the study was not without its limitations and challenges.

4.2.5 Challenges faced in the study

Obtaining a primary diagnosis was difficult in the context of the specialist paediatric service, as most patients had multiple co-morbidities. This was compounded by the difficulty of extracting the required data retrospectively from the medical records. Across the board notes were difficult to read and many details of diagnosis and treatment were absent or missing. ICD10 codes could not be ascertained as clinicians did not use this coding in determining the diagnosis and indication for IVIG. As a result of the wide variety of clinical indications and difficulty in ascertaining the primary indications for IVIG, consultants were asked to verify probable reasons for using IVIG in these very complex multi-morbid patients. Some provided evidence and some were uncertain of the use or considered it as 'last chance' medication.

Personal communication with the clinicians elucidated the challenges faced in dealing with complex, paediatric children presenting with rare and often life-threatening illnesses. Since RCWMCH operates as a specialist tertiary referral paediatric facility, the guidance on use is often absent and relies on evidence for which not much research undertaken has been undertaken due to the complexities and ethics of doing trials on rare illnesses in this vulnerable population. Often, expert opinion on clinical cases is the only information available. This has highlighted the need for a more coherent body to initiate the standardisation process for use of IVIG.

Other challenges include duplication of folders for the same patients with differing folder numbers on the dispensing database. This created initial errors that were later picked up in the database and lost or missing folders. Four attempts were made to retrieve folders after which a patient was described as missing. The sample size thus varied by indication (N=171) with 14 folders missing. These 14 patients constituted 44 IVIG issues. Only certain information was available for them in the pharmacy records allowing patient demographics to be ascertained for some variables.

A further 14 (8%) patients had uncertain indications for being prescribed IVIG or may be considered as in the case of the Cairo study, used because no other therapeutic option was available, lack of a suitable alternative or needing an urgent response. The disease ranges in these patients were varied, no trends

other than statistic doses could be found and six of these patients were issued IVIG whilst in the intensive care unit. IVIG could have been administered as 'last chance medicine' in acutely ill patients in a last ditch effort to improve outcome. Apart from the registered clinical categories, the unregistered ones listed as diagnoses needed to be evaluated for evidence and a clinical recommendation made for use in various conditions approved by the Provincial Pharmaceutics and Therapeutics Committee. There are varying levels of evidence available for potential use of IVIG. Within a resource constrained setting, the thorough evaluation of the evidence-base and a clinical guide to use should be an imperative step in IVIG administration.

4.2.6 Bias and measures to ensure validity

There were two significant sets of information bias arising from (a) the use of the JAC system and the ability to retrieve all the folders; and (b) the interpretation of the diagnoses by the investigator. In the former, all pharmacists will at some time or other have issued IVIG via the JAC system, so that the electronic record reflects the average accuracies/inaccuracies of all the staff over the past three years. In the latter, the investigator will have to interpret a number of usually clinician-specific diagnoses and reduce them to an International Classification of Diseases (ICD) 10 recognised diagnoses. Apart from the error that arises from the initial diagnosis, the secondary interpretation itself is also error-prone. In the latter, the investigator will have had to interpret a number of usually clinician-specific diagnoses and allocate them to a diagnostic category. Most clinical notes do not list all diagnoses, let alone the primary diagnosis, so that it may not have been clear which indication IVIG was prescribed for in the first instance. Due to this, it was not possible to apply International Classification of Diseases (ICD) 10 diagnostic labels in all cases.

The challenge in getting and reading off doctors' notes and diagnoses is a well-documented problem in retrospective studies using doctors' notes as primary or secondary data sources. Differential misclassification bias might arise from the fact that specific specialised clinics may themselves already be applying cut-offs and are therefore 'diluting' the figures for the hospital as a whole in terms of who is getting IVIG for what. One of the inherent features of this study was that it only reflected the prescribing practices of clinicians working at RCWMCH in the three years, and therefore reflecting their prescription and documentation habits.

Secondary reasoning that may have led to a prescription of IVIG may therefore not always have been included, an inherent weakness of a retrospective review. As such, the results will not be generalisable

to other populations because it is unique to this setting. At the same time, this served as an exploratory appraisal of actual paediatric use in an entire tertiary facility in a resource limited setting. Trends in usage can assist in determining future trends in usage and projections into infections treated annually that warrant the use of IVIG, quantities required as well as establish an initial picture on current usage. This information can further be used internally as well as externally for other paediatric populations within South Africa as a means of reflection and comparison.

4.2.6.1 Measures used to ensure validity

Internal

The JAC pharmacy database records all issues and returns of drug from the pharmacy to named patients or wards/clinics. Data was archived annually in the head office JAC database and available on written request.

- The pharmacy database relies on the manual inputting of all dispensing by pharmacists and pharmacy assistants and as such is prone to human error. Human error can result in false inputting of data against incorrect patient folder numbers, wards or clinics.
- Any emergency cupboard issues after hours that have not been recorded and issued from the JAC database the following day will escape the data collection in pharmacy.
- Any stock take where discrepancies in count of polyclonal IVIG occur lends itself to manipulation by stock adjustments on the JAC database. However, the past few stock takes have shown significant agreement with the JAC database.
- Any differences/errors in transcribing of data from source (patient folders) to data collection sheets and subsequent database (Excel or SPSS), though this is being minimised by dual entry and back-checking.

4.2.6.2 Selection bias

There is no way to reduce selection bias as purposeful sampling was utilised in this study. The aim was to measure trends in usage for the stipulated time period irrespective of other trends at different time periods. Thus this was a non-random cross-sectional sample.

Nevertheless, due to its sample size and that every patient during the study period were included if issued IVIG from the pharmacy database, the results presented here are a good indication of the

prescribing trends/indications observed at RCWMCH for this population receiving IVIG. It is evident that the majority of use is unregistered and seeing that IVIG is a costly therapeutic option, it becomes imperative to establish the evidence-base for use when designing a guideline/protocol for the paediatric use of IVIG. As compared to most other studies in paediatric IVIG use, which were limited by short review times, small sample sizes and /or restricted to specialised care, this study covered 39 months of continued usage within a whole hospital. It is important to note that this study was limited to describing clinical use by MCC registration status. The analysis of the evidence-base for each unregistered indication was beyond the scope of the study and more research is needed to ascertain and qualify this. The information gleaned by this study will be utilised by the Pharmacy and Therapeutics Committee to establish the criteria that would warrant: 1. use without motivation, 2. use with motivation and 3. use for which evidence is sparse and there is no clinical justification for administration. This process has already begun as a consequence of this study and clinical heads of departments have been requested to supply evidence justifying the need for and use in the clinical categories that are not registered by the MCC (Appendix E). The PTC will then forward this information on to the Provincial Pharmacy and Therapeutics Committee, where each off-label indication will reviewed and an established guideline drawn up for paediatrics. A similar scenario will need to take place in the adult setting.

4.3 ADDITIONAL RECOMMENDATIONS

Apart from the recommendations listed in the article and in the additional discussion, the following serve as recommendations for future studies that could enlighten, add to or assist in improving the work completed in this research.

1. A prospective study on IVIG utilisation: As this was a retrospective study, all the data collected was obtained from source notes. Consequently, missing information, incorrect data and illegibility of notes were some of the challenges encountered in retrospectively describing events. In addition ICD10 coding was hindered by the ability to make a definitive diagnosis in some instances. A prospective study would add further strength with definite end points and specific targets allowing a better quality of data to be analysed.
2. Assessing the evidence for each intervention: Secondary studies investigating the scientific evidence and literature available globally for each disease intervention would be the next progressive step for this research. One would need to consider the evidence by a classification system to assist in the drawing up of a protocol/guideline for IVIG use.

3. Subsequent to identifying the evidence available, any gaps in the literature with regards to IVIG use in specific diseases will need to be filled by primary studies. As the use by sub-specialties was wide and varied by duration, an in-depth analysis of IVIG indication for sub-specialties may present more substantial information in leading research within a low to middle-income setting.

4. Multihospital or regional setting: It is evident that this research was limited to a unique environment in a low to middle-income paediatric setting. Assessing the picture of IVIG usage within the Western Cape or in all tertiary/secondary hospitals is crucial for greater representation of the population.

5. IVIG usage in adults: From the literature reviewed, it was ascertained that the results presented on IVIG usage in paediatrics differ substantially from that of adults. This is due to the variance in diseases and afflictions affecting the paediatric population as opposed to the adult setting. One would need to conduct similar research in an adult facility in the Western Cape or elsewhere South Africa to determine the usage of IVIG in adults. The cost implications, dosages, durations of therapy, indication for use and adverse effects and monitoring would be interesting to analyse in an adult setting and with results compared.

6. Subcutaneous immunoglobulin (SCIG) use: There are obvious advantages of using a subcutaneous formulation, as opposed to IVIG: The subcutaneous route is easier to administer, (less costly in both consumables and potential in-patient time) and has a reduced chance of needle-stick injuries. However, there is no subcutaneous IVIG product currently registered with the MCC in South Africa. Drug trials on this dosage and formulation within our population could garner vital information like costs, ease of convenience, compliance, and efficacy of home therapy SCIG use versus hospital admissions for IVIG use.

CONCLUSION

This study was initiated following the casual observation that IVIG consumption at RCWMCH seemed to be increasing year-on-year and the subsequent shortage that necessitated the use of Intraglobin F under the section 21 licence. The initial assumption was that the majority of the use at the hospital was for registered uses. This assumption was proven wrong, as the analysis of the study period (January 2009 until 31 March 2012) showed that the majority of use was for unregistered indications, by patient numbers, and number of IVIG issues. What was even more revealing was that the biggest growth area in use was in liver transplants, increased usage mirrored in increasing use in this clinical area. Whereas IVIG has been tried in protean conditions as an immunomodulator, often these conditions are rare, resulting in the evidence for its use lacking. Though empirically attractive to use, the cost and clinical shortage means that wanton use cannot be encouraged. What this research has shown is that: a) there is room for standardisation of IVIG administration practices across conditions for which there is ample evidence, both in dosage and duration; b) the pre-/post administration IGG testing should be protocolled for the conditions in which IVIG is given as replacement therapy; c) the clinical notes need to be clearer on indications for individual therapies and side-effects; and d) there is a need for more research on the individual efficacy and effectiveness in a host of current clinical applications. Whereas this study did not specifically set out to systematically review the evidence behind each current clinical use at RCWMCH, the resultant findings of off-label use have rallied clinicians into starting to develop an evidence-based protocol to guide indication, dosage and duration for IVIG (see appendix E). This study will hopefully continue to assist with the responsible use of resources at the public health facility while optimising the care for those patients who will benefit most from it.

APPENDICES AND ADDENDA

Appendix A: Letter from NBI

Appendix B: NBI's process of IVIG manufacture and quality control

Appendix C: Immunoglobulins protocol for private medical scheme

Appendix D: Unlabelled uses of IVIG

Appendix E: Proposed indications for the use of Intravenous Immunoglobulins at RCWMCH

Appendix F: Protocol

Appendix G: Data collection sheet

Appendix H: BREC approval

Appendix I: Hospital approval

Appendix J: Amendment ratification and approval

Appendix K: Journal submission requirements

Appendix L: Consent from the author S Knight

Appendix M: Consent from the author T Welzel

Appendix N: Turnitin Summary Index

APPENDIX A:

LETTER FROM NBI

NATIONAL BIOPRODUCTS INSTITUTE

Association incorporated under Section 21
Registered under the Nonprofit Organisations Act, No 71 of 1997
Registration No.: [illegible]
(Registration No.: [illegible])

10 Eden Road, Pinetown, 3610.
Private Bag [illegible], Pinetown, 3600,
South Africa.

Telephone: (+27) (031) 714 6700
Fax: (+27) (031) 708 5614
Orders Fax: (+27) (031) 708 5618
Toll Free orders: 0800 [illegible]
E-mail: [illegible]
Website: [illegible]

6 December 2010
Our.Ref.NBI.7783

Prof. R Eastman
President: Neurological Association of South Africa
E8, Neurology
Groote Schuur Hospital
Cape Town
7925

Dear Prof Eastman

Supply of Polygam

We are aware that some of our customers are experiencing difficulty in sourcing Polygam. This is as a result of a country-wide increase in demand for this product. The trend of increasing usage of IVIG has been reported in the international literature and has been linked with increased off-label usage[1,2]. Intermittent shortages internationally have necessitated several countries like the UK[3], Australia[4] and Canada[5] to implement strict control measures on IVIG usage and availability.

As neurological indications form a significant percentage of the total usage of Polygam in SA, we respectfully request NASA to assist us by communicating to your members current restrictions on the availability of Polygam and in particular the critical need for appropriate usage.

In response to the increasing demand for all of our products, NBI has embarked on a 2 to 3 year complex facility upgrade plan that, once complete, will ensure that South African patients continue to have access to sufficient locally manufactured plasma-derived medicines. However, significant portions of this upgrade have to take place whilst routine manufacture continues, which has therefore necessitated longer project timelines. A critical phase in of the upgrade is scheduled to take place in April-May 2011, and for an approximate 8 week period, the plant will be shutdown to facilitate the installation of new plant and equipment. Sufficient stocks of product therefore have to be manufactured prior to April to ensure continuity of supply of these essential products. The key to a successful stock build, is maintaining current product usage over the same period. It is for this aspect of the programme that we request your support.

For the duration of the stock build period, during the shut down and at for least the following 6 months, supplies of Polygam will remain limited. It is therefore of paramount importance that the demand for Polygam remains at current usage levels for the next 12 months. Failure to do so will result in a periodic "out of stock" situation for Polygam.

NBI is a "not for profit" association committed to providing safe, cost effective, quality products

Directors: [illegible]
Company Secretary: [illegible]

APPENDIX B:
NBI'S PROCESS OF IVIG MANUFACTURE AND QUALITY CONTROL[7]

Voluntary non-remunerated donors (NBI site)

NBI's products are prepared from pooled human plasma sourced predominantly from non-remunerated healthy blood donors. Blood donors in South Africa are those people who voluntarily donate their blood or components to be used in accordance with the Human Tissue Act (Act 65 of 1983).

Donor screening

A range of questions on a confidential questionnaire determines the prospective donor's medical condition, health and any high-risk behaviour patterns. The donor is permanently deferred or deferred for a period of time depending on the answers to the questions.

Individual donation testing

All units of blood are individually tested and found non-reactive for hepatitis B surface antigen (HBsAg), antibodies to the hepatitis C virus, antibodies to the human immunodeficiency viruses, HIV-1 and HIV-2.

Approved plasma suppliers

The acquisition of plasma is predominantly from the South African National Blood Services (SANBS) and Western Province Blood Transfusion Service (WPBTS) and other internationally regulated suppliers.

Pooling of individual plasma units

Processes such as cold ethanol fractionation, have been introduced to enhance product safety, quality and efficacy.

Internationally accepted viral inactivation/reduction processes

The methods of manufacture include effective processes such as solvent-detergent treatment, pH 4 treatment and pasteurisation, which have been shown to inactivate the important transfusion transmitted lipid enveloped viruses, including the human immunodeficiency viruses (HIV-1 and HIV-2), hepatitis B and hepatitis C viruses.

Quality assurance for final product release

NBI plasma products fulfil the registration requirements of the South African regulatory authority, the Medicines Control Council, in terms of safety, quality and efficacy.

This plasma is pooled and must contain plasma from 1000 to 10 000 donors. The plasma undergoes five standard extraction processes in the Cohn alcohol fractionation II. These standards must adhere to WHO production criteria for IVIG to ensure that a safe, pure product of 90% mononumeric IgG is extracted, free from infections and other contaminant risks to the patient. This process can take up to 8 months.

[7] As taken from their site http://www.nbi-kzn.org.za/

APPENDIX C:
IMMUNOGLOBULINS PROTOCOL
FOR PRIVATE MEDICAL SCHEME

Intravenous Immunoglobulins

Definition

Intravenous immunoglobulin (IVIG) belongs to a group of medicines known as immunising agents. IVIG's are used to prevent or treat some illnesses that can occur when the body does not produce enough of its own immunity

Benefit

Hospital Benefit

This protocol applies to all plan types

Discovery Health funds intravenous immunoglobulins for the following conditions:

- Kawasaki syndrome
- Guillian 'Barre' syncrome
- X-linked agammaglobulinemia
- Swiss-type agammaglobulinemia
- Hyper IGM syndrome
- Wiscott-Alrich syndrome
- Common variable immunodeficiency with recurrent infection
- Selective deficiency of IgG sub-classes ie selective IgG deficiency with recurrent infection
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) also known as chronic relapsing polyneuropathy
- Dermatomyositis /Polymyositis
- Relapsing / remitting multiple sclerosis
- Myasthenia gravis-acute myasthenic crisis with decompensation (respiratory failure or disabling weakness requiring hospital admission)
- Warm-type Haemolytic Anaemia

Medical expenses incurred during an approved hospital admission will be paid from the Hospital Benefit, based on the member's chosen Discovery Health Plan, subject to preauthorisation. Clinical entry criteria will apply

Oncology Benefit

Discovery Health funds intravenous immunoglobulins for :

- Chronic B-Cell lymphocytic leukaemia with low IgG
- Multiple Myeloma with hypogammaglobulinaemia
- Idiopathic thrombocytopenic purpura (ITP) (paediatric) Idiopathic thrombocytopenic purpura (ITP) (adult, acute) Idiopathic thrombocytopenic purpura (ITP) (chronic refractory

Medical expenses incurred during an approved hospital admission will be paid from the Oncology Benefit based on the member's chosen Discovery Health Plan, subject to preauthorisation. Clinical entry criteria will apply

Stem Cell Benefit

Discovery Health will fund Immunoglobulins for:

- Allogenic Bone Marrow Transplantation (recipient) from the Stem Cell Benefit, based on the member's chosen Discovery Health Plan, subject to preauthorisation. Clinical entry criteria apply

Discovery Health does not fund

Any other condition not in this protocol

InHouse Schemes

Fund as per Discovery

Operational processes	
Preauthorisation process and clinical entry criteria	
Approve requests for the following indications without escalation.	
Diagnosis	**Clinical entry criteria and dosage**
Kawasaki Syndrome	Request should be from a paediatrician or immunologist • Approve treatment for a maximum of **five (5) days only** in hospital
Guillian Barre syndrome	Request should be from the neurologist, paediatrician or physician • Immunoglobulins should be initiated within two weeks of the onset of neuropathic symptoms and not later than four weeks. • Approve treatment for a maximum of five(5) days only in hospital
Refer requests for the following indications to DiscoveryCare Oncology Case Managers	
Multiple Myeloma or Chronic B-Cell lymphocytic leukemia with hypogammaglobulinaemia(low IgG)	Request should be from haematologist or oncologist Patient to be registered on the Oncology Programme for this condition and with the following history: • Recurrent or severe bacterial infection with evidence of hypogammaglobulinaemia or • Suboptimal response to antigenic stimulation Approve immunoglobulins every four weeks for six months from the Oncology Benefit: • If on chemotherapy continue for a further six months • If not on chemotherapy : o allow six to eight weeks break and request IgG trough levels **and** o If trough levels are normal, do not approve further treatment. If the trough levels are below normal, continue funding for a further three months only (total of 9 months)
Allogenic bone marrow transplantation (recipient)	Request should be from the haematologist or oncologist • Patient to be registered on the Oncology Programme • For prophylaxis of graft versus host disease Approve immunoglobulins from the **Stem Cell Benefit** for seven days prior to transplantation and up to three months thereafter at four months
Idiopathic thrombocytopenic purpura (ITP) (paediatric)	Request should be from the haematologist or paediatrician • IVIG as initial therapy if platelet count < 20,000/ul, especially when member has emergency bleeding or is at risk for severe life-threatening bleeding; or • Failure of other therapies or • Member at high risk for post-splenectomy sepsis Approve treatment for a maximum of **three** days in hospital

Idiopathic thrombocytopenic purpura (ITP) (adult, acute)	Requests from haematologist or physician for the following indications: • Other causes of thrombocytopenia have been ruled out **and** • Severe thrombocytopenia (platelet counts less than 20,000/ul) • considered to be at risk for intracerebral haemorrhage, **or** • Management of acute bleeding due to severe thrombocytopenia • (platelet counts less than 30,000/ul); **or** • To increase platelet counts prior to invasive major surgical procedures (e.g. splenectomy); **or** • Unresponsive to corticosteroid therapy; **or** • To avoid splenectomy Approve treatment for maximum of **three** days in hospital
Idiopathic thrombocytopenic purpura (ITP), chronic refractory	Requests should be from a haematologist or physician, paediatrician • Age of 10 years or older; and • Duration of illness of greater than six months; and • No concurrent illness or disease explaining thrombocytopenia; • and • Prior treatment with corticosteroids or splenectomy has failed; or • Member is at high risk for post-splenectomy sepsis
Refer motivational letter/treatment plan requests for the following indications to DiscoveryCare Medical Review Team (MRT)	
Warm Type Haemolytic Anaemia	Requests should be from haematologists, physicians , paediatricians • After failure of or intolerance to: o corticosteroids or Immunosuppressants • As a temporising measure prior to splenectomy Approve treatment for a maximum of **five** days in hospital
X-linked agammaglobulinemia	Request should be from the physician, paediatrician or haematologist • Markedly reduced or absent serum IgG, IgM, IgA or Absent B lymphocytes in the blood or • Suboptimal response to antigenic stimulation eg. tetanus, diphtheria, pneumococcal vaccine (adequate response is fourfold • increase in antibody titre) Approve immunoglobulins every **four** weeks for 6 months at a time
Swiss-type agammaglobulinemia	Request should be from the physician, paediatrician or haematologist Approve immunoglobulins every **four** weeks for 6 months at a time
Hyper IgM syndrome	Request should be from the physician, paediatrician or haematologist • Recurrent respiratory and intestinal infections and • Low or absent IgA, IgG, and IgE Approve immunoglobulins every **four** weeks for 6 months at a time

Common variable immunodeficiency with recurrent infection	Request should be from the physician or paediatrician Other causes of secondary antibody deficiency are excluded eg drug induced or nephrotic syndrome • Suboptimal response to antigenic stimulation eg tetanus, diphtheria, pneumococcal vaccine (adequate response is fourfold increase in antibody titre) **or** • Either serum IgG and, IgM below normal Approve immunoglobulins every **four** weeks for 6 months at a time
Selective deficiency of IgG sub-classes i.e. selective IgG deficiency with recurrent infection	Request should be from physician or paediatrician • Unexplained recurrent or persistent severe bacterial infections despite adequate treatment and • Deficiency of one or more IgG subclasses and • Suboptimal response to antigenic stimulation eg tetanus vaccine Approve immunoglobulins every **four** weeks for 6 months at a time
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); also known as chronic relapsing polyneuropathy	Request should be from the neurologist, physician or paediatrician • Elevated spinal fluid protein, with normal cell count • Motor: o IVIG given as first line treatment • Sensory: (where there is failure, or intolerance to corticosteroids or immunosuppressants or are contraindicated) o IVIG may be given as second line Approve treatment for up to 6 months and review , if responding to treatment approve additional 6 months Approve immunoglobulins every **two –six** weeks for 6 months at a time
Dermatomyositis /Polymyositis	Request should be from the neurologist, physician or paediatrician • Patients with muscle weakness or dysphagia who • Have failed or are intolerant to corticosteroids or immunosuppressive agents Approve immunoglobulins every **four** weeks for 6 months at a time
Relapsing/remitting multiple sclerosis	Request should be from a neurologist • Where there is intolerance to standard therapies; or • Where standard therapies have failed or are contraindicated Approve treatment for up to 6 months and review , if responding to treatment approve additional 6 months Approve immunoglobulins every **four** weeks for 6 months at a time
Acute myasthenic crisis with decompensation - respiratory failure or disabling weakness requiring hospital admission	Request should be from a neurologist or physician • Respiratory failure or disabling weakness requiring hospital admission and • Where there is intolerance to standard therapies, or where standard therapies have failed or are contraindicated or • As an alternative to plasma exchange in acute exacerbation Approve treatment for **five** days in hospital

References

Discovery Health Clinical Information Summaries

Search words

- Immunoglobulins
- Immune globulin
- Polygam
- Intravenous immunoglobulins

Coding

Code type	Code	Description
Click here for the Immunoglobulins codes		

Clinical Policy Unit review

Date of original draft: December 2006	**Original draft done by:** Martie Louw
Date of update:	**Reviewed by:**
November 2009	Thandi Tsintsing
September 2011	Thandi Tsintsing
Next review date:	September 2012
Reference number/Version control:	Version 1 of 2011
Publication Date:	28 October 2011

Disclaimer table

Discovery Health's coverage policies are developed using a rigorous, evidence-based decision-making process, consisting of a clinical and financial filter. The clinical filter uses evidence-based literature, the opinions of local and international leaders, and current treatment guidelines to ensure that the health care service is safe, ethical, clinically and cost-effective. Discovery Health reserves the right to review this protocol when required

Appendix D
Unlabelled Uses of IVIG
(Taken from Leong et al.)

Indication	Guideline Conclusion about Indication[a]						Mean Indication Score
	Ref 12[b]	Ref. 17	Ref. 16	Ref. 18[c]	Ref. 19[c]	Ref. 20	
Labeled							
Allogeneic bone marrow transplant	NI	1	NI	NI	NI	1	1.0
Chronic lymphocytic leukemia	NI	1	NI	2	2	2	1.8
Idiopathic thrombocytopenic purpura	NI	2	NI	2	2	2	2.0
Kawasaki disease	NI	2	NI	2	2	2	2.0
Pediatric HIV (to decrease bacterial infections)	NI	1	NI	2	2	2	1.8
Primary immunodeficiencies	NI	2	NI	2	2	2	2.0
Unlabeled							
Acquired hemophilia	0	1	NI	0	NI	NI	0.3
Acquired von Willebrand's disease	0	NI	NI	0	NI	NI	0.0
Adrenoleukodystrophy	0	0	NI	0	NI	NI	0.0
Alzheimer's disease	NI	NI	NI	0	NI	NI	0.0
Amyotrophic lateral sclerosis	0	0	NI	0	NI	NI	0.0
Anemia, aplastic	0	NI	NI	0	NI	NI	0.0
Anemia, hemolytic autoimmune, refractory	1	1	NI	2	NI	NI	1.3
Anemia, hemolytic neonatal	1	NI	NI	2	NI	NI	1.5
Angioedema	NI	NI	NI	0	NI	NI	0.0
Antiphospholipid syndrome in pregnancy	NI	0	NI	0	NI	NI	0.0
Asthma, severe and chronic chest symptoms	0	1	NI	0	NI	NI	0.3
Asthma, noncorticosteroid-dependent	0	0	NI	0	NI	NI	0.0
Autistic disorder	NI	0	NI	0	NI	NI	0.0
Autoimmune blistering skin diseases and manifestations of systemic disease	NI	1	2	2	2	NI	1.8
Autoimmune inner ear disease	NI	NI	NI	0	NI	NI	0.0
Bacterial infections in lymphoproliferative disease	NI	1	NI	NI	NI	NI	1.0
Behçet's syndrome	0	NI	NI	0	NI	NI	0.0
Cardiomyopathy, acute, dilated	0	0	NI	0	NI	NI	0.0
Cerebral infarctions with antiphospholipid antibodies	NI	1	NI	NI	NI	NI	1.0
Chronic fatigue syndrome	0	0	NI	0	NI	NI	0.0
Chronic inflammatory demyelinating polyneuropathy	2	2	NI	NI	2	2	2.0
Churg-Strauss syndrome, allergic granulomatosis	NI	NI	NI	2	NI	NI	2.0
Clostridium difficile colitis/pseudomembranous colitis	NI	1	NI	0	NI	2	1.0
Congenital heart block	0	NI	NI	0	NI	NI	0.0
Convulsive syndromes	NI	NI	NI	0	NI	NI	0.0
Cystic fibrosis	0	NI	NI	0	NI	NI	0.0
Dermatitis, atopic	NI	0	NI	0	NI	NI	0.0
Dermatomyositis, polymyositis	1	1	NI	2	2	2	1.6
Dermatosis, autoimmune blistering	0	NI	2	0	NI	NI	0.7
Diabetes mellitus	0	1	NI	0	NI	NI	0.3
Diamond-Blackfan anemia	0	NI	NI	0	NI	NI	0.0
Dysautonomia, acute idiopathic	0	1	NI	0	NI	NI	0.3
Eczema	NI	NI	NI	0	NI	NI	0.0
Encephalitis, demyelinative brain stem	NI	1	NI	0	NI	NI	0.5
Encephalomyelitis, acute disseminated	0	1	NI	0	NI	NI	0.3
Encephalopathy	NI	NI	NI	0	NI	NI	0.0
Endotoxemia	0	NI	NI	0	NI	NI	0.0
Enteritis, *Campylobacter* species-induced	NI	1	NI	NI	NI	NI	1.0
Enteroviral meningoencephalitis	NI	1	NI	NI	NI	NI	1.0
Epidermolysis bullosa acquisita	NI	NI	2	NI	NI	NI	2.0
Epilepsy, pediatric intractable	1	1	NI	0	NI	NI	0.7
Fetomaternal alloimmune thrombocytopenia	NI	1	NI	NI	NI	2	1.5
Goodpasture's syndrome	NI	NI	NI	0	NI	NI	0.0
Grave's ophthalmology	NI	2	NI	NI	NI	2	2.0

Continued on next page

Appendix (*continued*)

Indication	Guideline Conclusion about Indication[a]						Mean Indication Score
	Ref 12[b]	Ref. 17	Ref. 16	Ref. 18[c]	Ref. 19[c]	Ref. 20	
Guillain-Barré syndrome	2	2	NI	2	2	2	2.0
Hemolytic jaundice, neonatal autoimmune	NI	1	NI	NI	NI	NI	1.0
Hemolytic transfusion reaction	0	NI	NI	0	NI	NI	0.0
Hemolytic-uremic syndrome	NI	NI	NI	0	NI	NI	0.0
Hemophagocytic syndrome	0	NI	NI	0	NI	NI	0.0
Hyperimmunoglobulinemia E syndrome	NI	NI	NI	2	2	NI	2.0
IgA deficiency, isolated	NI	0	NI	NI	NI	NI	0.0
IgG subclass deficiency with severe infection	NI	NI	NI	2	NI	NI	2.0
IgG4 deficiency, isolated	NI	0	NI	NI	NI	NI	0.0
IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy	NI	1	NI	NI	NI	NI	1.0
Immunosuppression, secondary to major surgery and disease	NI	NI	NI	2	NI	NI	2.0
Inclusion body myositis	0	0	NI	0	NI	1	0.3
Infection prophylaxis, high-risk neonates	1	1	NI	0	2	NI	1.0
Infection prophylaxis, solid organ transplant	1	NI	NI	NI	NI	NI	1.0
Infection treatment, adults in surgery/trauma/burns	0	NI	NI	NI	NI	NI	0.0
Infection treatment, high-risk neonates	0	NI	NI	NI	NI	NI	0.0
Infection treatment, HIV infection (adults)	0	0	NI	NI	NI	NI	0.0
Infection treatment, surgery/trauma	0	NI	NI	NI	NI	NI	0.0
Lambert-Eaton myasthenic syndrome	1	1	NI	2	2	2	1.6
Leukemia, acute lymphoblastic	0	NI	NI	0	NI	NI	0.0
Liver disease, autoimmune	NI	1	NI	NI	NI	NI	1.0
Lower motor neuron syndrome	0	NI	NI	0	NI	NI	0.0
Lumbosacral or brachial plexitis	NI	1	NI	0	NI	NI	0.5
Malignancy, nonhematologic	NI	NI	NI	0	NI	NI	0.0
Miscarriage, recurrent	0	0	NI	0	NI	NI	0.0
Multifocal motor neuropathy	1	2	NI	2	2	2	1.8
Multiple myeloma	1	NI	NI	2	NI	NI	1.5
Multiple sclerosis, monoclonal gammopathy	1	1	NI	NI	NI	0	0.7
Multiple sclerosis, relapsing-remitting	NI	NI	NI	2	NI	0	1.0
Myalgia, myositis	NI	NI	NI	0	NI	NI	0.0
Myasthenia gravis	1	1	NI	2	2	1	1.4
Myelopathy, HTLV-1 associated	0	1	NI	0	NI	NI	0.3
Myelopathy, transverse	NI	NI	NI	0	NI	NI	0.0
Myocarditis, acute, viral	NI	1	NI	0	NI	NI	0.5
Necrotizing enterocolitis	NI	NI	NI	0	NI	NI	0.0
Neonatal lupus syndromes	NI	NI	NI	0	NI	NI	0.0
Nephritic syndrome	0	NI	NI	0	NI	NI	0.0
Nephropathy, membranous	0	NI	NI	0	NI	NI	0.0
Nephrotic syndrome	0	NI	NI	0	NI	NI	0.0
Neuromyelitis optica (Devic's disease)	NI	NI	NI	0	NI	NI	0.0
Neuromyotonia (Isaac's syndrome)	NI	NI	NI	0	NI	NI	0.0
Neurosarcoidosis	NI	NI	NI	0	NI	NI	0.0
Neuropathy, demyelinating associated with monoclonal IgM	NI	0	NI	NI	NI	NI	0.0
Neuropathy, sensory	NI	NI	NI	0	NI	NI	0.0
Neutropenia, immune mediated	1	1	NI	0	2	NI	1.0
Ophthalmopathy, euthyroid	0	NI	NI	0	NI	NI	0.0
Opsoclonus-myoclonus	0	1	NI	2	NI	NI	1.0
Optic neuritis, acute	NI	NI	NI	0	NI	NI	0.0
Oral use	0	NI	NI	0	NI	NI	0.0
Otitis media, recurrent	0	NI	NI	0	NI	NI	0.0
Paraneoplastic cerebellar degeneration	0	0	NI	0	NI	NI	0.0
Paraneoplastic opsoclonus-myoclonus-ataxia associated with neuroblastoma	NI	NI	NI	2	NI	NI	2.0

Appendix (*continued*)

Indication	Guideline Conclusion about Indication[a]						Mean Indication Score
	Ref 12[b]	Ref. 17	Ref. 16	Ref. 18[c]	Ref. 19[c]	Ref. 20	
Paraproteinemic neuropathy	0	1	NI	0	NI	NI	0.3
Parkinson's disease	NI	NI	NI	0	NI	NI	0.0
Parvovirus infection (general)	0	NI	NI	2	2	NI	1.3
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	NI	1	NI	0	NI	NI	0.5
Pemphigoid, bullous	NI	NI	2	NI	NI	NI	2.0
Pemphigoid, mucous membrane, cicatricial	NI	NI	2	NI	NI	NI	2.0
Pemphigus	NI	NI	2	2	2	2	2.0
Pemphigus foliaceus	NI	NI	2	NI	NI	NI	2.0
Pemphigus vulgaris	NI	NI	2	NI	NI	NI	2.0
POEMS syndrome	0	0	NI	0	NI	NI	0.0
Polyarteritis nodosa	NI	NI	NI	0	NI	NI	0.0
Polyneuritis cranialis	NI	NI	NI	0	NI	NI	0.0
Postinfectious cerebella ataxia	NI	1	NI	NI	NI	NI	1.0
Posttransfusion purpura	NI	1	NI	2	NI	2	1.7
Primary immune defect with normogammaglobulinemia and impaired specific antibody production	NI	1	NI	2	NI	NI	1.5
Progressive lumbosacral plexopathy	0	NI	NI	0	NI	NI	0.0
Pseudomembranous colitis/*Clostridium difficile* colitis	NI	1	NI	NI	NI	2	1.5
Pure red cell aplasia	1	NI	NI	0	NI	NI	0.5
Radiculoneuritis, Lyme	0	NI	NI	0	NI	NI	0.0
Rasmussen's syndrome	0	1	NI	0	NI	NI	0.3
Reiter's syndrome	0	NI	NI	0	NI	NI	0.0
Renal failure, acute	0	NI	NI	0	NI	NI	0.0
Rheumatic fever, acute	NI	0	NI	NI	NI	NI	0.0
Rheumatoid arthritis	0	1	NI	0	NI	NI	0.3
Rotaviral enterocolitis	NI	1	NI	NI	NI	NI	1.0
RSV lower-respiratory-tract infection	NI	1	NI	NI	NI	NI	1.0
Scleroderma	NI	NI	NI	0	NI	NI	0.0
Sepsis, neonatal	NI	1	NI	NI	NI	NI	1.0
Sepsis, postoperative	NI	1	NI	NI	NI	NI	1.0
Sinusitis, chronic	NI	NI	NI	0	NI	NI	0.0
Stiff-person (Moersch-Woltmann) syndrome	NI	1	NI	2	2	2	1.8
Sydenham's chorea	NI	NI	NI	0	NI	NI	0.0
Systemic lupus erythematosus	1	1	NI	2	NI	2	1.5
Systemic vasculitides	1	1	NI	0	NI	NI	0.7
Thrombocytopenia, HIV associated	NI	NI	NI	2	NI	NI	2.0
Thrombocytopenia, neonatal alloimmune/autoimmune	1	NI	NI	2	2	NI	1.7
Thrombocytopenia, nonimmune	0	NI	NI	0	NI	NI	0.0
Thrombocytopenia, posttransfusion purpura	2	NI	NI	NI	NI	NI	2.0
Thrombocytopenia, refractory to platelet transfusion	1	NI	NI	0	NI	NI	0.5
Thrombocytopenia, TTP/HUS	0	NI	NI	0	NI	NI	0.0
Tic disorders	NI	NI	NI	0	NI	NI	0.0
Toxic epidermal necrolysis, Stevens-Johnson syndrome	NI	1	NI	0	NI	1	0.7
Toxic necrotizing fascitis due to group A streptococcal bacteria	NI	NI	NI	2	NI	NI	2.0
Toxic shock syndrome, streptococcal or staphylococcal	0	1	NI	2	2	NI	1.3
Transplant, bone marrow, GVHD and infection prevention	NI	1	NI	NI	NI	NI	1.0
Transplant, bone marrow, prevention of chronic GVHD	NI	0	NI	NI	NI	NI	0.0
Transplant, bone marrow/stem cell, prevention of severe infections with marked hypogammagolinemia	NI	NI	NI	2	NI	NI	2.0
Transplant, renal, live donor with ABO incompatibility or positive cross-match	NI	NI	NI	2	NI	NI	2.0
Transplant, renal, prevention of acute humoral rejection	NI	1	NI	NI	2	NI	1.5

Continued on next page

Appendix (*continued*)

Indication	Guideline Conclusion about Indication[a]						Mean Indication Score
	Ref 1[b]	Ref. 2	Ref. 3	Ref. 4[c]	Ref. 5[c]	Ref. 6	
Transplant, renal, treatment of acute humoral rejection	NI	1	NI	NI	NI	2	1.5
Transplant, solid organ, CMV infection	NI	2	NI	NI	2	NI	2.0
Urticaria, chronic	NI	1	NI	0	NI	NI	0.5
Urticaria, delayed pressure	NI	1	NI	NI	NI	NI	1.0
Uveitis	0	1	NI	0	NI	NI	0.3
Vasculitis associated with other connective tissue disorders	NI	NI	NI	0	NI	NI	0.0
Vogt-Koyanagi-Harada syndrome	0	NI	NI	0	NI	NI	0.0
Wegener's granulomatosis	NI	NI	NI	0	NI	NI	0.0

[a]Score of 0 = IVIG not recommended, 1 = IVIG may be beneficial, and 2 = acceptable use of IVIG. NI = not included, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, HTLV = human T-cell lymphotropic virus, RSV = respiratory syncytial virus, TTP/HUS = thrombotic thrombocytopenia purpura/hemolytic-uremic syndrome, GVHD = graft-versus-host disease, CMV = cytomegalovirus.
[b]IVIG may be considered for treatment under certain circumstances; refer to full UHC guidelines for additional information. [c]Many conditions must meet specific criteria; refer to full policy for additional information.

References

1. Ratko TA. Technology assessment: intravenous immunoglobulin preparations. Oak Brook, IL: University HealthSystem Consortium; 1999 Mar.
2. Orange JS, Hossny EM, Weiler CR et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol.* 2006; 117(suppl 4):S525-53. [Erratum, *J Allergy Clin Immunol.* 2006; 117:1483.]
3. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol.* 2003; 139:1051-9.
4. Aetna Clinical Policy Bulletin. Intravenous immunoglobulins (IVIG). http://aetna-health.healthline.com/smartsource/search?q1=Intravenous+immunoglobulins&term=Intravenous+immunoglobulins&hmimuid=8128342&nodeid=0&type=rxg&subCat=MedicationsCat#DrugInformation (last accessed 30 Nov 2011).
5. Blue Cross of California Clinical UM Guideline. Intravenous immunoglobulins (IVIG). http://www.anthem.com/ca/medicalpolicies/guidelines/gl_pw_a053678.htm (last accessed 30 Nov 2011).
6. Intravenous immunoglobulin (IVIG). *Med Lett Drugs Ther.* 2006; 48:101-3.

APPENDIX E:

PROPOSED INICATIONS FOR THE USE OF INTRAVENOUS IMMUNOGLOBULINS AT RCWMCH

Condition	Selected	Dose	Frequency	Evidence / grade
Primary immunodeficiencies with defective antibody production (initiation of IVIG replacement therapy restricted to Paediatric Infectious Diseases Unit)	Yes			B, IIb
Pure red cell aplasia B19	No##$$			A, Ib
Haemolytic disease of the foetus and newborn (isoimmune haemolytic jaundice in neonates)	No			C, III
Auto immune haemolytic anaemia	No			C, III
Neonatal alloimmune thrombocytopenia	No$$			C,III
Post-transfusion purpura	No			C, III
Alloimmune thrombocytopenia, mother	Yes			C, III
Alloimmune thrombocytopenia — neonatal therapy	No$$			C, III
Auto immune thrombocytopenia	No##&&			A, Ia
Adult HIV associated thrombocytopenia	No			A, IB
Idiopathic thrombocytopenic purpura (<16 years)	No			A, Ia
Evan's syndrome	No			C, III
Myasthenia gravis	No**$$			B, Ia
Guillain-Barré syndrome	No**$$			**A, Ia**
Chronic inflammatory demyelinating polyradiculoneuropathy	No			A, Ia
Paraprotein associated demyelinating neuropathy (IgG or IgA)	No			A, Ia

Commented [AD1]: $$ = selected cases which would include parvovirus infection in immunocompromised cases.

Commented [AD2]: We suspect that neonatology would take issue with this!

Commented [AD3]: $$ = selected cases. Difficult: Although it's use has met with mixed results, it is cheaper than rituximab and would have to be considered for steroid resistant AIHA.

Commented [AD4]: $$ = selected cases. Active bleeding that is not responding to steroids.

Commented [AD5]: $$ = selected cases. Active bleeding that is not responding to steroids.

Commented [AD6]: $$ = selected cases would include [1] active bleeding in patients who are not responsive to steroids [2] intracranial or other forms of life-threatening haemorrhage [3] pregnant women with contraindications to steroid therapy.

Commented [AD7]: $$ = selected cases would include [1] active bleeding in patients who are not responsive to steroids [2] intracranial or other forms of life-threatening haemorrhage.

Commented [JMW8]: Specialist initiated absolutely – access must remain for our patients – we use it in crisis situations

Multifocal motor neuropathy	No	A, Ia
Lambert-Eaton myasthenic syndrome	No	A, Ib
Toxic epidermal necrolysis	Yes	B, IIa
Dermatomyositis	No	A, Ib
Kawasaki disease	Yes	A. Ia
Chronic lymphocytic leukaemia	No	A, Ia
Multiple myeloma	No	A, Ib
Pneumonitis induced by cytomegalovirus following transplantation	No	A, Ib
Rasmussen syndrome	No	B, IIb
Encephalitis lethargica	Yes	
ADEM / ADEM spectrum conditions	No $$	

Commented [JMW9]: Don't agree – we use it for severe cases where ambulation is threatened or there is severe threat to systemic health. Should be $$ - paed neuro happy to notify committee is use it.

Commented [JMW10]: Should be "$$" – beyond surgery there is little to do for these patients IVIG is effective in a few and may be patients only option.

Commented [JMW11]: Devastating condition – requires early and aggressive intervention. IVIG is part of this. Patients would be under or discussed with (country cases) neuro

Commented [JMW12]: We manage most successfully with IV methylpred. Some need IVIG as the disease process differs.

** May be approved to prevent ventilation and shorten stay in ICU in patients with decreasing lung functions.

May be approved to pregnant women with contraindications to steroid therapy.

$$ may be approved in selected cases.

&& May be approved for patients with intracranial bleeding

*Grade A: Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency evaluating the specific recommendation (evidence levels Ia, Ib).

Grade B: Requires the availability of well conducted clinical studies but not randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb).

Grade C: Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; indicates an absence

2012

Appendix F:
Protocol

MPH Dissertation Proposal

A review of the use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

This proposal is submitted in partial fulfilment of the MPH (Hospital Management) at the University of Kwa-Zulu Natal

Shenaaz Raiman - 9703187
University of Kwa-Zulu Natal
1/1/2012

STUDENT

Name: Miss Shenaaz Raiman
Student No. : 9703187
Pharmacy Council Nº : 19385
Contact details: (021) 683 3411
Department: Public Health Medicine
Tel.: (021) 658 5031 e-mail: SRAIMAN@pgwc.gov.za
Cell: 083 786 4059

Student's signature:

Co-Investigator:

Name: Dr T.B. Welzel
Department: Surgery, Division of Emergency Medicine, UCT
Tel.: 021 462 5493 Cell: 082 400 6780
Tyson.welzel@uct.ac.za

Signature:

INTERNAL SUPERVISOR:

Name: Dr S Knight
Department: Public Health
Tel.: 031 260 4226 Cell: 086 762 3123
e-mail: Knights@ukzn.ac.za

Signature:

Summary

Background;
Polyvalent intravenous immunoglobulin (IVIG) is registered for specific indications in South Africa and is being used off-label for a number of differing diseases. The majority of this use has been undocumented. In spite of no evidence based guideline existing in South Africa for IVIG, clinical demand is on the increase.

Purpose;
The aim of the study is to describe indications and frequency of use of IVIG at a tertiary paediatric hospital in South Africa for periods January 2009 to March 2012

Objectives;
The main objectives of the study are to determine the usage, demographic profile, indication and cost per patient of IVIG in the study period as well as the patient outcomes if available.

Study design;
An observational, cross-sectional descriptive study design will be used.

Setting;
A paediatric tertiary/ specialist referral centre located in Cape Town in the Western Cape.

Study population;
All patients who were issued polyclonal IVIG both as outpatients or inpatients.

Study sample;
The study involves a convenience sampling technique taken consecutively on a named patient basis from pharmacy dispensing records between 2009 and 2012.

Data collection;
Primary data will be obtained from the electronic dispensing database of named patients issues within the Pharmacy Department. A folder review will be conducted to extract all other relevant data. Thereafter the NHLS database will be used for collection of other data if not found sufficient in the folder review.Consultation with clinicians for verification may ensue.

Statistical methods;
The data obtained will be summarised using appropriate measures of central tendency and dispersion and presented in tables and graphs.

Table of Contents

1 Introduction /background

1.1. What is the problem?

1.1.1. Research Question?

What were the indications and actual usage of polyvalent human immunoglobulin (IVIG) at a paediatric tertiary referral hospital in South Africa between 2009 and 2012?

1.1 What is known so far?

Intravenous immunoglobulin has been used to treat several groups of conditions including primary imunodeficiencies, secondary immunodeficiencies, autoimmune diseases and neurological disorders. Several countries including the United States, United Kingdom, Canada and Australia[1] have published evidence-based guidelines for the administration of immunoglobulin therapy.[,2,3,4] In South Africa, intravenous immunoglobulin is registered for a narrow spectrum of indications[5]. However, beyond these registered indications, no evidence-based guideline exists. Individual clinical judgement determines consideration and use. Such subjectivity can lead to a very varied and occasionally indefensible practice.

1.2 What needs to be known?

To date there have been no known publications from sub-Saharan Africa, describing the pattern and spectrum of usage of intravenous immunoglobulin, neither in adults, nor in children.

Red Cross War Memorial Children's Hospital (RCWMCH) has shown an

increasing trend in usage over the last few years. Therefore, to gain an understanding into the indications of use of IVIGs at the hospital, a retrospective audit on the dosages and indications for use will be completed.

1.3 Why is the problem important?

Polyvalent Intravenous Human Immunoglobulin (IVIG) is available in South Africa as Polygam® produced by the National Bioproducts Institute which has been the sole supplier of human immunoglobulins up to 2010. Recently externally produced products have now entered the market.

In South Africa, high concentrations of IVIG are derived from pooled human plasma, sourced primarily from non–remunerated blood donors. Demand has increased indicating that either there is a generally longer duration of use or, the spectrum of usage has increased placing a higher demand on the supplier. Currently most of the plasma harvested in the country goes towards producing IVIG. This has meant that of late, plasma derived from blood donors within South Africa has been insufficient to meet the need. Hence plasma is now also being procured from Germany, thereby increasing the cost and time of production.[a]To meet the increasing demands, the sole supplier has embarked on a major refurbishment process.

At both national and hospital level, there is no standard policy guiding use and duration of treatment other than its registered uses. Anecdotal evidence suggests that the unregistered uses might outweigh the registered use. It is also unknown if clinical outcomes are measured routinely both for registered and

[a] Personal communication: Trisha Chetty, Head: Information of NBI, Sept 2011)

unregistered use or whether the intervention of IVIG administration has a desired response that is definable for the indication it is proposed for

RCWMCH is the only specialist paediatric government hospital in sub-Saharan Africa with a catchment area that is undefined due to specialist referrals from all of South Africa and beyond. These specialist tertiary and quaternary areas involve oncology, haematology, neurology, renal, and dermatology. RCWMCH holds 290 beds with a busy out-patient service. RCWMCH has seen approximately 28 200 admissions in 2009/ 2010 financial year and 26 400 in 2010/ 2011. Private medically funded patients tend to also access the highly specialised services offered at RCWMCH. Whilst theoretically, polyclonal IVIG is restricted in its use within government facilities by the Provincial Code List, it is not known for exactly what indications polyclonal IVIG is used for. IVIG is very expensive and is one of the top 50 cost drivers in the medicines budget for a number of years at RCWMCH (taken from the electronic dispensing record called JAC at the pharmacy department showing annual usage of drugs 2007-2012). This trend is evident in other tertiary referral centres in the Western Cape too, resulting in successively larger percentages of the pharmacy budget being attributed to the purchase of IVIG. It is uncertain if there is a greater therapeutic need for IVIG, in which case alternate suppliers of the immunoglobulin must be sought in order to keep up with supply or production of IVIG from the current sole supplier needs to increase. Other aspects that may present itself include an inappropriate use (clinically and cost effectively) of IVIG in the presence of other suitable alternatives or establishing the need for IVIG as newer therapeutic solutions to other disease states. The long-term risks associated

with the injudicious use of to IVIG in general are unknown, while the actual proportion of hypersensitivity reactions and other associated side effects from treatment at RCWMCH also remains undocumented.

Without all this information, pharmacy and management is unable to formulate an evidence-based strategy.

How will the study solve the problem?

Understanding the usage patterns and spectrum of use of IVIG at RCWMCH is integral to determining the frequency of off-label use at RCWMCH. An analysis of the past indications, evidence for use and outcome including side effects can assist in determining rationale for future use and duration of use in a broader context. In addition, a pattern of disease profiles in the paediatric setting that warrants the use of IVIG (outside the registered use) may be established including that of outliers. The study will compare registered use with off-label use.

Finally, this study will aim to calculate the average annual per patient cost of IVIG, which will allow future projections in the purchase thereof. Forecasting and creating a specific budget for the indications (will allow better control and management of IVIG that the Department of Health (DoH) may make use of in terms of planning for IVIG expenditure at an academic level in years to come Ultimately the aim would be to fuel further studies in this field within South Africa to enrich the knowledge base within the context of a developing world and the population it feeds and thereby aid future health systems in a collective policy or guideline for use of IVIG nationally

2 Literature Review

Polyclonal human IVIG is a plasma protein replacement therapy containing large concentrations of varying subclasses of (Immunoglobulin G) IgG antibodies as well as minute quantities of (Immunoglobulin A) IgA and (Immunoglobulin E) IgE found naturally in human plasma. It is obtained from pooling the plasma of not less than 1000 non-remunerated blood donors and then subjecting the plasma to a stringent fractionation and pasteurisation process to obtain the final useable product.[6] These IgG molecules reflect the collective acquired immunity of the donor pool from which it is derived.

Approximately 25 commercially available products are available globally but are not considered generic to one another due to the variances in source, manufacturing processes and ultimately product.[7] These differences include varying concentrations of immunoglobulin and IgG subclasses, differing infusion rates, side effects and antibody titre. In addition the various IgG formulations are thought to include small amounts of soluble CD4, cytokines, soluble cytokine inhibitors, major histocompatibility complex and stabilising agents that exhibit their own independent effect as determined from the donor plasma pool.[8]

Consequently, whilst all these products are therapeutically effective, the concentration and uses may differ in minor ways in the country in which they are registered.[9]

The mechanism of action of polyclonal IVIG is multifaceted lending itself as a therapeutic medium to a wide array of disease states, as evident from Table 1.

Table 1: Mechanism of action of polyclonal IVIG

- Modulation of complement activation;
- Saturation of idiotypic antibodies;
- Suppression of Fc receptors on macrophages and activation of dendritic cells to mediate anti-inflammatory effects helping to reduce the severity of the autoimmune disease or inflammatory states;
- Suppression of a multitude of inflammatory mediators including chemokines, cytokines and metalloproteinases[10,11]

For this reason, IVIG has an important role in the treatment of auto-immune and immune deficiency states by conferring a passive immunity, while also acting as an immunomodulator. These various mechanisms may be important in the different therapeutic uses of IVIG, including (1) replacement therapy for primary and secondary immunodeficiencies, i.e. antibody deficiencies, (2) specific passive immunotherapy, and (3) management of specific inflammatory and/or immunologic disorders. The complete mechanism of action of IgG however is not fully understood and further research is on-going with evidence for greater therapeutic outcomes with use in other infectious disease states as well as other autoimmune conditions coming to the fore.[12]

Registered and Non-registered Uses

IVIG is registered internationally and nationally for only a few specific indications. (Fig. 1) At the same time the majority of IVIG use can be attributed to the off label use with approximately 150 varied indications documented, as tabulated by Leong *et al*.[13] (See Appendix A). IVIG has had a huge impact clinically especially in the treatment of some rare disorders in the fields of neurology, haematology, immunology, nephrology, rheumatology and infectious diseases. The broad spectrum of activity as replacement or booster therapy for

Antibody IgG in humans does not preclude its use as adjunct therapy to a myriad of disease conditions. [14]

However the lack of sufficient randomized controlled trials speaking for the usage of IVIG in many of these unregistered conditions is concerning. Internationally some evidence based guidelines have been developed[1-4] but these do not exist for South Africa as such, usage remains uncontrolled or subject to registered restrictions. To what extent this is being monitored is unknown.

Table 2: Current Registered Use of Polyclonal IVIG 2011 in the USA and SA.

FDA Registered use Polyclonal IVIG (US)	MCC Registered use of Polyclonal IVIG (South Africa)
Primary immunodeficiencies	Replacement therapy in primary antibody deficiency syndromes.
Chronic lymphocytic leukaemia	Myeloma or chronic lymphocytic leukaemia with severe hypogammaglobulinaemia and recurrent infections.
Idiopathic thrombocytopenic purpura	**For immunomodulation in:** * Idiopathic Thrombocytopenic Purpura (ITP) in children and adults. * Kawasaki disease. * Guillain Barré Syndrome.
Allogeneic bone marrow transplant	Allogeneic bone marrow transplantation.
Paediatric HIV	Children with congenital AIDS and recurrent infections
Kawasaki disease	
Chronic inflammatory demyelinating polyneuropathy (CIDP).	
Kidney transplant with a high antibody recipient or with an ABO incompatible donor	
Alzheimers disease still undergoing phase III trials)	

Only the Gamunex® brand manufactured by Talecris is approved for CIDP (in 2008; under the U.S. Orphan Drug law provisions*; Source: Wikipedia*

Globally, increasing usage has led to concerns of a manufacturing shortfall.

Approximately 82 tons of IVIG was consumed worldwide in 2007 and 120 tons expected to be used in 2012. The shortage of plasma-derived medicines and in particular IVIG has had most impact in developing countries. High costs for production, long production times (6-8 months) as well as shortages in plasma from available donors contribute to this shortage. In addition both the on- and off-label uses are rare indications that health budgets in developing countries are not able to allocate sufficient resources towards.[15]

South Africa has had a sole supplier of polyclonal IVIG in the form of National Bioproducts Institute (NBI). Due to increasing demands for IVIG and other blood products, NBI have lately embarked on a major refurbishment process to their production plant. As such the supply of IVIG has been further limited. [7]NBI is reliant on a volunteer blood donor programme for plasma that is screened for hepatitis B surface antigen, HIV -p24 antigen, and antibodies to syphilis, HIV-1, HIV-2 and hepatitis C. Shortages in supply have resulted in NBI having to purchase plasma internationally to keep up with demand. In 2010, other registered products like Interferon B entered the market and Octapharma will be following shortly.

South Africa currently has dual public- and private-funded healthcare systems. Approximately 84% of all South Africans, generally lower income and unemployed citizens, make use of the public health medical service whilst higher income groups access their own private medical care.[16]

The public system geared towards prioritization key health issues aimed at meeting the majority of the public health needs, but cannot fully address

individual and rare disease conditions adequately at all times. Levels of health care exist in the public system restricting the use of specific drugs to different levels of care. In the Western Cape, usage of IVIG is restricted to central and tertiary level facilities for paediatrics and specialist usage only. Patients needing access to such therapies would have to be referred to these institutes. Occasionally secondary level hospitals have issued IVIG but hesitate to do so as it erodes the budget of these facilities greatly and requires them to purchase IVIG outside the coded restrictions.

Polyclonal IVIG is expensive, costing between ZAR 301.60 (2006) and ZAR 415.94 (2011) per gram IVIG at state level and approximately 20% more in private health facilities. Rather than being restricted by a coding list, usage in private is determined by what the funder is willing to cover and pay for. Varying medical systems offer varying levels of cover and have established norms for their own usage. (See Appendix B).

With clinical research continuously expanding the potential applications of IVIG this concern is valid. The broad mechanism of action allows IVIG as a therapeutically viable choice and often last resort in many disease and infectious states. Whilst attempts have been made to document the unregistered use in various institutes internationally, no such audit has been documented within South Africa. This information can then been used to formulate evidence based guidelines and policies regarding the unregistered use of IVIG.

3 Purpose of the study

The aim of the study is to assess the use and indications for use of Intravenous immunoglobulin at Red Cross War Memorial Children's Hospital a tertiary paediatric hospital in South Africa for periods January 2009 to March 2012 in order to develop recommendations for a guideline on future use.

4 Specific Objectives

The specific objectives of the study are:

1. To describe the total annual usage of IVIG;
2. To describe the demographic profile of children who have received intravenous immunoglobulin therapy;
3. To list the indications for usage as recorded in patient folders, and/ or by relevant clinician's judgement.
4. To correlate the indications for intravenous immunoglobulin therapy to registered and off-label use recommendations during this time period;
5. To estimate the expenditure on immunoglobulin therapy and relate this to the total drug expenditure during each financial year; To calculate the annual cost and cost per patient for forecasting budgets; and
6. To identify the main unregistered indications for use that will need to have treatment protocols developed for them.

5 Type of research

Heath systems research that can be applied clinically in assisting prescribing practices.

6 Definitions

There are no extraordinary definitions in this study.

7 Research Methodology

7.1 Study Setting

Red Cross War Memorial Children's Hospital is the only dedicated paediatric tertiary/quaternary hospital located in Cape Town, Western Cape province in South Africa. It has approximately 250 000 patient visits a year and is the centre for academic excellence in training, teaching and child healthcare as well as playing a pivotal role in Africa for the treatment of life limiting, life threatening and complex illnesses in children. As a consequence it sees specialist referrals from not only the Western Cape but other parts of South Africa and Africa.

7.2 Study Design

An Observational, cross-sectional descriptive study design will be used.

7.3 Target Population

Paediatric patients treated with polyclonal IVIG in tertiary care within South Africa.

7.4 Study population

All patients who were issued polyclonal IVIG, both as outpatients or inpatients at RCWMCH.

7.4.1 Inclusion Criteria

The inclusion criteria are:

- All patients issued or administered polyclonal IVIG between 1st January 2009 and 31 March 2012 as in-patients or out-patients from RCWMCH as based on dispensing data from the JAC dispensing programme in pharmacy;
- All issues from JAC data system of polyclonal intravenous immunoglobulin (Polygam® and Intraglobin F®) Both Private and Public patients irrespective of age that have been issued polyclonal IVIG from RCWMCH pharmacy data as in-patient or out-patients in the stipulated time periods; and
- Emergency cupboard issues for after hours as recorded on a named patient basis in the pharmacy dispensing system.

7.4.1 Exclusion Criteria

The exclusion criteria are:

- Any unknown administration of IVIG not recorded in pharmacy dispensing systems in the stipulated time period;
- Any other issue of monoclonal intravenous or intramuscular immunoglobulin e.g. Intragam®, basiliximab, ATG®, Rabigam®, Vazigam®, Tetagam® Habigam® etc.;
- Any lending of stock to other institutes that are recorded or not recorded in the pharmacy dispensing system; and
- Any incidental usage of polyclonal IVIG by patients at RCWMCH in the stipulated time period that has not been issued and recorded in the dispensing system i.e. use/administration of private stock.

7.5 Study Sample

The study involves a convenience sampling technique taken consecutively on a named patient basis from pharmacy dispensing records between 2009 and 2012. Data in a 3 year period is being assessed from the pharmacy database (JAC) of IVIG issues to different parts of the hospital. As this study is the first

known study of actual usage of polyclonal IVIG in a hospital in South Africa, it serves as an exploratory analysis of the current usage within a paediatric hospital. It is estimated that the last 3 financial years (containing approximately 6070 issues of polyclonal IVIG annually) will provide an adequate picture of current usage and trends. A larger and therefore older sample, e.g. looking back 5 - 10 years, might not reflect current prescription practice.

7.5.1 Method of selecting sample

The last completed 3 years, 2009, 2010,2011 and until March 2012 are being used as the sample.

7.5.2 Size of sample

Approximately 70 patients of IVIG annually from periods 2009 to March 2012 per year, i.e. approximately 200 patients in the total review.

7.6 Data sources

Data will be derived from the following sources:

- A list of named patient issues will be collected from the pharmacy dispensing database (JAC).
- The folders of the identified patients will be dawn and the data extracted per patient onto the data extraction form. (See Appendix C).
- Additional data not found in folders such as results of liver function tests, blood counts, Immunoglobulin G (IGG) trough testing and HIV status will be obtained from the National Health Laboratory Services (NHLS) data-base at the hospital.

- Relevant clinicians will be consulted informally to determine indication for use if necessary.

7.6.1 Measurement instruments / Data Collection Techniques

The JAC Database of polyclonal IVIG issues within the past 5 years is available and has been archived in an Excel™ spread sheet. This spread sheet will be converted to pivot tables to look at varying outcome variables and subsequently interpreted and described. This database will also form the primary basis of the folder review.

Appendix C shows the Data Collection Sheet that will be used to extract the data from patient folders. The final collected data will be dual inputted into an Excel™ database and compared for validity. The final product will be converted into an SPSS® database for further analysis and descriptions.

Measures to ensure validity

7.6.2 Internal

The JAC pharmacy database records all issues and returns of drug from the pharmacy to named patients or wards/clinics. Data is archived annually in the head office JAC database and available on written request.

- The pharmacy database relies on the manual inputting of all dispensing by pharmacists and pharmacy assistants and as such is prone to human error. Human error can result in false inputting of data against incorrect patient folder numbers, wards or clinics.
- Any emergency cupboard issues after hours that have not been recorded and issued from the JAC database the following day will escape the data collection in pharmacy.

- Any stock take where discrepancies in count of polyclonal IVIG occur lends itself to manipulation by stock adjustments on the JAC database. However, the past few stock takes have shown significant agreement with the JAC database.
- Any differences/errors in transcribing of data from source (patient folders) to data collection sheets and subsequent database (Excel or SPSS), though this is being minimised by dual entry and back-checking.

7.6.3 Reduction of bias

7.6.3.1 Selection bias

There is no way to reduce selection bias as purposeful sampling is being utilised in this study. The aim is to measure trends in usage for the stipulated time period irrespective of other trends at different time periods. Thus this will be a non-random cross-sectional sample.

7.6.3.2 Information bias

There are two significant sets of non-differential bias arising from (a) the use of the JAC system and the ability to retrieve all the folders and (b) the interpretation of the diagnoses by the investigator. In the former, all pharmacists will at some time or other have issued IVIG via the JAC system, so that the electronic record reflects the average accuracies/ inaccuracies of all the staff over the past three years. In the latter, the investigator will have to interpret a number of usually clinician specific diagnoses and reduce them to a standard recognisable diagnosis. To do this, consultation with the relevant clinician, if available, will be done to minimise misinterpretation of diagnoses. Apart from the error that arises from the initial diagnosis, the secondary interpretation itself is also error-prone.

Differential misclassification bias might arise from the fact that specific specialised clinics may themselves already be applying cut-offs and are therefore “diluting” the figures for the hospital as a whole in terms of who is getting IVIG for what. In addition, as some of the treatments might be controversial, there may be a higher emergency cupboard use of IVIG rather than pharmacy ordered IVIG, thereby circumventing the patient-recording mechanism of the JAC system.

7.6.4 External Validity / Generalisability

One of the inherent features of this study is that it will only reflect the prescribing practices of clinicians working at RCWMCH in the past three years. As such, the results will not be generalizable to other populations because unique to this setting. At the same time, this will serve as an exploratory appraisal of actual paediatric use in a tertiary setting. Trends in usage can assist in determining future trends in usage and projections into infections treated annually that warrant the use of IVIG, quantities required as well as establish an initial picture on current usage. This information can be used further internally as well as externally to other paediatric populations within South Africa as a means of reflection and comparison.

7.7 List of Variables

A complete list of variables to be measured is listed under appendix (See Appendix C) in the Data collection sheet. The main variables are listed below.

- Age in years: discrete
- Sex: Binary
- Mass: continuous
- Race: Nominal
- Patient profile: Nominal
- HIV Status: Nominal

- Indication for use: Nominal
- Quantity prescribed: continuous
- Dates issued: continuous
- Amount issued: continuous
- Wastage: continuous

7.8 Plan for Data collection

The captured data from JAC is a computer-based pharmacy dispensing platform, where all the variables are automatically captured in real time, archived and are transferred to a spread sheet. The manually obtained data collection sheets will be dual entered into an Excel™ 2010 (Microsoft Corporation) spread sheet, validated and plotted per annum. As described above, the JAC data will form the basis for the folder search. All patients identified via the JAC database will have their folders drawn and the data extracted as per the standard data extraction form. There will be three attempts to retrieve a folder within the three-month data collection period, after which it will be deemed to have been “lost” for purposes of this study.

7.9 Plan for Data handling/ processing

Any ambiguity in data interpretation will be reviewed by an independent person from the study and the final assessment made by consensus. If vital data fields are missing, such as age, body weight or diagnosis, that element will not be included in the section requiring that analysis, but could be used for the overall calculations.

It will then be analysed in SPSS® (IBM Corporation). The services of a statistician will be utilised to confirm the appropriateness of the statistical tests utilised and check any trend analyses.

All paper records will be stored in a secure, locked, fire-proof filing cabinet at the researcher's office. Electronic records will be pass-phrase protected using a commercial encryption technique and backed-up daily in a whole drive pass-phrase protected external hard drive, kept separate from the first database and stored in a fire-proof filing cabinet. Two different external hard drives will be used for the daily backup and alternated to allow for a reliable data record in case of hard drive failure.

7.10 Statistical methods

7.10.1 Descriptive statistics

Most of the statistics in the study will be descriptive, categorising the clinical uses into broad categories. The data obtained will be summarised using appropriate measures of central tendency and dispersion and presented in appropriate tables and graphs. Simple statistics for the Table 1 summary of patient characteristics, listing 95% CI, mean and median will be outlined. In addition, there will be summaries of the average duration of treatment, dose of treatment per kilogram body weight and average cost per patient year by year.

7.10.2 Analytic statistics

As this is an observational study, analytical statistics will not be utilised.

8 Ethical Considerations

8.1.1 Institutional Ethical Review Board

This study will be conducted with due regard to the ethical principles laid out in the Declaration of Helsinki and Good Clinical Practice (GCP). It will be

submitted for expedited review to the Human Research ethics Committee of both RCWMCH and the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee. This is a low-risk study from an ethics point of view, as it is essentially a retrospective record review, including the few months of data gathered in 2012, as it is an observational study, gathering the data relating to the cases “after the fact”. In addition, for the purposes of the analysis and publication, all patient-level data will be anonymised, with a master-identification sheet kept separately and only accessible to the principal investigator.

8.1.2 Permissions

This research project will be registered with the UKZN Postgraduate Education Committee for academic purposes. As RCWMCH is a government-run healthcare facility, in addition to the Institutional Review Board, permission will have to be obtained from the head of the institution, Dr L Lunga, as well as the Provincial Research Committee. Only after having obtained these permissions will the study commence.

8.1.3 Informed Consent and Information

We will request a waiver of informed consent, as this is a retrospective record review, as outlined above.

9 Work Plan

9.1 Budget

Budget				
April 2012 –July2013				
Item	**Description**	**Unit cost**	**Nº of Units**	**Total cost**
Consumables				
1. specialized services	Statistician	R 350.- / h	10h	R 3 500.-
2. office supplies, printing & reproduction for data collection	Papers, clipboards, photocopies to produce the 2-page data sheet for 240 study samples	R 500.-	1	R 500.-
3. office supplies, printing & reproduction for reports	Binders, copies of data reports with cover letters x 2		1	R 400.-
Research travel				
1. other, specify	Travel to get approvals	R 2.70 / km (AA rate)	300 km	R 810.-
2. Travel to supervisor	Three visits to Durban for Supervisor meetings and major reviews	R2000.-	3	R6 000.-
Minor research equipment				
1.	3G Internet access via dongle	R 1000.-	1	R 1 000.-
2.	External Hard Drives (500GB)	R 650.-	4	R 2 600.-
3.	Netbook	R 4600.-	1	R 4 600.-
Sub-Total				**R 19 410.-**
Total	**10% safety factor included**			**R 21 351.-**

9.2 Study period / Time lines

	April	May	June	July	Aug	Sept	Oct	Nov
Departmental Research Committee	X							
Ethics Committee		X						
Institutional & Provincial permissions		X						
Creating patient lists			X					
Obtaining folders & data extraction			X	X	X			
Statistical Analysis						X		
Compilation of final report						X	X	
Submission of final Thesis							X	

10 Acknowledgments

ALLAH, Theresa Blockman, Naiema Salie, Brian Eley,Liz Goddard and Trisha Chetty.

11. References

[1] Australian Health Ministers Advisory Council. Review of the use and supply of intravenous immunoglobulin in Australia. A report by the Blood and Blood Products Committee. June 2000. Last accessed 15 November 2011 from htpp://www.nba.gov.au/PDF/IVIg.pdf.

[2] Constantine MM, Thomas W, Whitman L et al. Intravenous immunoglobulin utilization in the Canadian Atlantic provinces: a report of the Atlantic Collaborative Intravenous Immune Globulin Utilization Working Group. Transfusion 2007; 47:2072-2080.

[3] Robinson P, Andersen D, Brouwers M et al. Evidence-based guidelines on the use of intravenous immune globulin for hematologic and neurologic conditions. *Transfusion Med Reviews* 2007;21:S3-S8.

[4] Chen C, Danekas LH, Ratko TA et al. A multicenter drug use surveillance of intravenous immunoglobulin utilization in US academic health centers*. Ann Pharmacother* 2000; 34:295-299.

[5] South African Electronic Package Inserts. Polygam. Last accessed on 10 August 2011, available online from: http://home.intekom.com/pharm/nbi/polygam.html .

[6] Sisti A.M, Vitali MS, Manfredi MJ, Zarzur JA. Preparation of lyophilized and liquid intravenous immunoglobulin G: development and scale-up. *Blackwell Science Ltd. Vox Sanguinis*. 2001;80:216-224.

[7] Chapel HM. Safety and availability of immunoglobulin replacement therapy in relation to potentially transmissible agents. *Clin Exp Immunol* 1999; 118**:** S29-S34.

[8] Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol* 2005; 142: 1-11.

[9] Romer J, Spath PJ, Skvaril F, *et al*. Characterization of various immunoglobulin preparations for intravenous application. II. Complement activation and binding to staphylococcus protein A*. Vox Sang*. 1982;42:74–80.

[10] Dalakas MC. Mechanisms of action of IVIG and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology*. Dec 24 2002;59(12 Suppl 6):S13-21.

[11] Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*. Sep 6 2001;345(10):747-55.

[12] Nydegger Urs E. Intravenous immunoglobulin, chapter 18, in : Simon, T. L., Snyder, E. L., Solheim, B. G., Stowell, C. P., Strauss, R. G. and Petrides, M. (eds) (2009) Front Matter, in Rossi's Principles of Transfusion Medicine, Fourth Edition, Wiley-Blackwell, Oxford, UK. doi: 10.1002/9781444303513.fmatter.p 260-272.

[13] Leong H, Stachnik J, Bonk ME, Matuszewski KA. Unlabeled uses of intravenous immune globulin. *Am J Health Syst Pharm*. Oct 1 2008;65(19):1815-24.

[14] Singh V.N, Riramulu E ,Siberil S, Graff-Dubois S, Mouthon L, Mitchel D *et al.* Intravenous Immunoglobulin: An Update on the Clinical Use and Mechanisms of Action *J Clin Imm*, Vol. 27, No. 3, May 2007 (C 2007).

[15] Cheraghali AM, Abolghasemi AB. Improving availability and affordability of plasma-derived medicines. *Biologicals* 38 (2010) 81–86.

[16] National Department of Health of South Africa. National Health Insurance in South Africa – Policy Paper. Last updated on 11 August 2011, last accessed on 13 August 2011, available online from http://www.info.gov.za/view/DownloadFileAction?id=148470.

[19] Hendriksen C, Hau J. 2003. Production of polyclonal and monoclonal antibodies. In: Handbook of Laboratory Animal Science. 2nd ed. Boca Raton: CRC Press LLC. p 391-411. http://dels-old.nas.edu/ilar_n/ilarjournal/46_3/pdfs/v4603Leenaars.pdf

[20] Nelson R E and Biberdorf R I. Nationwide Drug Shortages: It's Time to Take the Lead. *Nutrition in Clinical Practice.* 1998; 13:295-7.

[21] Schrand L M, Troester T S, Ballas Z K, Mutnick A H, and Ross M B. Preparing for drug shortages: One teaching hospital's approach to the IVIG shortage. *Formulary.* 2001; 36:52-9.

[22] Tyler LS, Fox ER, and Caravati EM. The Challenge of Drug Shortages for Emergency Medicine. *Ann Emerg Med.* 2002; 40:598-602.

[23] Goddard EA. Intravenous Immuonoglobulin Current Allergy & Clinical Immunology, March 2008 Vol 21, No. 1: 26 – 31

APPENDIX G:

DATA COLLECTION SHEET

THE ADMINISTRATION OF INTRAVENOUS IMMUNOGLOBULIN (IVIG) AT RED CROSS CHILDREN'S HOSPITAL FROM 2009 TO 2012

Demographic Data				**Data Capturer**
Date of birth				
Study number				
Sex				
Race	Black White Coloured Indian Other:			
HIV status if available				
Intravenous immunoglobulin – first time point from 2009				
Mass (kg to one decimal place) at the point of first administration from 1st April 2009 onwards				
Age (years and months to one decimal place) at time of administration of first dose in 2009 or onwards				
Indication for intravenous immunoglobulin therapy				
Primary Diagnosis				
Secondary Diagnosis				
Other diagnoses				
Amount (grams) prescribed and duration of treatment				
Amount (grams) issued by pharmacy	1 gram	3 gram	6 gram	12 gram
Wastage				
Concentration administered (grms/kg)				
Inpatient / outpatient administration Ward initiated				
Adverse events (Yes 2/No 1/unknown 0)				
Adverse events – describe, include date and time and relationship to IVIG infusion				
Repeat immunoglobulin therapy subsequently				
Was IVIG repeated during 2009 or thereafter (Yes/No)				
If yes, how many times during 2009 or thereafter				
List dates, amount prescribed, amount issued, concentration administered				

Date	Prescribed (grms)	Issued (grms)	Concentration (grms/kg body mass)	Wards

Has the patient responded favourably as judged by the clinician in notes (Yes 2/No 1/unknown 0)				
Have trough IgG concentrations been assessed (Yes 2/ No 1) as from laboratory source.				
Level of IGG				
Level of IGA				
Level of IgM				
Has an appropriate response been made to the trough level (Yes 2/No 1/unknown 0)				
Has liver functions been monitored regularly (Yes 2/No 1/unknown 0)				
Adverse events (Yes 2/No 1/unknown 0)				
Adverse events – describe, include date and time and relationship to IVIG infusion				
Previous IVIG administration – before 2009				
Has the patient received IVIG previously (Yes 2/No 1/unknown 0)				
If yes, since when (date)				
If yes, frequency of administration				
Has the patient responded favourable as judged by the primary clinician (Yes 2/No 1/unknown 0)				
Has trough IgG concentration been assessed (Yes 2/No 1/unknown 0)				
Has liver functions been monitored regularly (Yes 2/No 1/unknown 0)				
Adverse events (Yes/No)				
Adverse events – describe, include date and time and relationship to IVIG infusion				

APPENDIX H
BREC APPROVAL

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

28 October 2014

Ms. S Raiman
Department of Public Health
Nelson R Mandela School of Medicine
University of KwaZulu- Natal

Dear Ms Raiman

PROTOCOL: Three year review on the use of polyclonal intravenous human immunoglobulin at paediatric referral hospital in South Africa. REF: BE071/12.

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	03 October 2014
Expiration of Ethical Approval:	02 October 2015

I wish to advise you that your application for Recertification received on 08 October 2014 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

This approval will be ratified by a full Committee at its next meeting taking place on **09 December 2014.**

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics

APPENDIX I:

HOSPITAL APPROVAL

RESEARCH PROPOSAL SUMMARY	
Name of Institution / Organisation	Red Cross War Memorial Children's Hospital
Name and qualifications of Investigators	Ms. S.Raiman BPharm
Telephone number	0216585031
Fax number	0867234866
Cell phone number	0837864059
Email address	Shenaaz.Raiman@pgwc.gov.za
Institution giving ethics approval	University of KwaZulu Natal
Date of ethics approval	Awaiting hospital approval- see attached
Expected start date of research	1 May 2012
Expected end date	1 December 2012
Date reports expected	1 May 2012
Research title	A review of the use of polyclonal intravenous human immunoglobulin's at a paediatric referral hospital in South Africa between 2009 and 2012
Keywords	IVIG, polyvalent immunoglobulin, Red Cross War Memorial children's hospital
General research goal	The aim of the study is to describe indications and frequency of use of IVIG at a tertiary paediatric hospital in South Africa for periods January 2009 to December 2011 The main objectives of the study are to determine the usage, demographic profile, indication and cost per patient of IVIG in the study period as well as the patient outcomes if available.
Special research objectives	The specific objectives of the study are: 1. To describe the total annual usage of IVIG; 2. To describe the demographic profile of children who have received intravenous immunoglobulin therapy; 3. To list the indications for usage as recorded in patient folders, changes in the treatment indications over time and their recorded outcome; 4. To correlate the indications for intravenous immunoglobulin therapy to registered and off-label use recommendations during this time period; 5. To estimate the expenditure on immunoglobulin therapy and relate this to the total drug expenditure during each financial year; To calculate the annual cost and cost per patient for forecasting budgets; and 6. To identify the main unregistered indications for use that will need to have treatment protocols developed for them.
Brief description of methodology	All patients issued or administered polyclonal IVIG between 1st April 2009 and 31 March 2012 as in-patients or out-patients from RCWMCH as based on dispensing data from the JAC dispensing programme in pharmacy; Data will be derived from the following sources: A list of named patient issues will be collected from

	the pharmacy dispensing database (JAC). The folders of the identified patients will be drawn and the data extracted per patient onto the data extraction form. All patient names and folder numbers to be converted to study numbers to maintain patient anonymity.	
Budget for the research	Personal budget to be utilised	
Source of funding	Out of pocket	
	YES	NO
Additional load on nursing		x
Support services		x
Consumables		x
Laboratory tests		x
Equipment		x
Space		x
Communications	x	
Additional OPD visits		x
Admission of patients		x
The research will have implications for the requested facilities:		
If yes, what are these implications and how does your project plan to mitigate the impact?	Not applicable	
Operational manager informed of the research?	Yes	
How will results be disseminated?	On request	
What are your sustainability or exit plans?	Not applicable	

Approved/~~Not approved~~

Dr. T. Blake (Medical Manager Red Cross War Memorial Children's Hospital)

Date: 15/5/12

APPENDIX J:

AMENDMENT RATIFICATION AND APPROVAL

	the pharmacy dispensing database (JAC). The folders of the identified patients will be drawn and the data extracted per patient onto the data extraction form. All patient names and folder numbers to be converted to study numbers to maintain patient anonymity.	
Budget for the research	Personal budget to be utilised	
Source of funding	Out of pocket	
	YES	NO
Additional load on nursing		x
Support services		x
Consumables		x
Laboratory tests		x
Equipment		x
Space		x
Communications	x	
Additional OPD visits		x
Admission of patients		x
The research will have implications for the requested facilities:		
If yes, what are these implications and how does your project plan to mitigate the impact?	Not applicable	
Operational manager informed of the research?	Yes	
How will results be disseminated?	On request	
What are your sustainability or exit plans?	Not applicable	

Approved/~~Not approved~~
Dr. T. Blake (Medical Manager Red Cross War Memorial Children's Hospital)
Date: 15/5/12

	the pharmacy dispensing database (JAC). The folders of the identified patients will be drawn and the data extracted per patient onto the data extraction form. All patient names and folder numbers to be converted to study numbers to maintain patient anonymity.	
Budget for the research	Personal budget to be utilised	
Source of funding	Out of pocket	
	YES	NO
Additional load on nursing		x
Support services		x
Consumables		x
Laboratory tests		x
Equipment		x
Space		x
Communications	x	
Additional OPD visits		x
Admission of patients		x
The research will have implications for the requested facilities:		
If yes, what are these implications and how does your project plan to mitigate the impact?	Not applicable	
Operational manager informed of the research?	Yes	
How will results be disseminated?	On request	
What are your sustainability or exit plans?	Not applicable	

Approved/~~Not approved~~
Dr. T. Blake (Medical Manager Red Cross War Memorial Children's Hospital)
Date: 15/5/12

APPENDIX K:

JOURNAL SUBMISSION REQUIREMENTS

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually

observations or research of relevance to child health. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**.

Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e.

'women >40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.
Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...
Quotes should be placed in single quotation marks, i.e. The respondent stated: '...'
Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as '**supplementary files**'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...'

All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software.

Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3],[4],[5],[6]

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by *et al*. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references:

Price NC, Jacobs NN, Roberts DA, *et al*. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references:

Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book:

Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references:

World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002.http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format:
Author(s). Title. Publisher place: publisher name, year; pages.

Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

Unpublished observations and personal communications in the text must not appear in the reference

list. The full name of the source person must be provided for personal communications, e.g. '...(Prof. Michael Jones, personal communication)'.

PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

CHANGES OF ADDRESS

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

CPD POINTS

Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested after publication of the article.

CHARGES

There are no charges for the publication of manuscripts.

SUBMISSION PREPARATION CHECKLIST

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.

4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted as 'supplementary files' (not in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

http://www.sajch.org.za/index.php/SAJCH/about/submissions

APPENDIX L:

CONSENT FROM THE AUTHOR S. KNIGHT

UNIVERSITY OF KWAZULU-NATAL
Nelson R Mandela School of Medicine

MEMORANDUM

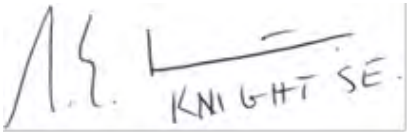
TO:	FROM:
The Editor **Journal of Child Health**	**Dr Stephen Knight** **Discipline of Public Health Medicine**

Date: 30 September 2014

Re: Use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

Dear Editors
I am happy to be involved with the preparation of this article and willing to have my name as one of its athours.

With thanks,
Regards
Stephen Knight



Dr Stephen Knight
Discipline of Public-Health Medicine
George Campbell Building
Howard College Campus
University of KwaZulu Natal
Durban 4041
knights@ukzn.ac.za
0837623123
+27 31 260 4226
+27 31 260 4211

APPENDIX M:

CONSENT FROM THE AUTHOR T. WELZEL

To Whom it May Concern:

Shenaaz Raiman: Use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

I have functioned as secondary supervisor on this project from its inception and am happy to be listed as a co-author. I have no conflicts of interests to declare.

Sincerely,

Dr T. Welzel

Cape Town, 28 September 2014

A review of the use of polyclonal intravenous immunoglobulin at a paediatric referral hospital in South Africa between 2009 and 2012

ORIGINALITY REPORT

18%	17%	6%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.sajch.org.za Internet Source	2%
2	dwdurl.eu Internet Source	1%
3	www.allergysa.org Internet Source	1%
4	www.aphanet.org Internet Source	1%
5	www.nbi-kzn.org.za Internet Source	1%
6	www.ncbi.nlm.nih.gov Internet Source	1%
7	www.aetna.com Internet Source	1%
8	researchspace.ukzn.ac.za Internet Source	1%
9	Submitted to 76830 Student Paper	<1%

REFERENCES[§§]

[1] National Bioproducts Institute. Registered under the Nonprofit Organisations Act, No 71 of 1997. 2014. South Africa. http://www.nbi-kzn.org.za (accessed 10 November 2014).

[2] Frauger E, Grassi J, Pradel V, *et al.* Use of Intravenous Immunoglobulins in Clinical Practice: Data from Three French University Hospitals. Fundam Clin Pharmacol 2011;25(6):753–61. [http://dx.doi.org/10.1111/j.1472-8206.2010.00908.x] [PMID: 21219439]

[3] Ruiz-Antoran B, Agusti Escasany A, Vallano Ferraz A *et al.* Use of Non-Specific Intravenous Human Immunoglobulins in Spanish Hospitals; Need for a Hospital Protocol. Eur J Clin Pharmacol 2010;66(6):633-641. [http://dx.doi.org/10.1007/s00228-010-0800-y] [PMID:20204337]

[4] National Blood Authority Australia. IVig Criteria for Use. 2nd ed. Lyneham: National Blood Authority, 2012. http://www.nba.gov.au/PDF/IVIg.pdf (accessed 10 November 2014).

[5] Constantine MM, Thomas W, Whitman L *et al.* Intravenous Immunoglobulin Utilization in the Canadian Atlantic Provinces: A Report of the Atlantic Collaborative Intravenous Immune Globulin Utilization Working Group. Transfusion 2007;47(11):2072-2080. [PMID: 17958537]

[6] Robinson P, Andersen D, Brouwers M et al. Evidence-Based Guidelines on the Use of Intravenous Immune Globulin for Hematologic and Neurologic Conditions. Transfusion Med Reviews 2007;21(1):S3-S8. [http://dx.doi.org/10.1016/j.tmrv.2007.01.004]

[7] Chen C, Danekas LH, Ratko TA *et al.* A Multicenter Drug Use Surveillance of Intravenous Immunoglobulin Utilization in US Academic Health Centers. Ann Pharmacother 2000;34(3):295-299. [PMID: 10917372]

[8] South African Electronic Package Inserts. Polygam. Malahyde Information Systems, 2014. http://home.intekom.com/pharm/nbi/polygam.html (accessed 10 November 2014).

[9] Sisti AM, Vitali MS, Manfredi MJ, Zarzur JA. Preparation of Lyophilized and Liquid Intravenous Immunoglobulin G: Development and Scale-up. Vox Sang 2001;80(4):216-224.

[§§] Stylistic format of References are consistent with Appendix K: Journals not italicized and DOI's and PMID's inserted where possible.

[http://dx.doi.org/doi/10.1046/j.1423-0410.2001.00041.x]

[10] Chapel HM. Safety and Availability of Immunoglobulin Replacement Therapy in Relation to Potentially Transmissible Agents. Clin Exp Immunol 1999;118(1):S29-S34 [http://dx.doi.org/doi/10.1046/j.1365-2249.1999.00000.x]

[11] Jolles S, Sewell WAC, Misbah SA. Clinical uses of Intravenous Immunoglobulin. Clin Exp Immunol 2005;142(1):1-11. [http://dx.doi.org/doi/10.1111/j.1365-2249.2005.02834.x]

[12] Romer J, Spath PJ, Skvaril F, Nyedegger UE. Characterization of Various Immunoglobulin Preparations for Intravenous Application. II. Complement Activation and Binding to Staphylococcus Protein A. Vox Sang 1982;42(2):74–80. [PMID: 6461133]

[13] Dalakas MC. Mechanisms of Action of IVIG and Therapeutic Considerations in the Treatment of Acute and Chronic Demyelinating Neuropathies. Neurology 2002;59(12/6):S13-21. [PMID: 12499466]

[14] Kazatchkine MD, Kaveri SV. Immunomodulation of Autoimmune and Inflammatory Diseases with Intravenous Immune Globulin. N Engl. J Med 2001;345(10):747-755. [PMID: 11547745]

[15] Nydegger UE. Immunoglobulins. In: Simon TL, Snyder EL, Solheim BG, Stowell CP, Strauss RG, Petrides M, eds. Front Matter, in Rossi's Principles of Transfusion Medicine. 4th ed. Oxford: Wiley-Blackwell, 2009:260-272.

[16] Ochs HD, Ament ME, Davis SD. Giardiasis with Malabsorption in X-linked Agammaglobulinemia. N Engl. J Med 1972;287(7):341-342. [PMID: 5041703]

[17] Saulsbury FT, Winkelstein JA, Yolken RH. Chronic Rotavirus Infection in Immunodeficiency. J Pediatr 1980;97(1):61-65. [http://dx.doi.org/10.1016/S0022-3476(80)80131-4] [PMID: 6247473]

[18] Roifman CM, Rao CP, Lederman HM, Lavi S, Quinn P, Gelfand EW. Increased Susceptibility to Mycoplasma Infection in Patients with Hypogammaglobulinemia. Am J Med 1986;80(4):590-594. [http://dx.doi.org/doi/10.1016/0002-9343(86)90812-0] [PMID: 3963038]

[19] Ballow M. Intravenous Immunoglobulins: Clinical Experience and Viral Safety. J Am Pharm Assoc 2002;42(3):449-458. [PMID: 12030632]

[20] Chapel H, Griffiths H, Brennan V, Bunch C, Lea J, Lee M. Hypogammaglobulinaemia in Low Grade B Cell Tumours; Significance and Therapy. Immunol Invest 1991;20(2):187-191. [http://dx.doi.org/10.3109/08820139109050786]

[21] Griffiths H, Lea J, Bunch C, Lee M, Chapel M. Predictors of Infection in Chronic Lymphocytic Leukaemia (CLL). Clin Exp Immunol 1992;89(3):374-377. [http://dx.doi.org/10.1111/j.1365-2249.1992.tb06965.x]

[22] Wu E, Frank MM. The Mystery of IVig. The Rheumatologist, 2012; March. [http://www.the-rheumatologist.org/details/article/1532121/The_Mystery_of_IVIg.html] (accessed 10 March 2014).

[23] Bruton OC. Agammaglobulinemia. Pediatrics 1952;9(6):722-728. [PMID 14929630]

[24] Imbach P, Barandun S, d'Apuzzo V, *et al*. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet. 1981;1(8232):1228-31.

[25] Rütter GH. Requirements for Safety and Quality of Intravenous Immunoglobulin G Preparations. J Neurol Neurosurg Psychiatry 1994;57(Suppl):2-5. [http://dx.doi.org/10.1111/j.1423-0410.2009.01226.x]

[26] Skoda-Smith S, Torgerson TR, Ochs HD. Subcutaneous Immunoglobulin Replacement Therapy in the Treatment of Patients with Primary Immunodeficiency Disease. Ther Clin Risk Manag 2010;6:1–10. [http://dx.doi.org/10.2147/TCRM.S4353]

[27] Webert K. Outbreak of Hepatitis C Associated with Intravenous Immunoglobulin Administration. MMWR Morb Mortal Wkly Rep 1994;43(28):505-509. [PMID: 8022396]

[28] Westphal RG. Donors and the US Blood Supply. Transfusion 1997;37(2):237–241. [http://dx.doi.org/10.1046/j.1537-2995.1997.37297203531.x]

[29] Weimer T, Streichert S, Watson C. Validation of a PCR Assay System to Screen Plasma for HBV, HCV, and HIV-1. Infusionsther Transfusionsmed 1998;25:139-146. [http://dx.doi.org/10.1159/000053411]

[30] European Agency for the Evaluation of Medicinal Products. Intramuscular Immunoglobulins: Nucleic Acid Amplification Tests for HCV RNA Detection. London: Committee for Proprietary Medicinal Products, 2001. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003613.pdf (accessed 10 March 2014).

[31] Berger M. A History of Immune Globulin Therapy, from the Harvard Crash Program to Monoclonal Antibodies. Curr Allergy Asthma Rep 2002;2(5):368–378. [PMID:12165202]

[32] Ballow M. Safety of IGIV Therapy and Infusion Related Adverse Events. Immunol Res 2007;38(1-3):122–132. [PMID:17917017]

[33] Buchacher, A, Iberer G. Purification of Immunoglobulin G from Human Plasma: Aspects of Yield and Virus Safety. Biotechnology J 2006;1(2):148-163. [PMID: 16892245]

[34] Robert P. Worldwide Supply and Demand for Plasma and Plasma Derived Medicines. Iranian J on Blood and Cancer 2011;3(3):111-120. http://build.jhousemedia3.com/nusep/user_files/1320293597_MRB%20Plasma%20Market%20Article%202011.pdf (accessed 11 March 2014).

[35] PRWeb. Increasing Awareness and Safety Drives the Intravenous Immunoglobulin (IVIG) Market, According to New Report by Global Industry Analysts, Inc. Global Industry Analysts Inc. California. http://www.prweb.com/releases/intravenous/immunoglobulin_IVIG/prweb9825314.html (accessed 8 August 2013).

[36] Robert P. IVIG/SCIG Global Usage Trends. Paper presented at the IPOPI Global Leaders Meeting, 2011 Nov 4-5; London: England. http://www.ipopi.org/uploads/Patrick%20Robert.pdf (accessed 11 March 2014).

[37] Cheraghali AM, Abolghasemi AB. Improving Availability and Affordability of Plasma-Derived Medicines. Biologicals 2010;38(1):81–86. [http://dx.doi.org/10.1016/j.biologicals.2009.10.004]

[38] ReportLinker. World Intravenous immunoglobulin (IVIG) Industry overview. An Analysis. 2011. Available for purchase online from http://www.reportlinker.com/p0395713-summary/Global-Intravenous-Immunoglobulin-IVIG-Market-An-Analysis.html. (Accessed January 2013)

[39] Robert P. Global Plasma Demand in 2015. Pharmaceuticals Policy and Law 2009;11:359–367. http://iospress.metapress.com/content/4012m3536460416n/fulltext.pdf (accessed 11 March 2014).

[40] World Health Organisation. Report of the WHO Expert Committee. WHO Technical Report Series, No 950. Washington, DC: World Health Organisation, 2007.

[41] Padila AA. WHO Initiative to Assure Safety and Availability of Blood Products in Developing Countries Washington, DC: World Health Organization, 2009. http://www.ipopi.org/uploads/media/PastEvents/presentations_november_2009/5%20WHO%20Achilles%20London4.pdf (accessed 11 March 2014).

[42] National Department of Health of South Africa. National Health Insurance in South Africa – Policy Paper. Pretoria: National Department of Health, 2011. http://www.info.gov.za/view/DownloadFileAction?id=148470 (accessed: 13 August 2011).

[43] Matsoso MP, Fryatt R. National Health Insurance: The first 16 months. S Afr Med J 2013;103(3):156-158. http://www.samj.org.za/index.php/samj/article/view/6601/4920 (accessed: 11 November 2014).

[44] Leong H, Stachnik J, Bonk ME, Matuszewski KA. Unlabeled Uses of Intravenous Immune Globulin. Am J Health Syst Pharm 2008;65(19):1815-1824. [http://dx.doi.org/10.2146/ajhp070582]

[45] Singh VN, Riramulu E, Siberil S, *et al*. Intravenous Immunoglobulin: An Update on the Clinical Use and Mechanisms of Action. J Clin Immunol 2007;27(3): 233-245. [PMID: 17351760]

[46] Food and Drug Administration (FDA). Immune Globulin Intravenous (IVIG) Indications. Washington, DC: Food and Drug Administration, 2009. http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm (accessed 18 October 2014)

[47] European Medicines Agency (EMA). Clinical Efficacy and Safety: Blood Products (including biotech alternatives). London: European Medicines Agency, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8 (accessed 18 October 2014).

[48] Food and Drug Administration (FDA). Immune Globulin Intravenous (IVIG) Indications. Washington, DC: Food and Drug Administration, 2009. http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm (accessed 18 October 2014)

[49] European Medicines Agency (EMA). Clinical Efficacy and Safety: Blood Products (including biotech alternatives). London: European Medicines Agency, 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8 (accessed 18 October 2014).

[50] O' Riordan J, Swingler RJ, Malek NM. Use of Intravenous Immunoglobulin in the Department of Neurology at Ninewells Hospital, 2008-2009: Indications for Utilization and Cost-Effectiveness. Ann Indian Acad Neurol 2010;13(4):271-275. [http://dx.doi.org/10.4103/0972-2327.74199] [PMID: 21264135]

[51] Frayha HH, Nuessle SJ, Arishi H, Rayes H, Qunibi WY, Bazarbashi MS. Improving Utilization of Intravenous Immunoglobulin Through Concurrent Use of an Indication Form. Eur J Clin Pharmacol 1997;52(4):255-260. [http://dx.doi.org/10.1007/s002280050286] [PMID: 9248761]

[52] Gurwitch KD, Goldwire MA, Baker CJ. Intravenous Immune Globulin Shortage: Experience at a Large Children's Hospital. Pediatrics 1998;102(3):645-647 [http://dx.doi.org/10.1007/s002280050286] [PMID: 9738190]

[53] Gajewski LK, Bailey EM, Brown PD, Chanrasekar PH. Immune Globulin Use at a Multihospital Centre. Am J Hosp Pharm 1994;51(6):801-805. [PMID: 8010320]

[54] Darabi K, Abdel-Wahab O, Dzik WH. Current Usage of Intravenous Immune Globulin and the Rationale Behind It: The Massachusetts General Hospital Database and a Review of the Literature. Transfusion 2006;46(5):741–753. [PMID: 16686841]

[55] Bayry J, Kazatchkine MD, Kaveri SV. Shortage of human intravenous immunoglobulin–reasons and possible solutions. Nat Clin Pract Neurol. 2007;3:120–121.

[56] Department of Health and Community Services. Utilization of Intravenous Immunoglobulin (IVig). Newfoundland and Labrador: Department of Health and Community Services, 2014. http://www.health.gov.nl.ca/health/bloodservices/resources/util_ivig.html (accessed 26 October 2014).

[57] Feasby T, Banwell B, Benstead T, *et al.* Guidelines on the use of Intravenous Immune Globulin in Neurologic Conditions. Trans Med Rev 2007;21(2):S57-S107. http://www.bloodmed.com/contentimage/guidelines/2871.pdf (accessed 26 October 2014).

[58] Hanna K, Poulin-Costello M, Preston M, Maresky N. Intravenous Immune Globulin use in Canada. Can J Clin Pharmacol 2003;10(1):11-16. [PMID: 12687032]

[59] Dashti-Khavidaki S, Khalili H, Farshadi F, Aghamohammadi A, Movahedi M, Hajibabaei M. Inpatient Paediatric Use of Intravenous Immunoglobulin at an Academic Medical Centre. Singapore Med J 2008;49(2):147-149. [PMID: 18301844]

[60] Galal, NM. Pattern of Intravenous Immunoglobulins (IVig) use in a Pediatric Intensive Care Facility in a Resource Limited Setting. African Health Sciences 2013;13(2):261-265. [http://dx.doi.org/10.4314/ahs.v13i2.9] [PMID:24235922]

[61] Wu J, Lee AJ, Goh AE, *et al.* Use of Intravenous Immunoglobulin in an Asian Paediatric Population Over a 10-year Period. J Paediatr Child Health 2013;49(8):629-634. [http://dx.doi.org/10.1111/jpc.12262] [PMID: 23750995]

[62] The South African Journal of Child Health. Submissions. Cape Town: The South African Journal of Child Health, 2014. http://www.sajch.org.za/index.php/SAJCH/about/submissions (accessed 12 November 2014).

[63] Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous Immunoglobulin for Treating Sepsis and Septic Shock. Cochrane Database Syst Rev 2002;1:CD001090. [PMID: 11869591]

[64] Dawoud T, Tatari H, Gebran N. A Utilisation Review of Intravenous Immunoglobulin in a Tertiary Care Hospital in United Arab Emirates. Eur J Hosp Pharm 2012;19(3):286–288. [http://dx.doi.org/10.1136/ejhpharm-2012-000070]

[65] De Meo MS, Pompilio A, Ciuccarelli F, *et al.* GRP-063 Evaluation of Intravenous

Immunoglobulin (IVIG) Prescriptions in an Italian Paediatric Hospital: An Overview of Off-Label Uses. Eur J Hosp Pharm 2013;20:A23. [http://dx.doi.org/10.1136/ejhpharm-2013-000276.063]

[66] Bucuvalas JC, Anand R. Studies of Pediatric Liver Transplantation Research G Treatment with Immunoglobulin Improves Outcome for Pediatric Liver Transplant Recipients. Liver Transpl 2009;15:1564–1569. [PMID:24788560]

[67] Winters JL, Brown D, Hazard E, Chainani A, Andrzejewski C. 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. [http://dx.doi.org/10.1186/1472-6963-11-101] [PMID: 21575219]