

# Intravenous immunoglobulin therapy among pediatric patients: labeled and off-labeled indications

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This study was designed to evaluate utilization patterns and clinical outcome of intravenous immunoglobulin (IVIG) therapy among pediatric patients in a tertiary hospital. Demographic data, IVIG prescribed, and clinical outcome were retrospectively reviewed from the pharmacy dispensing data and patient medical records between 2007 and 2014. One hundred and fifteen instances of IVIG administration to 108 pediatric patients were recorded. A total of 61 cases (53%) and 54 cases (47%) of the IVIG administered were for labeled and off-labeled indications, respectively. Age, weight, specialty, total IVIG usage, length of hospital stays, and mortality rate were found to be significantly associated with the indication being labeled or off-labeled ( $p < 0.05$ ). However, there was no significant difference in terms of adverse reactions between labeled and off-labeled indications ( $p > 0.05$ ). Guidelines should be developed and implemented for rational and evidence-based use of IVIG to avoid unnecessary wastage.

**Keywords:** Intravenous Immunoglobulin. Off-label indications. Pediatric patients. Malaysia hospital

## INTRODUCTION

Over the past two and a half decades, the administration of intravenous immunoglobulin (IVIG) has become an important therapy in clinical medicine. These preparations, which contain a broad range of antibody specificities, were originally used in antibody replacement therapy. However, many other clinical benefits of IVIG treatment have been demonstrated (Orange *et al.*, 2006). A rapid increase in the use of IVIG for an ever-growing number of conditions in children and neonates was also reported (Stiehm, Keller, Vyas, 2008).

In pediatrics, IVIG has been found to have a major impact in the treatment of conditions in the fields of neurology, hematology, rheumatology, dermatology, neonatology, immunology, cardiology, and infectious diseases (Prasad, Chaudhary, 2014). More than 150 off-labeled indications of IVIG in 128 clinical trials and 268 case reports were reported in another literature review by Leong *et al.* (2008). The most common off-labeled indications include multiple sclerosis, prevention of

antiphospholipid syndrome in miscarriage, Guillain-Barré syndrome, and progression of human immunodeficiency virus (HIV) after delivery. Health care institutions are strongly urged to closely monitor specific uses of IVIG to reserve supplies for the “best-evidence” uses because of the limited knowledge associated with off-labeled indications (Leong *et al.*, 2008).

IVIG is known to be a complex therapy with adverse effects. Adverse reactions associated with the regular administration of IVIG still occur despite the introduction of manufacturing steps that enhance purity, minimize damage to the Immunoglobulin G molecules, and result in a higher concentration of liquid IVIG (Bichuetti-Silva *et al.*, 2014). In 2002, a survey of more than 1000 patients with primary immunodeficiency conducted by the Immune Deficiency Foundation (IDF) found that 44% of the reported adverse reactions were not related to the rate of infusion but to the drug itself. Systemic reactions to IVIG infusion (not related to the rate of infusion) were reported to range from 3% to 15%, which include backache, abdominal pain, nausea, chills, rhinitis, asthma, low-grade fever, myalgia, and headaches (Goddard, 2008).

This study was designed to evaluate utilization patterns and clinical outcome of the IVIG therapy in a

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tertiary teaching hospital in Malaysia focusing on the off-label indications.

## MATERIAL AND METHODS

This observational retrospective chart review study was approved by the Research Ethics Committee of UKMMC (UKM 1.5.3.5/244/NF-009-15). Data collection was carried out from April to June 2015. Pediatric patients ranging in age from birth to 12 years who were administered IVIG from January 2007 to December 2014 during their hospital stay were traced using the IVIG usage logbook at the pharmacy department of UKMMC. Medical records were then retrieved from the Medical Record Unit and screened for confirmation of IVIG administration. Detailed clinical data including demographic data, primary diagnosis, dosing regimen of IVIG, indication, and clinical outcome were recorded using a designated data collection form.

The indication of IVIG is mainly divided into two categories, labeled and off-labeled. Labeled indication refers to the seven indications approved by the FDA as follows:

- a. Treatment of primary immunodeficiency
- b. Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent infection caused by B-cell chronic lymphocytic leukemia
- c. Prevention of coronary artery aneurysms in Kawasaki disease
- d. Prevention of infections, pneumonia, and acute graft versus host disease (GVHD) after bone marrow transplantation
- e. Reduction of serious bacterial infection in children with HIV
- f. Increase of platelet count in idiopathic thrombocytopenic purpura (ITP) to prevent or control bleeding
- g. Chronic inflammatory demyelinating polyneuropathy (CIDP)

Appropriate use of IVIG was placed into one of three a priori agreed upon categories. Off-labeled indication is defined as the indication of IVIG other than the seven indications approved by the FDA (Prasad, Chaudhary, 2014). Off-labeled indication is further categorized into 2 subgroups, “potentially indicated” or “not indicated.” “Off-labeled, potentially indicated” is the term used for disorders with clinical information supporting the use of IVIG as listed in the British Columbia IVIG Utilization Management Handbook and/or in the panel recommendations of the Canadian Blood Service 2000 national consensus conference. Clinical indications with no convincing evidence of benefit were defined as

“not indicated.” These were used for conditions with no evidence supporting the use of IVIG or for conditions in which IVIG use was deemed ineffective (Selin, 2002; Sher *et al.*, 2000). The level of evidence for the labeled and off-labeled indication is classified as category I, IIa, IIb, or III (Sher *et al.*, 2000).

As clinical outcomes, three parameters were documented: the length of hospital stay, mortality, and adverse reaction. Length of hospital stay is defined as the duration of hospital stay from the day of hospital admission until the patient is discharged or deceased. Mortality is defined as all-cause mortality. Adverse reaction related to IVIG infusion refers to a reaction that occurred during or within 48 hours after the infusion. It can be classified as mild, moderate, or severe as below (Brennan *et al.*, 2003):

- a. Mild reactions  
Symptoms included headache, flushing, muscle aches, shivering, feeling sick, itching, urticaria, anxiety, lightheadedness, dizziness, or irritability. These subsided when the infusion rate was decreased.
- b. Moderate reactions  
Symptoms included mild reactions becoming worse or other symptoms such as chest pain or wheezing, necessitating the infusion to be discontinued.
- c. Severe reactions  
Symptoms included moderate reactions persisting or becoming worse, or other symptoms such as tightness of the throat, severe headache and shaking, severe breathlessness or wheezing, severe dizziness or fainting, sensation of pressure in the chest, or collapsing. A severe reaction would require the administration of adrenaline and medical attention.

Statistical Package for the Social Sciences version 22 (SPSS®, Chicago, IL) was used to perform all statistical analyses. The indication, dosing regimen, and outcome of IVIG administration were descriptively analyzed. The Chi Square and Fisher’s Exact tests were used to compare two categorical variables, and the Mann-Whitney U test was used in comparing the numerical and categorical variables. All statistical tests were two-tailed. A p-value of <0.05 denoted statistical significance.

## RESULTS

A total of 162 patients with prescribed IVIG were identified through the computerized pharmacy system with only 118 patients having traceable medical records. The remaining 44 medical records were untraceable due to patients defaulting follow up for 5 years or more. Of the 118 patients, only 3 did not receive the IVIG therapy due to the patients’ worsening clinical condition. Hence, the

final sample size was 115 instances of IVIG administered to 108 patients from January 1, 2007 to December 31, 2014. The patient characteristics and clinical data are summarized in Table I.

Out of the 115 cases of IVIG administered, 61 cases (53%) were used for FDA approved indications while another 54 cases (470%) were used for off-labeled indications. The indications for IVIG had a category I evidence level in 68.9% of cases whereas the remaining 39.1% had category II and III evidence level (Table II).

Over the 8-year period, the total IVIG usage was 1396.42 g. A total of 1007.70 g and 388.72 g of IVIG were administered for labeled and off-labeled indications, respectively. The dose per course ranged from 0.4 mg/kg to 2.0 mg/kg with a median of 1.5 mg/kg. Sixty-nine percent of IVIG cases ( $n = 79$ ) were administered in a single dose and the remaining 31% ( $n = 36$ ) were administered as divided doses, up to 5 doses, with an interval of 2 to 5 days per case.

The length of hospital stays for a patient who received the IVIG ranged from 1 to 361 days, with a median of 23.8 days. After IVIG administration, 99 patients (86.1%) were discharged. Sixteen (13.9%) patients died but death was not related to IVIG administration. The cause of death comprised 15 cases of severe neonatal sepsis with underlying prematurity and 1 case of severe gastrointestinal bleeding.

Seven adverse reactions related to the IVIG administration were identified: 5 mild cases and 1 case each of moderate and severe adverse reactions. Patients with mild adverse reactions developed fever during the IVIG administration, and the symptom subsided when the infusion rate was reduced. Moderate adverse reaction was seen in patients who presented with chills, rigors, fever, mild bronchospasm, mild tachypnea, and tachycardia, which required additional intervention with antipyretic, bronchodilator, oxygen and necessitating the termination of IVIG infusion. In the severe adverse reaction case, the patient presented with general tonic-clonic seizure during IVIG infusion and required a loading dose of an antiepileptic drug, intubation for airway protection, and termination of IVIG infusion. The Naranjo scale was used to determine the probability of IVIG-related adverse reactions for the 7 cases, and the scores ranged from 5 to 8.

In this study, the patient's age, body weight, total usage of IVIG, specialty, length of hospital stay, and all-cause mortality were found to be significantly associated with the indication being labeled or off-labeled ( $p < 0.001$ ). There were no significant association between the indication of IVIG with adverse reaction related to IVIG infusion, gender and ethnicity ( $p > 0.05$ ) (Table III).

**TABLE I** – Patient demographics and clinical data ( $n=108$  patients)

Parameter	n
Courses of IVIG ( $n$ )	115
Age, years [median (IQR)]	0.58 (1.98)
Gender, $n$ (%)	
Male	65 (56.5)
Female	50 (43.5)
Body weight, kg [median (IQR)]	6.88 (8.76)
Ethnicity, $n$ (%)	
Malay	75 (65.2)
Chinese	33 (28.7)
Indian	2 (1.7)
Others	5 (4.3)
Setting, $n$ (%)	
PHDU	69 (60.0)
NICU	44 (38.3)
PICU	2 (1.7)
Specialty, $n$ (%)	
Neurology	7 (6.1)
Hematology	31 (27.0)
Immunology	4 (3.4)
Dermatology	25 (21.7)
Neonatology	44 (38.3)
Others	4 (3.4)
Primary diagnosis, $n$ (%)	
ITP	31 (27.0)
Neonatal sepsis	31 (27.0)
Kawasaki disease	24 (20.9)
Severe neonatal jaundice (NNJ) secondary	8 (7.0)
ABO incompatibility	
Primary immunodeficiency disease	3 (2.6)
Guillain-Barré syndrome	2 (1.7)
Perinatal acquired varicella infection (prophylaxis)	2 (1.7)
Neonatal autoimmune thrombocytopenia	2 (1.7)
CIDP	2 (1.7)
Multiple sclerosis	1 (0.9)
Acute graft versus host disease (GVHD)	1 (0.9)
Varicella pneumonitis	1 (0.9)
Anti-NMDA receptor encephalitis	1 (0.9)
Acute transverse myelitis	1 (0.9)
Viral myocarditis	1 (0.9)
Toxic epidermal necrolysis (TEN)	1 (0.9)
Acute disseminated encephalomyelitis (ADEM)	1 (0.9)
Evan's syndrome	1 (0.9)
Systemic lupus erythematosus (SLE)	1 (0.9)

**TABLE II** – Utilization of IVIG by indication and evidence category

Indication	Number of cases (%)	Category evidence*
<b>Labeled use</b>		
Kawasaki disease	31 (27.0)	I
ITP	24 (20.9)	I
Primary immunodeficiency	3 (2.6)	I
CIDP	2 (1.7)	I
Acute GVHD	1 (0.9)	IIa
<b>Off-labeled, potentially indicated</b>		
Neonatal sepsis	31 (27.0)	IIb
Severe NNJ secondary to ABO incompatibilities		I
Guillain-Barré syndrome	8 (7.0)	I
Perinatal-acquired varicella zoster infection (prophylaxis)	2 (1.7)	IIb
Neonatal autoimmune thrombocytopenia	2 (1.7)	IIb
Anti-NMDA receptor encephalitis	2 (1.7)	III
TEN	1 (0.9)	IIb
ADEM	1 (0.9)	IIa
Evan's syndrome	1 (0.9)	IIb
<b>Off-labeled, not indicated</b>		
SLE	1 (0.9)	III
Multiple sclerosis	1 (0.9)	IIb
Varicella pneumonitis	1 (0.9)	III
Acute transverse myelitis	1 (0.9)	III
Viral myocarditis	1 (0.9)	III

\* Classification of evidence levels (Selin, 2002):

- Category I: Medical conditions for which there is convincing evidence of benefit resulting from IVIG therapy.
- Category II: Medical conditions for which there is inconclusive evidence of benefit from IVIG therapy, because of either conflicting evidence, low level evidence, or limited research, possibly because the condition is rare. Category II is subdivided into “a” (high) and “b” (low), depending on whether there is a higher or lower level of evidence of benefit.
- Category III: Medical conditions for which there is convincing evidence that IVIG has no benefit, or for which there is no convincing evidence of benefit of IVIG therapy.

## DISCUSSION

In our study, nearly half of the IVIG treatment given through the years 2007-2014 were for off-labeled indications. This value is much higher than those reported in the other studies. A study conducted in Singapore over a 10-year period in two public pediatric hospitals reported that IVIG was used for off-labeled indications in only less than 25% of cases (Wu *et al.*, 2013). A study on IVIG use in the 10 institutions in Canada from 1997 to 1999 found that 38% of children received IVIG for off-labeled indications (Hanna *et al.*, 2003). Another report from Spain on the utilization of IVIG from 2000 to 2004 that included 273 patients found that only 14% of IVIG

courses were prescribed for off-labeled indications (Badia, Cardona, Massanes, 2006). The widespread use of IVIG for off-labeled indications, emergence of new therapeutic indications, and indefinite duration of use in neurological illnesses in addition to immune deficiencies have been linked with the shortage of IVIG supply (Provan *et al.*, 2007).

In this study, the utilization of IVIG in the adjunctive treatment of neonatal sepsis and severe neonatal jaundice secondary to ABO incompatibility contributed to the high usage of IVIG for off-labeled indications in the study. A meta-analysis of 110 cases of neonatal sepsis administered with IVIG found a 6-fold reduction in mortality compared to controls (Jenson, Pollock, 1997). Another meta-analysis

**TABLE III** – Association between demographics and clinical data with labeled and off-labeled indications

Parameter	Labeled (n=61)	Off-labeled (n=54)	p-value
Age, years [median (IQR)]	1.25 (0.67-2.42)	0.02 (0.01-0.17)	<0.001 <sup>b</sup>
Gender, <i>n</i> (%)			0.857 <sup>a</sup>
Male	34 (55.7)	31 (57.4)	
Female	27 (44.3)	23 (42.6)	
Ethnicity, <i>n</i> (%)			0.335 <sup>c</sup>
Malay	39 (63.9)	36 (66.7)	
Chinese	20 (32.8)	13 (24.1)	
Indian	2 (3.3)	2 (3.7)	
Others	0	3 (5.6)	
Body weight, kg [median (IQR)]	9.10 (7.12-11.80)	2.36 (0.96-3.28)	<0.001 <sup>b</sup>
Specialty, <i>n</i> (%)			<0.001 <sup>c</sup>
Neurology	2 (3.3)	5 (9.3)	
Hematology	31 (50.8)	-	
Immunology	3 (4.9)	1 (1.9)	
Dermatology	24 (39.3)	1 (1.9)	
Neonatology	-	44 (81.5)	
Others	1 (1.6)	3 (5.6)	
Total usage, g [median (IQR)]	14.00 (9.00-20.00)	2.50 (1.30-3.00)	<0.001 <sup>b</sup>
Length of hospital stay (day)	5.00 (3.00-8.00)	15.50 (5.00-53.00)	<0.001 <sup>b</sup>
All cause mortality, <i>n</i> (%)			<0.001 <sup>c</sup>
Yes	1 (1.6)	15 (27.8)	
No	60 (98.4)	39 (72.2)	
Adverse reaction, <i>n</i> (%)			0.705 <sup>c</sup>
Yes	3 (4.9)	4 (7.4)	
No	58 (95.1)	50 (92.6)	

a = Chi Square test; b = Mann-Whitney U test, c = Fisher's Exact test. \*p < 0.05 denoted statistical significant difference. IQR = interquartile range

on the assessment of its effectiveness found a significant reduction in mortality in infants with suspected or proven infection; however, a concern about the small sample sizes and study quality was raised (Ohlsson, Lacy, 2015). In 2011, the International Neonatal Immunotherapy Study (INIS) Collaborative Group published a placebo-controlled trial on 3493 low-weight infants and found no significant difference in the rate of death or major disability at the age of 2 years between patients receiving placebo or those under IVIG treatment for neonatal sepsis (Brocklehurst *et al.*, 2011). Based on the evidence from this latest prospective, randomized and placebo-controlled trial, the United Kingdom clinical guideline on IVIG use had listed neonatal sepsis as one of the “not recommended indication” for IVIG therapy with grade A recommendation and level Ia evidence level (Provan *et al.*, 2011).

Few studies on neonatal jaundice found the beneficial effect of IVIG administration in neonates with isoimmune hemolytic jaundice. Two systematic reviews demonstrated that IVIG significantly reduced the need for exchange transfusion in neonates with hemolytic disease of the fetus and newborn (Alcock, Liley, 2002; Gottstein, Cooke, 2003). Moreover, exchange transfusion was reported to be associated with morbidity and mortality (Anderson *et al.*, 2007).

For all labeled indications, the recommended IVIG dose and frequency are according to the guidelines of the British Columbia IVIG Utilization Management Handbook and the Canadian Blood Service 2000 national consensus conference on IVIG. For off-labeled indications, IVIG was administered using a variety of dosing regimens but still following the usual recommended dose in labeled



indications, which ranged from 0.4 g/kg to 2.0 g/kg per course in either a single dose or few divided doses (Prasad, Chaudhary, 2014).

The incidence of adverse reaction in this study was 6.1%, which falls in the range of 3-15% as reported in the literature (Goddard, 2008). The Naranjo scale, an adverse drug reaction probability scale, was used to assess the causality of IVIG-related adverse reaction in 7 reported cases in this study. All the 7 cases (5 mild cases, 1 moderate case, and 1 severe case) were interpreted as a probable level of IVIG infusion-related adverse reaction. The probable level of the Naranjo score is defined as the adverse reaction that occurred following a reasonable temporal sequence after drug administration and a recognized response to the suspected drug. It was confirmed by withdrawal but not by exposure to the drug and could not be reasonably explained by the known characteristics of the patient's clinical state (Naranjo *et al.*, 1981).

In the present study, the indication of IVIG as labeled or off-labeled was found to be associated with the patient's age, body weight, specialty, total IVIG usage, length of hospital stay, and all-cause mortality rate. Neonatal sepsis and severe NNJ secondary to ABO incompatibility were the most common off-label indications for IVIG administration. Hence, the lower total usage of IVIG for off-labeled indications compared to the labeled indications could be explained by the lower body weight of neonates. Other various factors such as underlying illness may contribute to the longer hospital stay and higher mortality rate seen in patients receiving IVIG for off-label indications.

In view of the high usage of IVIG for off-label indications, a strict approval system for IVIG prescription is needed. In many institutions, policies have been developed to monitor and control the dispensing process of IVIG. In a Spanish institution, the pharmacists assess the indication and categorize it upon receipt of prescription for IVIG. If the IVIG is requested for off-labeled indications, the pharmacist will contact the prescriber to obtain the documentation required to request authorization from the health authorities for compassionate use (Badia, Cardona, Massanes, 2006). A study conducted in Saudi Arabia had showed a clear improvement in the ratio of labeled to off-labeled use and correct dosing for various indications after the adoption of an IVIG indication form. Any off-labeled indication must obtain approval from the clinical research committee (Frayha *et al.*, 1997). Hence, all these strategies could be implemented for optimal IVIG utilization in the present setting.

There were several limitations of this study. First, there were medical records that could not be traced from

the years 2007 to 2010. For that reason, the exact usage of IVIG could be higher than that reported in this study. Second, the length of hospital stays and mortality rate could be affected by other comorbidities or coinfection present and not just due to the IVIG treatment.

## CONCLUSION

IVIG therapy used in this setting for off-labeled indications was high with indications that may not benefit from the IVIG therapy due to the lack of strong clinical evidence. The patient's age, body weight, specialty, total IVIG usage, length of hospital stays, and all-cause mortality rate were found to be associated with IVIG indications being labeled or off-labeled, although there are other confounding factors that may have influenced the results seen. A national policy on the prescription of IVIG needs to be urgently developed to guide physicians in appropriately prescribing IVIG for pediatric patients.

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