

## Original Article

# Intravenous Immunoglobulin Utilization Study in a Teaching Hospital

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## Abstract

**Background:** Intravenous immunoglobulin (IVIG) is an immunomodulating agent that has several actions. The aim of this study was to investigate the indications of IVIG according to available evidence and the cost in our center.

**Methods:** This retrospective study was conducted between September 2017 and June 2018 at a teaching hospital affiliated with Iran University of Medical Sciences, Tehran, Iran. Patients' demographic data and disease, indication for IVIG use, its dosage and treatment regimen and previous and concurrent treatments were assessed. The collected data were compared with the present criteria for the pattern of IVIG usage. The last version of Lexicomp® was used as the reference for indications of the administered drug and its dosage.

**Results:** A total of 119 patients received IVIG during the study period. The wards with the most frequent IVIG prescription were the neurology (46.2%) and neonatal intensive care unit (21%). The most common reasons of IVIG therapy were various inflammatory neurological disorders. IVIG was used in 22, 43 and 54 cases according to on-label, off-label and other indications, respectively. The total price was higher for off-label indications for IVIG (\$254 343.75) than on-label indications (\$152 625). As well, \$107 250 was exhausted for cases in which there was not sufficient evidence.

**Conclusion:** One important aspects of this study was the use of IVIG in cases other than on-label indications. Although a number of studies support IVIG therapy in some diseases, further trials are needed to establish efficacy and safety in these fields.

**Keywords:** Drug utilization evaluation, Inflammatory neurological disorders, Intravenous immunoglobulin, IVIG

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## Introduction

Immune globulin obtained from human plasma was first used in 1952 for management of primary immune deficiency. Intravenous immunoglobulin (IVIG) includes the pooled immunoglobulin G (IgG) from the plasma of approximately 1000-10000 donors. IVIG is an immunomodulating mediator that has numerous actions.<sup>1-3</sup>

Drug utilization evaluation (DUE) is an inclusive evaluation of the medication administration process. DUE programs contribute to improve the prescription, administration, medication use in health care systems. As well, given the importance of clinical usefulness and control of health system finance, most these studies are performed on medications with high cost and usage.<sup>4-6</sup>

Considering high prices for IVIG, increasing use of this agent, the difficult production process, and possible access to other more economical agents with equal effectiveness,

the utilization evaluation of IVIG is necessary. The goal of this study was to assess IVIG utilization patterns in a teaching hospital according to available evidence.

## Materials and Methods

This retrospective cross-sectional study was carried out between September 2017 and June 2018 at Firoozgar hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. In this period of time, patients who underwent IVIG therapy were included in this study. A retrospective evaluation of medical records was performed to cull patient's information (demographic data), their disease, IVIG indication, dosage and previous and concomitant management.

The collected data were compared with the current criteria for the pattern of IVIG use. The last version of Lexicomp® acquired by Wolters Kluwer and was used as the reference for indications of the administered drug and

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its dosage.<sup>7</sup>

Data was entered from the mentioned forms to SPSS® 20 Software for statistical analysis. The numerical and nominal variables are as mean values ± standard deviation (SD) and number/ percentage, respectively.

**Results**

During this study period, 119 patients received IVIG. Among these cases, 60 were male and 59 female, respectively. The mean age of included cases was 37.3 ± 24.9 years (range, 1 day to 81 years). The neurology ward (46.2%) accounted for the most part of IVIG administration. The rate of IVIG orders in other ward was mentioned in Figure 1. The most common reasons of IVIG therapy 69 (61.6%) were various inflammatory neurological disorders.

In 22 (18.5%) cases, IVIG were administrated based on FDA approval and in the remaining patients, 97 (81.5%) were not approved by the Food and Drug Administration (FDA). However, among 97 indications that were not approved by FDA, 43 (36.1%) cases were as off label indications of IVIG according to Lexicomp®. The list of on label and off label usages of IVIG was mentioned in Table 1. In fifty and four (45.3%) of cases, the cause of administration was not according to on label or off label indications. These indications include neonatal sepsis (19 cases), chronic myasthenia gravis (4 cases), systemic

lupus erythematosus (3 cases), autoimmune encephalitis (3 cases), neonatal icter (3 cases), autoimmune autonomic ganglionopathy (2 cases), progressive epilepsy (2 cases), neuromyelitis optica (2 cases), antibody mediated rejection (AMR) in kidney transplantation (2 cases), autoimmune hepatitis (1 case), Stevens-Johnson syndrome (1 case), Sjögren syndrome (1 case), Stiff-person syndrome (1 case). The IVIG indication was unknown in 10 patients.

The total amount of IVIG prescription for 119 patients was 12712.5 g that 4070 g was administrated for on label use indications and 6782.5 g for off label cases. 2860 g was used for other reasons.

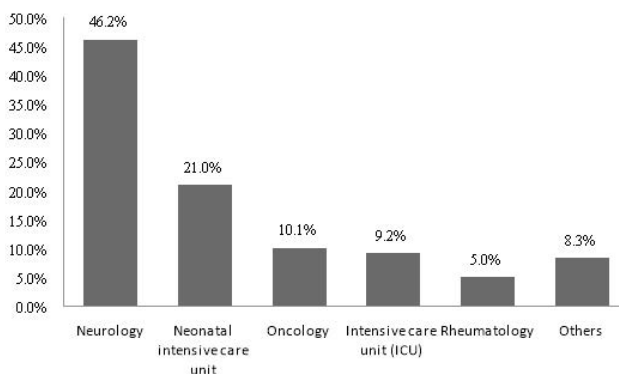
A wide range of dosing methods and schedules were recorded for various conditions. Some authorities allowed physicians to prescribe this agent according to their experience and patient’s condition. During this study, 106 patients (89%) received IVIG for one treatment cycle and 13 patients (11%) underwent IVIG therapy for more than one treatment cycle including 8 and 5 cases for on label and off label indications, respectively. Among these 13 cases, 5 patients received 2 treatment cycles, 5 patients 3 treatment cycles, 2 patients 4 treatment cycles, 1 patient 7 treatment cycles.

Other therapeutic interventions were administrated before or during IVIG therapy in 63 patients. These treatments included corticosteroids, phenytoin, phenobarbital, azathioprine, mycophenolate mofetil or mycophenolic acid, cyclosporine, rituximab and plasmapheresis.

The cost of 1 g of IVIG was \$37.5 according to the average cost designated by the Ministry of Health of Iran at the time of the study. The total cost was higher for off label indications IVIG (\$254 343.7) than on label indications (\$152 625). In addition, \$107 250 was spent for cases that there is not adequate evidence.

**Discussion**

In this study, we evaluated the pattern IVIG use in a referral hospital in Tehran. One important aspect of this study was the use of IVIG in cases different from on-label indications.



**Figure 1.** The Rate of IVIG Orders in Various Wards.

**Table 1.** On and Off Labeled Indications for IVIG Administration in 65 Cases

Indications	Frequency of On Labeled	Frequency of Off Labeled	Total
Chronic inflammatory demyelinating polyneuropathy	14 (11.7%)		14 (11.7%)
Idiopathic thrombocytopenic purpura	6 (5%)		6 (5%)
Multifocal motor neuropathy	2 (1.6%)		2 (1.6%)
Acquired hypogammaglobulinemia secondary to malignancy		5 (4.2%)	5 (4.2%)
Dermatomyositis/polymyositis (refractory)		7 (5.8%)	7 (5.8%)
GBS		24 (20.1%)	24 (20.1%)
Myasthenia gravis (acute exacerbation)		7 (5.8%)	7 (5.8%)
Total	22 (18.5%)	43 (36.1%)	65 (54.6%)

Abbreviations: GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin.

IVIg is a modulating agent which could modulate the complement system; suppress idiotypic antibodies; saturate Fc receptors on macrophages; and suppress various inflammatory mediators, including cytokines, chemokines, and metalloproteinases.<sup>1-3</sup> However, the process of producing IVIg is very difficult and costly. Therefore, the IVIg administration should be maintained for cases approved by the FDA or where the efficacy has been studied in large studies.

Neonatal sepsis has remained as one of the main reasons of mortality and morbidity among preterm infants.<sup>8</sup> Immunoglobulins are investigated as adjuvant treatment in the management of preterm neonatal sepsis. Although immunotherapy is an attractive approach, the results of a recent meta-analysis inspired people not to recommend this management.<sup>9-11</sup> So, the use of IVIg in neonatal sepsis needs further well-designed studies. In this study, IVIg was administered in 19 neonatal sepsis cases that is not currently rational use.

IVIg is well-known for treatment of various inflammatory neurological disorders, including chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy as first-line therapy.<sup>7,12</sup> In addition, IVIg therapy is an off-label indication in Guillain-Barré syndrome (GBS).<sup>7</sup> However, the evidence is variable and insufficient for other types of neuropathy such as Sjögren syndrome.<sup>12</sup> In acute exacerbation of myasthenia gravis, plasmapheresis is valuable. The use of IVIg instead of plasmapheresis for the treatment of exacerbations of myasthenia gravis has been evaluated in some clinical trials.<sup>13,14</sup> IVIg was as useful as plasmapheresis after 15 days in two studies.<sup>13,14</sup> However, in chronic management of myasthenia gravis, the role of IVIg has not yet been proven.<sup>15,16</sup> So, IVIg therapy may be considered as an alternative to plasmapheresis for acute exacerbation of myasthenia gravis but is not recommended for chronic disease control. In neuromyelitis optica and autoimmune epilepsy, IVIg therapy has been raised as a second line option in some guidelines.<sup>17</sup> In some case series, immunotherapies with corticosteroids, rituximab or IVIg could be effective in the treatment of autoimmune encephalitis but controlled studies were not performed.<sup>7</sup> The treatment efficacy of IVIg for the autoimmune autonomic ganglionopathy was evaluated according clinical observations in case reports or case series. The results of these studies supported the use of IVIg in this condition.<sup>18</sup> However; additional studies are needed to assess various immunotherapies for this condition. IVIg therapy significantly reduced stiffness scores and considerably improved walking and functions of daily activities in Stiff-person syndrome. Therefore, IVIg could be effective as complementary treatment in patients with this disease.<sup>7,19</sup> In our study, IVIg was used in 15 cases with various inflammatory neurological disorders that are not currently considered as on-label or off-label indications

of IVIg. However, in some cases, the studies support the use of IVIg therapy.<sup>7,12-19</sup>

One of the important points about IVIg therapy is attention to infusion reactions during injection. Many reactions are mild and include fever, chills, nausea, vomiting, backache, headache, facial redness or flush, dyspnea or shortness of breath, dizziness and hypotension or hypertension.<sup>3,20</sup> These reactions happen 3 mins to 1 h after the start of infusion.<sup>21</sup> The incidence of these complications increase with the presence of infection, high rate of infusion, use of the various commercial products, and first-time infusion.<sup>22</sup> Due to the retrospective nature of our study and incomplete clinical records, we could not assess infusion reactions.

During this study, 12712.5 g IVIg was administered and 4070 g was used for on-label use indications, 6782.5 g was used for off-label cases and 2,860 g was used for other reasons. This enforces extensive costs on the health-care system. The total cost was higher for off-label indications IVIg (\$254 343.7) than on-label indications (\$152 625). In addition, \$107 250 was spent for cases that did not have adequate evidence for its use. Even in on-label cases, in a study performed in the United States; direct costs of IVIg therapy were more than two fold relative to that of therapeutic plasma exchange in GBS patients.<sup>23</sup> Authors concluded, due to equal efficacy and similar severity of adverse reactions, therapeutic plasma exchange seems to be a less expensive first-line therapy choice for the treatment of GBS.

Therefore, cost is usually a subject of debate in the perspective of drug use in such examples as IVIg due to limited case-based evidence and uncertainty of the cost-benefit rate for some indications. For healthcare managers, physicians and patients, demands for reliable decision-making are necessary. Similarly, presence of a clinical pharmacist in the treatment system not only improves patient service but also reduces treatment cost.

In conclusion, our results indicated IVIg was used in various disorders other than on-label indications in this center. Although a number of studies show that IVIg therapy could be effective in some conditions, further studies are required to establish efficacy and safety in these fields. Also, cost effectiveness of treatment should be considered.

#### Authors' Contribution

Guarantor of integrity of the entire study: NR, BG, MF; Study concept and design: MF, MRM; Literature research: MF, ES; Clinical studies: MRM, ES, NR, MF; Statistical analysis: NP, BG; Manuscript preparation: MF.

#### Conflict of Interest Disclosures

The authors have no conflicts of interest.

#### Ethical Statement

The study protocol was approved by ethics committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC 1396.32298).

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