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Changing trends in IVIG use in pediatric patients: A retrospective review of practices in a network of major USA pediatric hospitals

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ABSTRACT

The use of immunoglobulins is gradually increasing. Intravenous immunoglobulins (IVIG) are used as replacement therapy for primary and secondary immune deficiencies, and as an anti-inflammatory and immunomodulatory medication for the treatment of neurologic, dermatologic, and rheumatologic diseases. The objective of this study was to analyze trends in the IVIG use in pediatric patients hospitalized to 47 US-based children's hospitals from 2007 to 2014.

IVIG was used for the treatment of > 2300 primary diagnoses in 53,648 unique patients. The number of IVIG admissions increased by 30.2% during the study period, while the mean rate of IVIG admissions/100,000 admissions increased only 5.8%. Most patients receiving IVIG were children and adolescents. IVIG was frequently used off-label or for the treatment of FDA-approved indications in children under two years of age and BMT patients < 20 years of age. Primary immune deficiencies represented only 1.2% of all IVIG admissions. Pediatric patients with mucocutaneous lymph node syndrome (Kawasaki disease, KD) and idiopathic thrombocytopenic purpura (ITP) were two primary consumers of the IVIG. Another top-ranked indications were acute infectious polyneuritis (Guillain–Barré syndrome, GBS) and prophylaxis of infections in patients receiving antineoplastic chemotherapy.

IVIG usage is a dynamic process guided by emerging evidence and FDA approval for new indications. IVIG was mostly prescribed for treatment of diseases with pathologic immune responses to foreign of self-antigens. These indications usually, require higher amounts of IVIG per admission. More studies are needed to understand whether IVIG treatments of off-label indications are effective and cost-efficient.

1. Introduction

Polyclonal immunoglobulin (IG) preparation as replacement therapy for patients with immune deficiency was first used in 1952 when an eight-year-old boy with agammaglobulinemia was treated for recurrent infections and sepsis by subcutaneous injections of “immune human serum globulin” [1]. The monthly immunoglobulin injections led to no sepsis occurrences for 14 months after treatment. The routine prophylactic treatment of patients with primary immune deficiencies (PID) by intravenous immunoglobulins (IVIG) started in the 1980s.

At present, IVIG preparations are made by pooling plasma collected from thousands of healthy donors. Immunoglobulin G (IgG) represents about 90% of all immunoglobulins present in a commercial IVIG preparation [2]. These preparations contain a broad range of opsonizing and neutralizing antibodies specific to a variety of bacterial and viral antigens [3]. IVIG is the treatment of choice for patients with humoral immune deficiencies but also can be used as an immunomodulatory or anti-inflammatory drug for the treatment of autoimmune disorders and systemic inflammatory diseases [3,4]. During 2007–2014, IVIG was approved by the FDA for use in six conditions: mucocutaneous lymph

Abbreviations: IVIG, Intravenous Immunoglobulin; ITP, Immune Thrombocytopenic Purpura; KD, Kawasaki disease; GBS, Guillain–Barré syndrome; ICD9, International Classification of Diseases 9; PHIS, Pediatric Hospital Information System; PID, Primary Immune Deficiencies

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node syndrome (Kawasaki disease, KD), immune thrombocytopenic purpura (ITP), primary immunodeficiency (PID), secondary immunodeficiency (chronic lymphocytic leukemia, CLL), pediatric HIV infection, and prevention of graft versus host disease or infection in bone marrow transplant (BMT) patients ≥20 years of age [5]. IVIG was also used off-label to treat a wide variety of neurologic, dermatologic, rheumatologic, hematologic, and infectious diseases. The evidence supporting these uses vary [5]. For some indications, the evidence is reasonably convincing and based on a meta-analysis of randomized clinical trials or at least one randomized clinical trial or trial without randomization, while the recommendation for other indications is based on expert opinion [5,6]. For example, the use of IVIG is probably or may be beneficial for the treatment of juvenile idiopathic arthritis, dermatomyositis, Lambert-Eaton Myasthenic syndrome, prevention of neonatal sepsis, primary immune defects with normal IgG, and unlikely to be beneficial demyelinating neuropathy associated with monoclonal IgM, and isolated IgE or IgA deficiency.

IVIG treatments may result in several adverse events, which may occur in 2–25% of patients [2,7]. IVIG related adverse events include pyrexia, malaise, headache, backache, nausea, raised blood creatinine levels, leucopenia/neutropenia/pancytopenia, acute renal failure, coronary and cerebral thrombosis, aseptic meningitis and in rare cases, anaphylactic shock in patients with agammaglobulinemia or IgA-deficient patients [8].

IVIG treatment becomes critical for pediatric patients, especially those with PID when diagnosed very early in their lives. IVIG therapy is beneficial for the treatment of pediatric patients with ITP, Kawasaki disease (KD), chronic inflammatory demyelinating polyradiculopathy (CIDP), acute inflammatory polyneuropathy (Guillain Barré syndrome, GBS) and hemolytic disease of the newborn due to ABO and Rh incompatibility [2,9]. IVIG treatment was successfully used for the treatment of acute disseminated encephalomyelitis and post-streptococcal neurodegenerative disorders in pediatric patients [10]. Advantages and disadvantages of the IVIG usage in pediatric patients with primary and secondary immune deficiencies, neurologic, infectious and other diseases were reviewed by the Work Group of the American Academy of Allergy, Asthma and Immunology based on the existing evidences in 2017 [5]. The work Group have found that IVIG treatment of primary immune deficiencies will benefit pediatric patients by reducing rate of infections. Interestingly, the group recommended the IVIG treatment of ITP in only pediatric patients with increased risk of bleeding or patients with refractory chronic disease. IVIG treatment is definitively benefit pediatric patients with KD [5], although the large percentage of African-American pediatric patients with KD were refractory to IVIG treatments [11]. More recent studies indicated that KD treatment with infliximab or steroids reduces need of additional therapies compared to IVIG treatment [12]. Recent systematic review of the literature suggest that IVIG treatment of children with acute myocarditis did not improve survival rate and cannot be routinely recommended for treatment of acute myocarditis in children [13]. Another study reviewed thirteen studies with 1534 cases of acute myocarditis in children and adults and came to the conclusion that IVIG treatments increases survival of patients with acute myocarditis and supports recovery of left ventricular function [14].

To our knowledge, there are no studies summarizing frequency and trends of IVIG use among pediatric inpatients. Our study analyses a retrospective data obtained from an administrative database of pediatric patients receiving IVIG following hospitalization to the pediatric hospitals during the 2007–2014 period. Data were collected from 47 U.S.-based pediatric hospitals participating in the Pediatric Hospital Information System (PHIS). PHIS is an administrative database maintained by the Children's Hospital Association (CHA) (Lenexa, KS). The PHIS data contains hospital and patient demographic data, admission characteristics (e.g., Length of Stay, Disposition, ICD9 coding, etc.) and detailed billing data. The data is reviewed by the CHA and participating hospitals to ensure data quality.

Our analysis indicates that IVIG was more often than not prescribed to pediatric patients for off-label indications. However, KD and ITP, two FDA-approved indications, were the top indications for which IVIG was prescribed during this period. The IVIG use significantly increased for indications like encephalitis and encephalomyelitis with immune pathogenesis, unspecified neutropenia, and septicemia, while the use for other indications (e.g., Erythema multiforme and fever) has decreased. IVIG usage is a dynamic process guided by emerging evidence and FDA approval for new indications.

2. Methods

This retrospective study analyzed IVIG used by 47 US-based children's hospitals between January 1, 2007, and September 31, 2014.

2.1. Inclusion criteria

Inpatients from PHIS database were included in this study, if they were of age < 18 discharged with pharmacy charges for IVIG (Pharmacy CTC Billing Code 164121 with a route of Intravenous).

2.2. Statistical analysis

Data were extracted from PHIS using SQL ™ v.13 and analyzed using SAS ™ v. 9.4. The primary diagnosis ICD9 codes were used to determine the indications for IVIG use. Data quality checks were performed on the pharmacy charges to ensure that only admissions billed for IVIG, which we assumed represented accurate IVIG administration, were included by excluding any reversed IVIG charges. Their primary ICD9 diagnosis code grouped patients, and for purposes of analysis, each observation reflects a single admission.

Several demographic parameters were evaluated in this study, such as gender, race/ethnicity, and age at the admission of the patient. Age stages were defined using National Institute of Child Health and Human Development (NICHD) pediatric terminology: neonates (birth to 27 days); infant (28 days to < 12 months), toddler (12 months to < 2 years), child (2 to 12 years), early adolescent (12 to 18 years) [15].

All Patient Refined-Diagnosis Related Group inpatient classification system (APR-DRG) was used to define the severity of illness (SOI) and risk of mortality (ROM) categories [16,17]. The APR-DRG assigns four levels (Minor, Moderate, Major, and Extreme).

Following indications were FDA-approved during study period: mucocutaneous lymph node syndrome (Kawasaki disease, KD), immune thrombocytopenic purpura (ITP), primary immunodeficiency (PID), secondary immunodeficiency (chronic lymphocytic leukemia, CLL), pediatric HIV infection, and prevention of graft versus host disease or infection in bone marrow transplant (BMT) patients > 20 years of age [5]. Off-label indications were considered all FDA-approved indications for children under two years of age since IVIG usage was approved only for children ≥2 years old. Additionally, off-label indication in our study was IVIG usage for pediatric BMT patients, since IVIG was approved only for BMT patients ≥20 years old.

Additionally, we evaluated the type of medical insurance that treatments were billed to and IVIG charges. For IVIG charge/gram, cost/gram and total admission cost, calculations, only data with provided dosage information and total admission cost (CTC Dosage Units of measure values 2 and 3) were included. All dollar amounts were also adjusted for the geographic area and inflation to 2014 dollars using the Health Care Finance Administration wage/price index and the All Urban Consumers Consumer Price Index. Categorical data were evaluated using SAS PROC FREQ and the SAS programming language was used to provide *t*-tests and level of significance for time trends in continuous variables.

Hospital sizes were quite diverse for hospitals in the PHIS network, ranging from 145 to 629 staffed beds. To have a comparable metric of use, rate of IVIG use was scaled by the number of annual admissions

and was presented as mean annual rates of IVIG admissions for patient subgroups per 100,000 total admissions. This also allows a calculation of variability between hospitals and between years. Comparisons between 2007 and 2014 rates were then based on a simple two independent sample *t*-test, and changes were considered significant if the two-sided *p*-value was < 0.05.

Summary statistics and t-statistics for trends were calculated using SAS ™ 9.4. Rates per 100,000 admissions were calculated for each hospital based on comparison to the overall quarterly admissions for each hospital in the PHIS network. Summary statistics were calculated for change from 2007 to 2014 for the top-ten primary diagnosis ICD9 groups.

3. Results

3.1. Demographic characteristics of pediatric patients treated with IVIG during hospitalization to the US-based pediatric hospitals

We identified 72,852 admissions in which IVIG was administered to 53,648 unique patients. Demographic characteristics of patients admitted to the 47 pediatric hospitals and treated with IVIG are summarized in Table 1. About 55% of patients receiving IVIG treatments were males. Majority of IVIG treated patients were White, non-Hispanic (50%), followed by Black, non-Hispanic group (15%) and White, Hispanic (13%). The median age at the admission was four years. Seventy percent of patients with IVIG treatments were children and adolescent. Forty-eight percent of children had government insurance. The IVIG varied widely from $3500 to 17,500 per admission and $ 30–517 per administered gram of the IVIG.

3.2. IVIG usage during 2007–2014 period

The number of IVIG admissions has increased by 30.2% from January 1, 2007, to September 30, 2014 (Fig. 1). However, the mean annual rate of IVIG admissions calculated as several IVIG admissions per 100,000 of total hospital admissions, has increased by only 5.8% from 1460.6 IVIG/100,000 admissions in 2007 to 1546.5 IVIG/100,000 total admissions by 2014 (Fig. 1).

The FDA has approved IVIG treatment for only a few indications in children older than two years old [5]. Among these indications are primary immunodeficiency, secondary immunodeficiency (CLL), KD, ITP, pediatric HIV infection, and prevention of graft versus host disease or infection in bone marrow transplant (BMT) patients > 20 years of age [5]. Our analysis has demonstrated that vast majority of IVIG usage was either off-label or for the treatment of FDA-approved IVIG indications in children under two years of age and BMT patients < 20 years of age (off-label indications) (Fig. 2). The admissions follow which immunoglobulins were administered to children with FDA-approved indications represented only 28.9% of total admissions (29.6% scaled by hospital size) from all IVIG admissions from 2007 to 2014. The mean rate of off-label IVIG admissions has increased by 6.3% and the mean rate of IVIG admissions for FDA-approved indications by 4.4% from 2007 to 2014 (Fig. 2). The difference was not statistically significant ($p = 0.908$).

Thirty-three percent of inpatients receiving IVIG were admitted to the ICU (Table 2). The most common diagnoses among children admitted to ICU were KD (mean rate of admissions 16.8 IVIG/100,000 admissions), Hypoplastic Left Heart Syndrome (mean rate of admissions 15.9 IVIG/100,000 admissions), Respiratory Distress Syndrome (mean rate of admissions 14.6 IVIG/100,000 general admissions) and GBS (mean rate of admissions 10.9 IVIG/100,000 general admissions). IVIG admissions distributed equally among all categories of severity of illness suggesting (Table 2). Most patients treated with IVIG (52%) had low risks of mortality.

3.3. Trends in the IVIG use among top 10 indications for 2007 and 2014 years

Retrospective data analysis revealed that five indications for the IVIG treatment were present in the top-10 list of IVIG indication in both the 2007 and 2014 years (Table 3). Kawasaki disease, an FDA-approved indication, ranked number 1 in both years with mean IVIG admission rates 266.1 and 286.1 per 100,000 admissions in 2007 and 2014, respectively. Immune thrombocytopenic purpura, another FDA-approved indication, was the second most often used indication for the IVIG treatment with a mean rate of IVIG admissions 145.8 and 162.3 per 100,000 admissions, respectively. These top two indications were followed by the prescription of IVIG treatments to inpatients undergoing antineoplastic chemotherapy, acute infectious polyneuritis (GBS), and hypoplastic left heart syndrome (Table 3). While the mean rates for these indications have changed between 2007 and 2014, the differences were not statistically significant.

Several indications for the IVIG treatment were present only in the top-10 list of IVIG indications in 2007. Among them were following indications: infections due to vascular device, acute lymphoid leukemia without remission, complications of transplanted bone marrow, fever, and erythema multiforme (Table 3). The mean rate of IVIG admissions of patients with infections due to a vascular device has dropped from 25.1 to 0.57/100,000 admissions and ranked only 325 in 2014. The mean rate of IVIG admissions of patients with complications of transplanted bone marrow decreased by 41.5%. IVIG treatment has not been used for the treatment of fever (ranked seventh in 2007) and erythema multiforme (ranked tenth in 2007) in 2014. The differences between mean rates of the IVIG admissions for these indications (with the exception of complications from those transplanted with bone marrow) were statistically significant.

Some IVIG indications present only in the 2014 top-10 indications list (Table 3). IVIG has not been used for the treatment of the bloodstream infection due to a central venous catheter (catheter-related

Table 1
Demographic characteristics pediatric patients receiving IVIG treatment in major US children's hospitals from the period of 2007–2014.

Characteristics	Number of admissions (% of total IVIG admissions)
Number of total admissions	72,852 (100%)
Gender	
Male	40,317 (55%)
Female	32,530 (45%)
Unknown	5 (< 1%)
Race/ethnicity	
White, Non-Hispanic	36,358(50%)
Black, Non-Hispanic	10,803(15%)
White, Hispanic	9180(13%)
Multiple	5703(7.8%)
Other	5154(7.1%)
Asian	3100(4.3%)
Unknown	1718(2.4%)
American Indian	401(0.55%)
Pacific Islander	224(0.31%)
Black Hispanic	209(0.29%)
Age	
Neonates (0–28 days)	5864 (8.1%)
Infants (> 28 days–12 mo.)	8887(12%)
Toddlers (> 12 mo.–2 years)	7072(9.7%)
Children (> 2–12 years)	34,294(48%)
Adolescent (> 12–18 years)	16,105(22%)
Payer group	
Government	35,011(48%)
Private	6714(9.2%)
Other	30,296(42%)
Unknown	831(1.1%)
IVIG cost, median (IQR)	
Per admission	7811 (3500–17,508)
Per gram	233 (30–517)

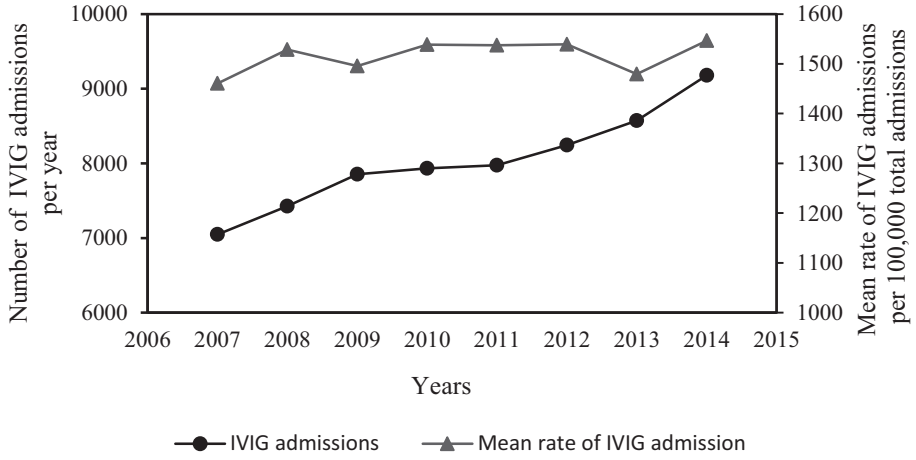

Fig. 1. The trend of the IVIG usage for the treatment of pediatric patients admitted to the US-based major pediatric hospitals from 2007 to 2014.

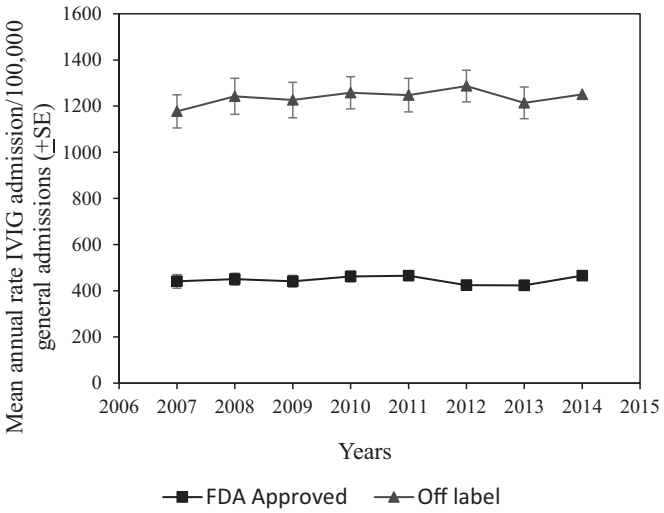

Fig. 2. Trends of the FDA-approved and off-label use of IVIG in pediatric inpatients.

Table 2
The association of the severity of illness and mortality risks with IVIG treatment.

	Number (%) of admissions
ICU/NICU admission	23,954(33%)
Severity of Illness (SOI)[a]	
Minor	19,586(27%)
Moderate	17,839(24%)
Major	17,745(24%)
Extreme	17,579(24%)
Not specified	103(< 1%)
Risk of Mortality[a]	
Minor	38,108 (52%)
Moderate	14,771(20%)
Major	10,902(15%)
Severe	8968(12%)
Not specified	103(< 1%)

[a] As defined by the guidelines Centers for Medicare & Medicaid Services (CMS) and implemented by 3M APR-DRG and SOI systems.

sepsis) in 2007, while this indication was ranked eighth in 2014 with mean rate admission 17.1 IVIG/100,000 admissions. In 2014, the mean rate of IVIG admissions for treatment of unspecified neutropenia and unspecified septicemia had increased 71.3% and 155.5%, respectively. The highest increase in the IVIG usage (+369%) was observed for the indication "Other causes of encephalitis and encephalomyelitis" belonging to the group of neurologic disorders and moved from the 63rd position in 2007 to ninth in 2014.

4. Discussion

Data analysis of the IVIG usage by patients hospitalized to the major US-based pediatric hospitals has revealed that the absolute number and mean rate of IVIG admissions per 100,000 admissions have increased from January 1, 2007, to September 30, 2014. This was due to a growing number of IVIG admissions and an increase in the number of indications for which IVIG was prescribed. During the 2007–2014 period, IVIG has been prescribed to pediatric patients diagnosed with 2343 distinct indications. The number of indications has increased by 20% during this period. At this time, IVIG has been approved by the FDA for the use in six conditions: KD, ITP, primary immunodeficiency, secondary immunodeficiency (CLL), pediatric HIV infection, and prevention of graft versus host disease or infection in bone marrow transplant (BMT) patients ≥20 years of age [5]. The FDA has not approved IVIG for use in children ≤2 years of age [5].

Consequently, in our study, 70% of IVIG treated patients were children and adolescent. There were no significant changes in the trend of the IVIG usage for FDA-approved and off-label indication between 2007 and 2014. The majority of IVIG admissions (~80%) were for off-label indications, FDA-approved indications for children under two years of age and indications for preventing of BMT complications (FDA-approved indication for patients ≥20 years of age). Our study included only patients, who were ≤ 18 years old. Therefore, the use of IVIG in BMT patients we considered as off-label use. However, the usage of IVIG for the treatment of complications of bone marrow transplant was quite high during the study period and ranked eighth in 2007 and sixteenth in 2014.

While IVIG treatment was not approved for numerous indications, it is possible that rationale for the IVIG use was based on a case report or small clinical trials suggesting positive effects of IVIG on the disease outcome. An immune nature of some off-label diseases also could lead to the decision to use IVIG. The proposed mechanisms of IVIG actions are multifaceted [18–21]. Immunoglogilins administered to the patient affect function of practically all types of immune cells. IVIG block Fc receptors, specifically Fcγ receptors on monocyte-derived macrophages; regulate Fc receptor expression on the surface of immune cells and activate inhibitory FcγIIb. Additionally, immunoglogulins may stimulate production of NK-cells via enhanced production of IL12 and modulation of T cell differentiation and cytokine production potentially via suppression of NFkB activation and IkB degradation. Immunoglobulins administered intravenously stimulate dendritic cell-

Table 3
Top IVIG indications used for the treatment of pediatric inpatients in 2007 and 2014.

IVIG indications	Mean usage rate (IVIG admissions/100,000 admissions) ± SE		Rank		% of change from 2007	*P* value
	2007	2014	2007	2014		
Indications present in the top-10 list in both 2007 and 2014						
Mucocutaneous lymph node syndrome (Kawasaki disease)	266.1 ± 18.3	286.1 ± 16.5	1	1	+7.5	0.418
Immune thrombocytopenic purpura	145.9 ± 20.1	162.3 ± 11.9	2	2	+11.2	0.479
Antineoplastic chemotherapy	35.8 ± 5.9	43.6 ± 5.2	4	3	+41.5	0.102
Acute infectious polyneuritis (Guillain–Barré syndrome)	30.8 ± 3.0	36.5 ± 2.9	3	4	+15.7	0.856
Hypoplastic left heart syndrome	16.2 ± 2.9	16.1 ± 3.5	9	10	−0.7	0.982
Indications present only in the top-10 list in 2007						
Infections due to vascular device	25.1 ± 3.8	0.57 ± 0.29	5	325	−97.7	< 0.00001
Acute lymphoid leukemia, without remission	23.9 ± 3.8	11.0 ± 2.1	6	17	−54	0.003
Complications of transplanted bone marrow	16.2 ± 3.8	11.6 ± 2.3	8	16	−41.5	0.292
Fever	19.1 ± 3.7	0	7	NA	−100	< 0.00001
Erythema multiforme	15.3 ± 2.7	0	10	NA	−100	< 0.00001
Indications present only in the top-10 list in 2014						
Unspecified Neutropenia	15.3 ± 2.5	25.7 ± 3.4	11	6	+71.3	0.011
Unspecified septicemia	7.2 ± 1.7	18.4 ± 2.4	34	7	+155.5	0.0001
Bloodstream infection due to central venous catheter	0	17.1 ± 3.3	NA	8	NA	NA
Other causes of encephalitis and encephalomyelitis	3.6 ± 0.8	17.0 ± 2.4	63	9	+369.4	< 0.00001

guided induction of regulatory T cells and neutralization of autoantibodies.

The mean rate of IVIG admissions for FDA-approved indications 29.6% of all IVIG admissions. The mean rate of IVIG admissions for primary immune deficiencies represented only 1.2% of all IVIG admissions and 4.1% of the FDA-approved IVIG admissions represented. The mean rate of the IVIG admissions for the treatment of KD and ITP was 28.2% of all IVIG admissions and 96% of FDA-approved category. IVIG treatment is intended to restore levels of immunoglobulins to normal levels in patients with hypogammaglobulinemia, antibody deficiency disorders, other immunodeficiency states, decrease susceptibility to infections or prophylaxis of serious complications of disease [5]. Predictably, ~ 50% of patients in the study cohort had negligible risk of mortality.

Kawasaki disease was ranked a number one among all pediatric IVIG admission in both 2007 and 2014. KD is an acute systemic vasculitis of small and medium-size arteries commonly affecting children under five years of age [22]. Clinically, KD is characterized by the fiver for five days or more, cracked and erythematous lips, strawberry tongue, polymorphous rash, bilateral conjunctivitis, unilateral cervical lymphadenopathy [22]. The primary complications of the KD are coronary arteries abnormalities, specifically coronary artery aneurysms that may occur in 20–25% of untreated children [23]. Specific causal factors of the KD are not known. Excessive production of inflammatory cytokines (e.g., TNFα and IL6) by the immune cells is capable of promoting endothelial cell damage, a critical component of the KD pathogenesis [22]. IVIG plus aspirin treatment is the mainstream treatment for the KD [19,22]. Usually, IVIG administration results in a quick resolution of fever, rash, and conjunctivitis [19,22]. Corticosteroid, cyclophosphamide, and anti-TNFα therapies along with repeated IVIG treatments are reserved for the refractory KD [22]. The main mechanisms of IVIG action that prevent KD complication development are a reduction of inflammation and endothelial cell damage by the inhibition of autoantibodies binding to Fc receptors, modulation of monocyte-derived macrophage activity, expansion of natural and inducible regulatory cells, production of anti-inflammatory IL10, and finally, increase of NK cell numbers [19]. In our study, the mean rate of IVIG admission for KD increased by 7.5% from 2007 to 2014, but differences were not statistically significant. IVIG admissions of patients with KD represented 17.6% of all IVIG admissions for this period. Darabi K. and colleagues reported that patients with KD admitted to the Massachusetts General Hospital represented only 2.6% of all IVIG admissions in 2004 [24]. The differences in the reported rates of usage of IVIG for the KD treatment between our and Massachusetts General Hospital studies could be due to several reasons. Darabi et all reported IVIG usage probably by an adult and pediatric patients with KD (no demographic characteristics were presented) hospitalized to one hospital during 2004, while we analyzed data of the IVIG usage by pediatric patients hospitalized to 47 pediatric hospitals during 2007–2014.

The mean IVIG admission rate for ITP has been ranked second among all IVIG admissions in both, 2007 and 2014 years. ITP is an autoimmune disease characterized by decreased platelet counts ($< 150 \times 10^9$/L) [25]. It affects patients of all ages. ITP is usually a self-limiting disease in children and typically has an uncertain probability of severe bleeding [26]. Children of 1–7 year old more frequently possess ITP than children of other ages [25]. The main complications of this disease was a risk of bleeding when platelet counts decreased below 10×10^9/L [27]. It is believed that immune dysregulation T and B cells is responsible for the generation of autoantibody and cytotoxic T lymphocyte targeting platelets and megakaryocytes [28]. In 1994, based on the results of RCT, Blanchette V. and colleagues recommended IVIG as an initial treatment for childhood acute ITP [29]. Administration of a single dose of IVIG (0.8 mg/kg) restored platelet counts above 20×10^9/L within 2–3 day in about two-thirds of children [29]. Patients with platelet counts below 20×10^9/L after initial treatment were recommended additional IVIG and oral prednisone treatments [29]. In 2013, the Intercontinental Cooperative ITP Study Group analyzed bleeding manifestations and treatment pattern in children with persistent chronic ITP [26]. The majority of patients had platelets counts above 150×10^9/L at six months after ITP was diagnosed, and only 7% of children had platelet counts below 20×10^9/L [26]. Three or more bleeding sites were reported in 26% of children with platelet counts below 20×10^9/L 6 months following diagnosis, while only 5% of children with platelet counts 20–150×10^9/L had ≥3 bleeding sites [26]. Conventional treatments provided to these patients with chronic ITP between 28 days and six months were corticosteroids (17%) and IVIG (14%) [26]. IVIG usage for this indication in our study has increased ~11%, but differences were not statistically significant.

Secondary hypogammaglobulinemia, another FDA-approved indication for IVIG usage, may occur in patients with CLL [5,24]. Infections are the primary cause of mortality and morbidity among these patients. It has been demonstrated that continuous IVIG treatment of CLL patients can significantly reduce the number of overall bacterial infections, but did not reduce the frequency of severe bacterial

infections as well as viral and fungal infections [30]. Since IVIG is an expensive procedure, the use of antimicrobial drugs may be a more -cost-efficient alternative for infection prophylaxis in CLL patient. In our study, IVIG admissions of pediatric patients with CLL represented only 0.05% of all IVIG admissions.

Acute lymphoid leukemia (ALL) is the most prevalent type of leukemias in children [31]. Pediatric patients with acute lymphoblastic leukemia may experience hypogammaglobulinemia [32]. During chemotherapeutic treatments, they are also at risk of acquiring infections and developing sepsis. In has been demonstrated that pediatric patients with ALL undergoing chemotherapy and receiving IVIG treatment have fewer infections and reduced antibiotic usage [32]. The use of IVIG concurrently with antibiotics may potentiate antibiotic treatment in ALL patients with fever and neutropenia. It has been reported that pediatric ALL patients with a high incidence of bacterial and fungal infections before chemotherapy have a higher chance to receive IVIG treatment during chemotherapy [32]. Unfortunately, there were no statistically significant differences in the number of bacteremia cases between patients receiving IVIG and those who did not IVIG treatment during chemotherapy [32]. In our study, the IVIG admissions for pediatric patients with ALL were ranked sixth in 2007 and then, dropped to 17th place in 2014. At the same time, the mean rate of the IVIG admissions of pediatric patients undergoing antineoplastic chemotherapy has increased by 41.5% by 2014. Significant increase in the rate of IVIG admissions was observed in patients admitted to the hospitals with ICD9 code “Unspecified Neutropenia” (+71.3%). More studies are needed to identify whether a decrease in the IVIG usage for the treatment of ALL patients and an increase IVIG usage in patients undergoing chemotherapy or patients with neutropenia was associated with changes in billing practices. However, it is reasonable to speculate that some ALL patients receiving IVIG treatments during hospitalization were billed as patients undergoing chemotherapy.

Acute infectious polyneuritis or Guillain Barre Syndrome (GBS) is an acute immune-mediated polyneuropathy often occurring after infections or stress. The development GBS was associated with *Campylobacter jejuni*, Epstein–Barr virus, cytomegalovirus, herpes viruses, *Mycoplasma pneumoniae*, and *Haemophilus influenza* infections [33,34] GBS may also occur after vaccination [35]. Most often, GBS was observed in older patients vaccinated with influenza and hepatitis vaccines. GBS was also reported in children after vaccinations with influenza A (H1N1) [36], measles vaccines [37], and quadrivalent human papillomavirus recombinant vaccine [38]. Based on the above-presented evidence, it becomes clear that deviant immune response to infection or vaccination could be a significant contributing factor of the GBS development. Molecular mimicry and cross-reactivity, complement activation and induction of anti-ganglioside antibodies are deriving mechanisms of the GBS [39].

Children are at lower risk of developing GBS. In the USA, the incidence of GBS are ranging between 0.3 and 1.5 cases per individuals younger than 18 years [40]. Typically, patients with GBS have symmetric weakness in the limbs, decreased or absent tendon reflexes [39]. It is challenging to diagnose GBS in younger children due to nonspecific symptoms [41]. Typical signs of GBS in preschool children may be a refusal to walk due to leg pain. Therefore, GBS is often misdiagnosed [41]. It has been determined that plasma exchange and IVIG treatments are equally efficient in adult patients with GBS [42,43]. Corticosteroids were not recommended for GBS treatment in adults [43]. Prospective multicenter studies of GBS in children reported that patients treated with IVIG in a few days after first symptoms' appearance had seen first improvements within 13 days after early symptoms, were able to walk unaided 27 days and were free of symptoms by 118 days after early symptoms' appearance [44]. However, 21% of patients had residual symptoms that did not affect their daily functions [44]. In our study, the rate of IVIG admission for treatment of GBS shared third and fourth places with antineoplastic chemotherapy in 2007 and 2014 with ~16% increase in the mean rate IVIG admission by 2014. “Other causes of encephalitis and encephalomyelitis” was another category of neurological disorder(s) present in the top ten list in 2014. It includes post-infectious or noninfectious acute disseminated encephalomyelitis, post-traumatic or autoimmune (lupus) encephalitis and Rasmussen's encephalitis. The mean rate of the IVIG admissions for this category has increased almost 4-fold. Darabi K. and colleagues reported that neurologic disorders were the number one indication for IVIG usage among patients admitted to the Massachusetts General Hospital [24]. Our data indicate that there was a significant increase by 37% in the IVIG usage for neurological disorders as an ICD9 group.

We believe that the IVIG usage in 47 US-based pediatric hospitals represents typical practices of the IVIG usage for the treatment of diseases and/or prophylaxis of complications in pediatric patients across all United States. IVIG treatment was used for the treatment of > 2300 diseases and conditions. Pediatric patients admitted with diagnoses KD and ITP were two significant users of the IVIG treatment. Primary immune deficiencies, two FDA-approved indications, represented only 1.2% of all IVIG admissions. The increase in the IVIG usage was observed in patients undergoing chemotherapeutic treatments and suggesting the effectiveness of the IVIG for treatment prophylaxis of complications of chemotherapeutic treatment in these patients. The usage of IVIG treatment has increased for neurological disorders, especially in patients with encephalitis and encephalomyelitis. It appears that the main IVIG consuming indications were those requiring modulation of pathologic immune responses (e.g., inflammation and autoimmunity) responsible for the development of diseases like KD, ITP, and GBS. More studies are needed to understand the effectiveness of IVIG usage for treatment of off-label diseases and conditions in pediatric patients.

References

[1] O.C. Bruton, Agammaglobulinemia, Pediatrics 9 (1952) 722–728.
[2] M. Garcia-Lloret, S. McGhee, T.A. Chatila, Immunoglobulin replacement therapy in children, Immunol. Allergy Clin. N. Am. 28 (2008) 833–849.
[3] J.S. Orange, E.M. Hossny, C.R. Weiler, M. Ballow, M. Berger, F.A. Bonilla, R. Buckley, J. Chinen, Y. El-Gamal, B.D. Mazer, R.P. Nelson Jr., D.D. Patel, E. Secord, R.U. Sorensen, R.L. Wasserman, C. Cunningham-Rundles, Primary Immunodeficiency Committee of the American Academy of Allergy, A., and Immunology, 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. 117 (2006) S525–S553.
[4] M.D. Kazatchkine, S.V. Kaveri, Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin, N. Engl. J. Med. 345 (2001) 747–755.
[5] E.E. Perez, J.S. Orange, F. Bonilla, J. Chinen, I.K. Chinn, M. Dorsey, Y. El-Gamal, T.O. Harville, E. Hossny, B. Mazer, R. Nelson, E. Secord, S.C. Jordan, E.R. Stiehm, A.A. Vo, M. Ballow, Update on the use of immunoglobulin in human disease: a review of evidence, J. Allergy Clin. Immunol. 139 (2017) S1–S46.
[6] J.S. Orange, H.D. Ochs, C. Cunningham-Rundles, Prioritization of evidence-based indications for intravenous immunoglobulin, J. Clin. Immunol. 33 (2013) 1033–1036.
[7] . Goddard, E. A. (2008) Goddard EA. Curr. Allergy Clin. Immunol. 21, 26–31.
[8] L.R. Pierce, N. Jain, Risks associated with the use of intravenous immunoglobulin, Transfus. Med. Rev. 17 (2003) 241–251.
[9] A.N. Prasad, S. Chaudhary, Intravenous immunoglobulin in pediatrics: a review, Med. J. Armed Forces India 70 (2014) 277–280.
[10] G. Vitaliti, O. Tabatabaie, N. Matin, C. Ledda, P. Pavone, R. Lubrano, A. Serra, P. Di Mauro, S. Cocuzza, R. Falsaperla, The usefulness of immunotherapy in pediatric neurodegenerative disorders: a systematic review of literature data, Hum. Vaccin. Immunother. 11 (2015) 2749–2763.
[11] B.S. Moffett, D. Syblik, S. Denfield, C. Altman, K. Tejtel-Sexson, Epidemiology of immunoglobulin resistant Kawasaki disease: results from a large, national database, Pediatr. Cardiol. 36 (2015) 374–378.
[12] S.R. Dominguez, M. Birkholz, M.S. Anderson, H. Heizer, P.N. Jone, M.P. Glode, J.K. Todd, Diagnostic and treatment trends in children with Kawasaki disease in the United States, 2006-2015, Pediatr. Infect. Dis. J. (2019), https://doi.org/10.1097/INF.0000000000002422 (Epublished 2019/08/01).
[13] C.Y. Yen, M.C. Hung, Y.C. Wong, C.Y. Chang, C.C. Lai, K.G. Wu, Role of intravenous immunoglobulin therapy in the survival rate of pediatric patients with acute myocarditis: a systematic review and meta-analysis, Sci. Rep. 9 (2019) 104–159.
[14] X. Huang, Y. Sun, G. Su, Y. Li, X. Shuai, Intravenous immunoglobulin therapy for acute myocarditis in children and adults, Int. Heart J. 60 (2019) 359–365.
[15] K. Williams, D. Thomson, I. Seto, D.G. Contopoulos-Ioannidis, J.P. Ioannidis, S. Curtis, E. Constantin, G. Batmanabane, L. Hartling, T. Klassen, R.C.H.G. Sta,

Standard 6: age groups for pediatric trials, Pediatrics 129 (Suppl. 3) (2012) S153–S160.
[16] Mortality Risk Adjustment Methodology for University Health System's Clinical Data Base (2008) Available at: https://archive.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/mortality/Meurer.pdf; University HealthSystem Consortium. Last accesed April 30, 2019.
[17] 3M health information systems, National Association of Children's hospitals and related institutions, Inc., medical advisory committee for NACHRI APR-DRG research project, ALL PATIENT REFINED DIAGNOSIS RELATED GROUPS (APR-DRGs), version 20.0, methodology overview, Available at: https://www.hcup-us.ahrq.gov/db/nation/nis/APR-DRGsV20MethodologyOverviewandBibliography.pdf , Accessed date: 30 April 2019.
[18] T. Sapir, Y. Shoenfeld, Uncovering the hidden potential of intravenous immunoglobulin as an anticancer therapy, Clin. Rev. Allergy Immunol. 29 (2005) 307–310.
[19] J.C. Burns, A. Franco, The immunomodulatory effects of intravenous immunoglobulin therapy in Kawasaki disease, Expert. Rev. Clin. Immunol. 11 (2015) 819–825.
[20] T. Sapir, Y. Shoenfeld, Facing the enigma of immunomodulatory effects of intravenous immunoglobulin, Clin. Rev. Allergy Immunol. 29 (2005) 185–199.
[21] C. Galeotti, S.V. Kaveri, J. Bayry, IVIG-mediated effector functions in autoimmune and inflammatory diseases, Int. Immunol. 29 (2017) 491–498.
[22] A. Saguil, M. Fargo, S. Grogan, Diagnosis and management of Kawasaki disease, Am. Fam. Physician 91 (2015) 365–371.
[23] E. Binder, E. Griesmaier, T. Giner, M. Sailer-Hock, J. Brunner, Kawasaki disease in children and adolescents: clinical data of Kawasaki patients in a western region (Tyrol) of Austria from 2003-2012, Pediatr. Rheumatol. Online J. 12 (2014) 37.
[24] K. Darabi, O. Abdel-Wahab, W.H. Dzik, Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature, Transfusion 46 (2006) 741–753.
[25] T. Kuhne, P. Imbach, P.H. Bolton-Maggs, W. Berchtold, V. Blanchette, G.R. Buchanan, I.T.P.S.G. Intercontinental Childhood, Newly diagnosed idiopathic thrombocytopenic purpura in childhood: an observational study, Lancet 358 (2001) 2122–2125.
[26] C.E. Neunert, G.R. Buchanan, P. Imbach, P.H. Bolton-Maggs, C.M. Bennett, E. Neufeld, S.K. Vesely, L. Adix, V.S. Blanchette, T. Kuhne, Intercontinental Cooperative, I. T. P. S. G. R. I. I. P, Bleeding manifestations and management of children with persistent and chronic immune thrombocytopenia: data from the Intercontinental Cooperative ITP Study Group (ICIS), Blood 121 (2013) 4457–4462.
[27] L.J. Butros, J.B. Bussel, Intracranial hemorrhage in immune thrombocytopenic purpura: a retrospective analysis, J. Pediatr. Hematol. Oncol. 25 (2003) 660–664.
[28] M. Perera, T. Garrido, Advances in the pathophysiology of primary immune thrombocytopenia, Hematology 22 (2017) 41–53.
[29] V. Blanchette, P. Imbach, M. Andrew, M. Adams, J. McMillan, E. Wang, R. Milner, K. Ali, D. Barnard, M. Bernstein, et al., Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura, Lancet 344 (1994) 703–707.
[30] Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic, L, R.P. Gale, H.M. Chapel, C. Bunch, K.R. Rai, K. Foon, S.G. Courter, D. Tait, Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial, N. Engl. J. Med. 319 (1988) 902–907.
[31] . Howlader, N., Noone, A. M., Krapcho, M., Miller, D. J., Brest, A., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, D. R., Chen, H. S., Feuer, E. J., and Cronin, K. A. (April 15, 2019) SEER Cancer Statistics Review, 1975-2016, Section 28 Childhood Cancer by Site Incidence, Survival and Mortalitybased on November 2018 SEER Data Submission, Posted to the SEER Web Site. Available at: https://seer.cancer.gov/csr/1975_2016/results_merged/sect_28_childhood_cancer.pdf Last Accessed April 30 2019. (Institute, N. C., ed), Bethesda, MD.
[32] P. Van Winkle, R. Burchette, R. Kim, R. Raghunathan, N. Qureshi, Prevalence and safety of intravenous immunoglobulin administration during maintenance chemotherapy in children with acute lymphoblastic leukemia in first complete remission: a health maintenance organization perspective, Perm. J. 22 (2018) 17–141.
[33] R.A. Hughes, D.R. Cornblath, Guillain-Barre syndrome, Lancet 366 (2005) 1653–1666.
[34] S. Grygorczuk, J. Zajkowska, M. Kondrusik, S. Pancewicz, T. Hermanowska-Szpakowicz, Guillain-Barre syndrome and its association with infectious factors, Neurol. Neurochir. Pol. 39 (2005) 230–236.
[35] N. Souayah, A. Nasar, M.F. Suri, A.I. Qureshi, Guillain-Barre syndrome after vaccination in United States: data from the Centers for Disease Control and Prevention/Food and Drug Administration Vaccine Adverse Event Reporting System (1990-2005), J. Clin. Neuromuscul. Dis. 11 (2009) 1–6.
[36] M.E. Tremblay, A. Closon, G. D'Anjou, J.F. Bussieres, Guillain-Barre syndrome following H1N1 immunization in a pediatric patient, Ann. Pharmacother. 44 (2010) 1330–1333.
[37] C.M. da Silveira, D.M. Salisbury, C.A. de Quadros, Measles vaccination and Guillain-Barre syndrome, Lancet 349 (1997) 14–16.
[38] B.A. Slade, L. Leidel, C. Vellozzi, E.J. Woo, W. Hua, A. Sutherland, H.S. Izurieta, R. Ball, N. Miller, M.M. Braun, L.E. Markowitz, J. Iskander, Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine, JAMA 302 (2009) 750–757.
[39] P.A. van Doorn, K. Kuitwaard, C. Walgaard, R. van Koningsveld, L. Ruts, B.C. Jacobs, IVIG treatment and prognosis in Guillain-Barre syndrome, J. Clin. Immunol. 30 (2010) S74–S78 Suppl 1.
[40] A. McGrogan, G.C. Madle, H.E. Seaman, C.S. de Vries, The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review, Neuroepidemiology 32 (2009) 150–163.
[41] J. Roodbol, M.C. de Wit, C. Walgaard, M. de Hoog, C.E. Catsman-Berrevoets, B.C. Jacobs, Recognizing Guillain-Barre syndrome in preschool children, Neurology 76 (2011) 807–810.
[42] R.A. Hughes, J.C. Raphael, A.V. Swan, P.A. Doorn, Intravenous immunoglobulin for Guillain-Barre syndrome, Cochrane Database Syst. Rev. (2004) CD002063.
[43] R.A. Hughes, E.F. Wijdicks, R. Barohn, E. Benson, D.R. Cornblath, A.F. Hahn, J.M. Meythaler, R.G. Miller, J.T. Sladky, J.C. Stevens, Quality Standards Subcommittee of the American Academy of, N, Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology 61 (2003) 736–740.
[44] R. Korinthenberg, J. Schessl, J. Kirschner, Clinical presentation and course of childhood Guillain-Barre syndrome: a prospective multicentre study, Neuropediatrics 38 (2007) 10–17.