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Retrospective Evaluation of IVIG Use: Appropriateness and Potential Cost Savings from Body-Weight dosing at a Northeastern Tertiary Hospital in the United States

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ABSTRACT

Background and objectives: This 1 year retrospective study evaluated the appropriateness of IVIG use as per protocol and the hypothesis that using adjusted bodyweight (AdjBW) (in obese patients) or ideal bodyweight (IBW) each instead of actual bodyweight (ABW) (which is used only in underweight patients with higher corresponding IBW) could save IVIG doses and costs.

Methods: Patient-level data (age, height, ABW, IBW and AdjBW computed; gender, IVIG dose, and dose duration) were collected from the electronic medical records at a northeastern tertiary care hospital in the United States.

Results: About 84.62% (44/65) of patients were ordered IVIG for a protocol approved indication. Applying the unit drug cost (average wholesale price from Red Book) to the differences in doses (grams) between ABW vs. IBW, and ABW vs. AdjBW; potential cost savings of minimum $20,472.63 and maximum $159,440.74, respectively could have been possible.

Conclusion: Despite limitations, this study informs stakeholders of the potential benefit monitoring appropriateness of IVIG use and evaluating cost-savings from implementing bodyweight dosing calculators for IVIG use.

INTRODUCTION

Intravenous immunoglobulin (IVIG) was reported as the number one of top 15 prescription medications by expenditure in non-federal hospitals in 2013 [1]. The IVIGs have been mainstay treatment options for primary immunodeficiency (PI) disorders for over 50 years. Primary immunodeficiency disorders are caused by inherent defects to B cells (in the immune system) that express immunoglobulin, often resulting in recurrent, severe or unusual infections [2-4].

According to the Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency by American Academy of Allergy, Asthma and Immunology, IVIG produces positive health outcomes like preserving organ function, improving quality of life, preventing infection-related death, and increasing lifespan [2]. Although IVIGs do not have an established definitive mechanism of action, it is believed that IVIGs act through multiple immunomodulatory effects [3,4]. As a result the Food and Drug Administration (FDA) has approved IVIG's use in six conditions: immune thrombocytopenic purpura (ITP), primary immunodeficiency, secondary immunodeficiency, pediatric immunodeficiency virus (HIV) infection, prevention of graft-versus host disease (GVHD) and infection in bone marrow transplant (BMT) patients, and Kawasaki disease (KD) [4].

Therapeutic uses of IVIG

For several reasons, prescribers may find it difficult to consistently deliver quality care in using IVIG. First, use of IVIG in hospitals is complicated by the fact that they are used more in off-label indications than FDA approved indications [5]. The literature reports greater positive clinical outcomes for FDA approved indications than for non FDA approved indications [6]. Furthermore, plasma collection from 10,000-20,000 healthy human donors is the limiting factor in IVIG's manufacture which leads to a finite supply of the product making IVIG highly expensive [7]. The average cost for one course of IVIG treatment is approximately $2,700 per infusion, [8] which could be much lesser with reimbursement by insurance companies.

Since 2005 hospitals have become a predominant setting for administration of IVIG [9]. Hospitals bill insurance providers for the services accumulated during a patient's hospital stay primarily using relevant diagnosis related group (DRG) in order to get reimbursed The institution receives a specified amount of funds from payers to reimburse expenses according to DRGs. Inpatient admissions are associated with a small profit margin and the use of high cost medications such as IVIG may lead to an overall financial loss associated with the patient's stay. However, in the outpatient (doctors' offices and homecare) settings, insurance coverage typically reimburses the cost of the medication including a modest profit margin. Institutions may use different methods (altering drug dose, drug manufacturer, infusion time, and lessening product preparation) to reduce total IVIG cost. At the study hospital IVIG was the second costliest drug with a total annual amount exceeding $1 million annually; a price that does not take into account the total treatment cost for each patient. Use of IVIG in the inpatient setting needs monitoring [10].

Differences in manufacturing processes and excipients bring major differences between currently marketed IVIG products [11]. With all currently available IVIG products on the market containing greater than 95% gamma globulin (IgG); it is well established that polyclonal IgG is the mainstay ingredient. Literature suggests currently available products are often considered equivalently efficacious based on clinical outcomes [11-13]. However, due to differences in formulation, concentration, and tolerability (altered by volume load, sugar content, sodium content, osmolarity, IgA (Immunoglobulin A) content, and pH)) products have different rates of adverse events that include; thromboembolic events, hemodynamic changes, hypertension, renal impairment, anaphylaxis [12]. Secondly, based on products; long infusion times, preparation times, added volumes, and refrigeration commonly add to costs, differences, and inefficiencies to the IVIG administration. The pharmacy and therapeutics committee at the author's institution selected Privigen IVIG (Human), 10% Liquid (CLS Behring) as their product of choice due to their several advantages. These include room temperature storage requirements, pre-mixed solution availability, and lack of sucrose as a stabilizer leading to a decrease in the likelihood of adverse effects

Summary of the study hospital's IVIG protocol

The study hospital implemented the *IVIG Appropriate Indications and Dosing Protocol* in the year 2013 with a list of approved and specific off label indications that could be supported with sufficient evidence for IVIG use **(Appendix 1).** A total of seventeen indications were listed, five of which are FDA approved while twelve were approved based on current clinical evidence. The protocol further specified that dosing will be based on the patient's ideal bodyweight (IBW) with a few exceptions: adjusted body weight (AdjBW) and actual body weight (ABW) are used for obese and underweight patients respectively (AdjBW and ABW are defined below).

1. Dosing weight=IBW; IBW (male)=50 kg+2.3 (inches greater than 5 feet) and IBW (female)=45.5 kg+2.3 (inches greater than 5 feet)
2. Exception: Dosing weight=ABW if ABW<IBW; AdjBW If Obese (BMI>30 or ABW is >20% above IBW)

The doses were then rounded to the nearest 5 g vial size to avoid waste. The rationale behind these rules were that ideal and adjusted each instead of actual body-weights would result in more accurate and smaller doses, ultimately minimizing expense.

Literature on IVIG use

Institutions may find it difficult to set standards for the use of IVIG due to the following problems: Conflicting evidence, product availability, drug costs, and lack of prescriber expertise. Currently there are no IVIG dosing recommendations in the American Academy of Allergy Asthma and Immunology guidelines addressing the use of ABW, IBW or AdjBW [13]. Many institutions use IBW due to IVIG's pharmacokinetic parameters [13,14]. Literature suggests that IBW gives a better estimate of weight due to the drug's low volume of distribution and absence of accumulation in the tissue [14]. Using AdjBW for dosing as opposed to ABW is preferred in obese patients as this accounts for increases in volume of body fluids [13,15]. Current studies show that pinpointed trough IVIG levels have a relationship to clinical outcomes [16]. A study conducted by Khan et al in 2011 in the United Kingdom, states the dose of IVIG required to produce a serum trough IgG level appears to be unrelated to body-weight [17]. This suggests no difference in outcomes between the three weight-based dosing options. In addition, previous studies suggest potential cost savings when IBW was used in place of ABW [14], A prospective study by Rocchio et al. in 2013 showed that for 262 inpatient cases in three FDA approved indications (recurrent infections, antibody desensitization in transplant patients, and immune thrombocytopenic purpura) a total of 3,880 g doses were averted by using IBW instead of ABW for calculating the dose. This resulted in a 20% reduction in the amount of IVIG dispensed in a hospital in the United States (U.S.) [14]. Similarly, a tertiary care center in Canada studied approval of IVIG orders and use of a weight based calculator. Weights were calculated in the same fashion as the hospital's protocol and doses were rounded to the nearest 5 g vial. They concluded that 34% of order forms were

modified based on weight or adherence to guidelines. The authors estimated a savings of $69,300 (during a 9-month period) if all orders were based on dosing weight (IBW or AdjBW) rather than ABW [18].

Study rationale and objectives

Proper use of IVIG in approved indications and using IBW or AdjBW (in the obese) instead of ABW has the potential to reduce cost to an institution. However, there are only two quality improvement studies that assess dose savings based on body-weight [14,18]. Despite a large volume of clinical knowledge on IVIG, no retrospective studies reported in the U.S. address evidence on appropriate/inappropriate prescribing or use. Further data on potential cost savings from using bodyweight dosing calculators, i.e., IBW and AdjBW each instead of ABW is limited to real- world settings. Because of the paucity of data to inform stakeholders (i.e., prescribers and the hospital payer), a retrospective observational study of IVIG use in the current institution was proposed. The objectives of this study were to evaluate 1) the appropriateness of IVIG use as per protocol in this institution and 2) the drug dose and cost savings from using ideal and adjusted bodyweight dosing each instead of actual bodyweight in eligible patients. The researchers hypothesize that using IBW (when lesser than ABW) and AdjBW (for obese patients only) would significantly decrease use and costs of IVIG. These study findings may help institutions monitor appropriate IVIG use, automate the use of IVIG dosing calculators and realize cost savings.

METHODS

Study design

A retrospective observational study by review of patients' electronic medical records was designed to evaluate frequency of approved indications for IVIG prescribing, and cost savings estimate associated with the use of IVIG dosing based on IBW or AdjBW.

Setting

The study hospital located in Northeast United States is an 867 bed tertiary teaching center serving 42,000 in-patients and 100,000 outpatient visits per year.

Data sources

Data were obtained from study hospital's Allscripts Sunrise Enterprise Manager (SCM) (Allscripts Healthcare Solutions Inc. Chicago, Illinois). Doses of IVIG were assumed to have been administered as per clinical evidence and FDA approved regimens. The institutional review board at the authors' institutions (hospital and university) reviewed and approved the study as "exempt" from human subject research requirements. The current study includes only use of Privigen, IVIG (Human), 10% Liquid (the preferred product on the study hospital's formulary) [16].

Inclusion and exclusion criteria

All inpatients or outpatients at the study hospital who had one or more doses of IVIG prescribed and ordered between the dates of June 1st, 2013 to June 1st, 2014 were included. Patients were excluded from this study if their age was greater than 88 years old to protect patient privacy and identity or if their weight was greater than 300 pounds (136 kg). Additionally, patients were also excluded if their height was not recorded or missing, as it would not be possible to calculate an IVIG dose using the IBW or adjusted BW dosing calculator without having the height variable.

Study sample rationale

The hospital protocol was updated June 1st, 2013 to include only the specified list of approved IVIG indications as determined by the pharmacy and therapeutics committee. Therefore, all patients fulfilling inclusion and exclusion criteria obtained through the SCM system from June 1st, 2013 to June 1st, 2014 were available at the time of the current study.

Data collection procedures

Data were collected from 69 patients at the study's institution from the SCM database in an excel document, consisting of variables specified in the *Study Variables* section. Three variables (patient date of birth, name, and date of admission) could identify patients so were considered Protected Health Information (PHI) and were subsequently removed to de-identify the data to protect patients' privacy and confidentiality. After deletion of these identifiers, a random numeric identifier replaced the patient's name, and the anonymous excel data file was used for further analyses.

Study variables

A retrospective chart review of the SCM database and IVIG pharmacy order placed by the prescriber were used to extract and categorize data at the patient level. Variables were - patient age (years), height (meters), ABW, IBW, AdjBW (Kg), gender, serum creatinine (sCr; if less than 0.8 mg/dL and the patient was 65 years or older, the sCR was rounded to 0.8 mg/dL), creatinine clearance CrCL (ml/min), IVIG dose (g/Kg; determined by prescribers based on clinical response), sum and total duration of IVIG use (days) (that was equivalent to number of doses of IVIG which is commonly dosed once daily); medical characteristics - indication for IVIG use (recorded by the prescriber requesting IVIG order in the SCM), primary diagnosis for admission to in-

patient/out-patient setting (from patient's admitting note), and number of comorbidities (as per patient's most recent encounter note), health service utilization variables included by reviewing admission and discharge dates for the hospital and ICU start and end dates; intensive care unit (ICU) and hospital length of stay (days). Outpatients were not considered to have had a length of stay. If the patient received IVIG, and had multiple values for relevant variables, mean values (SrCr, CrCL, IVIG dose, number of doses); were calculated and sum of the total number of doses (based on body-weights ABW, IBW, Adjusted BW) and duration days) were computed.

Dependent variables

Study outcomes (dependent variables) were 1) frequency of IVIG use by indication (approved/not approved per institution protocol) and 2) computed dose and cost differences between a) ABW and IBW and b) ABW and AdjBW. All daily doses each patient received contained the same indication; therefore frequency of IVIG use was categorized at the patient level as either "approved or not approved" based on the protocol indications listed in **Appendix 1.**

Statistical analysis

To address the first study objective, descriptive analyses of patient characteristics for two groups of patients were reported: IVIG administered and IVIG not administered. Patient characteristics were defined as categorical and continuous variables. In univariate analyses, the two patient groups were compared using Chi-square statistics for significant differences in proportions of categorical variables and using t-tests (if variables are normal) or Wilcoxon rank sum tests (if variables do not fit the normality assumption) for significant differences in continuous variables. For the second objective of determining potential dose and cost differences, a g/Kg dose was determined based on mean dose of IVIG and ABW for every patient. Patients were then identified as eligible candidates for protocol recommended IVIG-dosing for ABW, IBW, or AdjBW. The total dose of IVIG for each respective bodyweight was then calculated based on the number of doses administered that was equal to the duration of treatment in days based on IVIG once daily dosing. By comparing the total grams of IVIG administered using ABW to the total grams IVIG that could have been administered using IBW or AdjBW, total IVIG dose (in grams) that could be saved was determined. Using micro-costing procedures, the authors' estimated economic outcomes of possible IVIG cost savings. Thus, to estimate the corresponding potential drug cost saving values, the difference in total IVIG doses (in g) from using IBW instead of ABW and AdjBW instead of ABW was each multiplied by the unit IVIG drug cost of $133 per gram (the most updated AWP (average wholesale price) from the Red Book prescription product listings (Truven Health Analytics Inc., Ann Arbor, Michigan)). To test the effect of uncertainty of the unit drug cost on the outcome of potential drug cost saving estimate, a sensitivity analysis was conducted by varying the unit drug costs (AWP) by ± 20%. For this purpose, to generate respective potential cost saving estimates, the two dose differences were also further multiplied by the IVIG unit cost of 20% above and 20% below AWP costs per gram as follows; $107 (20% below AWP), $133(AWP), and $160 (20% above AWP).

RESULTS

Data were collected from 65 patients who had been ordered at least one dose of IVIG during the time period of June 1, 2013 to June 1, 2014. The distribution of indications for the 65 IVIG patients were Guillain Barre Syndrome (15.38%), hypogammaglobulinemia related (15.32%),antibody-mediated rejection (13.46%), Myasthenia Gravis (7.69%), and idiopathic thrombocytopenic purpura (5.77%).

Table 1 lists the patient characteristics and their respective frequency in the two patient groups: IVIG administered and IVIG not administered. Of the 65 patients included in the study, 54 (83.08%) received at least one dose of IVIG while 11 (16.92%) did not. For the IVIG administered group, the average age, height and comorbidities were 59.39 years, 1.67 m, and 5.5, respectively. Majority of the 54 patients were female [29 (53.70%) female; 25 (46.30%) male], were inpatients (40/54, 74.07%) and had an approved indication (84.31%). In addition, 12 patients (18.46%) were eligible to be dosed using ABW, 14 (21.54%) using IBW, and 28 (43.08%) with AdjBW. For the IVIG administered group, the average age, height and comorbidities were 53 years, 1.63 m, and 5.4 respectively. Majority of the 11 patients not administered IVIG were female [6 (54.55%) female; 5 (45.45%) male], were outpatients (11/11,100%) and had an approved indication (11/11,100%). None of the patient characteristics were significantly different for both groups (IVIG administered versus not administered) except service area. Patients administered IVIG were more likely to be inpatients than those not administered IVIG (40/54, 74.07% versus 0/11, 0%, p=<0.0001)

Table 2 shows the doses, possible dose savings, and the potential cost saving estimates by using appropriate bodyweight calculators for IVIG dosing as per protocol. The total IVIG dose administered based on ABW was 9357.02 g (n=54). However, using IBW (instead of the corresponding higher ABW in 14 eligible patients), and AdjBW (instead of ABW in 28 eligible obese patients) total IVIG doses would have been 2338.07 g, and 4513.72 g, respectively. Overall, the potential IVIG dose that could have been saved in non-obese patients if IBW was used instead of ABW would have been 153.93 g giving a potential cost saving estimate of $20,472.63. In addition, the potential IVIG dose that could have been saved in obese patients using AdjBW instead of ABW would have been 1198.8 g giving a potential cost saving estimate of $159,440.74. Reported at the patient level, the institution could theoretically have saved $1462.33 per non-obese patient using IBW and $5694.31 per obese patient using AdjBW patients. The sensitivity analysis showed a higher drug cost saving estimate if unit drug costs 20% above AWP were used and a lower drug cost saving estimate if unit drug costs 20% below AWP were used. For IBW if unit drug costs 20% above and below AWP were used the potential cost savings estimates could have been $24,628.73 and $16,470.46, respectively. A similar trend was evident for AdjBW if unit drug costs 20% above and below AWP were used the potential cost savings estimates could have been $191,808.41 and $128,271.87, respectively.

Table 1. Patient characteristics and protocol indications of IVIG administration in the study hospital.

Patient Characteristics (frequency, % unless otherwise specified)	IVIG Administered (n=54/65, 83.08%)	IVIG Not Administered (n=11/65, 16.92%)	p-value**
Age (mean ± SD)	59.39 ± 20.18	53 ± 15.23	0.4985
Gender			1.00
Male	25 (38.46)	5 (7.69)	
Female	29 (44.62)	6 (9.23)	
Height (mean +/- SD)	1.67 ± 0.10	1.63 ± 0.12	0.9488
Bodyweight for IVIG Dosing			0.91
ABW	12 (18.46)	2 (3.08)	
IBW	14 (21.54)	2 (3.08)	
AdjBW	28 (43.08)	7 (10.77)	
Comorbidities (mean ± SD)	5.5 ± 3.25	5.4 ± 4.19	0.2414
Service Area			<0.0001
Inpatient	40 (74.07)	0 (0)	
Outpatient	14 (25.93)	11 (100)	
Approved Indication*			1.00
Yes	43 (82.69)	1 (1.92)	
No	8 (15.38)	0 (0)	

* Frequency missing in 13 patients
SD: Standard Deviation
ABW: Actual Body-Weight
IBW: Ideal Body-Weight
AdjBW: Adjusted Body-Weight
Approved Indication: Study hospital Protocol approved
**p<0.05: statistically significant

Table 2. IVIG dosing and cost and related potential savings using bodyweight calculators across patients who received IVIG.

Characteristic		N	Sum	Mean (SD)		Median
IVIG doses						
Dose (g/kg) based on ABW		54	23.66	0.45 (0.16)		0.41 (0.38, 0.48)
Dose (g) per administration considering bodyweight (AdjBW in obese; IBW if IBW less than ABW)						
i.	based on ABW	54	1856.70	34.38 (20.72)		30.00 (25, 35)
ii.	based on IBW	14	408.12	29.15 (10.03)		27.76 (21.39, 34.86)
iii.	based on AdjBW	28	874.75	31.24 (16.31)		27.40 (21.97, 35.44)
Total Dose (g) per course considering duration (days) of treatment						
i.	based on ABW	54	9357.02	173.28 (250.56)		120.00 (35, 160)
ii.	based on IBW	14	2338.07	167.01 (342.62)		78.59 (37.13, 128.34)
iii.	based on AdjBW	28	4513.72	161.20 (190.80)		118.19 (38.42, 188.38)
Potential doses saved from						
a.	Using IBW versus ABW	14	153.93	10.99 (14.00)		5.10 (2.20, 20.01)
b.	Using AdjBW versus ABW (in obese)	28	1198.80	42.81 (47.05)		27.81 (13.27, 53.66)
Potential Cost savings from						
Estimates from using drug cost (AWP)*						
a.	using IBW vs. ABW	14	20472.63	1462.33	(1861.43)	678.36 (292.83, 2661.41)
b.	using AdjBW vs. ABW	28	159440.74	5694.31	(6257.58)	3698.70 (1765.53, 7136.78)
Estimates from sensitivity analyses at plus 20% of drug cost (AWP)**						
a.	using IBW vs. ABW	14	24628.73	1759.19	(2239.31)	816.08 (352.27, 3201.70)
b.	using AdjBW vs. ABW	28	191808.41	6850.30	(7527.91)	4449.57 (2123.95, 8585.60)
Estimates from sensitivity analyses at minus 20% of drug cost (AWP)***						
a.	using IBW vs. ABW	14	16470.46	1176.46	(1497.54)	545.75 (235.58, 2141.14)
b.	using AdjBW vs. ABW	28	128271.87	4581.14	(5034.29)	2975.65 (1420.39, 5741.62

Footnote: N: number of patients;
Red book Privigen *AWP: $133;
**plus 20%: $ 160;
***minus 20%: $107

DISCUSSION

To the authors' knowledge this is one of the first retrospective studies in a tertiary center in the United States to evaluate both IVIG use in approved indications based on the institution's protocol and estimate potential cost savings using relevant bodyweight dosing calculators. The indication for IVIG use varied in the current study population. However, majority (84.62%) of indications for IVIG use were "appropriate (approved)" as per the institution's protocol. Second, the authors' study demonstrated a substantial cost difference if IBW or AdjBW were each used instead of ABW in eligible patients suggesting a potential for savings costs with implementation of the IVIG bodyweight dosing calculators. Of note in the Canadian study 81% of IVIG administered to patients were based on Health Canada approved indications or cited guideline, similar to the current study in the Northeast United States where 85% of IVIG use was approved as per protocol. The IVIG use for approved indications was slightly higher in the current study than the earlier report. This may be because clinicians may be prescribing IVIG in approved indications as mentioned in protocols.

Standardization of IVIG prescribing through the use of protocols or dosing calculators may have facilitated prescribers to think carefully about patient specific factors such as distribution of drug in obese patients and evidence of positive clinical outcomes from the literature. Although no prior data about implementation of the protocol exists at the study hospital, there were no major deviations in non-approved indications. In the 15% of IVIG orders that were not appropriate per protocol, these indications required the prescriber to submit a study supporting use for that indication in literature. The study hospital protocol has only indications treated by the institution for which the pharmacy and therapeutics committee found data to support. Thus the protocol may have excluded indications supported in the literature but not treated at the study hospital. Because this information is not readily available to the authors on the subset of patients where IVIG was prescribed for indications outside the protocol, further evaluations in future need to consider this aspect of IVIG use. Also, supporting data for use of IVIG may not be of the highest quality in un-approved conditions. Therefore, the 8 guiding principles for IVIG use have expressed a concern that use in such off label indications would deplete a precious resource from use in the labeled indications [2] which could be monitored in future studies.

Several studies have previously reported drug dosing differences, better compliance with institutional protocols associated with drug cost savings and appropriateness of IVIG use by indication [13,14,18]. Similar to these studies, possible cost savings from using relevant bodyweight based dosing calculators were reported in the current study too. The current study findings are similar to another study from a tertiary care center Toronto, Ontario, Canada that used the same bodyweight definitions for administration of IVIG. In the study from Canada the authors studied their institution's use of a dosing weight calculator with preprinted approval forms on IVIG orders and how these affected prescribing practices over a nine-month period. Compared to 23 % (20/86) of patients in the Canadian study, about 78% (42/54) of patients in the current study who were administered IVIG were eligible for dosing adjustment based on body-weight. The authors' institution in the Northeast United States, likely saw this high percentage of patients requiring dosing adjustment by appropriate body-weight because 52% (28/54) of patients being considered were obese. Thus, in the current study, dose and cost savings could have been realized if 52% and 26% (14/54) patients eligible had used AdjBW and IBW each instead of ABW, respectively for dosing IVIG while only 22% (12/54) of patients eligible need to have used ABW.

Other findings not reported in earlier trials were also observed in the current study. Though more female than male patients were found to in IVIG administered and IVIG non-administered patient groups; gender was not significantly associated with the administration of IVIG. Height and number of comorbidities were not significantly different across both study groups. Though mean age of patients receiving IVIG was higher (59) than those who did (53), age was not associated with IVIG being administered. Another trend evident from the current study data is that there was a significant difference in IVIG administered by service area. Majority (61.54% versus 0%) of patients were inpatients being treated inside the hospital in IVIG administered versus IVIG non-administered groups, respectively. These results reflect the pattern that hospitals are the predominant setting for IVIG administration and call for the importance of using IVIG appropriately and efficiently in inpatients to balance quality while saving costs to hospitals [10].

This study has several limitations that could have affected the study estimates. First, because patient data were collected retrospectively, causation cannot be established and only association of patient characteristics to IVIG use could be reported. Second, Privigen [19] the brand of IVIG was the only product approved for use in the study institution. Therefore, applicability of the current study results to other institutions has to be done with caution if multiple brands of IVIG are being used in other institutions. Third, even though only this number of patients was available after protocol implementation at the time of the study, the patient cohort of 69 patients was small and may have affected our study findings. Consequently, these study results have to be routinely evaluated in a larger patient population as feasible. Fourth, the protocol in the current study was based on the historical use of IVIG in indications at the study institution. Therefore, indications for use of IVIG listed in **Appendix 1** may not be a comprehensive representation of all indications for IVIG use across all hospitals in the United States. Future studies in other institutions will need to evaluate the conditions for which IVIG was used in those institutions. Fifth, the current study was not able to compare historical data related to appropriateness of IVIG use and potential cost savings before the year 2013.

This is because the IVIG protocol was implemented in early 2013. However, the current study can be used as a first baseline analysis of IVIG use in the study hospital. Consequently, future monitoring of IVIG use will require routine future evaluations. Sixth, the authors were unable to include data on dosing based on target serum IgG levels and documentation on how the dosing was based on therapeutic effect because these were unavailable. Hence, there is a concern whether dosing on the basis of AdjBW or IBW could result in different total serum IgG levels or IgG increments. An objective analysis of the literature on IVIG dosing across several medical conditions [20-24] shows the correlation of dose, IgG levels and clinical outcomes. Further, bodyweight dosing by IBW or AdjBW in eligible patients may give similar clinical outcomes as dosing by ABW because IgG levels are not based on bodyweight. Like earlier literature [20-24], the authors used the "widely practiced" rationale of using IBW and AdjBW instead of ABW that was also supported by a recent retrospective study that reported different body-weight IVIG dosing correlated with similar IgG levels [25]. Because IVIG has a relatively small volume of distribution, IVIG has little accumulation in fat and tissue. Therefore, institutions adopt dosing adjustments by administering IVIG by IBW or AdjBW that is "theoretically appropriate in patients whose actual BW exceeds their IBW" that can save costs when supply of IVIG is limited.

Seventh, the authors were not able to compare clinical outcomes or possible reduction in the risk of life-threatening adverse events as a consequence of reduced dosing by IBW or AdjBW because it was beyond the scope of the study. Further, there were only few patients receiving IVIG, therefore, evaluating variable the clinical outcomes across different dosing weights and specific indications was also not possible as the reduced dosing was not implemented at the time of this baseline study. The current study objectives were reduced dosing eligibility and consequent dose and cost savings in IVIG use which informs payers and providers on the potential value in implementing dosing calculators in the future. To address the limitation in this study, when the IVIG dosing calculators are implemented within the new electronic medical record systems, prospective collection of data on IVIG dose, target IgG levels and patient outcomes may be more efficient in further studies. Thus, future studies need to address clinical and safety outcomes achieved with dosing adjustment of IVIG which is the next critical area of research that ties cost containment and dosing together.

Despite study limitations, the current study suggests that the use of a bodyweight (IBW or AdjBW) dosing calculator could result in potential IVIG cost savings in the study hospital. The study observations could be useful as the basis of discussion between P&T Committees and clinicians. As reimbursement rates continue to change and hospital pharmacy budgets continue to tighten, ensuring protocols are in place to secure appropriate prescribing of institutions' most expensive drugs is necessary for hospitals to remain viable. For successful implementation of cost saving measures, prescribers need to be educated of an institution's changing protocols.

Further, the study will provide baseline information for providers, payers, drug policy protocol makers, and researchers to evaluate such protocols in their own practice settings. Also, this study will help these stakeholders to adapt the study methods for automating the use of dosing calculators and for routine real-time evaluations of IVIG use using body weight dosing calculators. The cost savings demonstrated by this study will be utilized in the authors' institution to initiate further discussion on reducing IVIG expenditure complemented by implementing and securing the use of an IVIG protocol with related bodyweight dosing calculator. Although the authors' findings are institution specific, and cannot be extrapolated to other hospitals; the study methodology could be applied to other hospitals and cost reductions from altering dosing by appropriate body-weight will likely be seen in the majority of centers who institute an IVIG dosing protocol similar to the study.

CONCLUSION

In summary, the current retrospective evaluation of the study hospital's IVIG protocol demonstrated a high rate of appropriate prescribing as well as several missed opportunities for realizing potential savings in drug costs from dosing IVIG by IBW or AdjBW each instead of ABW in eligible patients. Despite study limitations, use of protocol based approved indications and bodyweight dosing calculators for IVIG prescribing warrants further consideration of hospital payers and providers.

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AUTHOR'S CONTRIBUTION

All authors conceived and designed the study. JS gained ethical approval. NT and JS got access to the data for the study. AF, CO and JS carried out the analysis of the data. CO and AF were involved in writing and revising the initial draft of the manuscript under the supervision of JS. All authors (AF, CO, JS and NT) reviewed and revised the final paper for intellectual content.

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