OBSERVATIONAL STUDY

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# Single-Center Experience of Outcomes and Prescribing Patterns of IV Immunoglobulin Use in Critically Ill Patients

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**OBJECTIVES:** Previous literature has not compared prescribing practices of IV immunoglobulin in medical ICU survivors and nonsurvivors. The objective of this study was to study IV immunoglobulin use in patients admitted to a medical ICU evaluating differences between hospital survivors and nonsurvivors in regards to level of evidence supporting use, prescribing patterns, and cost.

**DESIGN:** Retrospective, observational study.

**SETTING:** Single, academic medical center medical ICU.

**PATIENTS:** Adults who received greater than or equal to 1 dose of IV immunoglobulin during their medical ICU admission from 2011 to 2018.

**INTERVENTIONS:** Prescribing patterns, level of evidence supporting use, and cost.

**MEASUREMENTS AND MAIN RESULTS:** A total of 389 patients received greater than or equal to 1 dose of IV immunoglobulin for 46 discrete indications and 36.5% of indications had low-quality data supporting use of IV immunoglobulin. The primary indication for IV immunoglobulin was hypogammaglobulinemia (35.5%) followed by antibody-mediated lung transplant rejection (15.4%). Nonsurvivors received lower median dosing (g/kg) and number of doses compared with survivors (0.4 g/kg [0.4–1 g/kg] vs 0.5 g/kg [0.4–1 g/kg] [$p = 0.0003$] and 1.0 [1–2] vs 2 [1–3] doses [$p = 0.0001$], respectively). Dosing was based on ideal body weight in 258 patients (66%). High-quality data supported IV immunoglobulin use in 15 patients (4%). The median cost per dose of IV immunoglobulin in nonsurvivors was $4,893 ($4,078–$8,155) versus $5,709 ($4,078–$10,602) in survivors ($p = 0.04$).

**CONCLUSIONS:** IV immunoglobulin is prescribed for many indications in the medical ICU with low-quality evidence supporting its use and dosing regimens are variable. Hospital survivors received a higher dose and greater number of doses of IV immunoglobulin compared with nonsurvivors. National guidelines are needed to help inform IV immunoglobulin utilization and reduce healthcare costs.

**KEY WORDS:** critical care; intravenous immunoglobulin; mortality; prescribing patterns

IV immunoglobulin (IVIG) is used in critically ill patients for immunomodulation including replacement of endogenous stores of immunoglobulin and support of an impaired immune system (1). Data evaluating IVIG is of low quality and data including critically ill patients is often limited to case series



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and trials with low enrollment (1). An evaluation of IVIG utilization in the ICUs of a large health network found that the most common indications for use were necrotizing fasciitis, Guillain-Barre syndrome (GBS), and toxic epidermal necrolysis, accounting for 58% of prescribed indications (2). Other common indications for which IVIG is commonly prescribed, not specific to the ICU, include hypogammaglobulinemia related to hematological malignancies or other primary IVIG immunodeficiency diseases, chronic inflammatory demyelinating polyneuropathy (CIDP), myasthenia gravis (MG), and idiopathic thrombocytopenic purpura (1, 3–5).

Utilization of IVIG in the critically ill in the United States is plagued by the absence of a national consensus statement to recommend its appropriate utilization. The United Kingdom and Australia have critically appraised the evidence for IVIG utilization and apply a rating for the level of evidence to support each proposed indication based on the quality of the available literature (6, 7). The indications with the highest level of evidence include: Kawasaki disease, autoimmune thrombocytopenia, CIDP, GBS, MG, and hypogammaglobulinemia. These indications have randomized controlled trials and meta-analyses to support their use, whereas most other proposed indications for IVIG use are supported by case reports, case series, or expert opinion (6, 7). For indications in which IVIG has demonstrated benefit, studied dosing regimens have been variable (1, 3–5). IVIG is most often dosed based on body weight with reported dosing using ideal body weight (IBW), actual body weight (ABW) or an adjusted dosing weight due to lack of consensus guidelines (8).

In 2018 for the overall U.S. market, IVIG was ranked twentieth on the list of highest drug expenditures and second on the list of the highest drug expenditures in nonfederal hospitals with an annual cost exceeding $800 million (9). Globally, IVIG use increased by 39% from 2013 to 2018 in patients with immunodeficiencies (10). There is an interest among healthcare systems to develop protocols for appropriate, standardized use to help reduce the financial burden associated with IVIG. Evaluation of current prescribing practices and ideal clinical thresholds for initiating therapy and dosing regimens are needed to help inform protocol development. The objective of this study was to evaluate the use of IVIG in patients admitted to a medical ICU (MICU) evaluating differences between hospital survivors and nonsurvivors in regards to prescribing patterns, indications for use, level of evidence supporting use, and cost.

## MATERIALS AND METHODS

This study was a retrospective, noninterventional evaluation of IVIG use in a MICU between January 1, 2011, and December 31, 2018, conducted at the Cleveland Clinic main campus, a 1,400 bed, tertiary care, nonprofit, academic medical center. This study was approved by the Institutional Review Board prior to data collection (study number 17-1124). An electronic medical record was used for data collection and extraction. We included all patients who received greater than or equal to 1 dose of IVIG during their MICU admission for any indication. Patients were excluded if they received IVIG during the index hospital admission prior to admission to the MICU.

Patients were evaluated for dose, frequency, and quantity of IVIG prescribed. The documented patient weight used to calculate the dose and history of prior IVIG exposure was also collected. Indication for use, recommendation of IVIG use by specialist consultants, and pre-IVIG immunoglobulin G (IgG) levels were collected. Pharmacist documentation during order verification and progress notes entered by the prescribers or consult service were used to identify the indication for IVIG therapy. The severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] III score), duration of mechanical ventilation, ICU, and hospital lengths of stay, and mortality were collected. Finally, we applied cost data to our findings using the 2018 average wholesale price (U.S.$ 163.10/g) of GAMMAGARD LIQUID (immunoglobulin infusion [human]) 10% (11).

To describe the quality and strength of data supporting IVIG use, the level of evidence available to support each indication of IVIG use was applied to each patient. Given that the United States does not have a national guideline regarding the general use of IVIG in critically ill patients, we referenced the U.K.'s Clinical Guidelines for Immunoglobulin Use (6) and Australia's Criteria for the Clinical Use of IV Immunoglobulin in Australia (7) in addition to our institution's approved indications to help assign the level of evidence available to support each

ordered indication. The U.K.'s Clinical Guidelines for Immunoglobulin Use (6) make a recommendation for short-term and long-term use of IVIG per indication and provide the evidence grade to their recommendation and Australia's Criteria for the Clinical Use of IV Immunoglobulin in Australia (7) assigns an evidence level to each indication listed in their guidelines. If a discrepancy existed between guidelines in regards to the assigned level of evidence, the level of evidence was assigned based on author consensus after reviewing the available literature supporting use for the indication (**Table S1**, http://links.lww.com/CCX/A481). At our institution, IVIG may be prescribed for a limited number of indications based on Food and Drug Administration approved indications and those indications approved by our Pharmacy and Therapeutics Committee (Table S1, http://links.lww.com/CCX/A481). If prescribers wish to order IVIG for an indication or dosing strategy not listed on our formulary, the proposed regimen must be approved on a patient-by-patient basis by our formulary director or their designee.

The study variables were described using sample median with interquartile range or number with proportion as appropriate. The study group was divided into two groups based upon the mortality status. The decision to compare prognostic variables between hospital survivors and nonsurvivors was made a priori. Categorical variables were compared using Pearson chi-square test or Fisher exact test, whereas continuous variables were compared using the *t* test or nonparametric Wilcoxon test as appropriate. Univariate logistic regression model strategies were used to identify potential risk factors for hospital mortality. A multivariate logistic regression model was established, including variables that had biological plausibility of affecting hospital mortality. A Kaplan-Meier analysis with log-rank tests was implemented to analyze the time-to-event data. A subgroup analysis of patients by levels of evidence for IVIG indication, the severity of illness, and patients who received IVIG for our most commonly prescribed indications was performed. An APACHE III score of 80 was used as our threshold when comparing patients based on the severity of illness due to its associated mortality risk of approximately 50% (12). Because the percentage of missing data was small, only complete records were analyzed for the endpoint of interest. All analyses were two-tailed and were performed at a significance level of 0.05. SAS 9.3 software (SAS Institute, Cary, NC) was used for all analyses.

## RESULTS

A total of 389 patients were included in this analysis of which, 250 patients survived to hospital discharge. A total of 36 patients were excluded because they received IVIG during their hospitalization but prior to admission to the ICU. Nonsurvivors had higher median APACHE III scores at baseline (85.5 [64–112] vs 70 [53–87]; $p < 0.0001$) and a greater number required mechanical ventilation (96 [69.1%] vs 129 [51.6%] patients; $p = 0.0008$). There was no difference in the history of prior IVIG exposure between nonsurvivors and survivors ($p = 0.64$) (**Table 1**).

### Dose

Nonsurvivors received a lower median IVIG dose (30 g (25–50 g) vs 35 g (25–65 g); $p = 0.04$) and fewer median total doses of IVIG (1 [1–2] vs 2 [1–3] doses; $p = 0.0001$) compared with survivors. The majority of patients were dosed based on IBW when comparing survivors and nonsurvivors, respectively (93 [66.9%] vs 165 [66.0%] patients; $p = 0.45$) (**Table 2**).

### Indication

Hypogammaglobulinemia, an indication with level 2 supporting evidence for use, was the most common indication for IVIG use in both nonsurvivors and survivors, respectively (67 [48.2%] vs 71 [28.4%] patients). There was no difference in indication for use between both groups ($p = 0.06$) or in the level of evidence to support the prescribed IVIG indications ($p = 0.62$) (Table 2 and Table S1, http://links.lww.com/CCX/A481). Based on the Kaplan-Meier plot and the log-rank test ($p = 0.37$), there were no significant differences in hospital mortality among the four level of evidence groups (**Fig. S1**, http://links.lww.com/CCX/A481).

### Level of Evidence

Patients receiving IVIG for level 4 indications received the greatest median dose of IVIG (60 g [30–75 g]; $p < 0.0001$) and the highest median weight-based dose

**TABLE 1.**
**Baseline Characteristics**

| Variable | Nonsurvivors ($n = 139$) | Survivors ($n = 250$) | $p$ |
|---|---|---|---|
| Age, yr[a] | 61 (50–68) | 59 (43–67) | 0.10[b] |
| Male gender, *n* (%) | 87 (62.6) | 129 (51.6) | 0.04[c] |
| Weight, kg[a] | 73.0 (61.6–80.0) | 70.7 (60.5–82.2) | 0.64[b] |
| Acute Physiology and Chronic Health Evaluation III score[a] | 85.5 (64–112) ($n = 126$) | 70 (53–87) ($n = 235$) | < 0.0001[b] |
| Mechanical ventilation, *n* (%) | 96 (69.1) | 129 (51.6) | 0.0008[c] |
| Chronic dialysis, *n* (%) | 7 (5.0) | 21 (8.4) | 0.22[c] |
| Diabetes mellitus, *n* (%) | 32 (23.0) | 67 (26.8) | 0.41[c] |
| Septic shock, *n* (%) | 42 (30.2) | 36 (14.4) | 0.002[c] |
| Prior IV immunoglobulin exposure, *n* (%) | 44 (31.7) | 85 (34.0) | 0.64[c] |
| Immunoglobulin G level, mg/dL[a] | 411 (318–580), $n = 103$ | 471 (377–858), $n = 149$ | 0.008[b] |

[a]Median (interquartile range).
[b]Wilcoxon test.
[c]$\chi^2$ test.

of IVIG (1 g/kg [0.5–1 g/kg]; $p < 0.0001$). Patients receiving IVIG for level 1 indications received the greatest median number of doses ($p < 0.0001$) (**Table 3**).

## Cost

The median cost per dose of IVIG in nonsurvivors was $4,893 ($4,078–$8,155) versus $5,709 ($4,078–$10,602) in survivors ($p = 0.04$) (Table 2). The total cost for the entire cohort over the 8-year study period was $6.2 million. The cost per dose was significantly different among indications with patients receiving IVIG for level 4 indications resulting in the greatest drug expenditure ($p < 0.0001$) (Table 3).

## Multivariate Analysis

Age, APACHE III score, gender, weight-based IVIG dose, and weight were variables with biologic plausibility of affecting hospital morality and were included in the final multivariate logistic regression model. In the multivariate logistic regression model, one unit increase in APACHE III score was associated with a greater likelihood of hospital mortality (odds ratio [OR], 1.021; 95% CI, 1.013–1.029; $p < 0.0001$), whereas every 1 g/kg increase in IVIG dose was associated with decreased hospital mortality (OR, 0.325; 95% CI, 0.144–0.734; $p = 0.00068$) (**Table 4**) (receiver operating curve [ROC] = 0.71; [**Fig. S2**, http://links.lww.com/CCX/A481]).

## Evaluation of Most Common Indications

***Hypogammaglobulinemia***. Nonsurvivors had a higher APACHE III score than survivors (93.3 ± 30.9 vs 80.4 ± 27.5; $p = 0.01$), respectively. There was no difference in IVIG dose ($p = 0.99$), the number of IVIG doses ($p = 0.64$), or prior IVIG exposure ($p = 0.66$). Survivors did, however, receive a larger median g/kg dose of IVIG compared with nonsurvivors ($p = 0.007$) (**Table S2**, http://links.lww.com/CCX/A481). A one-point increase in the APACHE III score was associated with a higher risk of death (OR, 1.018; 95% CI, 1.004–1.032; $p = 0.0115$) (**Table S5**, http://links.lww.com/CCX/A481) (ROC = 0.68; [**Fig. S3**, http://links.lww.com/CCX/A481]).

***Lung Transplant Antibody-Mediated Rejection***. Patients with a history of lung transplantation were evaluated separately to describe IVIG prescribing practices in this population for antibody-mediated rejection.

## TABLE 2.
### IV Immunoglobulin Utilization and Outcomes

| Variable | Nonsurvivors (*n* = 139) | Survivors (*n* = 250) | *p* |
|---|---|---|---|
| IVIG dose, g[a] | 30 (25–50) | 35 (25–65) | 0.04[b] |
| IVIG dose, g/kg[a] | 0.4 (0.4–1) | 0.5 (0.4–1) | 0.0003[b] |
| Total number of doses[a] | 1 (1–2) | 2 (1–3) | 0.0001[b] |
| Cumulative IVIG dose, g[a] | 40 (30–100) | 90 (35–160) | < 0.0001[b] |
| Dosing weight, *n* (%) | | | 0.45[c] |
| Actual body weight | 18 (12.9) | 43 (17.2) | |
| Adjusted body weight | 28 (20.1) | 42 (16.8) | |
| Ideal body weight | 93 (66.9) | 165 (66.0) | |
| Cost per dose, U.S. dollar[a] | 4,893 (4,078–8,155) | 5,709 (4,078–10,602) | 0.04[b] |
| Cumulative cost, U.S. dollar[a] | 6,524 (4,893–16,310) | 14,679 (5,709–26,096) | < 0.0001[b] |
| IVIG indication level of evidence, *n* (%)[b,c] | | | 0.62[c] |
| Level 1 | 6 (4.3) | 9 (3.6) | |
| Level 2 | 82 (59.0) | 136 (54.4) | |
| Level 3 | 6 (4.3) | 8 (3.2) | |
| Level 4 | 45 (32.4) | 97 (38.8) | |
| Duration of mechanical ventilation, d[a] | 7 (3–13) (*n* = 77) | 6 (3–14) (*n* = 107) | 0.73[b] |
| ICU length of stay, d[a] | 10.0 (4.6–17.0) (*n* = 128) | 7.0 (3.3–14.0) (*n* = 237) | 0.05[b] |
| Hospital length of stay, d[a] | 18.0 (10.0–31.9) (*n* = 129) | 22.4 (12.8–38.4) (*n* = 237) | 0.06[b] |

IVIG = IV immunoglobulin.
[a]Median (interquartile range).
[b]Wilcoxon test.
[c]$\chi^2$ test.
Adjusted body weight = ideal body weight + 0.4 (actual body weight–ideal body weight).
Group NICRW (7).
Care UKDoHaS (6).

There was no difference in APACHE III scores between nonsurvivors and survivors (67.8 ± 28.6 vs 66.8 ± 20.8; $p$ = 0.89). There was no difference between nonsurvivors and survivors in terms of IVIG dose ($p$ = 0.51), total number of doses ($p$ = 0.40), and cost per IVIG dose ($p$ = 0.51) (**Table S3**, http://links.lww.com/CCX/A481). No variables in the multivariate logistic regression model were found to be associated with increased risk of death (Table S5, http://links.lww.com/CCX/A481) (ROC = 0.65; [**Fig. S4**, http://links.lww.com/CCX/A481]).

***Hematologic Disorders***. Patients receiving IVIG for a hematologic condition were evaluated. Hematologic disorders included in the analysis are listed below **Table S4**, http://links.lww.com/CCX/A481. Nonsurvivors had higher APACHE III scores compared with survivors (84.9 ± 33.5 vs 66.9 ± 28.6; $p$ = 0.02). There was no difference between nonsurvivors and survivors in terms of IVIG including dose ($p$ = 0.14), number of doses ($p$ = 0.29), and prior IVIG exposure ($p$ = 0.97) (Table S4, http://links.lww.com/CCX/A481). No variables in the multivariate logistic regression

**TABLE 3.**
**IV Immunoglobulin Utilization by Level of Evidence**

| Variable | Level 1 (*n* = 15) | Level 2 (*n* = 218) | Level 3 (*n* = 14) | Level 4 (*n* = 142) | *p* |
|---|---|---|---|---|---|
| Acute Physiology and Chronic Health Evaluation III score[a] | 71 (44–80) | 77.5 (61–99) (n = 202) | 68.5 (61–76) | 71 (54–90) (n = 130) | 0.09[b] |
| IVIG dose, g[a] | 30 (20–35) | 30 (25–35) | 30 (25–40) | 60 (30–75) | < 0.0001[b] |
| IVIG dose, g/kg[a] | 0.4 (0.4–0.4) | 0.4 (0.4–0.5) | 0.4 (0.4–0.5) | 1 (0.5–1) | < 0.0001[b] |
| Total number of doses[a] | 3 (1–5) | 1 (1–2) | 2 (1–3) | 2 (1–3) | < 0.0001[b] |
| Cost per dose, U.S. dollar[a] | 4,893 (3,262–5,708) | 4,893 (4,077–5,708) | 4,893 (4,077–6,524) | 9,786 (4,893–12,232) | < 0.0001[b] |
| Mortality, *n* (%) | 6 (40.0) | 82 (37.6) | 6 (42.9) | 45 (31.7) | 0.62[c] |

IVIG = IV immunoglobulin.
[a]Median (interquartile range).
[b]Kruskal-Wallis test.
[c]$\chi^2$ test.

model were found to be associated with increased risk of death (Table S5, http://links.lww.com/CCX/A481) (ROC = 0.69; [**Fig. S5**, http://links.lww.com/CCX/A481]).

***Severity of Illness***. Finally, we used an APACHE III score cutoff of 80 to classify patients based on the severity of illness (12). For severely ill patients with an APACHE III score of greater than or equal to 80, IVIG dose (g/kg) was not significantly associated with hospital mortality ($p = 0.0502$). However, for every 1 g/kg increase in IVIG dose in patients with an APACHE III score less than 80, patients were 0.296 times less likely to die ($p = 0.0376$) (Table S5, http://links.lww.com/CCX/A481).

## DISCUSSION

In our study, we report that prescribing practices of IVIG in MICU patients at a large, tertiary care hospital was variable, but hospital survivors received larger doses and a greater number of doses of IVIG compared with nonsurvivors. Nonsurvivors had higher APACHE III scores at baseline, lower IgG levels, more frequently required mechanical ventilation, and had a higher prevalence of septic shock. Over $6 million dollars were spent in an 8-year period for IVIG with indications having low-quality evidence supporting their use amounting to over one-third of the cost.

In an era where healthcare costs are under increasing scrutiny, opportunities for cost-avoidance need investigation. The Choosing Wisely campaign, led by the American Board of Internal Medicine and the Critical Care Societies Collaborative, is aimed at maximizing value in the ICU by avoiding unnecessary medical tests, treatments, and procedures, and there is an opportunity to add medications, such as IVIG, to this list (13). Altawalbeh et al (14) evaluated pharmacy-related ICU costs at a single center and opportunities for cost-avoidance, which consistently found IVIG to be within the top 10 medications for highest drug expenditure over a 10-year period. ICU drug costs accounted for an average of 31% of total hospital drug costs, and IVIG accounted for an average of 2.8% of the ICU drug costs.

With IVIG being one of the top three medication expenditures in our MICU, we sought to identify opportunities for cost-avoidance with this medication. First, we observed no differences in indication for IVIG use or level of supporting evidence for prescribed indication among nonsurvivors and survivors. Greater than one-third of our patients received IVIG for indications with low-quality evidence and 33% of patients received IVIG for indications not included in our institution's formulary restrictions. We additionally found that multiple dosing strategies existed for the same indication and deviated from previously described regimens (1, 6, 7). Our findings are in line

**TABLE 4.**
**Full Multivariate Logistic Regression for Overall Population Mortality**

| Variable | OR (95% CI) | *P* |
|---|---|---|
| Female vs male | 0.582 (0.350–0.968) | 0.0371 |
| Acute Physiology and Chronic Health Evaluation III score (1 U increase) | 1.021 (1.013–1.029) | < 0.0001 |
| Dose (1 g/kg increase) | 0.325 (0.144–0.734) | 0.0068 |
| Age (1 yr increase) | 1.003 (0.987–1.018) | 0.7326 |
| Weight (1 kg increase) | 0.999 (0.987–1.011) | 0.8689 |

OR = odds ratio.

with a retrospective review of IVIG prescribing practices in ICU patients published by Foster et al (2), finding that 74.5% of patients were prescribed IVIG for an off-label indication and 6.9% of orders were deemed to be not indicated based on reported indication. With IVIG being within the top five drugs nationally for drug expenditure (15), our study adds to this previously published study and further supports the need for national guidelines to help institutions establish approved indications for use with standardized dosing regimens to help facilitate IVIG stewardship.

Additionally, we found that increased IVIG doses in patients who were severely ill did not decrease mortality risk, whereas increased doses in patients who were less severely ill (APACHE III < 80) did decrease mortality risk, suggesting that there may be a severity of illness threshold at which IVIG may not provide additional benefit. Our finding that hospital survivors received higher doses and greater number of doses of IVIG compared with nonsurvivors should be interpreted with caution as hospital nonsurvivors with higher severity of illness at baseline may not have lived long enough to receive additional intended doses of IVIG. Additionally, the APACHE III score was used as our marker of disease severity, which primarily describes physiologic derangements with little emphasis on preexisting conditions which may impact mortality (16).

Although female patients are slightly underrepresented in our cohort (44.4% of the cohort), survivors were more likely to be female compared with male patients. Additionally, in our multivariate logistic regression models for overall mortality for the entire cohort, patients with hypogammaglobulinemia, and less severely ill patients (APACHE III < 80), female gender was associated with decreased mortality risk. This finding is likely due to female patients being less severely ill compared with male patients in our study, rather than a decreased mortality risk associated with gender, but prospective studies should evaluate the impact of gender on outcomes associated with IVIG use.

The two most common indications for which IVIG was prescribed in our MICU were hypogammaglobulinemia and antibody-mediated lung transplant rejection. Hypogammaglobulinemia is common in critically ill patients with a reported prevalence as high as 70% and is a risk factor for increased mortality (17, 18). Hypogammaglobulinemia is typically defined as an IgG level less than 400 mg/dL (6, 7, 19, 20), which is also the limit our institution uses in our restriction criteria for IVIG use for this indication. However, for patients in our analysis prescribed IVIG for hypogammaglobulinemia, 5% of patients did not have an IgG level checked before IVIG was prescribed and 5,475 g of IVIG were prescribed to patients with baseline IgG levels greater than our institution's IgG threshold of less than 400 mg/dL. These findings highlight an opportunity for cost-avoidance of almost $900,000 at our institution during our study period. A recently published study evaluating the impact of an IVIG stewardship program on cost and patient outcomes in patients with hypogammaglobulinemia found a significant reduction in IVIG use and cost without patient harm (21).

Similarly, the data evaluating IVIG for antibody-mediated rejection in lung transplant recipients have been limited. There are reports that IVIG reduces donor-specific human leukocyte antigen (HLA)

antibodies via immunomodulatory effects, neutralization of HLA antibodies, and disruption of antibody-mediated complement activation. However, the mortality rates in patients who develop antibody-mediated rejection are still high, questioning the clinical efficacy of IVIG in this setting (22–24). Similar to the findings of a small case series, we found that patients receiving IVIG for antibody-mediated rejection received variable weight-based doses and quantities (25). To improve the cost-effectiveness of IVIG in this setting, patients should be carefully evaluated to ensure they are appropriate candidates for IVIG treatment before initiation and a standard weight-based dose, frequency, and duration should be established. Additional studies evaluating this patient population are needed to determine these breakpoints.

In addition to variability in indications and dosing regimens for IVIG use, we found variability in dosing body weights used to determine IVIG doses. Published literature supports the use of IBW over ABW as a measure to reduce medication expenditure (8). Almost 35% of patients included in our study were not dosed based on IBW, resulting in an added cost of $62,800 in our studied cohort. Rocchio et al (8) reported a 20% cost savings with the adoption of a stewardship program which advocated for IVIG dosing based on IBW rather than ABW. Although the impact of hospital formulary restriction criteria on IVIG utilization is unknown, data evaluating the effect of restriction criteria for other medications demonstrates that when properly implemented, restriction criteria can reduce the usage of high-cost medicines (26, 27). These help prescribers identify appropriate indications for use based on best-practice guidelines and permit the institution of proper treatment regimens based on the clinical indication.

There are several limitations to our study. First, this was a single-center, retrospective study comparing IVIG utilization between MICU nonsurvivors and survivors, thus it may lack external validity; however, we believe this study adds to the literature advocating for national guidelines to help guide IVIG utilization in the United States. Our analysis relied upon accurate documentation in the medical record, and we were not able to control for factors associated with the clinical management that could have had an impact on mortality. Additionally, we were not able to measure efficacy related to IVIG therapy and establish whether patients achieved the desired effect of IVIG therapy. Likewise, we were not able to ascertain the prevalence of adverse effects related to IVIG therapy, which has ranged from 10% to 30% in published literature (28, 29). Also, we were not able to confirm prior exposure to IVIG if it was documented outside of our electronic health record. Finally, although we attempted to mitigate confounding by utilizing multivariate regression modeling, it is still possible that confounding by indication or disease severity may exist.

Despite these limitations, there are many strengths to this study. To our knowledge, this is the most extensive study comparing the prescribing practices of IVIG in MICU survivors and nonsurvivors, and our study may be representative of IVIG utilization in comparable practices. Additionally, the level of evidence supporting the indication for which IVIG was prescribed was applied to help identify indications for which the use of IVIG may be futile. Furthermore, cost analysis was employed to evaluate opportunities for cost-avoidance. Finally, multivariate logistic regression was performed to identify predictors of hospital mortality. Overall, the findings from this study advocate for the need for national guidelines related to IVIG use in critically ill patients and highlight opportunities for IVIG stewardship that other institutions can implement for cost-avoidance.

## CONCLUSIONS

Low-quality evidence and variable dosing patterns govern the utilization of IVIG in the MICU. Hospital survivors received higher doses and greater number of doses of IVIG compared with nonsurvivors. These findings support implementation of guidelines for use in critically ill patients and studies evaluating optimal dosing strategies are needed to help inform these management protocols.

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