Epidemiology of intravenous immune globulin in septic shock: a retrospective cohort analysis of the Premier Healthcare Database

Épidémiologie de l'utilisation de l'immunoglobuline intraveineuse dans les cas de choc septique : une analyse de cohorte rétrospective de la base de données Premier Healthcare

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Abstract
Purpose Intravenous immune globulin (IVIG) may improve survival in people with septic shock. Current utilization patterns of IVIG are unknown. We sought to characterize adult patients with septic shock requiring vasopressors who received IVIG, describes IVIG regimens, and evaluate determinants of IVIG use in patients with septic shock.

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Methods *We conducted a retrospective database study of adult patients with septic shock admitted to US hospitals in the Premier Healthcare Database (from July 2010 to June 2013). We described the proportion of patients with septic shock receiving IVIG, examined IVIG regimens across sites and employed random-effects multivariable regression techniques to identify predictors of IVIG use.*

Results *Intravenous immune globulin was administered to 0.3% (n = 685) of patients with septic shock; with a median [interquartile range (IQR)] dose of 1 [0.5–1.8] g·kg⁻¹ for a median [IQR] of 1 [1–2] day. Receipt of IVIG was less likely for Black patients (odds ratio [OR], 0.54; 95% confidence interval [CI] 0.41 to 0.72) and patients without private insurance (Medicare OR, 0.73; 95% CI 0.59 to 0.90; Medicaid OR, 0.41; 95% CI 0.30 to 0.57) and more likely for patients with immunocompromise (OR, 6.83; 95% CI 5.47 to 8.53), necrotizing fasciitis (OR, 9.78; 95% CI 6.97 to 13.72), and toxic shock (OR, 56.9; 95% CI 38.7 to 83.7).*

Conclusions *Intravenous immune globulin is used infrequently across the US in patients with septic shock. Regimens of IVIG in septic shock may be less intensive than those associated with a survival benefit in meta-analyses. Observed infrequent use supports apparent clinical equipoise, perhaps secondary to limitations of the primary literature. A clinical trial evaluating the role of IVIG in septic shock is needed.*

Résumé

Objectif *L'immunoglobuline intraveineuse (IGIV) peut améliorer la survie chez les personnes atteintes de choc septique. Les pratiques actuelles d'utilisation de l'IGIV sont inconnues. Nous avons cherché à caractériser les patients adultes en état de choc septique et nécessitant des vasopresseurs qui ont reçu de l'IGIV, à décrire les dosages administrés d'IGIV, et à évaluer les causes déterminantes d'une utilisation d'IGIV chez ces patients.*

Méthode *Nous avons réalisé une étude rétrospective de base de données portant sur des patients adultes atteints de choc septique admis dans des hôpitaux américains et inclus dans la base de données Premier Healthcare (de juillet 2010 à juin 2013). Nous avons décrit la proportion de patients en choc septique recevant de l'IGIV, examiné les posologies utilisées d'IGIV à travers les sites et employé des techniques de régression multivariable à effets aléatoires pour identifier les prédicteurs de l'utilisation d'IGIV.*

Résultats *L'IGIV a été administrée à 0,3 % (n = 685) des patients présentant un choc septique, avec une dose médiane [écart interquartile (ÉIQ)] de 1 [0,5–1,8] g·kg⁻¹ pour une médiane [ÉIQ] de 1 [1–2] jour. L'administration d'IGIV était moins probable chez les patients noirs (rapport de cotes [RC], 0,54; intervalle de confiance [IC] à 95 %, 0,41 à 0,72) et les patients sans assurance privée (RC Medicare, 0,73; IC 95 %, 0,59 à 0,90; RC Medicaid, 0,41; IC 95 %, 0,30 à 0,57) et plus probable chez les patients immunodéprimés (RC, 6,83; IC 95 %, 5,47 à 8,53), atteints de fasciite nécrosante (RC, 9,78; IC 95 %, 6,97 à 13,72), et en choc toxique (RC, 56,9; IC 95 %, 38,7 à 83,7).*

Conclusion *L'IGIV est rarement utilisée aux États-Unis chez les patients en choc septique. Les dosages d'IGIV utilisés en cas de choc septique pourraient être moins intensifs que ceux associés à un effet bénéfique en matière de survie dans les méta-analyses. L'utilisation peu fréquente observée appuie une équivalence clinique apparente, peut-être secondaire aux limites de la littérature princeps. Une étude clinique évaluant le rôle de l'IGIV dans le choc septique est nécessaire.*

Keywords Septic shock · IVIG · Intravenous immune globulin · Immunomodulation

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Sepsis and septic shock are associated with a significant burden of illness globally.[1–3] The cornerstone of therapy in septic shock is rapid administration of effective antimicrobial therapy[4] along with supportive care.[5] Despite existing therapies, hospital mortality from septic shock remains high, ranging from 35% to 54% in contemporary epidemiologic studies.[6] As antimicrobial resistance increases worldwide, effective available therapies are disappearing.[7] Intravenous immune globulin (IVIG) has the potential to improve outcomes in septic shock via an alternate immunomodulatory pathway, irrespective of antimicrobial susceptibility. Numerous randomized controlled trials (RCTs)[8–14] and systematic reviews[8,16–21] support a survival benefit of IVIG when used as an adjunctive therapy for septic shock. Nevertheless, studies to date have been largely of low quality and heterogeneous in their results, so that major society guidelines recommend against the routine use of IVIG in septic shock.[9] Meta-analysts have called for additional high-quality RCTs to determine the efficacy and safety of IVIG in septic shock prior to widespread adoption.[16,19]

Yet, the existing rate of adoption is unknown. In this study, we sought to characterize the patient populations in which clinicians are prescribing IVIG for septic shock to describe clinical utilization patterns of IVIG in patients with septic shock and to identify determinants of IVIG use in these patients.

Methods

We conducted a retrospective cohort study using the Premier Healthcare Database (PHD; Premier, Charlotte, NC, US), which contains detailed administrative data from approximately 20% of acute care hospitalizations in the US.[10] It contains information from hospital discharge files, Ninth International Classification of Disease Clinical Modification (ICD-9-CM) codes, Current Procedural Terminology codes, and detailed billing data with itemized, date-stamped logs of all medications, fluids, blood products, diagnostic tests and therapeutic services during hospitalization.[11,12] The PHD contains data from a variety of geographically and demographically diverse hospitals with a similar distribution to those of the American Hospital Association membership[13] whose participation is voluntary and fee-supported.[12]

Cohort

We developed a cohort of all adult patients with septic shock admitted to intensive care units (ICUs) in 518 hospitals from July 2010 to June 2013 in the PHD (Fig. 1). We identified episodes of sepsis using a previously validated administrative database definition of severe sepsis.[1] We further restricted this cohort of patients to those with septic shock by identifying episodes of severe sepsis in combination with the use of at least one vasopressor on one or more days during the hospital admission, an approach previously used to study this population.[10] We excluded patients with an ICD-9 code for any non-sepsis-based indication for IVIG use (Fig. 1) or who were either transferred from or to another acute care facility (as use of IVIG at those sites was not available). Only the first ICU admission of any hospitalization was considered. We also excluded patients receiving clinically implausible outlier doses of IVIG not consistent with use in septic shock (Fig. 1). We identified vasopressor and IVIG exposure via pharmacy billing codes. Of note, because the PHD did not include patient weight, the mean (standard deviation [SD]) weights used to estimate IVIG dose per kg were 83 (23) kg in male and 74 (22) kg in female patients with septic shock from US hospitals in the Cooperative Antimicrobial Therapy of Septic Shock database.[14]

Outcomes

Intravenous immune globulin receipt was our primary outcome. We considered IVIG to be administered as an adjunctive therapy in the management of septic shock if prescribed concomitantly with vasopressors on the first calendar day of IVIG receipt. Secondary IVIG utilization outcomes (clinical utilization patterns) included IVIG dosing, average duration of IVIG course, interval between admission to ICU and initiation of IVIG, interval between vasopressor onset and initiation of IVIG, and variation in IVIG use geographically and over time.

Statistical analysis

We summarized baseline demographic, patient illness, and hospital variables for our cohort. To characterize the populations in which clinicians are prescribing IVIG for septic shock, we compared patients with septic shock who received IVIG with those who did not. We described baseline characteristics using means (SDs) or medians [interquartile ranges (IQRs)] as appropriate. We performed two-sample comparisons of continuous variables using t tests and evaluated proportions of dichotomous variables using Chi square tests. Standardized differences were calculated and differences greater than 0.1 were typically considered meaningful.[15] We described dose, duration, and timing of IVIG prescription as medians [IQRs]. We summarized geographical variation in IVIG use using proportions and analyzed variation in IVIG use over time via logistic regression including each quarter year as an independent variable. To investigate factors that predict the receipt of IVIG, we developed a random-effects logistic regression model. Covariates considered for potential association with IVIG use included demographic variables, patient illness characteristics, receipt of mechanical ventilation or acute renal replacement therapy, year of admission, hospital site, hospital size, and geographic location, all of which were selected *a priori* based on clinical plausibility and data availability. Hospital site was anticipated to affect IVIG use due to variation in local practice and was therefore included as a random effect to explore variation in IVIG use at the individual hospital level. We reported results of this model as odds ratios (ORs) with 95% confidence intervals (95% CI). In general, *P* values less than 0.05 were considered significant for the multivariable regression model analysis, but the *P* values provided in the text and in Table 1 are considered descriptive and have not been adjusted for multiple inference. In considering our sample size we confirmed that there were at least ten outcome events for every predictor included in our multivariable regression model.
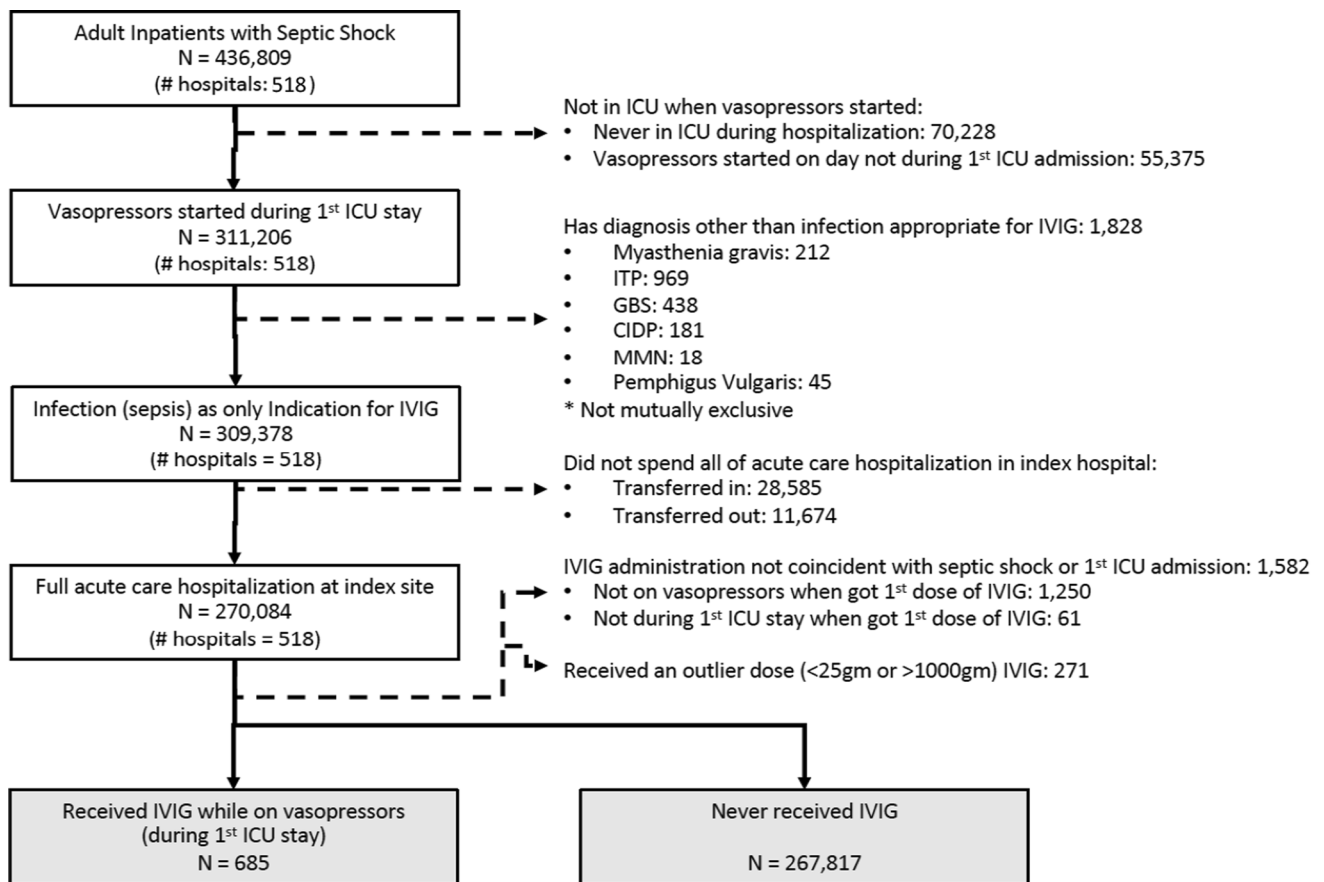
Fig. 1 Cohort creation. CIDP = chronic inflammatory demyelinating polyneuropathy; GBS = Guillain–Barre syndrome; ICU = intensive care unit; ITP = immune thrombocytopenic purpura; MMN = multifocal motor neuropathy

We obtained approval from the University of Manitoba Health Research Ethics Board for this study. We conducted all analyses using Stata (software version 13.1; StataCorp LP, College Station, TX, US).

Results

We identified 268,502 adult patients with septic shock in 518 US hospitals who met our inclusion criteria (Fig. 1); IVIG was administered to 685 (0.3%) of these patients.

Patient, illness, and hospital characteristics

Patient, illness, and hospital variables are summarized in Table 1. In univariate analyses, patients in the IVIG group were older (67 *vs* 62 yr, $P < 0.001$), with fewer Black patients, similar distributions of White patients and more "other" patients compared with patients who didn't receive IVIG (9% *vs* 13%; 67 *vs* 68%; and 24 *vs* 18%, all $P = 0.001$). Patients who received IVIG were more likely to have private health insurance (29% *vs* 15%, $P < 0.001$). Patients receiving IVIG had fewer baseline comorbid

illnesses but more acute organ failures during their hospitalization. More patients in the IVIG group were immunocompromised (16% *vs* 3%, $P < 0.001$).

A greater proportion of patients in the IVIG group had septic shock associated with necrotizing fasciitis or streptococcal toxic shock syndrome. Nevertheless, most patients with necrotizing fasciitis or streptococcal toxic shock syndrome did not receive IVIG. Patients receiving IVIG were more likely to have cellulitis or intra-abdominal infections as their source of sepsis and less likely to have urinary tract infections. Patients receiving IVIG were more likely to be mechanically ventilated. Intravenous immune globulin use varied geographically across the US. There was an association between a greater number of hospital beds and more IVIG use.

Clinical utilization of IVIG

In patients with septic shock who received IVIG, the median [IQR] total dose of IVIG per patient was 70 [40–146] g. This correlates to an estimated median patient weight-based IVIG dose of 1.0 [0.5–1.8] g·kg^{-1}. The median duration of an IVIG course was 1 [1,2] day, with a

Table 1 Patient, illness, and hospital characteristics[a]

Variable	IVIG group N = 685	Non-IVIG group N = 267,817	P value	Absolute standardized differences[b]
Age, mean (SD)	67 (15)	62 (16)	< 0.001	0.34
Female	331 (48%)	129,361 (48%)	0.99	0.00
Ethnicity				
White	461 (67%)	180,991 (68%)	0.001	0.02
Black	63 (9%)	34,827 (13%)		0.13
Other	161 (24%)	51,999 (19%)		0.12
Primary insurer				
Private	201 (29%)	40,807 (15%)	< 0.001	0.34
Medicare	377 (55%)	180,871 (68%)		0.27
Medicaid	52 (8%)	27,852 (10%)		0.07
Other/unknown	55 (8%)	18,287 (7%)		0.04
Admitting physician				
Intensivist	31 (5%)	10,437 (4%)	0.010	0.048
Surgical	58 (8%)	32,252 (12%)		0.13
Medical	347 (51%)	138,274 (52%)		0.02
Other	249 (36%)	86,854 (32%)		0.09
Elixhauser comorbidities, mean (SD)	4.64 (2)	5.18 (2)	< 0.001	0.24
	95% CI 4.47 to 4.81	95% CI 5.17 to 5.18		
Acute organ dysfunction[c]				
Cardiovascular	550 (80%)	179,711 (67%)	< 0.001	0.30
Pulmonary	489 (71%)	153,235 (57%)	< 0.001	0.30
Neurologic	170 (25%)	59,272 (22%)	0.09	0.07
Renal	495 (72%)	153,378 (57%)	< 0.001	0.32
Hepatic	96 (14%)	17,556 (7%)	< 0.001	0.23
Hematologic	302 (44%)	68,111 (25%)	< 0.001	0.41
Immunocompromised[d]	111 (16%)	7,633 (3%)	< 0.001	0.46
Source of infection				
Pneumonia	297 (43%)	111,532 (42%)	0.36	0.02
Urinary tract	152 (22%)	84,808 (32%)	< 0.001	0.23
Cellulitis	120 (18%)	26,020 (10%)	< 0.001	0.23
Bacteremia	8 (1%)	4,394 (2%)	0.33	0.08
Intra-abdominal	229 (33%)	51,103 (19%)	< 0.001	0.32
Necrotizing fasciitis	63 (9%)	1630 (0.6%)	< 0.001	0.40
Streptococcal toxic shock	57 (8%)	239 (0.09%)	< 0.001	0.41
Mechanical ventilation	529 (77%)	174,102 (65%)	< 0.001	0.27
Extra corporeal Membrane oxygenation	1 (0.1%)	33 (0.01%)	0.002	0.04
Urban hospital	620 (91%)	237,397 (89%)	0.12	0.07
Teaching hospital	234 (34%)	109,053 (41%)	< 0.001	0.15
Number of hospital beds				
>500	274 (40%)	79,140 (30%)	< 0.001	0.21
400–499	88 (13%)	44,743 (17%)		0.11
300–399	157 (23%)	56,228 (21%)		0.05
200–299	103 (15%)	48,322 (18%)		0.08
100–199	56 (8%)	32,539 (12%)		0.13
<100	7 (1%)	6,845 (3%)		0.14
Location				
Midwest	109 (16%)	46,725 (17%)	0.001	0.03

Table 1 continued

Variable	IVIG group N = 685	Non-IVIG group N = 267,817	P value	Absolute standardized differences[b]
Northeast	85 (12%)	41,759 (16%)		0.12
South	388 (57%)	127,713 (48%)		0.18
West	103 (15%)	51,620 (19%)		0.11

[a] Statistics are provided for descriptive purposes and as such, the P values have not been corrected for multiple inferences

[b] Standardized differences > 0.1 are considered meaningful.[15]

[c] ICD-9-CM based classification of acute organ dysfunction[1]

[d] ICD-9-CM based definition of immunocompromised[1]

CI = confidence interval; ICD-9-CM = Ninth International Classification of Disease Clinical Modification; IVIG = intravenous immune globulin; SD = standard deviation

median daily dose of 40 [30–67] g/day. Intravenous immune globulin was initiated within a median 1 [0–2] day of the onset of vasopressors in patients with septic shock and within a median of 1 [0–3] day of ICU admission.

Variation in IVIG utilization

To examine geographical variation in IVIG use, we calculated the proportion of patients with septic shock that received IVIG at each individual hospital site within our data set. There were 518 hospitals in our cohort. Proportion of IVIG use for patients with septic shock ranged from 0% to 8.4% across hospitals: in 300 hospitals there were no episodes of IVIG use, in 165 hospitals IVIG was used in 0.1–0.5% of cases, in 37 hospitals IVIG was used in 0.6–0.9% cases, and in two hospitals IVIG was used in 3.4% and 8.4% of septic shock cases (Fig. 2).

Considering variation in IVIG utilization over time, we examined proportional IVIG use per quarter year. In our cohort, the percentage of patients with septic shock receiving IVIG ranged from 0.2% to 0.4%. A univariate logistic regression analysis showed that consecutive quarter year was negatively associated with receipt of IVIG (OR, 0.97; 95% CI 0.95 to 0.99).

Predictors of IVIG utilization

Using multivariable random-effects logistic regression modelling, we found that female patients had greater odds of receiving IVIG, while Black patients with septic shock had decreased odds of receiving IVIG (Table 2). Patients with Medicare, Medicaid, or other primary insurance programs had decreased odds of receiving IVIG compared with those with private insurance.

Patients with more pre-existing comorbidities had decreased odds of receiving IVIG. Acute organ dysfunction of the cardiovascular, pulmonary, renal, and hematologic systems were all positively associated with receipt of IVIG. Immunocompromise was strongly associated with receipt of IVIG. Diagnoses of necrotizing fasciitis, streptococcal toxic shock syndrome, and septic shock due to cellulitis or intra-abdominal infections were all associated with receipt of IVIG. Acute renal replacement therapy was also associated with increased odds of receiving IVIG.

Year of discharge from hospital and geographical region were not associated with receipt of IVIG. Patients in small hospitals with less than 200 beds, however, had decreased odds of receiving IVIG compared with patients in hospitals with more than 500 beds (Table 2).

Discussion

Intravenous immune globulin use and predictors of use

In this large retrospective cohort study, IVIG was prescribed in a minority of patients with septic shock in the US from 1 July 2010 to 30 June 2013. Our finding that IVIG use decreased during the study period was marginally statistically significant but unlikely to be clinically significant based on the small absolute difference in proportion of patients prescribed IVIG during the time period. After adjusting for *a priori* specified demographic, clinical, and hospital variables, several independent predictors were associated with the use of IVIG. In particular, diagnoses of necrotizing fasciitis and streptococcal toxic shock were predictive of receipt of IVIG. The results from our national survey of Canadian
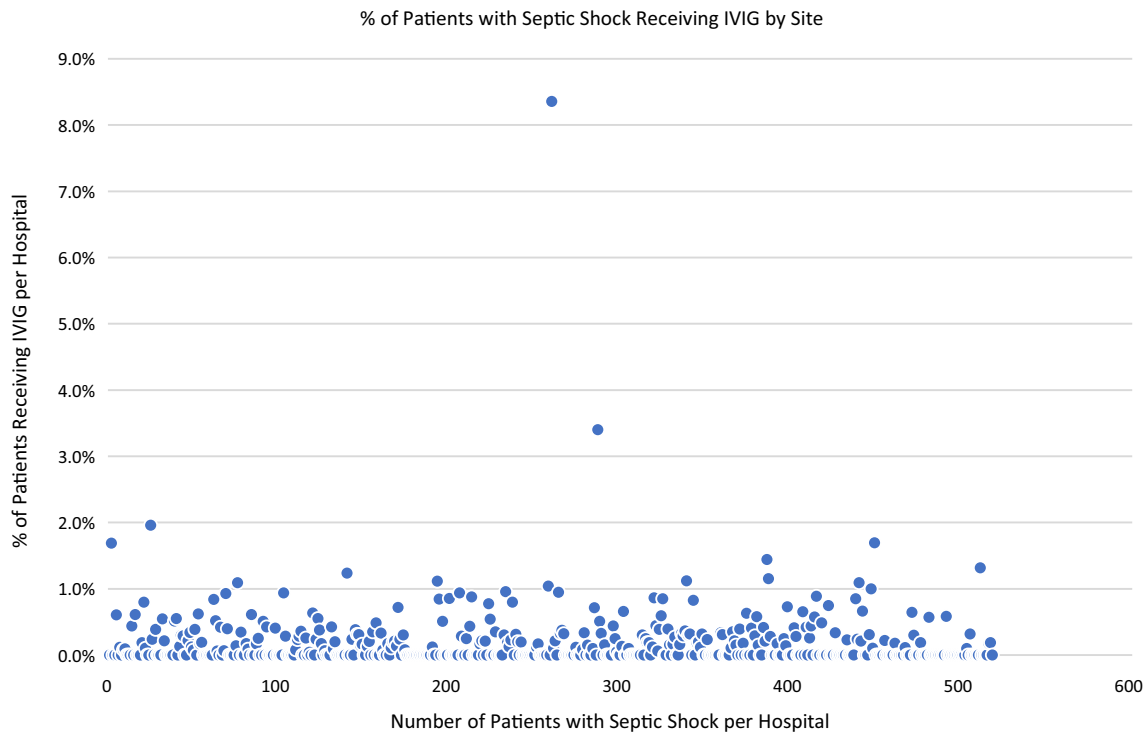
Fig. 2 Percentage of patients with septic shock receiving IVIG by site. CIDP = chronic inflammatory demyelinating polyneuropathy; GBS = Guillain–Barre syndrome; ICU = intensive care unit; ITP = immune thrombocytopenic purpura; IVIG = intravenous immune globulin; MMN = multifocal motor neuropathy. *ICU – intensive care unit; ITP – immune thrombocytopenic purpura; GBS – Guillan-Barre syndrome; CIDP – chronic inflammatory demyelinating polyneuropathy; MMN – multifocal motor neuropathy*

critical care and infectious diseases physicians were congruent with these findings where the vast majority of self-reported use of IVIG was for septic shock associated with necrotizing fasciitis or streptococcal toxic shock.[22] The pathobiology of septic shock is incompletely understood but IVIG is thought to have a role in bacterial toxin suppression, which might explain this clinical pattern of use in presumed bacterial toxin-mediated forms of shock despite limited published clinical studies. Nevertheless, most patients with necrotizing fasciitis and streptococcal toxic shock did not receive IVIG. This exposes an element of selectivity in prescriber practice that supports clinical equipoise regarding the use of IVIG for these historical indications. Further, results from existing systematic reviews reinforce that there is limited evidence to support the use of IVIG in necrotizing fasciitis, streptococcal toxic shock, and undifferentiated septic shock.[18–21]

Timing and therapeutic window in septic shock

Early, appropriate antimicrobial therapy has been found to be associated with increased survival in patients with septic shock.[14] This association has led to the recognition of a therapeutic window in septic shock wherein early targeted therapies can improve patient outcomes. While we

identified that the median time from onset of vasopressor use to the start of IVIG was one calendar day, we were not able to evaluate the timing of receipt of IVIG (or of antimicrobials) in increments of hours or minutes. Variability in timing of IVIG administration could have diluted a potential beneficial effect of early administration in our cohort if one existed. The impact of early IVIG administration within a therapeutic window in septic shock should be considered in future research.

Dose effects

As septic shock is an off-label indication for IVIG, the dose of IVIG is not standardized. In our cohort, the median total dose of IVIG used per patient was 1.0 $g \cdot kg^{-1}$ administered over a median course of one day. In published literature, the doses of IVIG administered are heterogenous and wide-ranging.[8,19,23] In a recent systematic review of IVIG in septic shock, variation in dosing of IVIG contributed significantly to between-study heterogeneity in treatment effects.[8] In another systematic review and meta-analysis of IVIG in septic shock, doses > 1 $g \cdot kg^{-1}$ body weight and duration of therapy > two days were both significantly associated with increased survival.[19] In our cohort study, variability in IVIG dose with median doses slightly lower

Table 2 Multivariable random-effects logistic regression model

Variable	OR	95% CI	*P* value
Age (per 1 yr increase)	0.99	0.98 to 0.99	< 0.001
Female	1.23	1.05 to 1.44	0.01
Ethnicity			
White	ref		
Black	0.54	0.41 to 0.72	< 0.001
Other	0.94	0.74 to 1.19	0.59
Primary insurer			
Private	Ref		
Medicare	0.73	0.59 to 0.90	0.003
Medicaid	0.41	0.30 to 0.57	< 0.001
Other	0.63	0.46 to 0.87	0.005
Admitting physician specialty			
Intensivist	Ref		
Surgical	0.82	0.51 to 1.34	0.43
Medical	1.05	0.69 to 1.61	0.82
Other	1.15	0.75 to 1.76	0.53
Elixhauser comorbidity score	0.93	0.90 to 0.97	0.001
Acute organ dysfunction			
Cardiovascular	1.66	1.36 to 2.03	< 0.001
Pulmonary	1.50	1.10 to 2.03	0.01
Neurologic	1.08	0.89 to 1.30	0.44
Renal	1.43	1.18 to 1.72	< 0.001
Hepatic	1.17	0.92 to 1.48	0.21
Hematologic	1.96	1.66 to 2.31	< 0.001
Immunocompromised[a]	6.83	5.47 to 8.53	< 0.001
Source of infection			
Pneumonia	1.20	1.02 to 1.42	0.03
Urinary tract	0.81	0.67 to 0.98	0.03
Cellulitis	1.46	1.16 to 1.85	0.001
Bacteremia	0.96	0.47 to 1.94	0.90
Intra-abdominal	2.07	1.74 to 2.45	< 0.001
Necrotizing fasciitis	9.78	6.97 to 13.72	< 0.001
Streptococcal toxic shock	56.93	38.70 to 83.75	< 0.001
Mechanical ventilation	1.15	0.83 to 1.60	0.40
AKI with acute RRT	1.99	1.62 to 2.46	< 0.001
Discharge year			
2011	1.14	0.93 to 1.39	0.21
2012	0.90	0.72 to 1.12	0.35
2013	0.91	0.69 to 1.19	0.49
Hospital type			
Urban	0.90	0.57 to 1.41	0.64
Teaching	0.78	0.55 to 1.11	0.17
Number of hospital beds			
>500	ref	Ref	Ref
400499	0.65	0.39 to 1.06	0.08
300–399	0.83	0.53 to 1.32	0.43
200–299	0.63	0.40 to 1.01	0.06
100–199	0.52	0.31 to 0.88	0.02

Table 2 continued

Variable	OR	95% CI	*P* value
<100	0.33	0.13 to 0.87	0.02
Location			
Midwest	Ref		
Northeast	0.72	0.44 to 1.19	0.20
South	0.94	0.63 to 1.40	0.77
West	0.71	0.44 to 1.15	0.17

[a] ICD-9-CM-based definition of immunocompromise[1]

AKI = acute kidney injury; CI = confidence interval; ICD-9-CM = Ninth International Classification of Disease Clinical Modification; OR = odds ratio; RRT = renal replacement therapy

than those described to be associated with a survival benefit in meta-analyses could potentially have confounded the association of IVIG with a survival benefit if it existed. Doses of IVIG at 2 g·kg^{-1} are commonly used for numerous indications in clinical practice and a dose-response effect of IVIG in septic shock must be considered in the critical appraisal of existing literature and the planning of future studies. An adequately designed clinical trial offers the opportunity to rationalize dosing of IVIG.

Limitations and strengths

The PHD is a rich administrative data set with detailed time- and date-stamped data but it is geared toward costs and billable healthcare items, and thus lacks many relevant clinical variables. In this study, while we were able to describe dosing regimens of IVIG, we were not able to identify time from onset of shock to receipt of IVIG by a margin of hours nor were we able to confirm whether calculated doses in g·kg^{-1} were accurate on an individual level given the absence of individual patient weights in the PHD, which limited our ability to compare IVIG doses used in this cohort with those in meta-analyses and patient outcomes. While no practice-changing trials regarding IVIG in septic shock have been published since 2013 (the end of our data period), clinical use of IVIG may have shifted in the interim. Further, observational cohort studies are limited in their ability to evaluate the effect of an intervention compared with clinical trials. Additionally, the cohort of patients with septic shock in this study are representative of a US population and the described utilization patterns should be extrapolated to alternate contexts with caution.

We described IVIG utilization patterns in real clinical practice in adult patients with septic shock using a large, detailed data set in the US. This data set allowed for the identification of a large number of patients for inclusion in our study and facilitated the granular exploration of IVIG utilization patterns in actual clinical practice. Our results offer novel insight into the clinical utilization of IVIG in adult patients with septic shock and will inform the design of a clinical trial.

Conclusions

Intravenous immune globulin is currently being used infrequently across the US for adult patients with undifferentiated septic shock. Use of IVIG is more common in cases of streptococcal toxic shock and necrotizing fasciitis. The doses of IVIG prescribed in septic shock are variable and may be below those doses associated with the observed potential survival benefit in systematic reviews of clinical trials. Our results highlight the need for an appropriately powered and designed randomized controlled trial studying IVIG as an adjunctive therapy in adult patients with septic shock.

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