MAJOR ARTICLE

Intravenous Immunoglobulin in Children with Streptococcal Toxic Shock Syndrome

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(See the editorial commentary by Valiquette et al, on pages 1377–9.)

Background. Streptococcal toxic shock syndrome (TSS) is a rare and severe manifestation of group A streptococcal infection. The role of intravenous immunoglobulin (IVIG) for streptococcal TSS in children is controversial. This study aims to describe the epidemiology of streptococcal TSS in children and to determine whether adjunctive therapy with IVIG is associated with improved outcomes.

Methods. A multicenter, retrospective cohort study of children with streptococcal TSS from 1 January 2003 through 31 December 2007 was conducted. Propensity scores were used to determine each child's likelihood of receiving IVIG. Differences in the primary outcomes of death, hospital length of stay, and total hospital costs were compared after matching IVIG recipients and nonrecipients on propensity score.

Results. The median patient age was 8.2 years. IVIG was administered to 84 (44%) of 192 patients. The overall mortality rate was 4.2% (95% confidence interval, 1.8%–8.0%). Differences in mortality between IVIG recipients ($n = 3$; 4.5%) and nonrecipients ($n = 3$; 4.5%) were not statistically significant ($P > .99$). Although patients receiving IVIG had higher total hospital and drug costs than nonrecipients, differences in hospital costs were not significant once drug costs were removed (median difference between matched patients, $6139; interquartile range, −$8316 to $25,993; $P = .06$). No differences were found in length of hospital stay between matched IVIG recipients and nonrecipients.

Conclusion. This multicenter study is, to our knowledge, the largest to describe the epidemiology and outcomes of children with streptococcal TSS and the first to explore the association between IVIG use and clinical outcomes. IVIG use was associated with increased costs of caring for children with streptococcal TSS but was not associated with improved outcomes.

Streptococcal toxic shock syndrome (TSS) is a rare and severe manifestation of infection caused by group A β-hemolytic streptococci. In adults, the mortality rate ranges from 30% to 70% despite antimicrobial therapy [1–3]. Streptococcal pyrogenic exotoxins, acting as superantigens, mediate systemic disease by bypassing traditional antigen-presenting mechanisms and attaching directly to T cell receptors [4]. In this manner, they induce a cascade of cytokine-mediated inflammation, leading to capillary leak and multiorgan failure.

Patients who develop streptococcal TSS often lack neutralizing antibody against pyrogenic exotoxins and other major streptococcal virulence factors [5–8]. Polyclonal human intravenous immunoglobulin (IVIG) contains neutralizing antibody to these streptococcal virulence factors [9], suggesting a potential mechanism for effective adjunctive therapy. In vitro, IVIG inhibits T cell activation by blocking or inactivating streptococcal superantigens, thereby decreasing the production of proinflammatory cytokines [9]. In a transgenic model of streptococcal TSS, mice treated with IVIG at the time of infection have improved survival rates [10].

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Extension of these findings to clinical practice is controversial. In an observational study of 53 adults with streptococcal TSS, IVIG therapy was associated with improved survival rates [11]. However, the difference in mortality rates between adult recipients of IVIG and placebo was not statistically significant in a subsequent randomized trial involving 21 patients [12].

The role of IVIG for streptococcal TSS in children is even less clear for several reasons: (1) children are less likely to develop streptococcal TSS than adults [1, 13, 14], limiting the available epidemiologic and outcome data; (2) mortality rates are substantially lower in children compared with adults, making this a less desirable outcome measure in pediatric studies of streptococcal TSS [13, 15, 16]; and (3) data regarding IVIG use in children with streptococcal TSS have been limited to case reports, making assessment of therapeutic effectiveness difficult [17–20]. We undertook this study to describe the epidemiology of streptococcal TSS in children and to determine whether adjunctive therapy with IVIG is associated with improved outcomes.

METHODS

Data source. Data for this retrospective cohort study were obtained from the Pediatric Health Information System, a national administrative database containing resource utilization data from 36 freestanding, tertiary care children's hospitals affiliated with the Child Health Corporation of America. For the purposes of external benchmarking, participating hospitals provide discharge data, including patient demographic characteristics, diagnoses, and procedures. Billing data are also available that detail all of the drugs, radiologic imaging studies, laboratory tests, and supplies charged to each patient. The protocol for the conduct of this study was reviewed and approved by The Children's Hospital of Philadelphia Committees for the Protection of Human Subjects with a waiver of informed consent.

Patients. Children aged <18 years with streptococcal TSS were eligible for this study if they were discharged from any of the 36 participating hospitals from 1 January 2003 through 31 December 2007.

Study definitions. Study participants were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) discharge diagnosis codes for the diagnosis of TSS (040.82) in combination with an *ICD-9* code for *Streptococcus* (041.xx) or with a billing charge for intravenous penicillin. Participants with varicella were identified using *ICD-9* discharge diagnosis code 052.x. Comorbid conditions considered in the study included malignant neoplasm, human immunodeficiency virus infection, postoperative infection, and sickle cell disease with use of *ICD-9* codes reported elsewhere [21]. Adjuvant corticosteroid therapy was defined as the receipt of dexamethasone, hydrocortisone, or methylprednisolone intravenously. Blood product transfusions included administration of packed red blood cells, cryoprecipitate, fresh frozen plasma, or platelets. Vasoactive infusions included dobutamine, dopamine, epinephrine, norepinephrine, and milrinone. Surgical debridement was defined using *ICD-9* procedure codes for excisional debridement of wound, infection or burn (86.22), and nonexcision debridement of wound, infection, or burn (86.28).

Measured outcomes. The primary outcomes of interest in this study were death, hospital length of stay (LOS), and total hospital costs. Total hospital charges in the Pediatric Health Information System database were adjusted for hospital location with use of the Centers for Medicare and Medicaid price/wage index. We then used hospital-level cost-to-charge ratios to convert the charges to costs. Secondary outcomes included the intensive care unit LOS and the following specific subcategories of hospital cost: drug, supply, laboratory, clinical (eg, clinical evaluation and consultation, surgical and nonsurgical procedures, wound care), and all other costs.

Measured exposures. The primary exposure of interest was the use of IVIG.

Statistical analysis. Categorical variables were described using frequencies and percentages, whereas continuous variables were described using mean, median, range, and interquartile range (IQR) values. We then characterized the variability among hospitals in the use of IVIG for streptococcal TSS. To account for a small signal (in this case, hospital effect) to noise (variation due to unmeasured patient factors) ratio, a bayesian shrinkage factor was applied to each hospital's observed IVIG prescribing practices. This process weights the proportion of patients with streptococcal TSS who received IVIG at a particular hospital on the basis of the degree of uncertainty in the calculation of prescribing rates. In this situation, bayesian shrinkage accounts for expected regression to the mean in IVIG prescribing [22].

In unadjusted analyses, patient characteristics and clinical outcomes of IVIG recipients and nonrecipients were compared using χ^2 or Fisher's exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Propensity scores accounted for potential confounding by observed baseline covariates, because the number of covariates within our study was large relative to the number of outcomes, a situation in which multivariable modeling may create unreliable estimates [23–25]. In addition, matching by propensity scores achieves a better balance of covariates between groups than other matching strategies [26, 27]. Propensity scores estimate the probability of receiving a specific treatment (in this case, IVIG) given an observed set of covariates in an observational study [28, 29]. We created a propensity score with use of multivariable logistic regression to assess the likelihood of exposure to IVIG with age, sex, race, comorbid conditions, and varicella diagnosis as risk factors for IVIG receipt. To account for severity of illness, the propensity model also included the following

Table 1. Characteristics of Patients with Streptococcal Toxic Shock Syndrome

Characteristic	Overall (N = 192)	Treatment		P[a]
		No IVIG (n = 108)	IVIG (n = 84)	
Male sex	95 (49.5)	61 (56.5)	34 (40.5)	.028
Age, years				
<2	20 (10.4)	9 (8.3)	11 (13.1)	.640
2–4	27 (14.1)	13 (12.0)	14 (16.7)	
5–9	69 (35.9)	41 (38.0)	28 (33.3)	
10–14	49 (25.5)	30 (27.8)	19 (22.6)	
15–18	27 (14.1)	15 (13.9)	12 (14.3)	
Race				
Non-Hispanic white	88 (48.1)	54 (52.4)	34 (42.5)	.100
Non-Hispanic black	29 (15.9)	19 (18.5)	10 (12.5)	
Hispanic	30 (16.4)	12 (11.7)	18 (22.5)	
Asian	12 (6.6)	8 (7.8)	4 (5.0)	
Other	24 (13.1)	10 (9.7)	14 (17.5)	
Comorbid condition				
Malignant neoplasm	3 (1.6)	1 (0.9)	2 (2.4)	.420
Hematologic disorder or immunodeficiency	7 (3.7)	1 (0.9)	6 (7.1)	.023
Diagnostic and therapeutic intervention				
Arterial blood gas measurement, median no. (IQR)	2 (0–8)	1 (0–4)	6 (2–10)	<.001
Blood product receipt	91 (47.4)	40 (37.0)	51 (60.7)	.001
Corticosteroid receipt	77 (40.1)	32 (29.6)	45 (53.6)	<.001
Vasoactive infusion	127 (66.2)	58 (53.7)	69 (82.1)	<.001
Intensive care unit admission	152 (79.2)	80 (74.1)	72 (85.7)	.049
Dialysis	3 (1.6)	0 (0.0)	3 (3.6)	.048
Mechanical ventilation	13 (6.8)	5 (4.6)	8 (9.5)	.181
Surgical debridement	15 (7.8)	6 (5.6)	9 (10.7)	.186

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; IVIG, intravenous immunoglobulin.

[a] $P < .05$ considered to be statistically significant.

variables if they occurred within 2 days of hospital admission: intensive care unit admission, requirement for mechanical ventilation, vasoactive infusions, blood product transfusions, intravenous corticosteroids, surgical debridement, and arterial blood gas measurements. The model's calculated C statistic was 0.776, indicating that the model provided a better estimate than expected by chance alone (ie, if the C statistic was equal to 0.5), but remained in a range that allowed for little concern over nonoverlapping propensity score distributions between the treatment and no treatment groups [30].

IVIG recipients and nonrecipients were matched on propensity score with use of nearest-neighbor matching with a caliper set at one-quarter of the standard deviation of the logit of the propensity scores [31]. We forced matches on intensive care unit status. The difference in outcomes was computed as the difference in outcomes between matched study participants. The median and IQR values of these differences were reported. There were too few patients at individual hospitals to permit hospital-level clustering in the analysis. Statistical significance for the difference in use (LOS or costs) was determined using the Wilcoxon signed rank test, and differences in mortality were determined using McNemar's test.

IVIG recipients who could not be matched to a control subject were removed from the analysis. To assess whether bias occurred in the matching process and how such bias would affect our interpretation of the results, we compared the characteristics and outcomes of matched and unmatched IVIG recipients with χ^2 or Fisher's exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables.

All statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute). For unadjusted comparisons, $P < .05$ was considered to be statistically significant. Because multiple comparisons were made on the same sample of discharges, we used the conservative Bonferroni correction to set the statistical significance at $P < .006$ when determining the significance of the 8 clinical outcomes in the propensity score analysis [32].

Table 2. Unadjusted Outcomes of Patients with Streptococcal Toxic Shock Syndrome

Outcome	Overall, median value (IQR)	Treatment, median value (IQR)	
		No IVIG	IVIG
Overall length of stay, days	10 (5–16)	7 (5–14)	14 (8–23)
ICU length of stay, days[a]	4 (2–9)	3 (2–5)	6 (3–11)
Total cost, $	24,206 (12,448–60,865)	15,520 (8706–34,824)	43,546 (24,358–93,466)
Drug cost, $	6315 (2383–14,002)	2665 (1520–6553)	13,060 (7202–21,972)
Supply cost, $	739 (179–2603)	521 (116–1577)	1486 (413–4208)
Laboratory cost, $	3784 (1483–10,778)	2464 (1186–4963)	7002 (3004–16,728)
Clinical cost, $	1352 (259–5515)	743 (212–3183)	3179 (655–7396)
Other cost, $	9006 (5039–19,216)	6406 (3859–13,274)	13,638 (7992–31,246)

NOTE. $P < .001$ for all entries ($P < .05$ considered to be statistically significant). ICU, intensive care unit; IVIG, intravenous immune globulin.

[a] Only patients requiring intensive care until hospitalization were included.

RESULTS

Patient characteristics. During the study period, 192 patients were diagnosed as having streptococcal TSS. There was a median of 4 patients (IQR, 3–8 patients) per hospital. Forty-three patients (22.4%) were transferred to a participating hospital after initial evaluation elsewhere. The characteristics of study patients are given in table 1. The mean patient age was 8.8 years (median, 8.2 years; IQR, 5.0–13.4 years). Most patients ($n = 182$; 94.8%) received adjunctive therapy with intravenous clindamycin in combination with either penicillin or vancomycin. Three patients (1.6%) had varicella zoster virus infection.

IVIG use. IVIG was administered to 84 children (44%) either as a single dose ($n = 51$; 61%) or once daily on 3 consecutive days ($n = 33$; 39%). No significant change was seen in the proportion of patients receiving IVIG over time: 44.1% in 2003, 29.7% in 2004, 50.0% in 2005, 50.0% in 2006, and 44.7% in 2007 ($P = .353$, by χ^2 test for trend). However, IVIG use varied by hospital; shrunken estimates of IVIG use ranged from 29% to 60% of patients with streptococcal TSS at any hospital. IVIG was administered to 12 (30%) of the 40 patients who did not require admission to the intensive care unit and 72 (47%) of 152 patients who were admitted to the intensive care unit; 5 (63%) of the 8 patients who died received IVIG.

Outcome measures. The overall mortality rate was 4.2% (95% confidence interval, 1.8%–8.0%). The unadjusted difference in mortality between patients receiving IVIG ($n = 5$; 6.0%) and those not receiving IVIG ($n = 3$; 2.8%) was not statistically significant ($P = .300$, by Fisher's exact test). The mean LOS was 14 days; ~25% of patients had a LOS >14 days, and 17% of patients had a LOS >21 days. In unadjusted analysis, the total hospital LOS and intensive care unit LOS were significantly longer for IVIG recipients than for nonrecipients (table 2).

The total cost for all patients was $9,392,968; drug costs accounted for $2,165,784 (23.1%) of the total hospital cost. The cost of hospitalization exceeded $115,000 for 10% of patients. Drug costs were significantly higher for patients receiving the 3-day IVIG regimen (median, $18,472; IQR, $10,910–$33,044), compared with the 1-day IVIG regimen (median, $9447; IQR, $5453–$16,698; $P = .002$). Patient outcomes are summarized in table 2. In unadjusted analysis, the total hospital cost, drug cost, and all other cost subcategories were greater in IVIG recipients than in nonrecipients. No significant difference was found in the proportion of IVIG recipients (22%) or nonrecipients (25%) admitted to the participating hospitals as transfers from other acute care institutions ($P = .832$, by χ^2 test).

When stratifying the unadjusted (ie, unmatched) analysis by age, no difference was found in LOS (median, 13 days; IQR, 7–18 days) or total hospital costs (median, $35,886; IQR, $18,606–$76,893) between IVIG recipients and nonrecipients aged <5 years. Among children aged ⩾5 years, the LOS was significantly longer for IVIG recipients (median, 14 days) than for nonrecipients (median, 7 days; $P < .001$). In this older age group, IVIG recipients also had higher total hospital costs (median, $43,488) than nonrecipients (median, $13,705; $P < .001$).

Analysis of patients matched by propensity scores. In the propensity score analysis, 67 (80%) of 84 patients receiving IVIG were matched to appropriate control patients (ie, IVIG nonrecipients). Differences between patients matched by propensity scores were not statistically significant with 1 exception: IVIG recipients had more arterial blood gas measurements than did nonrecipients (table 3). In propensity-matched analysis, the differences in mortality rates between IVIG recipients ($n = 3$; 4.5%) and nonrecipients ($n = 3$; 4.5%) were not statistically significant ($P > .99$, by McNemar's test). The other outcomes of the propensity-matched analysis are summarized in table 4. Patients receiving IVIG had higher total hospital and drug costs than did nonrecipients. Although patients receiving IVIG had a longer LOS and higher supply, clinical, and laboratory costs,

Table 3. Characteristics of Patients with Streptococcal Toxic Shock Syndrome Who Were Matched by Propensity Score

Characteristic	Treatment		P^a
	No IVIG (n = 67)	IVIG (n = 67)	
Male sex	31 (46.3)	26 (38.8)	.382
Age, years			
<2	8 (11.9)	8 (11.9)	.900
2–4	10 (14.9)	11 (16.4)	
5–9	20 (29.9)	23 (34.3)	
10–14	19 (28.4)	14 (20.9)	
15–18	10 (14.9)	11 (16.4)	
Race			
Non-Hispanic white	34 (51.5)	32 (50.8)	.382
Non-Hispanic black	14 (21.2)	8 (12.7)	
Hispanic	7 (10.6)	14 (22.2)	
Asian	4 (6.1)	3 (4.8)	
Other	7 (10.6)	6 (9.5)	
Comorbid condition			
Malignant neoplasm	1 (1.5)	2 (3.0)	.559
Hematologic disorder or immunodeficiency	1 (1.5)	0 (0.0)	.316
Diagnostic and therapeutic intervention			
Arterial blood gas measurement, median no. (IQR)	2 (0–7)	5 (1–9)	.048
Blood product receipt	34 (50.8)	36 (53.7)	.729
Corticosteroid receipt	29 (43.3)	32 (47.8)	.603
Vasoactive infusion	49 (73.1)	54 (80.6)	.306
Intensive care unit admission	59 (88.1)	59 (88.1)	>.99
Dialysis	0 (0.0)	1 (1.5)	.316
Mechanical ventilation	4 (6.0)	6 (9.0)	.511
Surgical debridement	3 (4.5)	6 (9.0)	.300

NOTE. Data are no. (%) of patients, unless otherwise indicated. IVIG, intravenous immune globulin.

[a] $P < .05$ considered to be statistically significant.

compared with nonrecipients, these differences were not statistically significant when accounting for multiple comparisons (table 4). The difference in the cost of hospitalization between IVIG recipients and nonrecipients was not significant once drug costs were subtracted from total hospital costs (median difference between matched patients, \$6139; IQR, −\$8316 to \$25,993; $P = .060$), suggesting that the differences in drug costs accounted for the differences in total costs.

In a secondary analysis, the characteristics and outcomes of unmatched and matched IVIG recipients were compared. No differences were found in age or sex between unmatched and matched patients. Unmatched patients had a greater number of arterial blood gas measurements and were more likely to receive blood product transfusions and corticosteroids, compared with matched patients. Unmatched IVIG recipients also had a significantly longer LOS (25 vs 12 days; $P = .003$) and higher total costs (\$115,500 vs \$38,120; $P = .001$) and drug costs (\$30,507 vs \$11,433; $P = .002$), compared with matched IVIG recipients.

DISCUSSION

This multicenter study, to our knowledge, is the largest to describe the epidemiology and outcomes of children with streptococcal TSS and the first to explore the association between IVIG use and clinical outcomes. There was variability in the use of IVIG among participating hospitals. Although overall mortality was low, the costs of caring for children with streptococcal TSS were substantial. Importantly, IVIG use was not associated with a reduction in mortality or hospital LOS. The total hospital costs were higher for children receiving IVIG, a difference that was attributable to higher drug costs for IVIG recipients, compared with nonrecipients. The results of our study suggest that IVIG use increases the costs of caring for children with streptococcal TSS but does not improve their outcomes.

Significant variation was found in the use of IVIG for TSS among hospitals. Increased illness severity incompletely accounted for this variation. It is likely that the variability among hospitals indicates poor consensus on best practices for treat-

Table 4. Results of the Propensity-Matched Analysis Comparing Differences in Outcomes between Intravenous Immunoglobulin Recipients and Nonrecipients with Streptococcal Toxic Shock Syndrome

Outcome	Median difference (IQR)	P[a]
Overall length of stay, days	2 (−4 to 9)	.036
ICU length of stay, days[b]	2 (−1 to 6)	.033
Total cost, $	12,056 (−8014 to 42,328)	.002
Drug cost, $	6555 (301–14,079)	<.001
Supply cost, $	346 (−282 to 2270)	.018
Laboratory cost, $	1029 (−2031 to 5707)	.098
Clinical cost, $	300 (−1426 to 3747)	.294
Other cost, $	3723 (−3324 to 12,456)	.008

NOTE. ICU, intensive care unit; IQR, interquartile range.

[a] $P < .006$, applying the Bonferroni correction, was considered to be statistically significant because of multiple comparisons.

[b] Only patients requiring intensive care until hospitalization were included.

ment, in part because of the lack of evidence supporting IVIG use. Institutional cultural differences also may drive variability; certain champions of therapies may define therapy at a particular institution, which may be more likely in cases of rare and potentially fatal diseases.

IVIG has been suggested as a potential adjunctive therapy for streptococcal TSS because of its ability to neutralize a wide variety of superantigens and to facilitate opsonization of streptococci [33, 34]. In an observational study of adults, the unadjusted 30-day mortality rate was significantly lower among 21 IVIG recipients (33%), compared with 32 nonrecipients (66%; $P = .02$) [11]. The odds of survival were 8-fold higher among IVIG recipients after adjusting for illness severity at presentation; however, a disproportionate number of IVIG nonrecipients did not receive clindamycin [11]. Darenberg et al [12] conducted a randomized trial involving 21 adults from 17 European hospitals. The trial was terminated early because of low enrollment. Although the mortality rate was lower in IVIG recipients (10%), compared with placebo recipients (36%), this difference was not statistically significant [12].

Our large multicenter study of children with streptococcal TSS did not find an association between IVIG use and mortality or LOS. Although substantial variability was found in IVIG use for children with streptococcal TSS, clindamycin was administered almost routinely. When given to mice at the time of experimental group A β-hemolytic streptococcal infection (and in the absence of antibiotic therapy), IVIG neutralized circulating superantigens and reduced systemic inflammatory response [10]. However, when used in combination with penicillin and clindamycin in delayed treatment situations (to mimic what occurs in the clinical situations), IVIG did not confer additional therapeutic benefit [10]. These experimental results raise 2 important points that lend credence to our findings that IVIG use was not associated with improved outcomes in children with streptococcal TSS. First, the benefit of IVIG may depend predominantly and perhaps exclusively on the timing of administration. IVIG may not have any clinical benefit if it is not administered sufficiently early in infection, a goal that may be difficult to accomplish in clinical practice. Second, the concurrent use of clindamycin therapy may improve outcomes to such an extent that detection of any additional benefit conferred by IVIG would require prohibitively large numbers of study participants.

This study has several limitations. First, the use of administrative data precluded the use of the formal case definition of streptococcal TSS [35] to identify the study cohort. We attempted to minimize such misclassification bias by using a rigorous definition of streptococcal TSS that incorporated *ICD-9* discharge diagnosis codes and billing data for receipt of intravenous penicillin. However, discharge diagnosis coding may be unreliable for specific diseases or pathogens. Furthermore, it is possible that IVIG recipients were more likely to have streptococcal TSS than were nonrecipients. If the outcomes of these groups of patients differed, then our approach would underestimate the actual benefit of IVIG.

Second, it is likely that we were underpowered to detect small benefits of IVIG use on mortality in streptococcal TSS. However, because the overall mortality rate in children with streptococcal TSS is considerably lower than the mortality rate in adults, any absolute reduction in mortality attributable to IVIG in children with streptococcal TSS is likely to be minimal. Furthermore, given the relative rarity of streptococcal TSS in children, it is unlikely that a randomized controlled trial of IVIG use in children with streptococcal TSS will ever be conducted. Despite the fact that streptococcal TSS occurs more commonly in adults, the only randomized trial of streptococcal TSS and IVIG use in adults was terminated early because of low enrollment; the number of patients in our study was 6-fold greater than the number enrolled in the randomized trial involving adults.

Third, the effectiveness of IVIG may be underestimated in our study because neutralizing activity against various streptococcal superantigens could not be determined for any of the IVIG doses administered. Titers against streptococcal superantigens vary in different IVIG preparations [36, 37], and such differences, at least in theory, could influence IVIG effectiveness. Finally, although matching patients on propensity score balances covariates between 2 groups (in this case, IVIG recipients and nonrecipients) better than other matching methods, the exclusion of unmatched patients may bias the study. This form of spectrum bias (ie, the most ill patients are excluded) would cause us to overestimate the benefit of IVIG.

In conclusion, the role of IVIG in children with streptococcal TSS has been controversial. Until now, pediatricians had to decide the extent to which findings from animal models and

adult studies were applicable to children with streptococcal TSS. In our large, multicenter, observational study of children with streptococcal TSS, the mortality rate was substantially lower than that reported in studies of adults. IVIG use increased the costs of hospitalization but was not associated with improved clinical outcomes. Although it may be reasonable to recommend IVIG as adjunctive therapy for adults with streptococcal TSS, our data do not support its use in children with streptococcal TSS.

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