Intravenous Immunoglobulin Therapy for Streptococcal Toxic Shock Syndrome—A Comparative Observational Study

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Twenty-one consecutive patients with streptococcal toxic shock syndrome (TSS) between December 1994 and April 1995 were treated with a median dose of 2 g of intravenous immunoglobulin (IVIG)/kg (cases) and were compared with 32 patients with streptococcal TSS between 1992 and 1995 who did not receive IVIG therapy (controls). The outcome measure was 30-day survival. Patient plasma was tested for its ability to inhibit T cell activation induced by the infecting strain. The proportion of cases with 30-day survival was higher than that of the controls with 30-day survival (67% vs. 34%, respectively; $P = .02$). Multivariate analysis revealed that IVIG administration and a lower Acute Physiology and Chronic Health Evaluation II score were associated with survival; the odds ratio for survival associated with IVIG therapy was 8.1 (95% confidence interval, 1.6–45; $P = .009$). IVIG therapy enhanced the ability of patient plasma to neutralize bacterial mitogenicity and reduced T cell production of interleukin-6 and tumor necrosis factor α. IVIG may be an effective adjunctive therapy for streptococcal TSS, possibly because of its ability to neutralize bacterial exotoxins.

Streptococcal toxic shock syndrome (TSS) is the most severe manifestation of invasive disease due to group A streptococcus (GAS); the case-fatality rate associated with streptococcal TSS is as high as 81% [1–6]. The mechanism whereby gram-positive organisms cause shock is as yet not determined, but there is increasing evidence that it is the result of cytokine induction by exotoxins(s) belonging to the family of gram-positive bacterial superantigens. This family includes the enterotoxins and TSS toxin-1 produced by *Staphylococcus aureus* and the streptococcal pyrogenic exotoxins of *Streptococcus pyogenes* [7, 8].

Superantigens bind to cells expressing major histocompatibility complex class II molecules and interact directly with the β chain of the T cell receptor to cause massive T cell prolifera-

tion and cytokine production [7]. Administration of intravenous immunoglobulin (IVIG) can block in vitro T cell activation by staphylococcal and streptococcal superantigens [8–10]. Several case reports have been published in which IVIG administration in the setting of streptococcal TSS appeared to correlate with clinical improvement [11–15], and there is evidence that IVIG contains superantigen-neutralizing antibodies [16].

The Ontario Streptococcal Study Group has conducted population-based surveillance for all invasive GAS disease in Ontario, Canada, since 1 January 1992 [6]. The case-fatality rate associated with streptococcal TSS has been >65% and has remained stable over time [6, 17]. In the winter of 1994, noting an increase in rates of streptococcal TSS [17] and recognizing the potential for IVIG to decrease the high case-fatality rates associated with this disease, we initiated an observational study of the use of IVIG to treat patients with GAS TSS.

Methods

Study Protocol

From 1 December 1994 to 30 April 1995, an observational evaluation of the utility of IVIG in the management of streptococcal TSS was performed. The study protocol and a request for recruitment were circulated to all Ontario Streptococcal Study Group collaborators (i.e., all microbiology laboratories, infection control practitioners, and public health units in Ontario) and to members of the Canadian Infectious Disease Society with a request to consider enrolling all identified patients

with GAS TSS. The treatment protocol recommended IVIG, clindamycin, and penicillin and early surgical debridement if appropriate. Physicians enrolling patients requested consent for the collection of detailed clinical data, the GAS isolate, and blood samples before and immediately after IVIG infusions. The IVIG used in this study was provided by the Canadian Red Cross and Cutter Biologicals (Toronto). Initial dosage recommendations were 0.4 g/kg daily for 5 days; in March 1995, the recommendation was changed to a single dose of 2 g/kg, with a repeated dose at 48 hours if the patient remained unstable. IgA deficiency was the only absolute contraindication to IVIG therapy, although patient hypervolemia might limit the rate of administration.

Because the magnitude of any therapeutic effect of IVIG was unknown and because severe GAS infections are seasonal (in Ontario, >70% of cases occur during the winter and spring months [6, 17]), an a priori decision was made to include in the treatment group patients enrolled during a single season, from 1 December 1994 to 30 April 1995. The study was approved by the Human Subjects Review Committee of the University of Toronto.

Study Enrollment

The efficacy of IVIG was assessed by comparing outcomes for IVIG-treated patients (cases) with those for patients receiving standard care (controls). Cases were patients with streptococcal TSS who received IVIG therapy within the study period; these patients were enrolled from across Canada. All cases were enrolled into the study before the administration of IVIG. Any patient with streptococcal TSS who was identified by active surveillance in southern Ontario between 1 January 1992 and 30 April 1995 was screened for possible inclusion in the control group. Controls were excluded from analysis if they had not received antibiotic therapy appropriate for GAS sepsis, if they died <12 hours after meeting the criteria for streptococcal TSS, if the severity of preexisting illness precluded aggressive supportive care, if they had received IVIG therapy outside of the study period, if their charts were not available for review, or if they had known IgA deficiency.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score [18] was calculated for each patient on the basis of age, underlying illness, and vital signs and laboratory results obtained at the time that the patient first met criteria for streptococcal TSS. For univariate analysis, cases and controls were stratified into four groups according to APACHE II score (1–19 points, 20–29 points, 30–39 points, and ≥40 points). The primary outcome was 30-day survival. Secondary end points were 7-day survival and the duration of survivors' mechanical ventilation and hospitalization.

Statistical Analysis

Univariate analysis was performed with use of Epi-Info Version 6.02 (Centers for Disease Control and Prevention).

Categorical variables were analyzed by Fisher's exact test, and continuous variables were analyzed by the Student's t test or Wilcoxon rank-sum or signed-rank test [19]. For stratified analyses of categorical variables, summary odds ratios were calculated, and significance was analyzed by the Cochran-Mantel-Haenzel χ^2 test. Multivariate analysis was carried out by two methods: generalized additive modeling in the S language [20] was performed, to remove possible nonlinear effects of continuous covariates, and propensity score analysis was performed [21–23], to assess group comparability before and after stratification by APACHE II score that was based on the estimated probability of receiving IVIG. The variables included in both multivariate models were those associated with survival in the univariate analysis ($P < .1$) and potential confounding variables. P values of ≤.05 were considered statistically significant.

Laboratory Methods

Clinical isolates were identified as GAS by conventional methods [24]. M typing and T typing, according to capillary precipitin and agglutination reactions, respectively, were performed with use of specific antisera at the National Reference Centre for the Streptococcus, Edmonton, Alberta, Canada [25, 26]. Specific PCR primers were used to detect the genes encoding streptococcal pyrogenic exotoxins A (speA) and C (speC) [27].

Additional immunologic analyses were performed on plasma samples from all 10 cases from whom both baseline and post–IVIG infusion specimens were available and on baseline plasma samples from the 10 controls most closely matching these cases according to age and APACHE II score. The ability of each patient's plasma to inhibit the mitogenicity of the culture supernatant from their own GAS isolate was assessed as previously described [10, 28]. Plasma samples resulting in ≥50% inhibition of mitogenic activity were considered to possess mitogen-neutralizing capacity [28].

The impact of a single IVIG infusion on the production of IL-6 and TNF-α by peripheral blood mononuclear cells (PBMCs) was assessed at the single cell level by staining with monoclonal antibodies according to previously described methods [10, 16, 29]. Data are presented as the mean percent of cytokine-producing cells ± SD; these mean values were calculated from duplicate runs, counting 1,000 cells per slide.

Results

Clinical and Microbiological Characteristics

Twenty-one cases were enrolled in the study. Twelve cases (57%) were identified through active surveillance in Ontario, and nine (43%) were identified through surveillance in other provinces of Canada, one of whom has been previously described [13]. Three patients were enrolled in December 1994,

Table 1. Clinical characteristics of 53 patients with streptococcal toxic shock syndrome who were treated with or without intravenous immunoglobulin.

Characteristic	Cases (n = 21)	Controls (n = 32)	P value	OR (95% CI)*
Mean age in y (SD)	52 (23)	60 (19)	.18	NA
No. (%) of males	11 (52)	18 (56)	.78	0.86 (0.25–3.0)
Mean APACHE II score (SD)	26 (8.7)	25 (8.6)	.99	NA
Median time in h (range)† to				
Admission	40.5 (4–240)	64.5 (3–240)	.31	NA
Antibiotic therapy‡	43 (5–241)	69 (3–246)	.26	NA
No. (%) who received				
Clindamycin	20 (95)	17 (55)§	<.01	15.7 (2.0–730)
Surgery	14 (67)	12 (38)	.04	3.2 (0.9–12.6)
No. (%) with site of infection				
Soft tissue	14 (67)	19 (59)	.10	2.5 (0.7–9.1)
Lung	4 (19)	5 (16)	.75	1.1 (0.2–6.7)
Other	3 (14)	8 (25)	.35	0.5 (0.1–2.5)
No. (%) infected with M serotype				
M1	10 (48)	2 (6)	<.01	12.5 (2.3–100)
M3	4 (19)	9 (28)	.46	0.6 (0.1–2.6)
Other	7 (33)	21 (66)	.02	0.3 (0.1–1.0)
No. (%) with toxin gene				
*spe*A	12 (57)	12 (38)	.16	2.2 (0.6–7.9)
*spe*C	6 (29)	17 (53)	.08	0.4 (0.1–1.3)

NOTE. APACHE II = Acute Physiology and Chronic Health Evaluation II [20]; NA = not applicable.
* Maximum likelihood estimate of odds ratio, with 95% confidence interval.
† Time from the onset of clinical symptoms of infection, as reported by the patient.
‡ Time to administration of parenteral antibiotics active against group A streptococcus.
§ Data on clindamycin were not available for one control.

and 18 were enrolled in the first 4 months of 1995. There was no difference in outcome between cases enrolled from active surveillance and those enrolled from elsewhere in Canada (7-day mortality: 0 of 12 vs. 2 of 9, respectively; 30-day mortality: 5 of 12 vs. 2 of 9, respectively; P = .64, Fisher's exact test).

Prospective surveillance in southern Ontario identified 63 patients with streptococcal TSS between 1 January 1992 and 30 April 1995 who were not enrolled as cases. The case-fatality rate among patients with streptococcal TSS who were from southern Ontario (66%) was not significantly different from that among patients from northern and eastern Ontario (83%; P = .24). Twenty-six of the patients with streptococcal TSS who were from southern Ontario were ineligible for the study (case-fatality rate, 92%): 2 had received IVIG therapy outside of the study period (both survived), 6 had not received aggressive supportive care (all died), and 18 died <12 hours after meeting criteria for streptococcal TSS. None of the patients had contraindications to IVIG therapy. Consent for additional chart review could not be obtained for four patients (two died), and medical records could not be traced for one patient who died. The remaining 32 patients were enrolled in the study as controls.

Four controls were enrolled from 1995 (3 deaths [75%]); 12, from 1994 (8 deaths [67%]); 3, from 1993 (2 deaths [67%]), and 13, from 1992 (8 deaths [62%]). These case-fatality rates were not statistically different (P = .97). Overall, case-fatality rates among controls also did not vary over the 4 years of the study: 1992, 13 (68%) of 19; 1993, 10 (83%) of 12; 1994, 16 (67%) of 24; and 1995, 13 (68%) of 19 (P = .76). Rates of surgical intervention and clindamycin use did not vary from year to year (data not shown). There was also no difference in the case-fatality rate among cases from Ontario who were treated between 1992 and 1995 in teaching and nonteaching hospitals (64% vs. 69%, respectively; P = .56).

Cases and controls were similar in regard to demographics, APACHE II score, and timing of interventions, although cases had more dysfunction of major organ systems, as defined by the Working Group on Severe Streptococcal Infections [5], than did controls (mean: 3.0 vs. 2.5 major organ systems, respectively; P = .05) (table 1). Cases were also more likely to have received clindamycin therapy and to be infected with organisms of M1 serotype (table 1).

Initial doses of IVIG were 0.2 g/kg (2 cases), 0.4 g/kg (11), 0.5 g/kg (2), 1 g/kg (3), and 2 g/kg (3). The median cumulative

Table 2. Study end points for 53 patients with streptococcal toxic shock syndrome who were treated with or without intravenous immunoglobulin.

End point	Cases (n = 21)	Controls (n = 32)	P value*	OR (95% CI)†
No. (%) who survived for				
7 d	19 (90)	16 (50)	<.01	16.0 (2.0–129)
30 d	14 (67)	11 (34)	.02	7.7 (1.5–14.3)
Median no. of d intubated (range)‡	7 (2–55)	8 (0–25)	.78	NA
Mean no. of d hospitalized (range)‡	29 (13–92)	39 (7–143)	.87	NA

NOTE.   NA = not applicable.

* Univariate analysis, with patients stratified according to the Acute Physiology and Chronic Health Evaluation II score [20].

† Mantel-Haenzel weighted odds ratio, with 95% confidence interval.

‡ Includes only those patients surviving for 30 days.

dose of IVIG was 2 g/kg (range, 0.2–3.6 g/kg). Neither the size of the initial dose nor the cumulative dose of IVIG administered was associated with outcome (data not shown). Treating physicians reported no significant adverse reactions to IVIG.

Univariate Analysis

The overall case-fatality rate associated with streptococcal TSS was 56% and increased as the APACHE II score increased (1–19 points, 31%; 20–29 points, 43%; 30–39 points, 77%; ≥40 points, 100%; $P = .02$, χ^2 test for trend). Cases were more likely than controls to survive for both 7 and 30 days in the stratified analysis ($P = .007$ and .02, respectively; tables 2 and 3). The duration of hospitalization and intubation for survivors did not differ significantly between the two groups (table 2).

Logistic and Propensity Score Analyses

Variables included in the multivariate model included APACHE II score (which incorporates the presence of underlying illness and age), IVIG therapy, clindamycin and penicillin therapy, surgery, presence of necrotizing fasciitis, *spe*A and *spe*C genotypes, and M1 and M3 serotypes. APACHE II score and IVIG therapy were the two variables retained in this modeling. The odds ratio for survival of cases as compared with controls was 8.1 (95% CI, 6–45; $P = .009$). The information for patients not treated with clindamycin is limited by the fact that 20 (95%) of 21 cases received clindamycin compared with 17 (55%) of 31 controls. This circumstance occurred because the treatment protocol recommended by the study included clindamycin as well as IVIG therapy. In a secondary multivariate analysis, considering only those cases and controls treated

with clindamycin, APACHE II score and IVIG therapy remained the only variables significantly associated with survival (OR for survival associated with IVIG therapy, 5.5; 95% CI, 0.98–30; $P = .03$). Because of uncertainty about optimal model selection given the small sample size, we looked at the estimated IVIG effect for all possible models. The minimum estimated odds ratio for survival associated with an IVIG effect was 4.3.

For the propensity score stratification to adequately remove imbalances on covariates, at least a stepwise selection from the covariates was required. The df needed for this stepwise selection was 12, considerably more than that recommended given the small number of outcome events [22, 23]. This number of covariates and the small sample size resulted in the lowest stratum having no cases and the highest stratum having only one control. An analysis based on the middle three strata identified an IVIG effect, with an estimated odds ratio for survival associated with IVIG therapy of 10 (95% CI, 1.4–70).

Neutralization of Streptococcal Mitogenic Activity

Baseline and post–IVIG infusion plasma samples from 10 cases were analyzed, as were baseline plasma samples from 10 controls matched for mean age (52 vs. 47 years, respectively; $P = .6$) and mean APACHE II score (24.6 vs. 25.6, respectively; $P = .8$). The inhibitory capacity of baseline plasma varied from 0 to 97%, and there was no significant difference between cases and controls ($P = .20$; figure 1). There was a significant increase in mitogen-neutralizing capacity after a single dose of IVIG ($P = .004$, Wilcoxon signed-rank test), with eight of 10 cases exhibiting mitogen-neutralizing activity after one dose (figure 1). Plasma from one of the two remaining cases exhibited neutralizing activity after a second IVIG dose. IVIG therapy resulted in a statistically significant decrease in IL-6 production by PBMCs for all four patients treated (for each patient, $P < .05$ by the t test) and in TNF-α production by PBMCs for three of the four patients treated (figure 2).

Discussion

The advent of antibiotics dramatically reduced the mortality rate associated with invasive bacterial infections [30]. However, despite antibiotic therapy and intensive care unit support, rates of early death due to serious streptococcal infections remain high [6, 30, 31], suggesting that new therapeutic approaches are needed. Recently, a number of case reports have suggested that IVIG may fulfill this role [11–15]. These case reports are supported by the fact that there is a biologically plausible mechanism for this effect and by the fact that IVIG may have an impact on mortality due to sepsis caused by other gram-positive organisms [32].

Double-blind, randomized, controlled trials are the standard method for evaluating new therapies. The advantages of this approach are that investigators, blinded to assignment of ther-

Table 3. Influence of clinical and microbiological characteristics on the 30-d survival of 53 patients with streptococcal toxic shock syndrome.

Variable	No. of survivors with factor present/total no. of patients (%)	No. of survivors with factor absent/total no. of patients (%)	P value*	OR (95% CI)†
Medical therapy				
Intranveous immunoglobulin	14/21 (67)	11/32 (34)	.02	7.8 (1.5–41.3)
Clindamycin	22/37 (59)	3/15 (20)‡	.11	4.8 (1.0–25)
Surgery	17/26 (65)	8/27 (30)	.09	4.0 (1.0–14.3)
Clinical diagnosis				
Pneumonia	2/9 (22)	23/44 (52)	.56	0.4 (0.1–2.5)
Fasciitis	16/23 (70)	9/30 (30)	.03	4.9 (1.3–17.9)
M serotype				
M1	7/12 (58)	18/41 (44)	.64	1.8 (0.4–7.5)
M3	5/13 (38)	20/40 (50)	.76	0.6 (0.2–2.5)
Other	12/25 (48)	13/28 (46)	.88	1.0 (0.3–3.6)
Toxin gene				
*spe*A	11/24 (46)	14/29 (48)	.79	1.0 (0.3–3.4)
*spe*C	9/23 (39)	16/30 (53)	.50	0.5 (0.2–1.8)

* Univariate analysis, with patients stratified by the Acute Physiology and Chronic Health Evaluation II score [20].
† Mantel-Haenzel weighted odds ratio, with 95% confidence interval.
‡ Data on clindamycin were not available for one control.

apy, cannot introduce bias in classifying outcomes and that prospective, randomized assignment to treatment group should lead to an equal distribution of potential confounders between therapies. A randomized, controlled trial, however, may be logistically extremely difficult when a rare condition requiring immediate therapy is being studied. In the face of increasing population-based rates of streptococcal TSS in 1994, we designed a comparative observational study, combined with an in vitro assessment of effect, to further our understanding of the value of IVIG therapy.

The major concern in assessing results from observational studies is the comparability of the treatment and control groups. Patients are not randomly assigned to treatment group; therefore, potential sources of bias must be recognized and minimized, and potential confounders must be controlled for in the analysis. In this study, we did this by analyzing the results with both a multivariate analysis model and a propensity score model [22, 23]. Multivariate modeling expresses the risk of the outcome as a function of the exposure of interest and the confounders. Propensity score analysis stratifies on the basis of a propensity score, which is obtained from a logistic regression model that assesses the probability of the exposure itself as a function of the confounders. Although the finding of an IVIG effect in both types of models is reassuring, the success of both models depends on the appropriate identification and control of the effects of bias and confounding.

Thus, the results of this study must be considered in the context of several potential sources of bias. The choice of death as the primary outcome avoids issues of bias in classifying outcomes; however, bias may have been introduced because cases were from throughout Canada and controls were only from Ontario. This difference could affect study outcome if cases were enrolled from facilities where more aggressive treatment and supportive care were provided and a larger number of controls were enrolled from facilities providing varying quality of care. However, we found no difference in outcome between cases enrolled from active surveillance and those enrolled from elsewhere in Canada or between cases from teaching and nonteaching hospitals in Ontario. Bias might also have been introduced in our exclusion of some patients with streptococcal TSS as controls or because cases and controls were enrolled during different times. These practices would bias results toward finding an effect of IVIG if excluded persons were less likely to die or if patients enrolled in 1995 were less likely to die than those affected in previous years. We found, however, that the case-fatality rate was significantly higher among excluded controls than among included controls (87% vs. 68%, respectively; P = .05) and that there was no change in the case-fatality rate associated with streptococcal TSS among controls between 1992 and 1995.

We took other potential sources of bias into account in the analysis. We controlled for potential differences in age and severity of illness between groups by including APACHE II scores in both univariate and multivariate analyses. The APACHE II scoring system is a validated severity of illness scale that accurately predicts in-hospital mortality rates among critically ill patients [18, 33]. The only two statistically significant differences between demographic and clinical characteristics of groups at baseline, major organ dysfunction at study enrollment (P = .05) and M1 serotype (P < .01), tended to bias toward a more favorable outcome for the controls [34, 35]. It is important to remember, how-
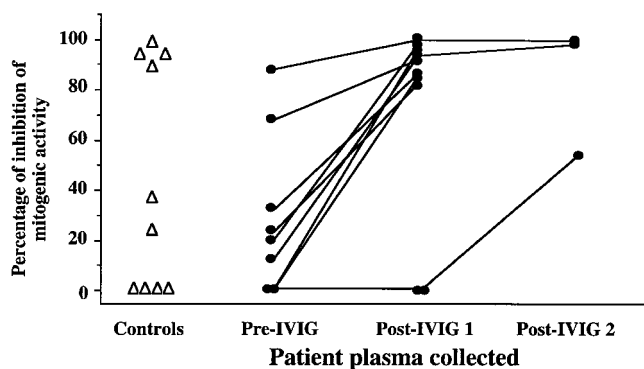
Figure 1. Inhibition of mitogenicity of bacterial culture supernatants by plasma from patients with streptococcal toxic shock syndrome who were treated with (cases, ●) and without (controls, △) intravenous immunoglobulin (IVIG). Supernatants from infecting strains of group A streptococci were used to stimulate peripheral blood mononuclear cells from a healthy individual. Cells were cultured in 10% fetal calf serum in the presence or absence of 1% patient plasma and stimulated with 1% supernatant produced by the infecting group A streptococcus isolate. Post–IVIG 1 = plasma sample obtained within 24 hours of the completion of the first IVIG infusion; post–IVIG 2 = plasma sample obtained within 24 hours after the second IVIG infusion. There was no difference in the mitogen-neutralizing capacity at baseline for cases and controls ($P = .20$, Wilcoxon rank-sum test); however, post–IVIG plasma had significantly greater neutralizing capacity than did pre–IVIG plasma ($P = .004$, Wilcoxon signed-rank test).

ever, that there remains considerable controversy about the importance of various GAS virulence factors and that the small sample size limited our ability to identify and adjust for all the potential confounders.

Because cases were enrolled prospectively and recommendations were made regarding the need for clindamycin therapy and aggressive surgery, cases were more likely to have been treated with both clindamycin and surgery than were controls. Studies with animals have suggested that clindamycin is more active against GAS than several antibiotics, including penicillin, and that it may reduce exotoxin production by inhibiting bacterial protein synthesis [36, 37]. Because all cases but one were also treated with clindamycin, we cannot assess the efficacy of IVIG in the absence of clindamycin or rule out the possibility that clindamycin is a necessary cofactor for the efficacy of IVIG in streptococcal TSS. However, in the subgroup analysis including only patients treated with clindamycin, the estimate of the size of the IVIG effect did not change, suggesting that the improvement in outcome seen for cases was not solely due to the use of clindamycin.

There is considerable evidence that mitogenic streptococcal exotoxins contribute to the pathogenesis of streptococcal TSS and that this contribution may be through their ability to function as superantigens [10, 16, 34, 35, 38–40]. In this study, the ability of patient plasma to inhibit the mitogenicity of the bacterial supernatant was significantly increased after IVIG therapy. These data suggest that IVIG may have inhibited T

cell stimulation and subsequent cytokine release induced by one or more superantigens [41]. It has been shown that different IVIG preparations vary in their ability to inhibit GAS supernatant–induced mitogenicity and that they vary in their ability to induce this activity in postadministration patient plasma [42]. However, the clinical relevance of this observation is not clear at present.

This study adds to data from case reports suggesting that IVIG is associated with improved outcomes for persons with
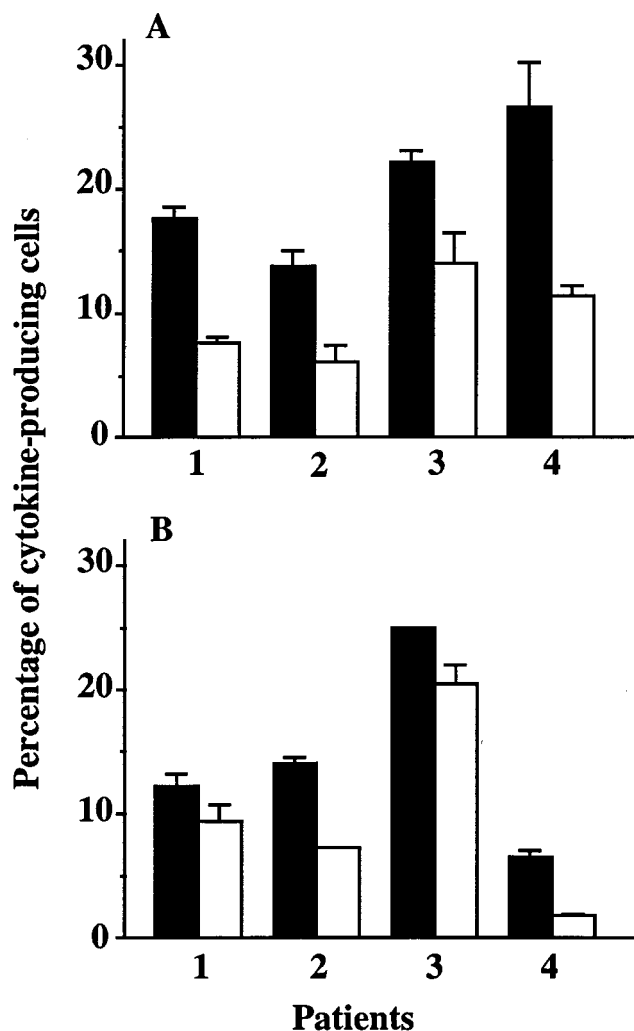

Figure 2. Inhibition of cytokine production in peripheral blood mononuclear cells from patients with streptococcal toxic shock syndrome following intravenous immunoglobulin treatment. Peripheral blood mononuclear cells obtained from the same patient before (■) and after (□) intravenous immunoglobulin treatment were fixed on glass slides and stained with monoclonal antibodies specific to IL-6 (A) and TNF-α (B). Cells displaying dense juxtanuclear staining after application of an avidin-biotin label were visually quantified as the mean percentage of cytokine-producing cells ± SD. IL-6 production was significantly (for each patient, $P < .05$ by the t test) reduced in all four patients; TNF-α production was significantly reduced in patients 2, 3, and 4 ($P < .05$).

streptococcal TSS [11–15] and information from the preantibiotic era that serum therapy improves outcomes for persons with severe scarlet fever and erysipelas [30, 43, 44]. On the basis of the results of our study, we believe that IVIG therapy should be considered for patients for whom streptococcal TSS is diagnosed. It is unlikely that a randomized, controlled trial to test the use of this therapy can be performed. In the absence of such a randomized controlled trial, data from both continued surveillance and laboratory studies of the pathogenesis of streptococcal TSS and the IVIG effect should help to clarify the appropriate indications for IVIG as adjunctive therapy for streptococcal TSS.

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References

1. Hoge CW, Schwartz B, Talkington DF, Breiman RF, MacNeill EM, Englender SJ. The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome. JAMA **1993**;269:384–9.

2. Demers B, Simor AE, Vellend H, et al. Severe invasive group A streptococcal infections in Ontario, Canada: 1987–1991. Clin Infect Dis **1993**; 16:792–800.

3. Davies HD, Matlow A, Scriver SC, et al. Apparent lower rates of streptococcal toxic shock syndrome and lower mortality in children with invasive group A streptococcal infections compared with adults. Pediatr Infect Dis J **1994**;13:49–56.

4. Stevens DL, Tanner MH, Winship J, et al. Reappearance of scarlet fever toxin A among streptococci in the Rocky Mountain west: severe group A streptococcal infections associated with a toxic shock-like syndrome. N Engl J Med **1989**;321:1–7.

5. The Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome: rationale and consensus definition. JAMA **1993**;269:390–1.

6. Davies HD, McGeer A, Schwartz B, et al. Invasive group A streptococcal infections in Ontario, Canada. N Engl J Med **1996**;335:547–54.

7. Kotb M. Bacterial pyrogenic exotoxins as superantigens. Clin Microbiol Rev **1995**;8:411–31.

8. Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains antibodies inhibitory to activation of T-cells by staphylococcal superantigens. J Clin Invest **1993**;91:602–7.

9. Skansen-Saphir U, Andersson J, Bjork L, Andersson U. Lymphokine production induced by streptococcal pyrogenic exotoxin-A is selectively down-regulated by pooled human IgG. Eur J Immunol **1994**;24: 916–22.

10. Norrby-Teglund A, Kaul R, Low DE, et al. Plasma from patients with severe invasive group A streptococcal infections treated with normal polyspecific IgG inhibits streptococcal superantigen-induced T cell proliferation and cytokine production. J Immunol **1996**;156:3057–64.

11. Nadal D, Lauener RP, Braegger CP, et al. T cell activation and cytokine release in streptococcal toxic shock-like syndrome. J Pediatr **1993**;122: 727–9.

12. Barry W, Hudgins L, Donta ST, Pesanti EL. Intravenous immunoglobulin therapy for toxic shock syndrome. JAMA **1992**;267:3315–6.

13. Lamothe F, D'Amico P, Ghosn P, Tremblay C, Braidy J, Patenaude J. Clinical usefulness of intravenous human immunoglobulins in invasive group A streptococcal disease: case report and review. Clin Infect Dis **1995**;21:1469–70.

14. Perez CM, Kubak BM, Cryer HG, Salemugodam S, Vespa P, Farmer D. Adjunctive treatment of streptococcal toxic shock syndrome with intravenous immunoglobulin: case report and review. Am J Med **1997**; 102:111–3.

15. Chiu CH, Ou JT, Chang KS, Lin TY. Successful treatment of severe streptococcal toxic shock with a combination of intravenous immunoglobulin, dexamethasone and antibiotics. Infection **1997**;25:47–8.

16. Norrby-Teglund A, Kaul R, Low DE, et al. Evidence for the presence of streptococcal superantigen-neutralizing antibodies in normal polyspecific immunoglobulin G. Infect Immun **1996**;64:3595–8.

17. McGeer A, Green K, Cann D, et al. Changing epidemiology of invasive group A streptococcal infection: population-based surveillance, Ontario, Canada 1992–95 [abstract 1945]. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1995**:312.

18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med **1985**;13: 818–29.

19. Colton T. Statistics in medicine. Boston: Little, Brown and Company, **1974**.

20. Hastie TJ. Generalized additive models. In: Chambers JM, Hastie TJ, eds. Statistical models in S. Pacific Grove, California: Wadsworth and Brooks/Cole Advanced Books and Software, **1992**:249–304.

21. Cook EF, Goldman L. Performance of tests of significance based on stratification by a multivariate confounder score or by a propensity score. J Clin Epidemiol **1989**;42:317–24.

22. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med **1996**;15:361–87.

23. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med **1997**;127:757–63.

24. Facklam RR, Washington JA. Streptococcus and related catalase-negative gram-positive cocci. In: Balows A, Hausler WJ, Herrmann KL, Isenberg HD, Shadomy HJ, eds. Manual of clinical microbiology. 5th ed. Washington, DC: American Society for Microbiology, **1991**:238–57.

25. Swift HF, Wilson AT, Lancefield RC. Typing group A hemolytic streptococci by M precipitin reactions in capillary pipettes. J Exp Med **1943**; 78:127–33.

26. Griffith F. Serological classification of Streptococcus pyogenes. J Hyg (Lond) **1934**;34:542–84.

27. Musser JM, Gray BM, Schlievert PM, Pichichero ME. Streptococcus pyogenes pharyngitis; characterization of strains by multilocus enzyme genotype, M and T protein serotype, and pyrogenic exotoxin gene probing. J Clin Microbiol **1992**;30:600–3.

28. Norrby-Teglund A, Pauksens K, Holm SE, Norgren M. Relation between low capacity of human sera to inhibit streptococcal mitogens and serious manifestations of disease. J Infect Dis **1994**;170:585–91.

29. Sander B, Andersson J, Andersson U. Assessment of cytokines by immunofluorescence and the paraformaldehyde-saponin procedure. Immunol Rev **1991**;119:65–93.

30. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med **1964**;60:759–76.

31. Hook EW, Horton CA, Schaberg DR. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. JAMA **1983**; 249:1055–7.

32. De Simone C, Delogu G, Corbetta G. Intravenous immunoglobulins in association with antibiotics: a therapeutic trial in septic intensive care unit patients. Crit Care Med **1988**;16:23–6.

33. Berger MM, Marazzi A, Freeman J, Chiolero R. Evaluation of the consistency of Acute Physiology and Chronic Health Evaluation (APACHE II) scoring in a surgical intensive care unit. Crit Care Med **1992**;20:1681–7.

34. Talkington DF, Schwartz B, Black CM, et al. Association of phenotypic and genotypic characteristics of invasive *Streptococcus pyogenes* isolates with clinical components of streptococcal toxic shock syndrome. Infect Immun **1993**;61:3369–74.

35. Holm SE, Norrby A, Bergholm AM, Norgren M. Aspects of pathogenesis of serious group A streptococcal infections in Sweden, 1988–1989. J Infect Dis **1992**;166:31–7.

36. Stevens DL, Gibbons AE, Bergstrom R, Winn V. The Eagle effect revisited: efficacy of clindamycin, erythromycin and penicillin in the treatment of streptococcal myositis. J Infect Dis **1988**;158:23–8.

37. Wannamaker LW, Schlievert PM. Exotoxins of group A streptococci. In: Hardegree MC, Tu AT, eds. Bacterial toxins. New York: Marcel Dekker, **1988**:267–96.

38. Norrby-Teglund A, Norgren M, Holm SE, Andersson U, Andersson J. Similar cytokine induction profiles of a novel streptococcal mitogenic factor, MF, and pyrogenic exotoxins A and B. Infect Immun **1994**;62: 3731–8.

39. Norrby-Teglund A, Newton D, Kotb M, Holm SE, Norgren M. Superantigenic properties of the group A streptococcal exotoxin SpeF (MF). Infect Immun **1994**;62:5227–33.

40. Watanabe-Ohnishi R, Low DE, McGeer A, et al. Selective depletion of Vβ-bearing T-cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. J Infect Dis **1995**;171:74–84.

41. Aukrust P, Hestdal K, Lien E, et al. Effects of intravenous immunoglobulin in vivo on abnormally increased tumour necrosis factor-α activity in human immunodeficiency virus type 1 infection. J Infect Dis **1997**;176: 913–23.

42. Norrby-Teglund A, Basma H, Andersson J, McGeer A, Low DE, Kotb M. Varying titers of neutralizing antibodies to streptococcal superantigens in different preparations of normal polyspecific immunoglobulin G: implications for therapeutic efficacy. Clin Infect Dis **1998**;26: 631–8.

43. Symmers D, Lewis KM. The antitoxin treatment of erysipelas: further observations. JAMA **1932**;99:1082–3.

44. Lucchesi PF, Bowman JE. Antitoxin vs no antitoxin in scarlet fever. JAMA **1934**;103:1049–51.