Clinical Efficacy of Polyspecific Intravenous Immunoglobulin Therapy in Patients With Streptococcal Toxic Shock Syndrome: A Comparative Observational Study

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Background. Streptococcal toxic shock syndrome (STSS) and necrotizing fasciitis are the 2 most severe invasive manifestations caused by group A Streptococcus (GAS). Intravenous immunoglobulin (IVIG) therapy has been suggested as adjunctive treatment with a beneficial effect on mortality. However, the clinical evidence is limited. Here we aim to further document the clinical efficacy of administered IVIG therapy in a comparative observational study of well-defined patients with STSS.

Methods. The effect of IVIG was evaluated in patients with STSS prospectively identified in a nationwide Swedish surveillance study conducted between April 2002 and December 2004. Detailed data on symptoms, severity of disease, treatment, and outcome were obtained from 67 patients. Crude and adjusted analyses with logistic regression were performed.

Results. Twenty-three patients received IVIG therapy compared with 44 who did not. No significant difference in comorbidities, severity of disease, organ failures, or sex was seen, but the IVIG group was slightly younger and had a higher degree of necrotizing fasciitis (56% vs 14%). The primary endpoint was 28-day survival. Adjusted analysis revealed that factors influencing survival in STSS were Simplified Acute Physiology Score II (odds ratio [OR], 1.1; \( P = .007 \)), clindamycin (OR, 8.6; \( P = .007 \)), and IVIG (OR, 5.6; \( P = .030 \)).

Conclusions. This comparative observational study of prospectively identified STSS patients demonstrates that both IVIG and clindamycin therapy contribute to a significantly improved survival in STSS.

Keywords. clindamycin; necrotizing fasciitis; polyspecific intravenous immunoglobulin; Streptococcus pyogenes; streptococcal toxic shock syndrome.

Group A Streptococcus (GAS), or Streptococcus pyogenes, is a pathogen causing a wide array of infections in humans, ranging from mild upper respiratory tract infections and skin infections to severe invasive infections such as bacteremia, pneumonia, necrotizing fasciitis (NF), and streptococcal toxic shock syndrome (STSS). It is estimated to be among the 10 most common causes of death due to an individual pathogen globally [1]. Although antimicrobial resistance is low among GAS strains and all strains are susceptible to penicillin, the severe invasive GAS infections, such as STSS and NF, are associated with a high mortality rate exceeding 40%–50% [2–4].

A prominent feature of severe invasive GAS infections is the massive inflammatory response that contributes to systemic toxicity as well as tissue pathology [5, 6]. Main mediators of these responses are the streptococcal superantigens [7, 8] as well as the surface-attached M protein [9, 10]. Importantly, the outcome

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of infection is also influenced by host factors—both genetic factors, such as human leukocyte antigen class II types that determine the magnitude of superantigen-induced responses [11, 12] and a lack of protective antibodies against M protein and superantigens [13, 14]. In light of this, polyclonal intravenous immunoglobulin (IVIG) was suggested as a potentially beneficial adjunctive therapy [6]. There are robust mechanistic data of the effect of IVIG in this setting, including opsonization and improved phagocytic killing, direct toxin neutralization (both superantigens and M-protein), and general anti-inflammatory effects mediated through Fc-receptor interaction or through soluble immune components [15–17]. Clinical data are more limited. In sepsis overall, results of clinical trials on IVIG as adjunctive therapy have been conflicting, and the usage of IVIG is still controversial. In the latest Cochrane review [18], the authors concluded that although IVIG reduced mortality among adults with sepsis, this benefit was not seen in trials with low risk of bias. However in the subgroup of STSS, studies including an observational cohort study as well as a small, prematurely terminated, placebo-controlled trial, have reported decreased mortality rates in patients treated with IVIG [19, 20]. These reports, together with the detailed mechanistic action where superantigen neutralization and dampening of the hyperinflammatory state are prominent features, support the use of IVIG as adjunctive therapy in STSS. Nevertheless, the level of clinical evidence is low and there has been a debated retrospective study of IVIG in pediatric STSS that did not demonstrate an effect [21, 22]. To this end, we conducted a comparative observational study of adjunctive IVIG therapy in well-defined STSS patients identified in a nationwide prospective surveillance study. In addition, subgroup analysis of the presence of NF was performed, as in this patient group only anecdotal data on IVIG therapy are available [23], and an experimental murine study indicated limited effect [24]. The impact of other factors expected to contribute to improved survival, such as clindamycin [25] and surgery [26], were also analyzed.

MATERIALS AND METHODS

Patient Material and Study Protocol

This study is based on 75 patients with STSS identified through a national Swedish prospective surveillance study conducted between 23 April 2002 and 31 December 2004, in which a total of 746 cases of invasive GAS infections were identified based on reports from all 29 Swedish microbiological laboratories to the Swedish Institute for Communicable Disease Control (now the Public Health Agency of Sweden) [27]. The isolates were collected and characterized by T-typing, emm-typing, and superantigen gene profile [27]. Attending physicians were asked to complete a questionnaire regarding clinical information about the patients; diagnosis including, among others, presence of STSS and NF; treatment; and outcome. STSS was defined as isolation of GAS from a normally sterile site or from a nonsterile site, hypotension (blood pressure ≤90 mm Hg), and ≥2 of the following signs: renal impairment, coagulopathy, liver involvement, acute respiratory distress syndrome, erythematous rash, or soft tissue necrosis, in accordance with the definition proposed by the Working Group on Severe Streptococcal Infections [28].

For the 75 STSS patients identified, new questionnaires were sent out to the physicians asking for more detailed information regarding severity of disease, manifestation, underlying condition, and treatment strategies including antibiotics, IVIG, and surgery. The severity of disease was defined using the Simplified Acute Physiology Score II (SAPS II) [29]. The patient charts and journals were well documented throughout their hospital stay in the intensive care unit as well as in the common wards, and thus the requested information was readily available for the majority of patients. Sixty-nine questionnaires were returned properly filled out. Two patients were excluded for not fulfilling the STSS criteria, leaving 67 patients for further analysis (Figure 1).

Consent from patients or their legal guardians were obtained for collection and retraction of detailed clinical data. The study was approved by the ethical committee at Karolinska Institutet (Stockholm, Sweden).

Study Endpoint, Analytical Plan, and Statistical Analysis

Primary study endpoint was 28-day survival. The potential predictors (IVIG, SAPS II, clindamycin therapy, and surgery), expected to affect survival and outcome of the study [25, 26, 29–32], were first analyzed by simple logistic regression (crude results). These variables were then analyzed in a multiple logistic regression model (adjusted results), which was finally

![Figure 1](https://academic.oup.com/cid/article-abstract/59/6/851/2895714/2895714)
RESULTS

Clinical and Microbiological Characteristics
In a prospective surveillance study of invasive GAS infections reported by Darenberg et al [27], 75 STSS cases were identified for which additional clinical and therapeutic information was collected in this study (Figure 1). Among the 67 patients eligible for this study, that is, those who had completed questionnaires and fulfilling STSS definition criteria, 23 (34%) patients had received adjunctive IVIG therapy, whereas 44 (66%) had not. Comparison of baseline characteristics of the IVIG-treated vs non-IVIG-treated groups revealed that they were well matched with respect to sex, SAPS II scores, organ failure, presence of acute respiratory distress syndrome, underlying conditions, and microbiological characteristics (ie, emm types or presence of specific superantigen genes) (Table 1). However, the groups differed in age with median ages of 60 and 65 years in the IVIG and non-IVIG groups, respectively. Although a soft tissue focus of infection was common in both groups, there was a significant difference in the severity of tissue manifestations, with NF being significantly more common in the IVIG group, whereas erysipelas was more prevalent in the non-IVIG group (Table 1).

Antibiotic Treatment and Surgery
All patients, except one, received a β-lactam antibiotic, most commonly penicillin, and most received this in combination with clindamycin (78%). There was a difference, although not statistically significant, in clindamycin therapy in the 2 groups, with clindamycin administered in 91% of the IVIG group vs 70% in the non-IVIG group (Table 1). Data on time to adequate antibiotics were available in 42 (63%) of the patients. Median time was 1.3 hours (range, 0.1–4.2) with no difference between the groups, which indicates that most patients received antibiotic treatment against GAS quite promptly. The IVIG group was significantly more likely to have had surgery than the non-IVIG group (Table 1), which was expected as this group had a more frequent diagnosis of NF, for which surgery is the recommended therapeutic strategy. Among the patients diagnosed with necrotizing fasciitis, 17 of 19 had surgery, the extent of which ranged from explorative (n = 6), to debridement (n = 5) or amputation (n = 6). Only 2 patients received plasmapheresis, and none were administered recombinant activated protein C.

IVIG Treatment
Most of the patients were initiated on IVIG therapy during the first day of onset of illness. The dosage of IVIG was 0.5 g/kg in all except 1 patient who received 1.0 g/kg, during days 1–6 (8 cases for 1 day, 5 cases for 2 days, 2 cases for 3 days, 4 cases for 4 days, 3 cases for 5 days, and 1 case for 6 days). Only 1 patient had a possible adverse reaction consisting of a general rash.

Study Endpoints
Among the 67 STSS patients, 25 died; 3 cases in the IVIG group and 22 in the non-IVIG group. Thus, there was a significant difference in outcome between the 2 groups, favoring the IVIG group with a 28-day survival of 87% vs 50% for the non-IVIG group (P < .01). This difference was seen already after 7 days, where corresponding figures were 91% and 59% (P < .001), respectively. This resulted in an improved survival in the crude analysis with an odds ratio (OR) of 6.7 (95% confidence interval [CI], 1.7–25.7) (Table 2). When the subgroups with and without NF were analyzed separately, differences of the same magnitude were found (Table 3). Although not reaching statistical significance, this result indicates a similar effect in patients with NF as in those without. The crude results showed as expected that SAPS II, clindamycin treatment, and surgery all had significant effects on survival in STSS (Table 2). Surgery demonstrated the lowest P value and was not close to significance in the adjusted model; therefore, it was subsequently discarded in the final analysis. In addition, surgery was strongly correlated with both clindamycin and IVIG therapy, indicating multicollinearity. In the final adjusted model, SAPS II (OR, 1.1; P = .007) and clindamycin (OR, 8.6; P = .007) precipitated as significant factors for survival (Table 2). In this analysis, IVIG demonstrated a significant effect on survival with an OR of 5.6 (95% CI, 1.2–26.9; P = .03). Because there was only 1 patient who was not treated with clindamycin among the NF patients and the SAPS II scores did not differ between IVIG and non-IVIG patients with and without NF, adjusted subgroup analysis did not give any further information.

There was an unexpected significant difference in age (Table 1). Therefore, a post hoc analysis was performed that analyzed the influence of age on the effect of IVIG using the age of 80 as a cutoff. This cutoff was chosen as patients in this age group receive the highest score in the age parameters of SAPS II and are associated with a peak in incidence of invasive GAS infections, indicating an increased susceptibility in this group.
Table 1. Clinical and Treatment Characteristics of 67 Patients With Streptococcal Toxic Shock Syndrome Treated or Not Treated With Intravenous Immunoglobulin Therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IVIG (n = 23)</th>
<th>Non-IVIG (n = 44)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, median (range)</strong></td>
<td>60 (31–87)</td>
<td>65 (32–92)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Sex, male, No. (%)</strong></td>
<td>8 (34.8)</td>
<td>20 (45.5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SAPS II score</strong>, median (range)</td>
<td>43 (21–71)</td>
<td>48 (24–84)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Organ failures, median (range)</strong></td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>ARDS, No. (%)</strong></td>
<td>9 (39.1)</td>
<td>13 (29.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Manifestations**, No. (%)

- Soft tissue: 16 (69.6) vs. 27 (61.4), NS
- Necrotizing fasciitis: 13 (56.5) vs. 6 (13.6), <.001
- Erysipelas: 1 (4.3) vs. 15 (34.1), <.01
- Cellulitis: 2 (8.7) vs. 6 (13.6), NS
- Tonsillitis: 1 (4.3) vs. 1 (2.3), NS
- Puerperal: 1 (4.3) vs. 0 (0), NS
- Pneumonia: 1 (4.3) vs. 9 (20.5), NS
- Meningitis: 1 (4.3) vs. 1 (2.3), NS
- STSS without focus: 6 (26.1) vs. 10 (22.7), NS

**Underlying conditions**, No. (%)

- Previous healthy: 9 (39.1) vs. 7 (15.9), NS
- Alcohol: 1 (4.3) vs. 6 (13.6), NS
- Drug: 1 (4.3) vs. 0 (0), NS
- Cardiovascular disease: 10 (43.3) vs. 22 (50.0), NS
- Lung: 2 (8.7) vs. 10 (22.7), NS
- Liver: 1 (4.3) vs. 4 (9.1), NS
- Blood disease: 0 (0) vs. 4 (9.1), NS
- Kidney: 0 (0) vs. 5 (11.4), NS
- Diabetes: 2 (8.7) vs. 9 (20.5), NS
- Skin disease: 4 (17.4) vs. 13 (29.5), NS
- Malignancy: 0 (0) vs. 5 (11.4), NS
- Autoimmune disease: 1 (0) vs. 5 (11.4), NS
- Immunosuppressive treatment: 2 (8.7) vs. 6 (13.6), NS

**Major emm types**, No. (%)

- emm1: 8 (34.8) vs. 11 (25.0), NS
- emm89: 4 (17.4) vs. 5 (11.4), NS
- emm81: 1 (4.3) vs. 7 (15.9), NS
- emm28: 3 (13.0) vs. 4 (9.1), NS
- Other: 7 (30.4) vs. 17 (38.6), NS

**No. (%) with toxin gene**

- speA: 6 (26.1) vs. 7 (15.9), NS
- speC: 12 (52.7) vs. 21 (47.7), NS
- speA plus speC: 2 (8.7) vs. 3 (6.8), NS
- Clindamycin treatment, No. (%): 21 (91.3) vs. 31 (70.5), NS
- Surgery, No. (%): 16 (69.6) vs. 11 (25.0), <.001
- Hospital stay, d, median (range): 28 (9–102) vs. 24 (6–155), NS

Abbreviations: ARDS, acute respiratory distress syndrome; IVIG, intravenous immunoglobulin; NS, not significant; SAPS, Simplified Acute Physiology Score; STSS, streptococcal toxic shock syndrome.

a SAPS score missing for 1 IVIG patient and 3 non-IVIG patients.
b Some patients may have several manifestations, but only 1 of the soft tissue involvements.
d Based on data from the 20 and 22 survivors in the IVIG or non-IVIG groups, respectively.
Table 2. Predictors Expected to Influence Survival in Streptococcal Toxic Shock Syndrome Patients: Crude and Adjusted Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude Logistic Regression (Crude Results)</th>
<th>Adjusted Logistic Regression (Adjusted Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>SAPS</td>
<td>1.05 (1.0–1.1)</td>
<td>1.10 (1.0–1.1)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>7.5 (2.0–27.3)</td>
<td>8.6 (1.8–40.4)</td>
</tr>
<tr>
<td>IVIG</td>
<td>6.7 (1.7–25.7)</td>
<td>5.6 (1.2–26.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4.4 (1.4–13.9)</td>
<td>.012</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IVIG, intravenous immunoglobulin; OR, odds ratio; SAPS, Simplified Acute Physiology Score.

* The adjusted model was validated with Hosmer-Lemeshow test (2.729, P = .95). Surgery was deleted from the adjusted model in accordance with the analytical plan (see statistics in the Methods).

[33]. The analysis demonstrated that IVIG significantly improved survival in patients aged <80 years (Table 4). Eleven patients in the STSS cohort were aged ≥80 years. Although no significant effect was observed, data suggest improved survival by IVIG also among these patients, as the 2 patients given IVIG both survived, in comparison to only 2 of the 9 patients that did not receive IVIG.

DISCUSSION

Invasive GAS disease, and STSS in particular, are conditions associated with significant morbidity and mortality despite adequate antibiotic treatment. IVIG has been suggested as adjunctive therapy contributing to improved survival [19, 20], but these studies are small and associated with confounding factors. As shown by Valiquette et al [34], there is a substantial variability between physicians in the use of IVIG for STSS, which demonstrates the need for further clinical data on this topic. In this study, we demonstrate a significant reduction in mortality in patients treated with IVIG as adjunctive therapy in STSS. The 28-day survival was as high as 87% in the IVIG-treated group compared with 50% in the nontreated group. The latter is in line with previously reported mortality rates in STSS [2–4]. The survival rates are also comparable to those reported in the prematurely ended multicenter placebo-controlled trial with IVIG (90% vs 64% survival in the IVIG vs placebo groups, respectively) [20]. The study is an observational study with a similar design as that by Kaul et al [19]. However, whereas Kaul et al used largely historical controls, our study uses a prospectively identified STSS cohort including both treated and nontreated cases. Another study that has addressed the efficacy of IVIG in STSS is a retrospective study on a pediatric patient cohort [21]. This report concluded that IVIG had no effect on survival as the mortality was 4.5% in both the IVIG and non-IVIG groups. However, several major concerns have been raised regarding this study [22]. Most important, it was markedly underpowered considering the low mortality rate and the inclusion criteria used did not follow conventional STSS definition criteria, and were therefore likely to result in inclusion of patients with a milder disease, as also evidenced by the low mortality rate [22].

In the present study, clinical and demographic characteristics were similar between the IVIG and non-IVIG groups, with the exception that patients in the IVIG group were slightly younger and more often affected by NF and, consequently, more often received surgery. It seems likely that the presence of a clinically identifiable NF might lead to a more rapid diagnosis of potential STSS for which aggressive therapy such as IVIG is proposed, thereby resulting in this skewness between the cohorts. Considering the severity of NF, addition of this complicating factor should reasonably influence the outcome negatively, making our results on survival even more impressive. It was further expected that the presence of NF might also skew the use of surgery and treatment with clindamycin. Because surgery and treatment with clindamycin might both affect survival and be imbalanced between the cohorts, the analytic plan included

Table 3. Simple Logistic Regression of Factors Expected to Influence Survival in Streptococcal Toxic Shock Syndrome Patients With or Without Necrotizing Fasciitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>NF Patients (n = 19)</th>
<th>Non-NF Patients (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>SAPS</td>
<td>1.0 (1.0–1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>IVIG</td>
<td>6.0 (4.9–85.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery</td>
<td>7.5 (3.3–173.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IVIG, intravenous immunoglobulin; NA, not applicable; NF, necrotizing fasciitis; NS, not significant; OR, odds ratio; SAPS, Simplified Acute Physiology Score.

* Only 1 patient who died was not treated with clindamycin.

Table 4. Post Hoc Analysis of the Effect of Intravenous Immunoglobulin on Survival in Streptococcal Toxic Shock Syndrome Patients, by Age

<table>
<thead>
<tr>
<th></th>
<th>Age &lt;80 y</th>
<th>Age &gt;80 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>Non-IVIG</td>
<td>P Value</td>
</tr>
<tr>
<td>Survival</td>
<td>18 (85.7)</td>
<td>20 (57.1)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%). Abbreviations: IVIG, intravenous immunoglobulin; NS, not significant.
simple as well as multiple regression analyses of their effects on survival. Furthermore, because severity of disease as classified by SAPS II is a strong factor affecting outcome in critically ill patients [29, 32], even smaller differences between the groups not reaching statistical significance might affect the outcome. Therefore, SAPS II was also included in the analytical plan as a possible confounding factor. As expected, clindamycin, surgery, and SAPS II were all significant factors for survival in the crude analysis. However, only clindamycin, SAPS II, and IVIG treatment had a significant effect in the adjusted analysis. Thus, even when the differences between groups in clindamycin treatment, surgery, and SAPS II score were taken into account, treatment with IVIG had a demonstrable and significant beneficial effect. The ability of immunoglobulin to penetrate into necrotic tissue might be limited, and an experimental murine study failed to demonstrate an effect on the course of NF [24]. From this, it could be speculated that STSS might be further fueled by the presence of NF, and treatment with IVIG might have less effect. However, the result from this study does not support this theory and IVIG seemed to have a similar effect in patients with or without NF.

It should be noted that updated treatment recommendations including IVIG as adjunctive therapy in STSS was published by the Medical Products Agency in Sweden in the later period of the study (ie, February 2004). The percentage of IVIG therapy in the patient group increased from 27% to 56% in the period following the recommendation. This reflects the fact that in Sweden, even with a recommendation in place, IVIG is not routinely used and it cannot be excluded that younger, previously healthy individuals with a complicated manifestation (eg, STSS in combination with NF), might be more likely to receive IVIG. However, in the post hoc analysis, the oldest patients with the highest mortality seemed to benefit from IVIG, which was also the case for the younger patients.

A secondary major finding in this study was the significant effect on survival noted for the combination treatment with addition of clindamycin to penicillin (adjusted OR, 8.6). Ever since the report by Stevens et al [35], the recommended antibiotic regimen has been penicillin in combination with the protein synthesis inhibitor clindamycin. However, the clinical data to support this are fairly scarce and include 2 reports showing a beneficial effect, particularly in those with NF/deep tissue infections caused by GAS [25, 30], as well as a recent study of Carapetis et al [36]. The latter study reports on 84 cases of severe invasive GAS infections identified through a population-based, prospective, active surveillance of invasive GAS infections in Australia. The data revealed that clindamycin-treated patients had more severe disease than clindamycin-untreated patients but significantly lower mortality rates. Analyses of subsets of STSS, NF, or both had a minimal impact on the results. Similarly, in our subgroup analyses of STSS patients without NF, clindamycin remained significantly associated with improved survival (OR, 4.6; P = .028). This analysis could, however, not be conducted in the subgroup of STSS patients with NF, as the group included only 1 patient not treated with clindamycin. This patient died in comparison with 2 of 18 treated with clindamycin.

The present study has several limitations. First and most important, the number of patients is small. Although being the largest study to include prospectively identified STSS patients, the limited number of patients makes analysis of data more difficult and uncertain. In addition, there were, as discussed above, differences between the cohorts, and data for the extended questionnaire were collected up to 10 years after the patients had been identified. However, the patient medical records and journals were well documented, and all requested information was easily identifiable, which limits the potential impact of the latter point.

In conclusion, the results of this study provide evidence for IVIG as a safe adjunctive therapy that contributes to increased survival in STSS. In STSS, as in all rare diseases, large randomized clinical trials are most difficult to achieve, and therefore, we need to rely on comparative observational data such as those presented in this study. Taken together with the high morbidity and mortality of these infections as well as a detailed mechanistic action of IVIG, our results strongly suggest that clinicians ought to consider the use of IVIG in the treatment of STSS. In addition, this study gives further clinical support for combination therapy with penicillin and clindamycin.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


