EDITORIAL COMMENTARY

Assessing the Impact of Intravenous Immunoglobulin in the Management of Streptococcal Toxic Shock Syndrome: A Noble but Difficult Quest

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(See the article by Shah et al, on pages 1369–76.)

The annual incidence of invasive group A streptococcal disease in the developed world has been stable for at least 2 decades at 2.0–4.0 cases per 100,000 persons per year [1–3]. Streptococcal toxic shock syndrome (TSS) and necrotizing fasciitis are among the most severe manifestations of invasive group A streptococcal infection, with case-fatality rates of 30%-70% in adult patients with streptococcal TSS [2, 4–6]. Fortunately, these syndromes and their severe complications are rare in pediatric populations. In a recent study of 10 sites in the United States, covering a population of 29.7 million persons, 572 patients aged <10 years had invasive group A streptococcal infection [2]. Of these, only 5 (0.9%) developed necrotizing fasciitis and only 26 (4.6%) developed streptococcal TSS, and the case-fatality rate in patients with streptococcal TSS was 7.2%.

Only 2 prior publications have attempted to assess the efficacy of intravenous immunoglobulin (IVIG) in the treatment of streptococcal TSS. Both the underpowered trial performed by Darenberg et al in 2003 [4] and the case-cohort study by Kaul et al published in 1999 [5] excluded children from their analysis because of ethical considerations and lower mortality rates in this subgroup. In this edition of Clinical Infectious Diseases, Shah and colleagues reactivate this controversial topic in a pediatric cohort [6].

This attempt is appealing because pediatric data regarding the use of IVIG in streptococcal TSS are limited to a handful of case reports [7–12]. Consequently, the American Academy of Pediatrics Committee on Infectious Disease recommendation for IVIG in streptococcal TSS management is based on the adult literature cited herein. The committee recommends that IVIG be considered for streptococcal TSS that is refractory to several hours of aggressive therapy or in the presence of an undrainable focus or persistent oliguria with pulmonary edema [13].

The relatively low mortality rates among children with streptococcal TSS mean that demonstrating a reduction in mortality is a difficult challenge. Even in adults, for whom the case-fatality rate is higher, a randomized controlled trial of IVIG versus placebo would need to include at least 140 patients (70 per arm) to detect and label as statistically significant a decrease in the mortality rates from 60% to 40% [14]. A total of 1102 children would be needed to show the same relative reduction in mortality rates—from 10% to 6.7%. Although mortality is clearly the preferable primary outcome for retrospective analyses such as this study, the study was, a priori, underpowered to detect a difference. Consequently, one of the most important challenges in this study, which is unmet by the authors, was to select a significant outcome to replace all-cause mortality. The authors selected total hospital cost, hospital length of stay, intensive care unit length of stay, and specific subcategories of hospital cost as alternative outcomes. Hospital cost (total or subdivided) is a suboptimal choice in the context of such a severe syndrome in a cohort of very young patients because it does not take into account saved productivity years or the impact on society of long-term disability. Length of stay is somewhat more interesting because it gives an indication of recovery time and burden of the disease in patients with streptococcal TSS. However, it is easily influenced by variability in physician practice, hospital policies, and ambulatory care infrastructure. Outcomes that would have been more valid are or-
gan dysfunction, need for surgery, and need for vasopressors; however, these outcomes may be difficult to measure reliably in studies that rely on administrative databases.

Requirement for surgery would have been particularly interesting, given the descriptive data on the surgery-sparing potential of IVIG in patients with streptococcal necrotizing fasciitis [15]. In a small case series, aggressive medical therapy was administered with either no surgery or exploration alone. All included patients fared well [15]. These data are in contrast to those from a large retrospective cohort [16], which suggested an important role for surgery in patients with streptococcal TSS and necrotizing fasciitis. Further information on the impact of IVIG therapy in necrotizing fasciitis would be welcome but difficult to obtain.

In recent years, the use of propensity scores in clinical research has increased significantly [17]. Confounding by indication is often the main challenge to validity in pharmacoepidemiology. The propensity score focuses directly on the indications for use and nonuse of the drug under study. This study is a typical example where propensity score analysis is likely to be helpful, with a small number of outcomes (only 8 patients died from streptococcal TSS) and a desire to evaluate a common treatment (more than one-half of the cohort received IVIG). When a limited number of outcomes occur relative to the number of independent variables, both overfitting and underfitting become significant concerns in logistic regression models; regression coefficients for individual variables may then represent spurious associations, effects may be estimated with low precision, and important variables may be omitted from the model [18]. A matched propensity score analysis offers an improved option to adjust for potential confounders [17, 19]. Nonetheless, in some circumstances, even this type of analysis may be confounded and result in inaccurate estimates of the true effect [20]. The persisting difference in the number of measurements of arterial blood gases in patients in whom IVIG was administered in this study suggests that patients who received IVIG had significantly more severe disease than those who did not receive IVIG, which may not have been completely compensated for, even in careful multivariate analysis.

Some data that are not presented would have assisted an informed interpretation of this study. These data include administered IVIG dose, timing of administration, IVIG adverse effects, source of infection, proportion of patients with necrotizing fasciitis, proportion of patients undergoing surgical procedures, severity scores [21, 22], and specific streptococcal TSS criteria used. Severity assessment and streptococcal TSS criteria are particularly important; there is a significant difference between patients with short duration hypotension with good response to fluid and a rash and patients with refractory hypotension, severe acute respiratory diseases, and extensive tissue necrosis. The low crude mortality rate reported in this analysis might be explained by the inclusion of a substantial number of patients with relatively mild disease.

In conclusion, although this analysis may shake physicians’ faith in the efficacy of IVIG for routine management of streptococcal TSS in children, it must be remembered that the authors’ conclusion is based on the overall low mortality rate in untreated patients more than on the identification of lack of efficacy of IVIG in reducing mortality and morbidity. In addition, the most sophisticated analyses cannot replace the ability to clearly define inclusion criteria and adequate sample sizes. Thus, the difficult question of whether IVIG is of benefit for adults with streptococcal TSS or for children who meet the American Academy of Pediatrics Committee on Infectious Disease criteria for IVIG use in children with streptococcal TSS remains unresolved.

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References


