Editorial Response: Rationale for the Use of Intravenous Gamma Globulin in the Treatment of Streptococcal Toxic Shock Syndrome

Since the 1980s there has been a marked increase in the recognition and reporting of highly invasive group A streptococcal infections, with or without necrotizing fascitis, associated with shock and organ failure [1]. Such dramatic cases have been defined as streptococcal toxic shock syndrome (Strep TSS) [2]. Associated mortality rates have been reported to be between 30% and 70%, and those who survive often require extensive surgical debridement, including amputations, and a prolonged hospital stay for ventilatory support, hemodialysis, and reconstructive surgery. We must diligently seek better therapeutic modalities.

It is my sense that mortality rates associated with Strep TSS in 1997 may be less than those recorded nearly 10 years ago. If this is true, it is likely due to several factors. First, there is earlier recognition by both the patient and the physician, a fact that is largely attributed to heightened media attention and to the publication of several hundred clinical reports. Second, the increased use of protein synthesis inhibitors, such as clindamycin, in this setting may also have reduced the severity of infection by suppressing bacterial toxin synthesis and/or by modulating the host immune response [3].

In fact, it is clear that the extent of clinical disease is the consequence of the encounter of the human immune system with the numerous virulence factors of these invasive streptococci, although the exact contribution of each virulence factor to the pathogenesis of Strep TSS remains unclear. It has been hypothesized, however, that only those individuals who lack neutralizing antibody against the major streptococcal virulence factors, such as the pyrogenic exotoxins and M-protein, develop invasive infections such as bacteremia and Strep TSS [4]. Supporting this concept are the studies by Holm that demonstrated that patients with bacteremia and Strep TSS did indeed lack antibodies against streptococcal pyrogenic exotoxin (Spe) B [5]. Furthermore, Norrby-Teglund et al. found that sera from patients with group A streptococcal bacteremia had lower titers of neutralizing antibodies against SpeB and SpeF than did patients with tonsillitis [6]. These authors also found that acute sera from patients with postpartum sepsis contained elevated levels of antibodies against pyrogenic exotoxins but that these antibodies were nonneutralizing [6].

Extending this hypothesis, one might ask, “Can passive immunization with antitoxins improve the outcome for patients with established group A streptococcal infections?” There is some clinical precedent for this. In the 1920s, George and Gladys Dick demonstrated that convalescent serum from patients with scarlet fever attenuated, and in some cases prevented, severe scarlet fever [7], suggesting the presence of neutralizing antibodies to the scarlatina toxin (pyrogenic exotoxins). Because these pyrogenic exotoxins likely contribute to Strep TSS by virtue of their ability to stimulate production of both potent monokines [8–11] and lymphokines [9, 11–13], it is logical to believe that convalescent serum from patients with severe streptococcal infection may also have beneficial therapeutic effects in patients with active Strep TSS.

Thus, a second question arises: “Does pooled human gamma globulin contain neutralizing antibodies against the streptococcal pyrogenic exotoxins?” Dr. Norrby-Teglund has studied this in detail [5, 14, 15], and the most current results are reported in this journal. It is interesting that there was great variation in the neutralizing activity of different brands and batches of immunoglobulin preparation. Pyrogenic exotoxin A–induced mitogenic activity was the most difficult to neutralize for all the brands of immunoglobulin tested. In a different study, Skansen-Saphir et al. demonstrated that pooled human IgG demonstrated marked suppression of lymphocyte blastogenesis and strongly inhibited TNF-β and IFN-γ production by mononuclear cells from normal donors [16].

One must keep in mind that there may also be a nonspecific inhibition of monokine production, since intravenous immunoglobulin (IVIG) suppressed TNF production by monocytes stimulated in vitro with lipopolysaccharide [17] and by splenocytes from animals with adjuvant-induced arthritis [18]. The mechanism of nonspecific inhibition of the immune system by IVIG is largely unexplained although inhibition of uptake of C3 fragments by target cells has been demonstrated [19]. In addition, Leung et al. demonstrated that IVIG inhibited the release of IL-1 from monocytes from patients with Kawasaki syndrome [20]. Other possibilities include an IVIG-mediated Fc receptor blockade of reticuloendothelial cells and monocytes and an IVIG modulation of Fc receptor expression or affinity [21]. Finally, it is possible that IVIG somehow inhibits the interaction of superantigen, T-cell receptor, and major histocompatibility complex class II molecules by means other than toxin inhibition.

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Nonetheless, in light of the above findings by Norrby-Teglund et al. and Skansen-Saphir et al., there is reason to ask, ‘‘Does infusion of IVIG preparations improve the clinical outcome for patients with Strep TSS?’’ Two case reports have been published that describe two patients who dramatically improved following administration of IVIG [22, 23]. In another series, four patients received either intramuscular or intravenous gamma globulin preparations and seven others received fresh frozen plasma [24]. In a larger series, IVIG adjunctive therapy for Strep TSS was associated with a reduction in mortality (from 67% to 34%) [25], compared with that for case controls. None of these studies was performed as a randomized clinical trial.

What are the potential negative aspects of IVIG therapy in patients with Strep TSS? First is cost, although this is likely a small consideration if the treatment improves outcome and shortens hospital stay. Second, many side effects following IVIG administration have been described, ranging from anaphylaxis to maculopapular eruptions, although these are likely most common in patients with immunoglobulin deficiencies.

What is the optimal therapeutic regimen of IVIG? Results of the present study suggest that one dose may not be sufficient to neutralize all the potential pyrogenic exotoxins, but this can vary greatly among different batches and different manufacturers. If IVIG is to be given, it should be given as soon as Strep TSS is recognized or suspected and well before exotoxins have induced sufficient cytokines to result in shock and organ failure. However, even later in the course, IVIG could be useful to prevent further activation of lymphocytes and monocytes.

In summary, there is ample basic science information and a modest amount of positive, albeit nonrandomized data from IVIG administration have been described, ranging from anaphylaxis to maculopapular eruptions, although these are likely most common in patients with immunoglobulin deficiencies.

References


