Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach

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Abstract
Intravenous polyspecific immunoglobulin G (IVIG) has been reported to be efficacious as adjunctive therapy in patients with toxic shock syndrome caused by group A streptococci (GAS). GAS is also an important cause of necrotizing fasciitis, for which an early and extensive surgical intervention is currently advocated. Here we report on the use of an aggressive medical regimen including high-dose IVIG together with a conservative surgical approach in severe GAS soft tissue infection. We describe 7 patients with severe soft tissue infection caused by GAS, who all were treated with effective antimicrobials and high-dose IVIG. Surgery was either not performed or only limited exploration was carried out. Six of the patients had toxic shock syndrome. All patients survived. Immunostaining of tissue biopsies from 2 of the patients revealed high levels of GAS, superantigen and pro-inflammatory cytokines initially, which were dramatically reduced in a repeat biopsy of the initial operative site collected from 1 of the patients 66 h post-IVIG administration. The study suggests that the use of a medical regimen including IVIG in patients with severe GAS soft tissue infections may allow an initial non-operative or minimally invasive approach, which can limit the need to perform immediate wide debridements and amputations in unstable patients.

Introduction
Streptococcal toxic shock syndrome and necrotizing fasciitis caused by group A streptococci are rapidly progressive invasive diseases that are associated with significant morbidity and mortality [1,2]. Group A streptococci secrete several exotoxins with superantigenic activity that are thought to play a major role in the pathogenesis of these infections [3–6]. Superantigens circumvent the normal rules of antigen processing and presentation, resulting in potent activation of T-cells and antigen presenting cells and consequently excessive production of pro-inflammatory cytokines [7]. Another important pathogenic mechanism of group A streptococci was recently identified by Herwald et al. [8] who demonstrated that the streptococcal M-protein, aside from its well-known anti-phagocytic activity, also induces vascular leakage through complex formation with fibrinogen and subsequent activation of neutrophils.

Medical therapy of severe group A streptococcal infections includes fluid replacement, antimicrobial therapy, and general supportive measures. There is growing evidence to support the use of intravenous polyspecific immunoglobulin G (IVIG) in patients...
with streptococcal toxic shock syndrome [9,10]. These studies include 1 observational cohort study based on Canadian patients identified through active surveillance of invasive group A streptococcal infections [9], and 1 European multicentre placebo-controlled trial [10]. The mechanistic actions of IVIG in this setting are believed to include inhibition of the superantigen activity through neutralizing antibodies, opsonization through M-specific antibodies, and a general anti-inflammatory effect (reviewed in [11]). Prompt and aggressive exploration of suspected deep-seated group A streptococcal infections is currently advocated in order to determine the presence or absence of necrotizing fasciitis [12,13]. Despite only anecdotal evidence [14–20], the current medical literature as well as standard surgical and medical reference textbooks advocate an early and aggressive surgical approach for patients with suspected or proven necrotizing fasciitis [21–27]. Drainage plus complete removal of all infected tissue is felt to be lifesaving [26,27]. We present here the successful management of 7 patients with severe group A streptococcal soft tissue infections treated with a medical regimen including IVIG in whom surgery was either not performed or where only limited exploration was carried out.

**Material and methods**

**Definitions**

Streptococcal toxic shock syndrome was defined by criteria established by The Working Group on Severe Streptococcal Infections [28], i.e. group A streptococcus isolated from a sterile site, and hypotension in combination with 2 or more of the following: acute renal failure, coagulation abnormalities, liver abnormalities, acute respiratory distress syndrome, generalized rash and necrotizing fasciitis.

Necrotizing fasciitis is defined by infection of the subcutaneous tissue and fascia that often results in necrosis with relative sparing of the underlying muscle. Histopathology demonstrates both necrosis of superficial fascia and polymorphonuclear infiltrates, as well as oedema of the reticular dermis, subcutaneous fat, and superficial fascia. In the absence of examined specimens, the diagnosis required the presence of gross fascial oedema and necrosis detected at surgery [2].

For the purpose of this study, we defined patients as having severe soft tissue infection if group A streptococcus was isolated from site of infection and/or blood, if they manifested 2 or more of the following conditions: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or PaCO₂ <32 mmHg; white blood cell count >12,000/mm³, <4000/mm³, or >10% immature (band) forms, and if they had 2 or more organ dysfunction (as defined in [28]) and/or hypotension not responding to a fluid bolus.

**Patients**

The study included patients identified through retrospective screening of the database of the population-based surveillance of invasive group A streptococcal infections in Ontario, ongoing since 1992 and previously described in detail [29]. The database contained 7 patients who fulfilled the study selection criteria, i.e. they presented with severe group A streptococcal soft tissue infections, had received high-dose IVIG, and had not had extensive surgical intervention. High-dose IVIG was defined as 2 g/kg body weight usually infused over 3 h, and the IVIG preparation used in all patients was Gamimmune® N (Bayer Corporation). The patients, 3 male and 4 female, had been treated for severe group A streptococcal soft tissue infection in Toronto, Canada from November 1996 to February 2002. The study was performed in accordance with the declaration of Helsinki and the Human Subjects Review Committee of the University of Toronto approved it. Informed consent was obtained from the patients from whom tissue biopsies were collected.

**Laboratory analysis**

Isolates were confirmed as Streptococcus pyogenes with the use of standard techniques. M protein typing was performed at the Canadian National Centre for Streptococcus in Edmonton [30].

From 2 patients (patients 1 and 6), snap-frozen biopsies stored at −80°C were available for immunostaining. The biopsies were cryo-sectioned, fixed, and immunohistochemically stained for group A streptococci, the superantigen streptococcal pyrogenic exotoxin F (SpeF), and intracellular cytokines using antigen-specific antibodies as detailed elsewhere [5]. Isotypic control antibodies were used as controls for non-specific staining. The immunostainings were evaluated by acquired computerized image analysis as detailed elsewhere [5].

**Results**

The patients were all previously healthy individuals aged 31 to 52 y, who had severe soft tissue infection caused by group A streptococci. Clinical and laboratory parameters of the patients are presented in Table I. Six of the patients had elevated serum creatine kinase levels, which has previously been shown to be a predictor of the presence of
necrotizing fasciitis or myositis [24,31]. The majority of patients (n/C30/C6) fulfilled the case definition for streptococcal toxic shock syndrome. Serotyping of the bacterial isolates revealed that strains of the M1 serotype were most prevalent (patients 3, 5 and 6; Table I), which is consistent with previous findings that the M1 serotype is 1 of the most common types in severe streptococcal infections [1].

Common clinical features at admission included fever, rash and severe pain at the site of infection, and the majority of the patients also had influenza-like symptoms including myalgia, chills, nausea and vomiting. Three of the patients had experienced events that were probably associated with the subsequent infection, including blunt trauma at the site of infection (1 and 3 d prior to admission in patients 5 and 7, respectively) and childbirth (4 d prior to admission, patient 4). All patients received intravenous antibiotic therapy consisting of a b-lactam antibiotic, most commonly cefazolin, and clindamycin. Two of the patients (patients 1 and 2) required vasopressor agents, and 2 (patients 1 and 3) were intubated and mechanically ventilated for acute respiratory distress syndrome.

The soft tissue infections of all 7 patients were classified as severe based on the clinical appearance, elevated creatine kinase and/or imaging compatible with deep tissue oedema, often involving large areas. Patient 3 had necrotizing fasciitis, as confirmed by histopathological examination of tissue specimens obtained through exploratory surgery. The initial impression of the surgical team was that extensive tissue debridement was required for patients 1, 2 and 3, and amputation of the involved arm of patient 6. However, surgery was deferred in these patients because of the haemodynamic instability and/or the extensive nature of the required operation, as in patient 1 who had approximately 60% soft tissue involvement (see below and Figure 1). High-dose IVIG was administered to the patients on d 1 or 2 of admission. In patient 1, a dramatic clinical improvement was evident 18 h after IVIG administration (see below). Haemodynamic improvement within 24 h of IVIG administration was also noted in patients 2, 5 and 6, whereas patients 3 and 4 required a second dose of IVIG after 2 and 3 d, respectively, since their soft tissue infections had not improved clinically. Two patients had limited exploratory surgery without debridement and 1 had repeated bedside drainage of her olecranon bursa. No other patient had surgery, and all 7 patients survived. On average the patients were discharged home 30 d after admission.

Patient 1 developed severe right shoulder pain 1 week before admission. At admission she was febrile and found to have an erythematous rash involving the skin of her right breast, axilla and flank. She had bullae on her right breast that grew group A streptococci, as did her blood culture. Her clinical condition deteriorated and she required vasopressor therapy, intubation and mechanical ventilation for acute respiratory distress syndrome. The erythema then extended from the right axilla to the right arm, right chest wall, right and left breast, right flank and perineum (Figure 1). IVIG was started. The surgical team felt that she would require extensive debridement, but surgery was deferred because of her unstable condition and the extensive nature of the

<table>
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<th>Features of patients</th>
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<td>Severe or disproportionate pain at site of infection</td>
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<td>Bullae or discoloration of skin at site of infection</td>
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<td>Peak levels of creatine phosphokinase, U/l</td>
<td>1400</td>
<td>4260</td>
<td>963</td>
<td>1423 normal&lt;sup&gt;a&lt;/sup&gt;</td>
<td>614</td>
<td>&gt;800</td>
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<td>Imaging compatible with deep tissue oedema</td>
<td>MRI U/S</td>
<td>CT</td>
<td>MRI N/D</td>
<td>CT</td>
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<td>10</td>
<td>20</td>
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<td>N</td>
<td>Y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N</td>
<td>N</td>
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<td>N</td>
<td>Y&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>4</td>
<td>1</td>
<td>1</td>
<td>5</td>
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Y: yes; N: no; MRI: magnetic resonance imaging; U/S: ultrasound; N/D: Not done; CT: computed tomographic scan; ICU: intensive care unit.

<sup>a</sup> According to the threshold values used at Mount Sinai Hospital, i.e. 0–240 U/l for males.

<sup>b</sup> Because of the findings on CT scan compatible with extensive involvement of deep tissue, exploratory surgery was performed.

<sup>c</sup> Shock was defined as hypotension not responding to a fluid bolus.

<sup>d</sup> Group A streptococci isolated from non-sterile site, i.e. the patient had probable streptococcal toxic shock according to the consensus definition [28].
Approximately 18 h after admission she had improved dramatically, with a reduction in the erythema and oedema of her soft tissue and the requirement for vasopressors. Magnetic resonance imaging of involved areas demonstrated oedema of subcutaneous tissue, deep fascial planes and muscle. She was taken to the operating room for exploratory surgery, which showed that the subcutaneous tissue and fascia of the breast were inflamed but not necrotic (Figure 1). There was a minimal amount of perifascial necrosis of the external oblique muscle that was debrided. Approximately 66 h after admission she was again taken to the operating room at which time both previous operative sites were found to be less inflamed. A repeat biopsy of subcutaneous tissue was taken at the original operative site of the right breast. Analyses of the tissue biopsies revealed a pronounced reduction in bacterial load, expression of the superantigen SpeF, and levels of interleukin 1α (IL1α), IL1β, IL1 receptor antagonist (IL1ra), and interferon γ (IFNγ) biopsies collected 66 h, as compared to 18 h, post-IVIG administration (Figure 1). Biopsies were also obtained from patient 6 and both fascia and muscle biopsies collected pre-IVIG administration revealed a high bacterial load, SpeF expression and pro-inflammatory response. Unfortunately, no subsequent acute phase biopsies were available from this patient.

**Discussion**

There is convincing evidence that streptococcal toxic shock syndrome and necrotizing fasciitis are different entities, although sharing several important pathogenic mechanisms, including among others the superantigen-induced hyper-inflammatory state [5,6]. Two studies have reported that adjunctive therapy with IVIG reduces the mortality associated with streptococcal toxic shock syndrome [9,10]. The first report is a Canadian observational cohort study [9], which showed significant improvement in survival among IVIG-treated cases. However, there were confounding factors that could have affected the outcome of the trial, including the fact that the majority of the controls were historical and that IVIG-treated cases were more likely to have received clindamycin therapy than the controls. Importantly,
in a secondary multivariate analysis considering only cases and controls that had received clindamycin, APACHE II score and IVIG therapy remained the 2 variables associated with survival. Further support for the use of IVIG in STSS was provided by a multicentre placebo-controlled trial [10]. Due to a low incidence of STSS during the study period, the trial was prematurely terminated after enrolment of 21 patients. The results revealed a trend towards a reduced mortality rate in IVIG-treated cases compared to those receiving placebo (10% vs 36%). Importantly, this trend in reduced mortality was supported by significantly better improvement of organ dysfunction following treatment in the IVIG group, whereas no such change could be noted in the placebo group. IVIG has also been shown to reduce the morbidity associated with severe soft tissue infection such as toxic epidermal necrolysis [32,33], and anecdotal reports have suggested that IVIG may improve outcome when used to treat necrotizing fasciitis [2,34].

In this study, we report the successful management of 7 patients with severe soft tissue infections caused by group A streptococci using a medical regimen containing IVIG together with a conservative surgical approach. All of these patients had soft tissue infection caused by group A streptococci severe enough that most current standards would have mandated immediate and aggressive surgical approach. Serum creatine kinase levels were significantly elevated in 6 of the patients, indicating the involvement of muscle necrosis [24,31,35]. Previous studies have reported a positive predictive value of serum creatine kinase ranging between 58% and 61% in necrotizing fasciitis, whereas in a series of 101 erysipelas patients, 95% had normal levels [31]. Furthermore, a recent study showed that serum creatine kinase levels were significantly higher in patients with necrotizing fasciitis caused by group A streptococci than in those with other aetiology [35]. Considering that 6 of these patients also had toxic shock syndrome, the fact that all patients survived without extensive surgery is impressive. A case fatality rate of 67% has been reported in patients with combined streptococcal toxic shock syndrome and necrotizing fasciitis [2]. This suggests that the use of high-dose IVIG in patients with these infections may allow an initial non-operative or minimally invasive approach, which can limit the need to perform immediate wide debridements and amputations in haemodynamically unstable patients.

Despite this it may be that these patients were somewhat different in a way we are not able to measure at present, and their type of soft tissue disease never required surgical intervention, as evidenced by their outcomes. Would then delay of surgery in a patient with streptococcal toxic shock and necrotizing fasciitis increase their morbidity and mortality? In patients with streptococcal toxic shock the mortality ranges from 30% to 80% [1,13,29], whereas, in patients with necrotizing fasciitis without streptococcal toxic shock the mortality is <5% [2]. Delaying surgery may decrease morbidity by allowing the development of a line of demarcation separating necrotic from vital tissue, thereby limiting the extent of tissue resection. It may also decrease mortality by allowing the patient to stabilize haemodynamically prior to surgery. Early versus late surgical debridement has been a matter of debate also in acute necrotizing pancreatitis, where a common therapeutic approach in the past was early surgical intervention and debridement. However, Mier et al. [36] found that early surgical intervention in severe necrotizing pancreatitis was in fact deleterious resulting in mortality rates exceeding 50%, whereas delayed surgical debridement along with close supportive care in an intensive care unit improved the clinical outcome. Thus, the concept that the existence of infected tissue in the acute stages of pancreatitis worsens the outcome may not be true, and in fact the more crucial process may be the inflammatory response that results. However, any necrotic tissue should eventually be removed, but if the use of an immunomodulating agent, such as IVIG that neutralizes the toxins and the pathological levels of pro-inflammatory cytokines, allows for the tissue debridement to be performed at a later stage this may be beneficial for the patient.

One of the main mechanisms of action of IVIG in invasive group A streptococcal infections is suppression of the hyperinflammatory state through neutralizing antibodies against the superantigens and a general immunosuppressive effect [11]. Snap-frozen biopsies were available from 2 of the patients, and analysis revealed a high bacterial load, superantigen expression and pro-inflammatory response in biopsies collected pre- or 18 h post-IVIG administration, respectively. From the latter patient, a repeat biopsy from the same operative site was collected 66 h post-IVIG and demonstrated a pronounced reduction in bacterial load, expression of the superantigen SpeF, and levels of pro-inflammatory cytokines compared to 18 h post-IVIG administration. In our previous study of tissue biopsies of patients with severe group A streptococcal soft tissue infection [5], group A streptococci and pro-inflammatory cytokines, in particular the ones studied here, could be demonstrated for an extended period of time, up to 20 d after onset of infection. Hence, the significant drop in pro-inflammatory activity seen in patient 1 seems likely to be at least partially due to therapy with IVIG.
We recognize that this study which reports a conservative ‘wait and see’ approach in patients with severe soft tissue disease goes against the standard purported in the literature. Most published reports on the management of patients with suspected or proven necrotizing soft tissue infections, including those due to group A streptococci, advocate early radical surgery [14–17,21,37,38]. This observational study, although limited in numbers, suggests that an initial conservative surgical approach combined with the use of immune modulators, such as IVIG, may reduce the morbidity associated with extensive surgical exploration in haemodynamically unstable patients without increasing mortality. The fact that 7 patients with severe group A streptococcal soft tissue infections survived with this approach definitely warrants further studies to be conducted on the use of IVIG in these severe infections.

Acknowledgements

This work was supported by grants from the Canadian Bacterial Diseases Network, Magn. Bergvalls Foundation, Swedish Foundation for Strategic Research, Swedish Research Council, and the Karolinska University Hospital Huddinge Research Foundation.

References


