

Infections Due to Group A Streptococcus: New Concepts and Potential Treatment Strategies

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Abstract

Important new information has been gained on the pathogenesis and treatment of life-threatening invasive infections caused by group A streptococci (GAS), i.e. the streptococcal toxic shock syndrome (STSS) and necrotizing fasciitis (NF). Both STSS and NF lead to superantigen reactions with activation of up to 10% of the CD4+ lymphocytes and release of large amounts of cytokines; mainly tumour necrosis factor beta, interferon gamma, interleukin 1 and interleukin 6. Streptococcal products known to trigger the superantigen reactions are the pyrogenic exotoxins, spe A, spe B and spe C and the M-proteins. Therapeutically clindamycin has been shown to reduce mortality in animal experiments in comparison to penicillin treatment. A possible mechanism is the effect of clindamycin on protein synthesis which might decrease the production of superantigens. In man, the use of intravenous immunoglobulin has been shown to significantly reduce mortality in STSS and NF. The most probable mechanism is neutralisation of superantigens by antibodies in the immunoglobulin preparations used.

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Introduction

Group A streptococci (GAS; *Streptococcus pyogenes*) cause a variety of infections which can be superficial (e.g. impetigo), localised (e.g. tonsillopharyngitis, wound infection or erysipelas), or systemic (e.g. septicaemia). In patients with bacteraemia GAS toxins may lead to streptococcal toxic shock syndrome (STSS). This term has been coined due to the marked similarities, in terms of pathogenesis and clinical presentation, between STSS and staphylococcal toxic shock syndrome (TSS).¹

Another manifestation of GAS infections, which has been widely publicised in the lay press, is necrotizing fasciitis (NF); GAS has been called "the flesh eating bacteria". None of these syndromes are new clinical entities but have been described as surgical scarlet fever and postpuerperal fever. This overview deals with some of the available information about the epidemiology, pathogenesis and treatment of invasive GAS infections, particularly STSS and NF.

Epidemiology

The incidence of invasive GAS infections with or without STSS or NF varies and depends on which GAS strains that are predominant in a population at a given time and on the toxins produced by those strains. As

pointed out below, the immunity in the population to certain toxins in GAS seems to be a critical factor for the frequency of invasive GAS infections.

In Europe and North America outbreaks of invasive GAS infections have been described during the last decade.^{2,5} In Scandinavia, GAS of serotype M1T1, which had been infrequent in those countries for many years, caused an outbreak at the end of the 1980s.^{2,3} Data for the outbreaks in Norway and Sweden are shown in Table I. The increase of invasive infections was probably somewhat smaller than those reported, since the awareness increased markedly due to reports both in medical journals and in the news media.

It is important to realise that only a small fraction of all GAS infections are invasive and an increased incidence of such infections follows from increased frequency of other GAS infections such as pharyngotonsillitis, scarlet fever and impetigo. When such infections, which are normally benign, become more common in a population, an awareness of an increased risk for invasive and life-threatening infections is essential. It is also important to realise that there are no reports indicating that underlying diseases and /or immune deficiencies are of importance for the risk of developing invasive GAS infections.

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TABLE I: OUTBREAKS OF INVASIVE GROUP A STREPTOCOCCAL (GAS) INFECTIONS IN SCANDINAVIA¹,

	Norway	Sweden
Period studied (month/year)	8/87 to 7/88	8/88 to 7/89
Incidence of non-invasive GAS-infections (cases/100 000 inh)		
During outbreak	1863	No data
Previous year	1157	No data
% increase during outbreak	61	No data
Incidence of invasive GAS-infections (cases/100 000 inh)		
During outbreak	2.02	2.92
Previous year	0.86	1.73
% increase during outbreak	135	69
Mortality rate in invasive infection	25%	18%

A majority of invasive GAS infections are community acquired and sporadic. It is rare to see more than one case in a family or other defined small group of individuals. Nosocomial infections are seen mainly in obstetrical units as puerperal fever and neonatal infections.

Pathogenesis

STSS is characterised by rapid onset of septic shock and multiorgan failure in patients who often lack complicating underlying diseases. NF is a localised infection with extensive and very rapidly progressing tissue damage. In that situation, the patient is threatened both by the consequences of the infection itself and by the toxic effects of products released from necrotic tissues.

It has been convincingly shown that severe manifestations of GAS infections are superantigen reactions.⁶⁻⁹ The mechanisms leading to such reactions as well as their nature and consequences have been reviewed by Kotb.^{6,7} Briefly, in a superantigen reaction, antigen-presenting cells (normally macrophages) expose the microbial antigen, bound to major histocompatibility complex (MHC) class II molecules on their surfaces without previous intracellular processing. This results in activation and cytokine production of up to 10% of the CD4 lymphocytes, i.e. 1000 times or more than is the case when the antigen-MHCII-complex is presented on the macrophage surface following intracellular processing and degradation to short-chain peptides. The result of the activation of large numbers of CD4 lymphocytes in a superantigen reaction is the liberation of very high amounts of inflammatory cytokines, mainly tumour necrosis factor (TNF), interferon (INF) and interleukin 1 and 6 (IL-1 and IL-6). The extensive amounts of cytokines released in superantigen reactions is the most probable explanation for the high mortality in invasive GAS infections; up to 80% in patients manifesting with septic shock.^{5,10}

Streptococcal antigens capable of eliciting superantigen

reactions are the streptococcal pyrogenic exotoxins (Spe's) and the M-proteins.^{6,7} A recent *in vitro* study suggested that other, yet not characterised, streptococcal antigens are superantigens and contribute to the manifestations of severe GAS disease.⁷

Spe A, Spe B, Spe C and Spe F have convincingly been shown to be superantigens and it has also been demonstrated that immunity to such antigens are lacking in patients developing STSS or NF.¹¹ Thus, patients at risk for invasive GAS infections are those who acquire a GAS strain producing toxins against which antibodies have not been developed following previous exposures to the toxins. Interestingly very few of the patients who developed STSS or NF in the Swedish material had tonsillopharyngitis as the primary focus of infection.³ An explanation for that may be that tonsillar tissue has a high capacity to contain and combat infections.

One reason for the lack of immunity to GAS toxins may be that, although the patients have been exposed previously, early antibiotic treatment has resulted in rapid elimination of the bacteria and hence of the antigens.

Therapeutic Approaches

Invasive GAS infections require prompt antibiotic treatment, e.g. with benzylpenicillin or a cephalosporin. Resistance against these antibiotics in GAS has not been described and seems unlikely to occur (Tomasz, unpublished data).

Antibiotic treatment will remove the offending organisms from the blood and the focus of infection. However, β -lactam antibiotics seem to have little effect on the clinical course in patients who have developed STSS or NF. In such patients two regimens seem to offer a better prognosis. The first is clindamycin, which in streptococcal infections in mice, has been shown to be superior to benzylpenicillin in reducing mortality.¹² A possible explanation is that clindamycin is an inhibitor of bacterial protein synthesis, which might result in liberation of lower amounts of the superantigens. A caveat is that resistance to clindamycin has been reported to occur in up to 4.3% of GAS isolates in Spain and the possibility of cross-resistance between clindamycin and macrolides cannot be excluded.¹³ Thus, if clindamycin is used in patients with invasive GAS infections, it is recommended that it is combined with benzylpenicillin or a cephalosporin.

The second therapeutic approach is far more innovative and promising. In 1995, Kaul and McGeer¹⁴ reported on 15 patients with STSS who were treated with very high doses (0.5 g/kg body weight) of intravenous immunoglobulin (IVIG). As outlined in Table II, IVIG treatment significantly and markedly increased survival rates in their material. The IVIG used was shown to inhibit the *in vitro* effects of purified Spe's and of

TABLE II: EFFICACY OF INTRAVENOUS IMMUNOGLOBULIN (IVIG) IN INVASIVE STREPTOCOCCAL INFECTIONS¹⁴

No. of patients	15
No of matched historical, controls	15
Mean APACHE II scores	
Patients	26
Controls	26
IVIG dose in patients	0.5 g/kg
Mortality of any cause	
Patients	40%*
Controls	80%*
7-day mortality	
Patients	13%**
Controls	66%**

** $P = 0.035$; * $P = 0.01$

superantigenic culture supernatants prepared from clinical GAS isolates. Most importantly the patients' plasma samples inhibited the *in vitro* mitogenic activity of these toxins significantly more efficiently after than before IVIG treatment.¹⁵ The post-IVIG plasma samples almost completely inhibited Spe C and GAS culture supernatant induced production of TNF β and INF. Thus, this project has convincingly proven that IVIG containing antibodies against the Spe of the GAS strain causing STSS or NF neutralises the GAS toxins. Although the trial is not double-blind and uses a historical control, its results very strongly indicate that IVIG reduces mortality in invasive GAS infections. Findings should preferably be confirmed in a randomised trial using placebo or no treatment as controls. Other issues which remain to be addressed are whether all preparations of IVIG contain the same amount and type of antibodies or if there are variations between available IVIG preparations and/or intra- or inter-batch variations for one and the same product. Unpublished data indicate that there are indeed considerable variations between various brands of IVIG (Norrby-Teglund et al, unpublished data).

In patients with NF, aggressive surgical treatment is needed in addition to antibiotics and IVIG.¹⁶

Summary and Conclusions

Reactions elicited by GAS superantigens, mainly uncontrolled release of vast amounts of inflammatory cytokines, explain the exceedingly high mortality in STSS and NF. Early treatment with antibiotics seems to affect the survival rates only marginally while the

results obtained with IVIG are promising and may lead to new therapeutic strategies for these important infections.

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