Group A Streptococcal Fasciitis

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ABSTRACT

Objective: *To review the current understanding of group A streptococcal fasciitis; the different bacterial serotypes, the role of superantigens, antibiotic and other therapies, and transmission to house hold contacts and health care workers.*

Data sources: *Articles and published abstracts on the mechanisms and management of group A streptococcal fasciitis.*

Summary of review: The *development of streptococcal fasciitis depends on the inoculation of a susceptible individual (i.e. one who has not been previously exposed to that particular serotype or superantigen) with a virulent streptococcus that has the ability to produce superantigens. The superantigens produce an excessive stimulation of the immune system, with a subsequent outpouring of inflammatory cytokines causing the multiorgan failure that characterises both streptococcal necrotising fasciitis as well as streptococcal toxic shock syndrome.*

Effective management of streptococcal necrotising fasciitis requires an early diagnosis, appropriate surgery, administration of clindamycin (600 mg/70 kg i.v. 6-hourly), penicillin G (1.2 g/70 kg i.v. 2 to 4-hourly), and polyvalent immunoglobulin (0.2 – 0.4 g/kg/day i.v. for 3 – 5 days). Household and health workers in close contact with the patient need to be warned to present to medical care early if they develop any signs of an infection.

Conclusions: *Necrotising fasciitis is a severe disorder which is commonly caused by group A streptococcus. Early diagnosis and effective management with surgery, antibiotics and polyvalent immunoglobulin will reduce mortality. Further studies concerning the risk of transmission of the organism to close contacts need to be performed.* (**Critical Care and Resuscitation 1999; 1: 63-68**)

Key words: Streptococcus pyogenes, necrotising fasciitis, streptococcocal toxic shock syndrome

Streptococci are spherical gram positive bacteria that form characteristic chains when grown in liquid media. While no single scheme for classification of this organism is completely satisfactory, several are used, although the beta haemolytic streptococci (i.e. those that produce a zone of complete haemolysis around the colony when cultured on blood agar) are usually classified by the Lancefield system (a serological grouping based on the reaction of specific antisera with the bacterial cell wall carbohydrate antigens). The Lancefield groups A, B, C and G are all associated with characteristic patterns of human disease. Streptococci that produce partial haemolysis (i.e. a green appearance surrounding the colony on blood agar) are known as alpha haemolytic streptococci, whereas non haemolytic streptococci are said to have a gamma haemolysis pattern.

Lancefield group A streptococcus (*Streptococcus pyogenes*) is associated with a variety of clinical disorders including, pharyngitis, impetigo, scarlet fever, cellulitis and necrotising fasciitis. Necrotising fasciitis is a rapidly spreading destructive disease of the fascia investing the muscles of a limb or trunk. While necrotising fasciitis can be caused by other bacteria, in over 60% of cases it is caused by group A streptococci, either alone or in association with *Staphylococcus aureus* or enteric flora (e.g. *Bacteroides* or Gram-negative enterobacteria). In the remaining cases it may be caused by a mixed enteric infection which includes *Bacteroides*, *Peptostreptococcus* and Gram-negative

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enterobacteria, or, rarely, a marine vibro (e.g. *Vibrio vulnificus*).[1]

The necrotising fasciitis caused by *Streptococcus pyogenes* (sometimes known as haemolytic streptococcal gangrene) continues to have a high mortality and morbidity. This article will review the current understanding of the different bacterial serotypes, the role of superantigens in the development of toxic shock, antibiotic and other therapies, and transmission to house hold contacts and health care workers.

Pathophysiology

Extracellular proteins and toxin production

Group A streptococci have a number of cell surface proteins and extracellular substances that promote its virulence. The major surface protein is the M protein which is anchored in the cell membrane with its amino-terminal end projecting from the surface. The amino acid sequence nearest the cell is highly conserved while more distally it is variable, accounting for the more than 80 antigenic subtypes. The M protein confers increased resistance to phagocytosis by binding fibrinogen to the surface of the bacteria which interferes with complement activation and attachment of opsonic complement fragments on the bacteria.[2] The incidence of invasive streptococci with M proteins types 1 and 3 has increased in the last few years.[3] A comprehensive study on invasive Group A streptococcal infections has been undertaken in Ontario, Canada where all cases of invasive streptococcal infections had been examined prospectively since 1991.[4,5] Over the period 1992 to 1993 the incidence of invasive disease caused by the M1 serotype had increased from 15 to 32 percent.

Group A streptococci produce a number of exotoxins that have been linked to an increased severity of clinical infection. Streptococcal pyrogenic exotoxin A (SPEA) is often produced by streptococci with the M1 and M3 serotype,[6] with a strong correlation existing between M1 serotype and the production of the SPEA. Patients with bacteria producing SPEA have been found to be much more likely to develop Streptococcal toxic shock syndrome and die when compared with patients infected with other streptococcal strains.[7] It would appear that patients without prior exposure to the particular serotype and therefore lacking neutralising antibodies to the respective exotoxin will develop toxic shock,[8] whereas patients who have antibodies due to a previous exposure, do not develop invasive disease.

There are a wide variety of streptococcal toxins, including SPE A, B and C mitogenic factor (MF), and streptococcal superantigen (SSA) all of which appear to act as superantigens. During the normal immune response, foreign antigens are processed and presented to the immune system on antigen presenting cells. Superantigens have the ability to react with the major histocompatibility complex class II antigens on antigen presenting cells and specific Vβ regions of the T cell. The T cell receptor is made up of an α and β chain. Each of these chains have constant and variable regions. In humans there are 24 major Vβ families separated on the basis of specific amino acid sequences in the variable region of each β chain. Each superantigen has the ability to activate a specific set of T cells.[9] This causes the release of large amounts of proinflammatory mediators such as TNF,[10] IL1, and IL6, often resulting in the development of septic shock.

The development of Staphylococcal toxic shock syndrome, which shows a number of similar clinical features to streptococcal toxic shock syndrome (see later), is due to the preferential stimulation of Vβ2 T cells.[11] The streptococcal exotoxins A and C can also, in the presence of interferon-gamma, up regulate the production of inducible nitric oxide synthase in murine macrophages.[12]

Non steroidal anti-inflammatory drugs (NSAIDs)

As the initial presentation of necrotising fasciitis is often pain in the affected area with few other signs suggestive of an infective process, a number of patients are treated with analgesic medication. There have been a large number of reports of streptococcal necrotising fasciitis, in association with the use of non steroidal anti-inflammatory drugs (NSAIDs), which has led to the suggestion that the inhibition of white cell function secondary to the administration of NSAIDs may contribute to the development of the disease (and lead to a higher mortality).

However, animal data and a recent review of the literature do not support this view[5,13] In rabbits given diclofenac 24 hours after inoculation with group A streptococci, the diclofenac group developed less inflammation and lower bacterial density on bacteriological and histological studies performed daily from day 1 to 10, compared with the control group.[14] As pain is the most common presenting complaint it is most likely that the administration of the NSAID delays the diagnosis and hence the treatment of the infection.

Clinical features

Necrotising fasciitis

The onset of necrotising fasciitis is usually rapid with the presenting features consisting of pain overlying the site of involvement (in one study, this occurred in 85% of cases, some of whom had no other physical findings[7]), fever, malaise, rigors and a toxic or shocked physical appearance. The overlying skin may be only

slightly erythematous but within a short period of time can become dusky, mottled and oedematous. In severe cases the affected skin may become anaesthetic due to infarction of peripheral nerves.

The portal of entry for the streptococcus is usually a skin wound, which may not be obvious on cursory examination, and is often a considerable distance from the clinically affected area. Group A streptococci are among the few bacteria that can cause a wound infection, cellulitis or necrotising fasciitis in the first 24 hours following surgery. If the source is from the bowel, the necrotising fasciitis is usually caused by a mixed aerobic/anaerobic infection from either the surgical trauma or an intra-abdominal abscess.[15]

Streptococcal toxic shock syndrome

In the late 1980's there were a number of reports of patients with group A streptococcal infections developing shock and multiple organ failure. As this condition shared a number of features seen in patients with Staphylococcal toxic shock, the syndrome was called Streptococcal Toxic Shock Syndrome, (STSS). In 1993 a case definition was proposed.[6] The requirements were based on the isolation of Group A Streptococci (GAS) from either a normally sterile site (e.g. blood, CSF, tissue) or a non sterile site such as throat, vagina or skin lesion; and clinical features indicating severity of infection. The clinical signs required were hypotension, systolic blood pressure less than 90 mmHg for adults or in the 5th percentile for children, plus two of either; renal impairment, coagulopathy, liver function abnormalities, acute respiratory distress syndrome, generalised macular rash or soft tissue necrosis.

Most patients who develop STSS are bacteraemic, which is in sharp contrast to staphylococcal toxic shock where bacteraemia almost never occurs (sometimes it is difficult to isolate *Staphylococcus aureus* from the wound). The most common streptococcal infection sites are fascia (necrotising fasciitis) and skin (cellulitis, impetigo), although the syndrome has also been caused by streptococcal infections of the lower respiratory tract, joints and pelvic organs.

In the first paper from the Ontario group 323 patients with invasive GAS infections and their close contacts were prospectively studied.[4] The second study followed 77 patients who had necrotising fasciitis over a 3.5 year period. In the first study the overall death rate was 15 percent, although for patients over the age of 64 it rose to 29% and in those who developed STSS the death rate was 81%. Necrotising fasciitis occurred in 20 patients, 11 developed STSS, 9 of whom died. The other site of infection which was associated with a significantly higher death rate was the lower respiratory tract. Forty two patients were classified as having STSS, although only 31 fulfilled the consensus definition, the other 11 were either dead on arrival at hospital or died shortly after admission without sufficient data being collected to allow classification. These patients were older, had a history of underlying chronic disease (e.g. cancer, heart disease, diabetes or lung disease), and were more likely to have contracted the infection in the community. Additional risk factors were HIV infection, alcohol (in the group aged from 20 - 60 years), and in patients under the age of 16 years, a recent infection with chickenpox.

The second study concentrated on necrotising fasciitis only.[5] The relevant findings were:

1) the incidence of the disease had increased from 0.085 per 100,000 to 0.4 cases per 100,000 over the period 1991-1995, with a higher rate observed in winter and in older people.
2) at least one underlying chronic medical condition (e.g. cancer, diabetes, respiratory, renal or heart disease) was found in 71 % of cases.
3) in four of the five cases occurring in children under 10 years of age, the disease was complicated by a varicella infection.
4) the mortality rate was 34% (0/19 who were under 35 years, 7/26 in the age range of 35 to 64 years, and 19/31 in patients who were older than 65 years).
5) patients with STSS, as defined by the consensus conference, had a 67% mortality rate compared with a 4.9% mortality rate in those who did not meet the criteria.
6) Patients who were bacteraemic were 3 times more likely to die.
7) the predominant serotypes were M1 (35%) and M3 (25%).
8) treatment with clindamycin appeared to result in a better outcome, although just failing to reach significance (relative risk 0.55, 95% confidence interval 0.23 to 1.02; p = 0.06)

Management

The mainstay of treatment is surgical debridement and antibiotics with increasing evidence of the benefits of administering polyvalent immunoglobulin.

Surgery

Initial reports on the surgical management of necrotising fasciitis were first published in the 1920's where the reported mortality was 20 %.[16] Surgery with extensive debridement and or amputation is recommended, as the areas of affected fascia is usually much greater than indicated by changes in the overlying skin.

Antibiotics

Group A streptococci remain very sensitive to the penicillin *in vitro*, and *in vivo* in most cases. Despite the introduction of penicillin, the death rates in some reports continued to be excessive (e.g. up to 85% despite penicillin therapy).[17] However there may be a number of *in vivo* conditions such as an impaired blood supply, an increase in bacterial inoculum size or changes in bacterial growth rate, which reduces the sensitivity of the organism to penicillin.

Eagle, in the late 1940's, demonstrated in a mouse model of myositis that penicillin was only effective if given early in the course of the infection.[18] If the number of organisms were allowed to increase by using either a larger inoculum or delaying the start of antimicrobial treatment, the effectiveness of penicillin was reduced. He felt that once the bacteria had reached a steady state stationary growth phase, penicillin would be less effective as its antibiotic effect requires actively growing and dividing cells. More recently it has been demonstrated that streptococci in the stationary growth phase lose penicillin-binding proteins.[19] This loss may be responsible for the inoculum effects described by Eagle and the lack of effect of penicillin in severe infections.

Stevens *et al* in a similar mouse model found that clindamycin was superior to penicillin in the treatment of streptococcal myositis.[20] This effect of clindamycin may be due to a number of factors, although the ability of clindamycin to inhibit protein synthesis (decreasing the production of M proteins[21] and reducing superantigen production), may be one of its more important effects. The drug is rapidly bactericidal and unaffected by inoculum size.[12] Clindamycin has also been showed in increase opsonization of bacteria. This may also be relevant, given reports of the apparent successful use of pooled immunoglobulin in the management of patients with invasive GAS infections.[22]

The current antibiotic approach is to combine penicillin G (1.2 g/70kg i.v. 2 to 4-hourly) with clindamycin (600 mg/70 kg i.v. 6-hourly).[5]

Immunoglobulin

Lancefield, in 1962, showed that the presence of antibodies to specific subtypes of M proteins conferred resistance by increasing phagocytosis, and that for invasive disease to occur there must be an absence of the particular anti M antibody. With invasive disease, the activation of millions of clones of T cells, instead of just a few, by the streptococcal superantigens, and the excessive activation of cytokines (with TNF alpha playing a key role), complement, and clotting cascades, leads to symptoms and signs of shock and multiorgan failure.

The discovery that intravenous immunoglobulin G can reverse the hyperproliferation of T cells, neutralise superantigens,[23] and down regulates the production of TNF,[24] has prompted some to use intravenous gamma globulin to reverse the adverse superantigen effects.[25] Norrby *et al*, treated 12 patients with invasive streptococcal disease with polyvalent immunoglobulin with reduction in the death rate.[26] Plasma samples collected from the patients before and after the infusion of IgG were tested for activity against a wide variety of superantigens. The post infusion plasma from each patient completely blocked production cytokine production from the respective group A streptococcus.

Other therapies

There have been no prospective randomised controlled studies that have demonstrated beneficial effects of hyperbaric oxygen treatment in patients with invasive streptococcal disease.

Transmission to household contacts

It is recognised that close contacts of patients with meningococcal infection are at risk of contracting meningococcal disease.[27] However, there has not been as much emphasis on the risk of close contacts to patients with streptococcal disease developing invasive streptococcal disease. Concerning the epidemiology of the disease, the Ontario group had seven cases (2%) of invasive disease in household contacts, one community transmission and 14 cases in 12 geriatric homes. In four of the seven geriatric homes that agreed to be studied, 3.3% to 9.6% of patients had had a GAS infection (mainly cellulitis) in the previous 3 months. Furthermore, 2.2% to 7.1% of the staff or residents were colonised with the same strain of GAS.

DiPersio *et al*, described two family groups where household transmission had occurred.[28] In one case the father in law of the index case (who had frequently contacted the patient) developed an infection on the right hand. He had been seen in a general practice clinic 2 days prior to admission, with a four day history of right arm pain. A diagnosis of a strained ligament had been made and he was treated with paracetamol, naprosyn and an arm sling.

On presentation he was in shock with an obviously painful and infected arm. Despite amputation of the arm, supportive treatment in an intensive care unit, administration of clindamycin and vancomycin, extensive necrosis of the trunk occurred and he died the following day. Three hospital staff had streptococcal infections which developed over the next 2 days. An emergency department doctor developed an exudative pharyngitis, a paramedic developed scarlet fever and another doctor, who had minimal exposure to the

patient, was colonised with a GAS that was identical on DNA analysis to the index and fatal cases. The organism from the emergency doctor and the paramedic were not available for analysis.

There are a number of other cases documenting spread of the infection to health care workers, including the death of a paramedic who had treated a young girl with STSS.[29] The Ontario group calculated the risk to the patient's household contacts developing invasive disease as 2.9 per 1000 (95% confidence interval 0.8 - 7.5 per 1000), which is almost 200 time greater than the risk in the general population.

The risk of disease and fatality rates are the same as for meningococcal disease, however the role and the approach to prophylaxis remains unclear and needs to be investigated further. The risk of colonization is associated with a younger age and four or more hours of contact with the infected person.

What precautions does one take when managing a patient with severe streptococcus infections? The National Center for Infectious Diseases (NCID) guidelines recommends gowns and gloves be worn when handling patients with 'major' GAS wound infections. The use of face masks may also decrease the risk of developing pharangitis. While close contacts and hospital workers are at risk of becoming colonised by the patient's organism, most will be asymptomatic or at worse have a mild infection. Staff treating patients with severe GAS infections should be vigilant about developing sore throats or painful limbs and seek medical advice early.

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