Diabetes and necrotising tissue infection: What challenges lie ahead?

John Timmons

ARTICLE POINTS

1 Necrotising fasciitis is a relatively rare but potentially life-threatening type of tissue infection.

2 People with diabetes appear to be at greater risk than those without diabetes.

3 *Streptococcus pyogenes* (Group A beta-haemolytic *Streptococcus*; GAS) is the most well recognised species of bacteria that causes necrotising fasciitis.

4 GAS enters the body through long-standing chronic wounds or an acute entry site and presentation varies depending on the site and presence/absence of a chronic wound.

5 Infection should be treated immediately with antibiotics and aggressive debridement to minimise the effects of the condition.

KEY WORDS
- **Necrotising fasciitis**
- **Group A beta-haemolytic *Streptococcus***
- **Tissue infection**
- **Diabetes**
- **Risk profile**

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Introduction

Necrotising fasciitis is a relatively rare but potentially life-threatening type of tissue infection. The condition is a rapidly progressing infective process involving the skin and subcutaneous tissues (Wong et al, 2003). The ability of certain organisms to cause such devastation in tissue is of concern to all practitioners, however, more worrying is the percentage of people with diabetes who appear particularly susceptible to this condition. Some studies have identified that patients with diabetes make up to 70% of the total number of patients in their affected population (Wong et al, 2003). This article discusses the various types of infection, the organisms involved, risk factors, and how it might present in practice.

The literature on necrotising fasciitis suggests that early recognition and treatment are paramount to minimise tissue damage and, in many cases, reduce mortality (Wong et al, 2003). Awareness of risk factors may assist in prompt treatment being administered, however, there are many patients who are normally healthy, who present for the first time with early-stage necrotising infection. Awareness, therefore, of the signs of early stage disease may be more important in these instances (Poromanski and Andriessen, 2004). Some authors have attempted to identify the common factors with which patients present using retrospective data in order to create a 'risk scoring system' (Poromanski and Andriessen, 2004). However, such a system has not yet been tested in practice. There does appear to be an increase in the incidence of this disease but there is little empirical evidence to support this belief (Kaul et al, 1997).

What is more obvious is the increased public awareness of the issue and the often much-inflated media attention it receives.

Necrotising fasciitis is often used as a blanket term to describe the infection, inflammation and destruction of tissue caused by one or more types of bacteria (Loudon, 1994). The most well recognised of these is the Group A beta-haemolytic *Streptococcus* (GAS) or *Strep. pyogenes*. In cases of GAS, large areas of tissue are literally destroyed, with advanced disease potentially leading to organ involvement. Early recognition and treatment are essential in order to minimise the extent of tissue damage or, indeed, for the patient to survive the episode.

Three distinct types of necrotising infection have been identified:

- Type 1: Referring to a polymicrobial infection which may or may not include the GAS organism.
- Type 2: Infection caused by the GAS (Loudon, 1994). Identification of this type is often confused due to the ability of other organisms to cause significant tissue destruction once the infection takes hold.
- Type 3: Tissue infection caused by *Clostridium perfringens* organism which causes myonecrosis.

Streptococcus pyogenes (GAS)

Strep. pyogenes is a Gram-positive non spore-forming coccus that occurs in chains or in pairs. In vitro, the bacteria requires an enriched medium containing blood in which to grow. This organism is one of the most frequent pathogens of humans and is believed to be present in 5–15% of the population, normally

occurring in the respiratory tract (Todar, 2002).

When bacteria are introduced or transferred to vulnerable areas, suppurative infection may ensue. Puerperal fever (post-childbirth sepsis) was largely attributed to the presence of *Strep. pyogenes* during the last century.

Acute episodes of *Strep. pyogenes* may present as pharyngitis, impetigo, cellulitis, toxic shock syndrome and necrotising fasciitis (Hackett and Stevens, 1993). Darenberg et al (2003) carried out a study on 21 patients identified as having streptococcal toxic shock syndrome to test the role of intravenous immunoglobulin (ivlg) on the symptoms. A mortality rate of 30% in the placebo group versus 14% in the ivlg group, while encouraging, was not statistically significant given the small numbers involved in the trial.

The streptococcal organism has largely been classified using agar plating to note the type of haemolytic reaction displayed. The reaction of GAS on agar is the complete lysis of the red blood cells present compared with the haemolytic reaction of some bacteria, which results in only partial haemolysis of the red blood cells leaving a green residue on the plate (Todar, 2002).

The outer capsule of the bacteria consists of hyaluronic acid (HA), which is not recognised by the host as a foreign substance, HA being a naturally-occurring component of the host's connective tissue. Due to this, the organism is unrecognised as being antigenic. This results in the reduced functioning of polymorphonuclear leucocytes, allowing greater proliferation of the organism (Caputo et al, 1997; Poromanski and Andriessen, 2004).

Table 1. Possible presentations of necrotising infections. Adapted from Fink and De Luca (2002) and Headley (2003).

- Pain (usually greater than site implies)
- Erythema
- Pyrexia
- Bullae
- Apparent bruising
- Extensive necrosis
- Swelling
- Signs of organ failure (late diagnosis)
- Sweating
- Tachycardia
- Toxic delirium

Pathophysiology

Once GAS has entered the body through an acute or chronic wound entry site, the bacteria releases toxins. These toxins come in the form of invasins and exotoxins. Streptolysin-O is an oxygen labile enzyme that is leucotoxic, causing leucocyte malfunction (Darenberg et al, 2003). Hyaluronidase is also produced, which not only destroys local HA in the host's connective tissue but also the capsule surrounding the organism. Proteases released also contribute to the tissue necrosis.

Streptococcal pyrogenic exotoxins (SPE) stimulate T-cells to release massive amounts of cytokines, which creates signs of shock, fever, rash and hypotension.

Due to the tissue and microvascular destruction, the resultant reduction in blood supply results in secondary tissue ischaemia. Clotting and thrombosis occurs within the vessels, thereby affecting the local tissues which become ischaemic and die. This results in the killing of host cells, which provokes a further and potentially damaging inflammatory response. The histamine reaction that follows causes fluid to leak out of the local capillaries into the extravascular space (Fink and De Luca, 2002).

The patient may appear with an erythematous lesion but this will change over time to appear 'dusky blue' in colour. In some patients, bullae can be noted on the skin surface, and these are filled with foul smelling 'dish-water pus'. Left untreated the lesion may spread and a systemic toxic reaction may follow once the toxins enter the bloodstream (Headley, 2003). The toxins released by GAS infection may lead to abscesses and

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1 Acute episodes of *Strep. pyogenes* may present as pharyngitis, impetigo, cellulitis, toxic shock syndrome and necrotising fasciitis.

2 In vitro there is complete lysis of red blood cells by GAS, whereas with some bacteria there is only partial haemolysis.

3 Once GAS has entered the body through an acute or chronic wound entry site, the bacteria releases toxins.

4 Streptococcal pyrogenic exotoxins stimulate T-cells to release massive amounts of cytokines, which creates signs of shock, fever, rash and hypotension.

5 Patients may present with an erythematous lesion or bullae, which left untreated may spread and may be followed by a systemic toxic reaction that may lead to abscesses and eventual organ failure.

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1 In polymicrobial infections, a number of organisms work synergistically to destroy tissue by a similar means to monomicrobial streptococcal infection.

2 A majority of necrotising infections are caused by more than one organism.

3 Necrotising fasciitis presentation varies depending on the site and presence or absence of a chronic wound from which the infection propagates.

4 Patient history may reflect recent trauma, surgery or a chronic wound. In some cases there is no prior indication.

5 Characteristics include: increase in pain (in wounds), rapidly spreading cellulitis, tissue swelling and pyrexia.

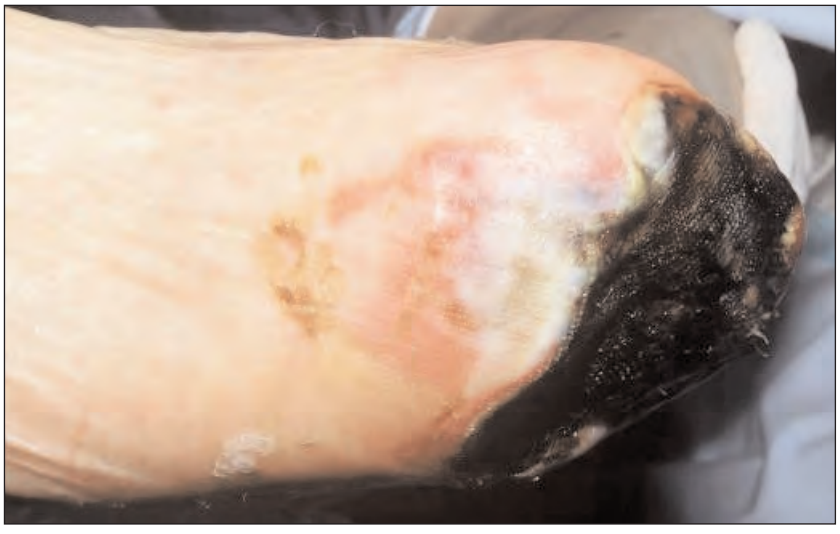
eventual organ failure. Other complications include disseminated intravascular coagulopathy and multisystem organ failure.

Aetiology

Many of the studies carried out disagree as to the exact causative organisms in cases of necrotising fasciitis. Despite many infections being identified as monomicrobial, some studies have shown there to be a number of polymicrobial infections also. In the case of polymicrobial infection, a number of organisms work synergistically to destroy tissue by similar means to a monomicrobial streptococcal infection. In a study by Elliott et al (2000), only 28 of 182 patients with necrotising skin infections had a single pathogen infection, the other 154 patients had a polymicrobial infection, with an average of 4.4 different causative organisms present on culture. The most common single organism in this study was GAS.

In another study by Childers et al (2002), of 145 patients with necrotising infection, only 29% had a single organism pathogen, the remaining 79% had up to six different organisms present. In a similar study, Wong et al (2003) found that 25 out of 89 patients (28.1%) had infection caused by a single organism compared with 48 patients (53.9%) having polymicrobial infections. In 16 cases, no single organism was identified. In the patient group who were diagnosed as having polymicrobial infections, the organisms found included streptococcal species, staphylococcal species, enterococci and *Enterobacteriaceae*, such as *Escherichia coli, Pseudomonas* and *Klebsiella* (Wong et al, 2003). A common finding is the low number of *Clostridium* isolates in cases where GAS is common (Wong et al, 2003; Childers et al, 2002; Elliott et al, 2000).

Figure 1. Spreading necrotising infection from an initial heel ulcer. (Credit: Lynne Watret)



Presentation

The presentation of necrotising fasciitis varies, depending on the site and also the presence or absence of a chronic wound from which the infection propagates (see *Table 1,* and *Figure 1*). The history may therefore reflect recent trauma, surgery or – in the cases of those patients with chronic wounds – the patients may be known to the healthcare team. In other cases there may be no distinct recollection of trauma or skin damage, for example in cases of 'Fournier's gangrene' the patient may develop sudden cellulitis and infection in the groin region having had no prior indication (Headley, 2003).

This can make diagnosis difficult; however, there are a number of key characteristics that may be observed. In cases of acute infection of previously unbroken skin, the time from injury to development of severe symptoms can be very short (0–2 hours in some cases). In long-standing wounds an increase in pain, possibly associated with an increase in exudate levels, may indicate a change in the bioburden of a wound and may precipitate an acute streptococcal infection.

A rapidly spreading cellulitis and swelling of tissue is noted, which moves from red to dusky blue as the local vascular network is destroyed. Studies report patients experiencing pain beyond that which would be associated with 'normal' wound pain, therefore, this may be a useful clinical indication (Childers et al, 2002). It must be added that patients with diabetes with neuropathy may not experience pain to this degree, making diagnosis more difficult (Caputo et al,

1997). There is little evidence relating to the initial clinical findings, such as pain and fever, in those with diabetes with necrotising disease.

In addition to the cellulitis, the formation of purple bullae may be obvious as previously stated. Pyrexia is common but not always present and temperature should be monitored as soon as infection is suspected. Some studies report a temperature of greater than 38 °C as indicative of more severe systemic infection (Childers et al, 2002).

The link with diabetes

Although there are no conclusive studies that describe all the risk factors for development of necrotising fasciitis, many authors agree that there are certain factors which, if present, may predispose a patient to a necrotising infection (see *Table 2*). Most studies carried out to date have been presentations of retrospective data, highlighting the key common factors that were present in a group of patients over a given period of time. These studies, despite agreeing on many of the key risk factors, show very different rates of occurrence when comparing the risk factors involved. Childers et al (2002) examined retrospective data for a group of 163 patients. The study found that 58% of the patients were smokers, 35% had diabetes and 27% were intravenous drug users. In 1997, a population-based surveillance study of 77 patients identified diabetes in 27% of of the patients, with 13% of cases overall having chronic skin lesions (Kaul et al, 1997). This study also highlights a number of patients with diabetes and lower limb ischaemia (12%).

Wong et al (2003) found that of 89 patients recruited with suspected necrotising skin infection, 63 (70.8%) had diabetes – this an extremely high figure – however, the authors give no explanation as to why this may be the case. In the same study 20 (22.5%) had peripheral vascular disease. Chronic liver disease and cancer were also implicated in this study, with only 12 (13.5%) having no co-morbid factors. These studies show a huge range in the numbers of necrotising fasciitis cases with concommittant diabetes – 27–70%. This highlights the concern that people with diabetes would appear at significantly higher risk of developing a necrotising skin infection. Neither study was able to report on the sites of the lesions in the patients with diabetes.

Significantly, all of the studies stated that mortality and morbidity were adversely affected by an increase in the length of time from onset of symptoms to diagnosis and then time to operation (Kaul et al, 1997; Childers et al, 2002; Wong et al, 2003). Knowing the severity and speed at which the disease can progress, the implications of this for practitioners in both primary and acute care settings are far reaching. Awareness of the risk factors and also of early disease presentation is therefore essential in order to prevent complications and to ensure swift treatment.

Due to microvascular and neuropathic damage, the patient with diabetes is well

Table 2. Risk factors for necrotising soft tissue infections. Adapted from Fink and De Luca (2002) and Headley (2003).

- Age (greater than 50)
- Atherosclerosis
- Presence of chronic wound
- Cancer or immunocompromised
- Alcoholic liver disease
- Corticosteroid use
- Diabetes mellitus
- Hypoalbuminaemia
- Intravenous drug abuse
- Renal failure
- Trauma
- Obesity
- Malnutrition
- Occult diverticulitis
- Post-operative infection
- Peripheral vascular disease
- Strangulated femoral hernia
- Use of non-steroidal medication (inconclusive)

PAGE POINTS

1 Factors that may predispose a patient to a necrotising infection include: being a smoker, having diabetes, using intravenous drugs, and peripheral vascular disease.

2 Studies highlight the concern that people with diabetes would appear to be at significantly higher risk of developing a necrotising skin infection.

3 All studies stated that mortality and morbidity were adversely affected by an increase in time from symptom onset to diagnosis and operation.

4 Due to microvascular and neuropathic damage, the patient with diabetes is well recognised as 'at risk' of infection.

PAGE POINTS

1 Studies agree that immediate action should be taken to minimise risks to the patient.

2 Intravenous antibiotics should be administered; benzyl penicillin for streptococcal bacteria and broad-spectrum agents (e.g. clindamycin, gentamycin or metronidazole) for polymicrobial infections.

3 Aggressive surgical debridement with removal of non-viable tissue leaving a wide margin of unaffected tissue is required.

4 When surgery is involved, adequate psychological preparation is necessary.

recognised as 'at risk' of infection (Caputo et al, 1997) (see *Figure 2*). Limb ischaemia can contribute to impaired defence against infection, there is also evidence that polymorphonuclear leucocyte function is affected. Some studies suggest there are problems of adherence, altered chemotaxis, phagocytosis and antibacterial activity in people with poor glycaemic control (Bagdade et al, 1974).

In GAS infection, polymorphonuclear leucocytes are destroyed by streptolysin-O. This could mean, in theory at least, that in patients with diabetes the risks of infection and necrosis are further increased due both to the action of the bacteria and the patients' intrinsic leucocyte malfunction.

Diagnosis and treatment

The diagnosis of necrotising infection is often delayed due to the lack of early signs of infection (Wong et al, 2003). All of the studies cited agree that immediate action should be taken in order to minimise risks to the patient. In some cases there may be no apparent predisposing factors, however in others, for example cases in which a chronic wound is present, the nurse may suspect a change in the wound status or in the overall patient condition.

Intravenous antibiotics should be administered as soon as is possible in order to attempt to slow the progress of the organism. It is recommended that benzyl penicillin 600 mg four times daily (dependent on local practice) should be used to treat the streptococcal bacteria present. The high proportion of polymicrobial infections should also be accounted for and there is a need to use broad spectrum agents, such as clindamycin, gentamycin (1mg per kg body weight, eight hourly) and metronidazole (500 mg three times daily) to cover for other types of bacteria that may be present (Jackson et al, 2003). The addition of clindamycin to the treatment also reduces the likelihood of the 'Eagle effect', in which the penicillin is seen as less effective against the pathogen as a result of the pathogen being in a stationary phase or non-growth phase (Eagle, 1952).

Aggressive surgical debridement is essential in order to minimise the effects of this condition. The non-viable tissue is removed leaving a wide margin of unaffected tissue in order to minimise the risk of recurrence. Patients may be surprised by the extent of the excision, as the initial wound will not be representative of the final wound that the surgeon creates.

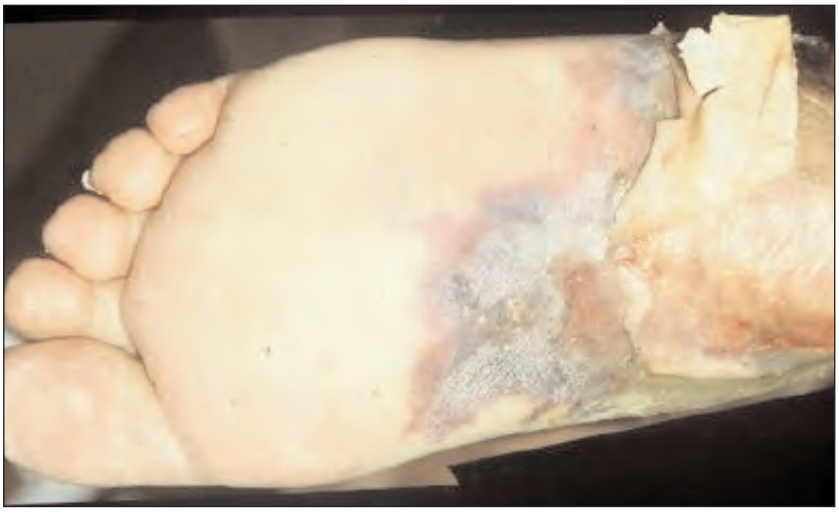
Adequate psychological preparation is necessary in the preoperative phase, however, this may prove difficult given the speed of the disease process. Any delay in treatment is associated with an increase in mortality (Aronoff and Bloch, 2003; Headley, 2003). Caring for relatives is also essential, however, there are few studies that examine the before and after care of this patient group in sufficient depth as to examine the psychological responses of patient and relative.

Treatment with hyperbaric oxygen has also been used to some effect in a few studies, with the increase in oxygen in the wound assisting in faster wound healing and also a reduction in bacterial numbers (Bissett, 2002). The results are inconclusive and this therapy should only be used as an adjunct to surgery and antibiotics, not a replacement (Bissett, 2002).

Challenges

Not apparent in many of the studies cited are more exact details of the

Figure 2. The spreading streptococcal infection in a patient with diabetes. (Credit: Lynne Watret)



patients with the infection in terms of wound sites, depth of tissue damage, and whether treatment regimens are more or less successful in patients with diabetes. The challenge for the practitioner is to be aware of the patient's risk profile and to promptly diagnose the early signs of the disease and initiate treatment.

The fact that many studies report greater numbers of patients with diabetes is of concern to practitioners in all settings. From the studies cited there are large pieces of information missing that may provide more guidance for specific management of the patient with diabetes and a necrotising infection.

Further study must be done in order to find out the following:

- What combinations of factors may precipitate a necrotising infection?
- Is mortality in patients with diabetes and necrotising infection increased?
- Which wound sites are most vulnerable? (will require accurate documentation of wound sites.)
- How good was the patient's glycaemic control?
- Which treatment regimens, including antibiotics and wound dressings, can promote the most favourable outcomes?

Furthermore, it is essential that accurate analysis of wound bacteria is carried out in order to identify those patients with existing ulcers who may have the potential to develop streptococcal and/or polymicrobial tissue infection. ■

PAGE POINTS

1 It is essential that accurate analysis of wound bacteria is carried out to identify patients with existing ulcers with the potential to develop streptococcal and/or polymicrobial tissue infection.

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