Necrotizing soft tissue infection: principles of diagnosis and management

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Abstract

Necrotizing soft tissue infection (NSTI) is a rare and sometimes deadly infective condition affecting the subcutaneous tissue and fascia, with or without involvement of the muscle. This paper reviews the broader definition of necrotizing infections, including infective myositis. The symptoms, signs and laboratory-based diagnostic tools are discussed. Early diagnosis of NSTI is often a challenge due to inconsistent features of necrosis at presentation; however, features of necrosis can also develop within hours. Clear risk factors and patterns of bacteriology exist, some of which define prognosis. Modern concepts, including debridement zones and an operative strategy are discussed. Time to debridement significantly impacts mortality outcomes and is a key message of this article.

Keywords infection; myositis; necrotizing fasciitis; *Streptococcus pyogenes*; toxic shock syndrome

Introduction

Necrotizing soft tissue infection (NSTI) is a rare and sometimes deadly infective condition affecting the subcutaneous tissue and fascia, with or without involvement of the muscle.

NSTIs are rapidly progressive with high associated mortality. In the UK, these infections maybe treated by a wide variety of teams including Infectious Diseases, General Surgery, Maxillofacial, Urology, Plastics and Orthopaedic Surgery. Given the low incidence and division of caseload over different specialities, exposure to these conditions remains low. It has been well established that delay in diagnosis leads to increased mortality.[1–3] This necessitates the need for rapid diagnosis and early appropriate debridement to reduce mortality from NSTI.

There has been, quite correctly, an increased focus on necrotizing fasciitis with media coverage of "flesh eating bacteria". However, deeper infections involving muscle have a similar aetiology, progression and high mortality rate. These infections are commonly misdiagnosed as cellulitis or abscesses. It is essential therefore, that these conditions are considered together as a spectrum.

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Epidemiology

NSTI is most common in men (1.3:1) and in the 5th and 6th decades of life.[4,5] It is rarely seen in children, but is associated with newborn omphalitis and recent *Varicella zoster* infection, both with a high mortality.

NSTI has a seasonal variation, with a higher incidence reported between January and April in Denmark.[6] A population-based surveillance study from Canada identified that 85% of monomicrobial NSTIs occur sporadically in the community, 10% are hospital acquired, 4% are from care homes and 1% from a direct exposure.[7]

As yet unpublished data from UK suggest that the incidence of necrotizing fasciitis has doubled from 2003 to 2011.[8]

A large-scale study with a cohort including 1509 NSTI patients had an incidence of 15.5 per 100 000 population across three provinces of Thailand.[5] It is estimated that surgeons encounter at least one NSTI during their clinical practice.[9]

Risk factors

In general, conditions leading to immunocompromise are associated with NSTI.

It is believed that at least two-thirds of NSTI patients have one or more conditions such as diabetes, peripheral vascular disease, chronic liver disease or cancer.[2,5,10] Intravenous drug use is also a strong risk factor.[9] Decompensated liver disease is associated with higher mortality ($p = 0.015$).[11] Group A Streptococcus (GAS) necrotizing fasciitis or myositis may, however, occur in healthy individuals.

Pathophysiology

The predominant tissue layers implicated are the subcutaneous fat and the deep fascia; hence the commonly used term 'necrotizing fasciitis'. The pathogens responsible for NSTI are known to cause infections that generally are not normally life threatening. The exact reasons for these becoming lethal infections are unknown as yet. Host factors, including immunocompromise, do play a permissive role; however, there is evidence that Group A Streptococcus may undergo random single nucleotide mutation, increasing the pathogen's ability to cause necrotizing fasciitis.[12]

Regardless of the type of microorganism, a common pathway ensues following inoculation. The pathogenesis of NSTI involves a three-staged attack with i) local angiothrombotic bacterial invasion, ii) local tissue necrosis and then, subsequently, iii) release of toxins (Figure 1). The exotoxins are responsible for early systemic features. Bacterial invasion leads to secretion of local cytokines, leading to activation of platelets. Along with activated white cells, these platelet clumps lead to microvascular occlusion. Cutaneous blood supply and lymphatic channels undergo thrombosis. Subsequent local hypoxia and local inflammatory marker release, including TNF alpha and IL-6, lead to cellular dysfunction and death. Early local ischaemia encourages necrosis as well as preventing access to antibiotic therapy. This local anoxia leads to progressive cutaneous nerve damage, leading to severe pain followed by local anaesthesia. Rapid

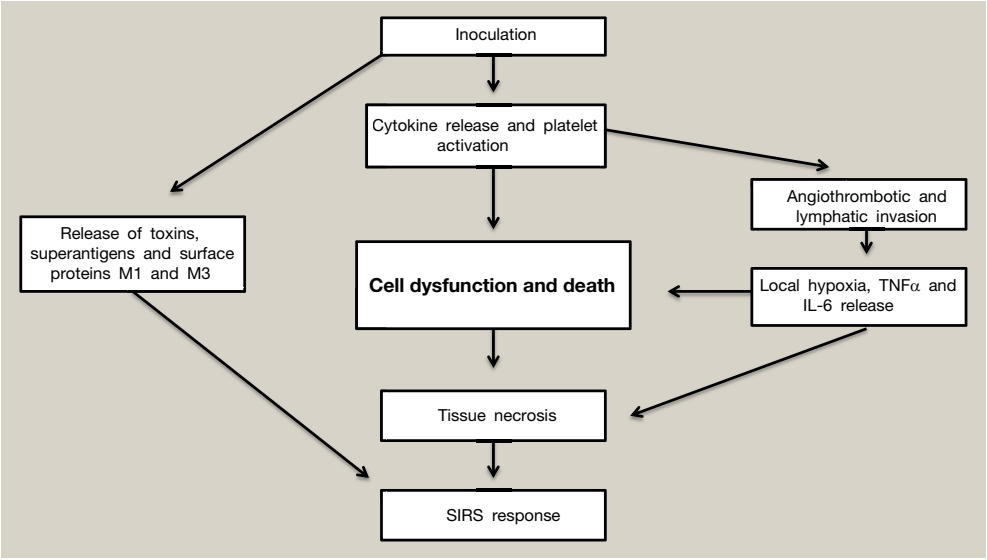

Figure 1 Pathogenesis of necrotising soft tissue infections.

thrombosis of local vasculature explains lack of lymphatic spread of these conditions. This may also explain the low incidence of NSTIs travelling across the fascia to deeper muscular compartments. Spread of infection is therefore contiguous and horizontal.

Group A Streptococcus also displays surface proteins M1 and M3, which resist phagocytosis. The presence of superantigens leads to excessive activation of T-cells, leading to an accelerated immune response. Progression to Streptococcal Shock Syndrome carries a mortality risk of up to 40%.[13]

Presentation

The presentation of NSTI can also be separated into local and systemic features. NSTIs are notoriously difficult to diagnose early due to the paucity of early skin manifestations (Tables 1 and 2).

A key early feature of NSTI is severe pain, which is disproportionate to all visible clinical signs. This is due to subcutaneous neural hypoxia and may extend beyond any visible erythema.

Up to 50% of patients will have a visible portal of entry, such as an ulcer, wound or injection site.[2] The vast majority of cases involve the peripheries, with 70% affecting the lower limb and 10% the upper limb (the other 20% affect the trunk).[2]

A paucity of the classic but late signs of NSTI at presentation can delay the diagnosis. Level II evidence suggests that only 14.6% (13/89 patients) had the correct diagnosis of NSTI made on admission, with the majority diagnosed as cellulitis (58%) or abscess (16%).[2] Wong et al speculate that the cause for the reduction in multiple organ failure and systemic signs of sepsis at presentation is due to an increase in antibiotic prescribing at a primary care level; 70% of their patients had pre-hospital antibiotics. As the clinical findings on presentation can be misleading, it is important to continually re-assess the high-risk patient.

Investigation and diagnosis

As the evidence for early debridement has been established, a recent trend in the literature has focused on the early diagnosis of NSTI through objective parameters.

Wall et al developed the first laboratory-based diagnostic tool for NSTI.[14] The presence of either a WBC $>15.4 \times 10^9$/L or a serum Na^{2+} <135 mmol/L was shown to be have 90% sensitivity and 76% specificity for NSTI. The positive predictive value (PPV) was 26% and the negative predictive value (NPV) was 99%, meaning that this is a good tool to rule out NSTI, but not useful to confirm an NSTI diagnosis.

Serum lactate >2.0 mmol/L at presentation identifies the tissue necrosis of NSTI, with a sensitivity of 100% and specificity of 76%.[15] Lactate in isolation has not been validated in other papers, but has been integrated in other biochemical prediction tools.

In 2004, Wong et al published the results of their Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC).[16] This was a multicenter observational study that performed a univariate and multivariate logistical regression analysis to identify the most useful blood tests to differentiate between NSTI and severe (non-necrotizing) soft tissue infections. The serum blood parameters for the LRINEC scoring and their associated weighting are seen in Tables 3 and 4, with a maximum LRINEC score of 13. A raised C-reactive protein (CRP) is attributed 4 points on the LRINEC scoring system. It is important to stress that a CRP will not be raised in a patient with chronic hepatic failure, a known risk factor for NSTI. In addition, a diabetic patient with renal failure may have a very high LRINEC index even with just cellulitis. Despite these limitations, the LRINEC index is used widely to escalate the response to severe infections.

An LRINEC score of ≥6 had a PPV of 92% and NPV of 96% to diagnose NSTI, a significant improvement on the initial predictive model suggested by Wall et al. Analysis of the LRINEC scoring tool was based on 89 consecutive NSTI cases and it demonstrated that LRINEC is a statistically strong model.[16] However, a validation assessment of LRINEC from an independent unit (who assessed 233 NSTI patients) found that an LRINEC score of ≥6 had a sensitivity of just 59%, a specificity of 84%, a likelihood ratio of 3.89, a positive predictive ratio of 38% and a negative predictive ratio of 93%.[17] The conclusion of this