Necrotizing fasciitis

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Key points
Patients with necrotizing fasciitis (NF) have pain disproportionate to their physical findings.
During the early stages of NF, an apparently normal-looking skin is seen.
The LRINEC score (Laboratory Risk Indicator for Necrotising Fasciitis) is a scoring system, surgical exploration, and tissue biopsy can detect necrotizing soft tissue infections.
Delays in diagnosis and surgical intervention increase tissue loss and risk of mortality.
Communication and teamwork between the intensivist, surgeon, anaesthetist, and microbiologist are essential.

Necrotizing fasciitis (NF) is a progressive, fulminant bacterial infection of subcutaneous tissue that spreads rapidly through the fascial planes causing extensive tissue destruction. NF can affect any part of the body and is the most serious presentation of necrotizing soft tissue infection (NSTI); it is a rare but potentially fatal condition. Prompt recognition and intervention is essential, as mortality is directly proportional to time to intervention.

The UK incidence of reported NF is ~500 new cases each year, although this is likely to be an underestimate. In Canada, it is estimated that 90–200 cases of NF occur each year in all age groups. The USA reports an annual age-adjusted incidence of 4.3 invasive infections per 100,000 of the population. In Australian studies, it is reported as a maximum yearly incidence of 3.8 cases per 100,000. Reported mortality in the literature varies widely with more recent studies reporting a mortality of around 25%.

Classification
NSTIs vary from mild pyodermas to NF. NSTI can be classified in multiple ways (Table 1 and Fig. 1) but is most commonly classified by microbial source of infection (Table 2). Types I and II are responsible for the majority of cases of necrotizing fasciitis in the UK, whereas Types III and IV are extremely rare.

Type I
Type I infections are the most common form of the disease. They are polymicrobial and wound tissue isolates identify on average four different organisms. Causative microbes include a combination of Gram-positive cocci, Gram-negative rods, and anaerobes. Type I infections most frequently occur in the perineal and trunk areas in immunocompromised patients, particularly diabetics and patients with peripheral vascular disease. Fournier’s gangrene refers to NF of the perineal, perianal, and genital regions and is a relatively common presentation in the UK. Other risk factors (Table 3) include obesity, chronic renal failure, HIV, alcohol abuse, abscess, i.v. drug use, blunt or penetrating trauma, insect bites, surgical incisions, indwelling catheters, chicken pox, vesicles, and (rarely) perforation of the gastrointestinal tract (e.g. carcinoma or diverticulitis).

Type II
An infection caused by the group A streptococcus (Streptococcus pyogenes) either alone or in association with Staphylococcus aureus, classically located on the extremities of the body but truncal involvement has also been reported. Group A streptococci can survive and replicate in macrophages, thereby escaping antibiotic therapy even in those tissues that remain well perfused and considered amenable to antibiotic penetration.

Type II is the only NSTI associated with toxic shock syndrome. Type II is far less common than type I infection; however, this incidence is increasing, reflecting the rise in the incidence of community-acquired methicillin-resistant S. aureus (MRSA) in some parts of the world. MRSA soft tissue infection has been reported particularly in i.v. drug abusers, athletes, and institutionalized groups. Type II NSTIs often occur in healthy, young, immunocompetent hosts, although frequently there is a history of recent trauma or operation to the tissue involved.

Type III
Type III is a Gram-negative monomicrobial NF. The most common Gram-negative responsible are Vibrio spp., such as V. damselae and V. vulnificus. Type III is uncommon but carries a very high mortality of 30–40%, despite prompt diagnosis and aggressive therapy.

Type IV
Type IV describes fungal cases of Candida NF. These are very rare. Fungal invasion most commonly occurs in patients with traumatic wounds and burns and in those who are severely immunocompromised.
Pathophysiology of NF

Microbial invasion of the subcutaneous tissues occurs either through external trauma or direct spread from a perforated viscus (particularly colon, rectum) or urogenital organ. Bacterial growth within the superficial fascia releases a mixture of enzymes and endo- and exotoxins causing the spread of infection through this fascia. This process results in poor microcirculation, ischaemia in affected tissues, and ultimately, cell death and necrosis.

Thrombosis of small veins and arteries passing through the fascia causes profound skin ischaemia. This skin ischaemia is the fundamental process for the soft tissue presentation of NF as it progresses. Importantly, during the early pathological stages, an apparently normal-looking skin is seen, despite extensive infection of the underlying fascia. Haemorrhagic bullae, ulceration, and skin necrosis subsequently manifest with further involvement of the deeper structures.

The initial clinical skin findings underestimate the tissue infection present, although thrombosis of penetrating vessels to the skin is the key feature in the pathology of NSTI. Thrombosis of large numbers of dermal capillary beds must occur before skin changes suggestive of necrosis occur.6

Risk factors and prognosis

Most patients with NF are immunocompromised with one or more chronic debilitating diseases. Table 3 lists known predisposing risk factors for NF. There may be a history of minor trauma such as gardening scratches or penetrating soft tissue injuries by insect, dog, or human bites and injections. A history of more major trauma should also be sought, for example, a recent operation, skin

Table 1 Classification of soft tissue necrotizing infections

<table>
<thead>
<tr>
<th>Classification</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic location</td>
<td>Cervical, thoracic, abdominal (Meleney’s), pelvic, Fournier’s gangrene</td>
</tr>
<tr>
<td>Depth of infection</td>
<td>Epidermis and dermis</td>
</tr>
<tr>
<td></td>
<td>Erysipelas</td>
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<tr>
<td></td>
<td>Impetigo</td>
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<tr>
<td></td>
<td>Folliculitis</td>
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<td></td>
<td>Ecthyma</td>
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<td></td>
<td>Furunculosis</td>
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<tr>
<td></td>
<td>Carbunculosis</td>
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<tr>
<td></td>
<td>Cellulitis</td>
</tr>
<tr>
<td></td>
<td>Superficial fascia, subcutaneous tissue, subcutaneous fat, nerves, arteries, veins, Deep fascia</td>
</tr>
<tr>
<td>Microbial cause</td>
<td>Types I, II, III, and IV</td>
</tr>
</tbody>
</table>

Fig 1 Depth of infection and clinical classification of soft tissue infections. Reproduced with permission from the American College of Chest Physicians.
infection, or ulcer. Independent markers of mortality from NF in order of severity are: streptococcal toxic shock syndrome, immunocompromise, and advanced age.7

Clinical presentation and diagnosis

Many patients with NF are initially misdiagnosed with cellulitis, delaying appropriate management and increasing morbidity and mortality. Despite some similarities in the clinical presentation of cellulitis and NF, it is very important to correctly identify symptoms and signs allowing the correct diagnosis. The most critical early distinctive symptom of NF is a disproportionate level of pain compared with physical findings.

Unlike cellulitis where the infection begins at the junction between the dermis and superficial fascia, in NF, the infection starts at the level of subcutaneous fat and deep fascia. It is because of this sparing of the epidermal and dermal layers in the early stages of the disease that erythema and oedema of skin are not obvious,6 and so the extent of infection clinically is not clear. Lymphangitis is rare in NF. Blister or bulla formation is an important but late feature of necrotizing fasciitis. Blisters result from ischaemia as the penetrating vessels that perfuse the skin are largely thrombosed due to the inflammatory process. In contrast, blistering and bullae are rare findings in cellulitis.

The rate of progression of NF can vary from several days from presentation to, in contrast, a rapid decline and death within hours from presentation. Patients with NF in the later stages of the disease often show symptoms and signs of septic shock, toxic shock syndrome, and multiorgan failure. Tachycardia, tachypnoea, fever or hypothermia, hypotension, cardiac arrhythmias, confusion, metabolic acidosis, abnormal renal and liver function, coagulopathy, and thrombocytopenia may occur. These patients carry a high rate of mortality.

Clinical dermatological features of NF can be classified into three stages:

Stage 1: defined with signs such as erythema, tenderness beyond the erythema, swelling, and hot skin.
Stage 2: defined by the formation of skin bullae, blister, and skin fluctuation.
Stage 3: manifests with haemorrhagic bullae, crepitus, skin necrosis, and gangrene.

Investigations

Diagnosis of NF is essentially clinical. The gold standard is surgical exploration and tissue biopsy. The presence of fascial necrosis and myonecrosis or loss of fascial integrity along tissue planes and frank evidence of muscle involvement are diagnostic. There is a lack of resistance to blunt dissection of the normally adherent superficial fascia, accompanied by a lack of bleeding and the presence of foul-smelling ‘dishwater’ pus.6

These tests are all adjuncts to diagnosing NF. Many are non-specific, reflecting changes that occur in severe sepsis.

Haematology

Haematological changes in NF are consistent with any septic process. These changes include leucocytosis, leucopenia, coagulopathy, and thrombocytopenia. Anaemia can be dilutional from fluid resuscitation or from haemolysis. Disseminated intravascular coagulation is not uncommon in any severe sepsis.

Biochemistry

Raised serum creatinine kinase indicates myositis or myonecrosis, and the effects of circulating toxins or ischaemia.8 Hypocalcaemia

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### Table 2 Micro-organisms causing NF

<table>
<thead>
<tr>
<th>Types of NF</th>
<th>Aetiology</th>
<th>Organism(s)</th>
<th>Clinical progress</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (70–80% cases)</td>
<td>Polymicrobial, synergistic, often bowel flora-derived</td>
<td>Mixed anaerobes and aerobes</td>
<td>More indolent, better prognosis, easier to recognize clinically</td>
<td>Variable; depends on underlying co-morbidities</td>
</tr>
<tr>
<td>Type II (20–30% cases)</td>
<td>Often monomicrobial, skin- or throat-derived</td>
<td>Usually group A β-haemolytic streptococcus (GAS), occasionally S. aureus</td>
<td>Aggressive, protean presentations, easily missed</td>
<td>&gt;32%, depends if associated with myositis or toxic shock</td>
</tr>
<tr>
<td>Type III</td>
<td>Gram-negative, often marine-related organisms</td>
<td>Vibrio spp. mainly</td>
<td>Seafood ingestion or water contamination wounds</td>
<td>30–40%</td>
</tr>
<tr>
<td>Type IV (fungal)</td>
<td>Usually trauma associated, immunocompetent patients</td>
<td>Candida spp. immunocompromised patients. Zygomycetes immunocompromised patients</td>
<td>Aggressive with rapid extension especially if immunocompromised</td>
<td>&gt;47% (higher if immunocompromised)</td>
</tr>
</tbody>
</table>

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### Table 3 Predisposing factors for NF

| | Immunosuppression | Diabetes | Chronic disease | Drugs, for example, steroids | Malnutrition | Age >60 | I.V. drug misuse | Peripheral vascular disease | Renal failure | Underlying malignancy | Obesity | Blunt or penetrating trauma | Soft tissue infections | Surgery | I.V. drug use | Childbirth | Burns | Muscle injuries |
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is a sign of fat necrosis and calcium deposit in necrotic tissues. Bacterial infection, inflammation, and necrosis cause raised C-reactive protein (CRP). As in severe sepsis, abnormal renal function, hypoalbuminaemia, hyponatraemia, abnormal liver function, metabolic acidosis, and high serum lactate concentrations may occur.

**Microbiology**

Blood cultures are positive in 11–60% of the patients with NF caused by group A streptococci. Percutaneous needle aspiration of the advancing edge is useful but a tissue biopsy is the investigation of choice. Tissues and aspirates should be Gram stained and cultured. Fungal culture is recommended in high-risk immunocompromised patients.

**Histology**

Deep incisional biopsies and frozen sections with Gram staining of tissues are all diagnostic of NF. Samples should include the advancing edge and central necrotic areas. It reveals the underlying thrombi, necrosis, polymorphonuclear infiltrates, microorganisms, and vasculitis.

**Laboratory scoring systems for the prediction of NF**

The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) scoring system was designed to distinguish NF from other soft tissue infections. A comparison of laboratory tests between these two groups of patients showed that the most reliable and significant indicators of the underlying NF rather than cellulitis were CRP, creatinine, haemoglobin, white cell count, sodium, and serum glucose. The score is calculated by adding up each of six predictive factors (Table 4). A score of >6 has a positive predictive value of 92% and a negative predictive value of 96%. A score of ≥8 is strongly predictive of NF, with a positive predictive value of 93.4%.

**Imaging**

Computed tomography (CT) scan, ultrasound, and magnetic resonance imaging (MRI) have all been used to image NSTIs. It is important to emphasise that imaging is not a definitive procedure and should not delay surgery. However, with the increasing use of imaging, it may be possible to diagnose early NF, despite lack of clinical suspicion. CT scans demonstrate deep fascial thickening and enhancement, and the presence of fluid and gas within soft tissue planes in and around the superficial fascia. Ultrasound identifies features suggestive of thickening, distortion, and fluid collections along the deep fascia. MRI with gadolinium differentiates necrotic and inflamed or oedematous tissue. T2-weighted images on MRI are probably the best radiological adjunctive investigation for NF.

### Table 4 Laboratory Risk Indicator for Necrotising Fasciitis score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>C-reactive protein</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>0</td>
</tr>
<tr>
<td>≥150</td>
<td>4</td>
</tr>
<tr>
<td>WBC (cells mm$^{-3}$)</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
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<tr>
<td>15–25</td>
<td>1</td>
</tr>
<tr>
<td>≥25</td>
<td>2</td>
</tr>
<tr>
<td>Haemoglobin (g d$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>&gt;13.5</td>
<td>0</td>
</tr>
<tr>
<td>11–13.5</td>
<td>1</td>
</tr>
<tr>
<td>&lt;11</td>
<td>2</td>
</tr>
<tr>
<td>Sodium (mmol litre$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>≥135</td>
<td>0</td>
</tr>
<tr>
<td>&lt;135</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine (µg litre$^{-1}$)</td>
<td></td>
</tr>
<tr>
<td>≤141</td>
<td>0</td>
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<tr>
<td>&gt;141</td>
<td>2</td>
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<tr>
<td>Glucose (mmol litre$^{-1}$)</td>
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</tr>
<tr>
<td>≤10</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1</td>
</tr>
</tbody>
</table>

**Treatment**

Early diagnosis, aggressive resuscitation, surgical debridement, antibiotic therapy, and supportive intensive care are necessary for managing patients with NF. Effective communication between the intensivist, surgeon, anaesthetist, and microbiologist is essential.

**Resuscitation and supportive care**

The aim of resuscitation is to establish an adequate tissue perfusion and oxygen delivery. Invasive arterial pressure monitoring and central venous access may be required; goal-directed therapy targets for haemodynamic resuscitation in patients with sepsis secondary to NF are as suggested by the Surviving Sepsis Campaign. Adequate nutritional support and treatment of nosocomial infections are crucial. Critical care admission is strongly recommended in view of the aggressive clinical course, high risk of multiorgan failure, and significant mortality rate.

**Surgical debridement**

Several studies have shown that the most important factor affecting mortality is timing and adequacy of initial surgical debridement. Delayed or inadequate debridement dramatically increases mortality. Radical debridement may necessitate limb amputation. Debridement removes the source of infection and toxins, and furthermore, removal of infected tissue improves the subsequent penetration of antibiotics. The infection is rarely eradicated after a single debridement and serial debridements are almost always needed. Optionally, three debridements spaced 12–36 h apart are required to obtain control of gross infection. Debridement may result in significant intraoperative blood loss and inability to close surgical wounds. Vacuum-assisted dressings and skin expansion
devices may have a role. Reconstructive surgery should be considered only when the patient has been stabilized and the infection fully eradicated.

Antibiotic therapy

Antibiotics are unable to penetrate infected necrotic tissue because of the thrombogenic nature of the process, so aggressive surgical debridement remains the first priority. Due to complex microbiology and fulminant nature of the infection, seeking advice from a senior microbiologist is crucial.

Empiric therapy requires an antibiotic combination that covers the variety of organisms that may cause NF. A broad-spectrum agent such as Tazocin, containing piperacillin (a penicillin which kills a wide variety of bacteria by interfering with the formation of bacterial cell walls) and tazobactam (a β-lactamase inhibitor which prevents bacteria from inactivating piperacillin leaving them susceptible to attack) or a carbapenem (such as meropenem), can be combined with clindamycin. If Group A streptococcus alone is responsible, antibiotics may be rationalized to a combination of penicillin and clindamycin. Clindamycin is included in antibiotic therapy as it is known to switch off toxin production. Likewise, when MRSA is suspected, Linezolid is preferred to vancomycin as it inhibits exotoxin production.

I.V. immunoglobulin therapy

The use of i.v. immunoglobulin (IVIG) is based on the theoretical mechanism that it can bind staphylococcal- and streptococcal-derived exotoxin, so limiting the systemic cytokine release associated with systemic inflammatory response syndrome.

There is very limited evidence which suggests a decreased mortality from using IVIG in group A streptococcal NF. IVIG use in other forms of NF has not been studied. Currently, IVIG should be restricted to consideration of use for critically ill patients with either staphylococcal or streptococcal NF.5,12

Hyperbaric oxygen

For synergistic infections, particularly involving Clostridium spp., hyperbaric oxygen (HBO) switches off toxin production. HBO is believed to increase the bactericidal action of neutrophils. However, the overall evidence of benefit in non-clostridial NF is weak. In addition, there are few hospitals with easy access to HBO units, appropriate staffing, and chambers large enough for patients receiving intensive care support.8

Anaesthetic implications

Anaesthesia for patients with NF is often challenging and should be undertaken by a senior anaesthetist. Patients with NF need multiple general anaesthetics for surgical debridement, reconstruction, and skin grafting. It frequently involves dealing with a severely septic patient. Surgical debridement is often more extensive than expected before operation, and this and coagulopathy can result in substantial blood loss.

Preoperative assessment should focus on the severity of sepsis, anatomical involvement, the presence of shock or multiorgan dysfunction, and the adequacy of haemodynamic resuscitation.13

The need for aggressive fluid resuscitation and the requirement for inotropic support should be pre-empted and often necessitate invasive blood pressure and central venous pressure monitoring. Cardiac output monitoring may be required to optimize cardiac output, inotropic state, and vasopressors response. It should be noted that cervicothoracic NF may limit the options for central venous access.

The postoperative care period is crucial and intensive care admission is recommended, with organ support as appropriate. Close observation of the debrided wound is necessary and multiple debridements are very common. Adequate analgesia must be provided; patient-controlled analgesia is often preferable in cases with extensive debridement.

The safety of health-care workers and close contacts of patients with NF must be considered. Currently, antimicrobial prophylaxis is not recommended for adults with close contact to patients with NF and group A streptococcus. However, the UK Health Protection Agency recommends increased vigilance and the seeking of early medical advice if signs and symptoms of infection develop in any such individual.

Summary

NF is a progressive, fulminant bacterial infection of subcutaneous tissue that spreads rapidly through the fascial planes causing extensive tissue destruction. NSTI is most commonly classified by microbial source of infection. Prompt recognition, diagnosis, and intervention are essential. Delays increase tissue loss, and mortality is directly proportional to time to intervention.

Clinically, pain precedes skin changes by 24–48 h and apparently normal-looking skin is seen during the early pathological stages, despite extensive infection of the underlying fascia. Common misdiagnoses are muscular pain and cellulitis. The LRINEC scoring system and the gold standard surgical exploration and tissue biopsy distinguish NF from other soft tissue infections.

Most patients with NF have one or more chronic debilitating diseases. Patients with NF may show symptoms and signs of sepsis, severe sepsis, septic shock, toxic shock syndrome, and multiorgan failure. Early diagnosis, aggressive resuscitation, surgical debridement, antibiotic therapy, and supportive intensive care are necessary for managing patients with NF. Preoperative assessment should focus on the severity of sepsis, anatomical involvement, the presence of shock or multiorgan dysfunction, and the adequacy of haemodynamic resuscitation. Anaesthesia is challenging, and haemodynamic instability of the septic patient, large blood loss, and fluid shifts should be anticipated. Invasive arterial and central venous pressure and cardiac output monitoring are often necessary. Effective communication between the intensivist, surgeon,
anaesthetist, and microbiologist is essential in the successful management of these patients.

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Declaration of interest

None declared.

References


Please see multiple choice questions 13–16.