Necrotizing soft tissue infections

John D Urschel

Necrotizing soft tissue infections are a highly lethal group of infections that require early and aggressive surgical debridement. These infections may occur in almost any anatomic area, but they most frequently involve the abdomen, perineum, and lower extremities. Surgery and trauma are common aetiologies, but in some cases the aetiology remains uncertain. Immunosuppressed patients, especially those with diabetes, are more likely to develop necrotizing infections. A great deal of attention has been directed toward classifying these infections by bacteriological features or layers of tissue involved, but it is useful to view necrotizing infections as a spectrum of clinical conditions with similar pathophysiological features and common treatment principles. In this review, the common treatment concepts applicable to all necrotizing soft tissue infections will be emphasized, and the more important specific disease entities will be described.

Clinical features of necrotizing soft tissue infections include wound pain, crepitus, foul watery wound discharge, skin blistering, and rapid progression to septic shock. The external appearance of the skin wound may initially betray the seriousness of the necrotizing infection beneath it (figure 1); this contributes to diagnostic delay. Soft tissue gas, detected clinically or radiologically, is a classic sign, but its absence does not exclude the presence of a necrotizing infection. This common misconception is also responsible for delayed diagnosis in some cases. The infection spreads rapidly through the soft tissue planes, and produces severe systemic sepsis. Progression to septic shock, multiple organ failure, and death ensues if aggressive treatment is not instituted immediately. Even with timely and skilled treatment, death from necrotizing soft tissue infections is all too frequent.

Some necrotizing infections are caused by single organisms. Myonecrosis (gas gangrene) from Clostridium infection and necrotizing fasciitis from group A Streptococcus are two classic examples of monomicrobial necrotizing infection. However, most necrotizing soft tissue infections are caused by a mixture of aerobic and anaerobic bacteria, that act synergistically to cause fulminant infection. Organisms commonly identified include aerobic and anaerobic streptococci, coagulase-negative and coagulase-positive staphylococci, facultative and aerobic Gram-negative rods, Bacteroides species, and Clostridium species. Facilitative organisms lower the oxidation-reduction potential of the wound microenvironment, and promote favourable conditions for the growth of anaerobes. Anaerobes interfere with host phagocyte function, and thereby facilitate the proliferation of aerobic bacteria. Several bacteria, such as Bacteroides fragilis, produce β-lactamase enzymes that interfere with antibiotic activity.

Bacterial necrotoxins, such as those produced by Clostridium perfringens and Streptococcus pyogenes, cause tissue necrosis. In addition, the infectious process activates the coagulation system that in turn produces local vascular thrombosis and infarction. Bacterial heparinase production contributes to this process. As the infection progresses, pressure increases within the soft tissues causing further impairment of blood supply.

The diagnosis of necrotizing soft tissue infections is usually made at the time of surgical exploration. Securing a diagnosis non-invasively is very difficult; this contributes to diagnostic delay, and the ultimate demise of many patients. The clinical presentation is often mistaken for simple cellulitis. However, pain in the affected region and systemic toxicity are more pronounced than would be expected in simple cellulitis. Despite recommendations for the diagnostic use of computed tomography and magnetic resonance imaging studies in these infections, the best diagnostic strategy is to perform surgical exploration when clinical features raise the possibility of necrotizing soft tissue infection.

Initially, diagnostic surgical exploration can be very limited in scope; small incisions under local anaesthesia serve to establish the presence or absence of fascial and muscle necrosis. Frozen section examination of tissue specimens will establish the diagnosis if the gross findings at surgical exploration leave any doubt.
cells (haematoxylin and eosin, connective tissue and acute inflammatory wall necrotizing fasciitis involving the abdominal patient suicide). Figure 2. Histology shows necrotic within 24 hours of amputation amputation, fulminant sepsis led to death betray the seriousness of underlying process has been arrested.23 24 The clinical suspicion indicates that the broad general principles of diagnosis and treatment outlined above are not relevant for the initial care of patients; confused clinicians were similar for all of the entities within the spectrum. Previous complex classification schemes were not relevant for the initial care of patients; confused clinicians were left without practical management algorithms. Nevertheless, there are several distinct clinical–bacteriologic infectious entities (reviewed below).

Hyperbaric oxygen therapy has an uncertain role in the management of necrotizing soft tissue infections. Some studies suggest a survival benefit,21 30 31 but others do not.24 32 Survival from clostridial myonecrosis is probably improved by hyperbaric oxygen therapy.32 33 For other types of necrotizing soft tissue infection, hyperbaric oxygen therapy may hasten local wound healing and closure.9 30 Most investigators agree on one point: hyperbaric oxygen therapy is not as important as urgent surgical intervention. Debridement should take priority over patient transfer to a hyperbaric oxygen facility.

Despite aggressive therapy, and modern intensive treatment unit care, the mortality of necrotizing soft tissue infections remains high (15–50%).1 8 13 Factors associated with increased mortality include extent of soft tissue involvement, delay in diagnosis, inadequate debridement, advanced age, and truncal involvement.20 21 24 Chest wall involvement is particularly ominous, and survival is rare.5 34 Considering the seriousness of necrotizing soft tissue infections, and the complexity of treatment, a multidisciplinary team approach is needed. Surgeons, anaesthetists, intensive care physicians, and infectious disease consultants must work together.

### Specific syndromes

Many authors have stressed the importance of a unified approach to necrotizing soft tissue infections,1 8 13 and the initial diagnostic and management approach is similar for all of the entities within the spectrum. Previous complex classification schemes were not relevant for the initial care of patients; confused clinicians were left without practical management algorithms. Nevertheless, there are several distinct clinical–bacteriologic infectious entities that should be recognised (table). After initial treatment has been instituted, subtle differences in management for the various specific syndromes become important.30 13 However, it is worth reiterating that the broad general principles of diagnosis and treatment outlined above are undoubtedly more important than the specifics discussed below. Three of the major necrotizing soft tissue infections will be reviewed: necrotizing fasciitis type I (polymicrobial), necrotizing fasciitis type II (group A streptococcal), and Clostridial myonecrosis (gas gangrene). Finally, several other necrotizing soft tissue infectious entities will be briefly described.

#### NECROTIZING FASCIITIS TYPE I (POLYMICROBIAL)

Necrotizing fasciitis usually occurs after trauma or surgery (figure 4).8 35 The subcutaneous fat and fascia overlying muscle are prominently involved, but in the late stages extension occurs into the muscle tissue itself. Anaerobes and facultative bacteria act synergistically to cause tissue destruction. The clinical pace...
Necrotizing soft tissue infections — major clinical entities

Table

<table>
<thead>
<tr>
<th>Necrotizing fasciitis type I (polymicrobial)</th>
<th>Predisposing factors</th>
<th>Microbiology</th>
<th>Dominant features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, trauma, diabetes mellitus</td>
<td>Anaerobes, Gram-negative aerobic bacilli</td>
<td>Necrosis of fat and fascia, may have gas</td>
<td>Debridement, broad-spectrum antibiotics, ITU support</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Necrotizing fasciitis type II (group A streptococcal)</th>
<th>Predisposing factors</th>
<th>Microbiology</th>
<th>Dominant features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, minor trauma, varicella</td>
<td>Streptococcus pyogenes</td>
<td>Rapidly progressing necrosis of multiple tissue layers, no gas, shock</td>
<td>Debridement, penicillin &amp; clindamycin, ITU support</td>
<td></td>
</tr>
</tbody>
</table>

| Clostridial myonecrosis (gas gangrene)              | Clostridial species | Fulminant myonecrosis, prominent gas formation | Debridement, penicillin & clindamycin, ITU support, hyperbaric oxygen |

Necrotizing fasciitis may occur in the perineum. This type of infection is usually secondary to urogenital or anorectal infections. It is termed Fournier’s gangrene. Patients usually have a predisposing systemic illness, such as diabetes mellitus. Another distinct form of necrotizing fasciitis is that caused by salt-water contamination of an otherwise minor skin wound. Vibrio species are responsible. The affected patients usually suffer from a predisposing condition, such as chronic liver disease. This form of necrotizing fasciitis is highly lethal.

Necrotizing fasciitis type II (group A streptococcal)

Type II necrotizing fasciitis is caused by virulent subtypes of Streptococcus pyogenes. It has gained considerable recent attention in the lay press where the bacteria is often referred to as a flesh-eating bacteria. The incidence of this infection seems to have increased in the last two decades, but this could simply reflect improvements in diagnosis and reporting. Alternatively, there is some evidence to suggest a true increase in incidence. It could be the result of an evolutionary trend towards greater organism virulence in the setting of a more immunologically naïve population. The presence of the M1 and M3 proteins is associated with virulent infection. The occurrence of outbreaks of streptococcal necrotizing fasciitis has set it apart from related infections, and captured the public’s attention. Most of the general features of necrotizing soft tissue infections apply to this particular entity, but the presence of gas in tissues is unusual. There are some other unique aspects of this condition that warrant further discussion.

Two specific predisposing factors are varicella infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs). Although necrotizing fasciitis is rare in children, almost half of cases occur in the setting of varicella. NSAIDs may attenuate host immune responses and therefore they may predispose to, and adversely effect the outcome of, streptococcal necrotizing fasciitis. However, some investigators have failed to find an increased incidence or severity of streptococcal necrotizing fasciitis in patients using NSAIDs. Another distinct feature of this form of necrotizing fasciitis is its frequent association with streptococcal toxic shock syndrome. This syndrome is similar to that originally described for staphylococcal infections. Its features include a high fever, early onset of shock, multiple organ failure, and a very high mortality rate. Approximately 50% of patients with streptococcal toxic shock syndrome have streptococcal necrotizing fasciitis as the initiating infection.

Treatment of type II necrotizing fasciitis is generally in keeping with the principles outlined above. Once the diagnosis has been established, penicillin combined with clindamycin replaces the previous broad-spectrum empiric antimicrobial therapy. The combination of clindamycin and penicillin appears to be superior to the traditional treatment with penicillin alone. Finally, there is of disease is usually somewhat slower than that seen with type II (streptococcal) necrotizing fasciitis and clostridial myonecrosis, but its overall severity and lethality should not be underestimated. Clinicians often mistake it for simple wound cellulitis, but severe pain and systemic toxicity point to a more sinister underlying infection. The diagnosis is easily established by making a small skin incision and passing a haemostat or probe through the subcutaneous tissues. In necrotizing fasciitis the subcutaneous and fascial layers lack resistance to this manoeuvre, a feature that indicates widespread tissue necrosis underneath seemingly viable skin. Gas may or may not be present in the soft tissues. Histology of affected tissues shows widespread necrosis of subcutaneous fat and fascia, with relative sparing of muscle. An acute inflammatory reaction, with many polymorphonuclear cells, is seen. Thrombosis of blood vessels and abundant bacteria are other typical histologic findings. Aggressive surgical debridement is the key to successful treatment.
some evidence to support the use of intravenous immunoglobulin as an immu-
nomodulator in this condition.13 39

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)
Clostridial myonecrosis is a distinct necrotizing infection of skeletal muscle.43 44
As the older term gas gangrene suggests, muscle necrosis and gas production are
prominent features of this illness. Most cases arise in the setting of recent surgery
or trauma, but some arise spontaneously. Clostridium perfringens (formerly C
welchii) is the most common causative organism. This anaerobic Gram-positive
spore-forming bacillus is widely distributed in soil, and it can be found within the
gastrointestinal tract of animals and humans. The organism produces over 10
different exotoxins of which the α-toxin is the most important.45 The α-toxin
hydrolyses cell membranes. It causes tissue necrosis, inactivates leukocytes, and
haemolyses red blood cells. In addition, the α-toxin has direct cardiodepressive
effects.

The pathologic features of clostridial myonecrosis are very dramatic. Grossly,
there is obvious release of gas upon surgically entering the involved muscle com-
partment. The muscle is oedematous, pale or grey, and it does not bleed or con-
tract when cut. Unlike the other necrotizing infections described above,
clostridial myonecrosis shows very little inflammation on histologic examination.
This lack of inflammatory host response goes along with the classic fulminating
clinical course of clostridial myonecrosis. The infection rapidly advances, often
over a matter of hours.

Surgical debridement and antibiotics are the mainstays of treatment. As for
necrotizing infections caused by group A Streptococci, clindamycin combined
with penicillin is preferable to penicillin alone.1 Hyperbaric oxygen is of greater
benefit for clostridial myonecrosis than it is for other necrotizing infections.46 47
This is logical, since clostridial myonecrosis is a monomicrobial anaerobic infec-
tion. After aggressive debridement and stabilisation, hyperbaric oxygen therapy
should be instituted if available. It inhibits clostridial growth and arrests α-toxin
production.48

Spontaneously occurring clostridial myonecrosis is usually caused by Clostrid-
ium septicum.49 The organism spreads to muscle haematogenously from a small
break in the normal gastrointestinal mucosal barrier. It usually occurs in patients
suffering from either colon cancer or leukaemia. Patients surviving Clostridium
septicum infection should undergo colonoscopy to check for an occult colon can-
cer.

OTHER NECROTIZING SOFT TISSUE INFECTIOUS ENTITIES
Anaerobic streptococcal myonecrosis is a necrotizing infection of skeletal mus-
cle that clinically resembles clostridial myonecrosis.50 51 Compared to clostridial
myonecrosis, the pace of this infectious process is slower and gas production is
not as marked. Anaerobic streptococcal myonecrosis is a polymicrobial
infection. General treatment principles of necrotizing soft tissue infections are
applicable.

Group A streptococci can occasionally cause myonecrosis, although these
organisms more commonly cause necrotizing fasciitis (type II).42 52 The clinical
features and treatment are similar to clostridial myonecrosis, but gas production
is not typically present.

Aeromonas hydrophilia is a facultatively anaerobic, Gram-negative bacillus,
which causes a fulminant myonecrosis.53 54 The rapidity of the infectious process
is similar to that of clostridial myonecrosis, but gas production is not a consist-
ent feature. The infection usually occurs in the setting of penetrating freshwater
trauma. Aggressive surgical debridement and antibiotic coverage for Gram-
negative rods are the essential features of treatment.

Clostridial cellulitis is a necrotizing soft tissue infection that clinically resem-
bles necrotizing fasciitis, but the infection is more superficial.14 55–57 It usually
occurs in the setting of surgery or trauma (Clostridium perfringens), but it can
occur spontaneously in association with malignancy (Clostridium septicum). The
skin and subcutaneous fat are involved. Gas production is a prominent feature.
Since the infection is more superficial than clostridial myonecrosis, the
associated toxicity is usually not as severe. Surgical exploration reveals viable
fascia and muscle; this distinguishes clostridial cellulitis from necrotizing fasci-
tis and gas gangrene. The differentiation is obviously important. Clostridial cel-
lulitis requires debridement of skin and subcutaneous fat, but more aggressive
and extensive surgical therapy is not needed. A very similar superficial necrotiz-
ing infection can also be caused by a variety of anaerobic bacteria, either alone
or as a mixed infection. This is termed nonclostridial anaerobic cellulitis, or syn-
ergistic necrotizing cellulitis.14 56 57 Diabetes mellitus is often a predisposing fac-
tor. The treatment approach is the same as for clostridial cellulitis.
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