Necrotizing soft tissue infections

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Purpose of review

The purpose of this review is to consider recent advances in the definition, pathogenesis, diagnostic criteria, and treatment of necrotizing soft tissue infections.

Recent findings

The efficacy of early surgical debridement combined with antimicrobial therapy, close monitoring and physiologic support is strongly demonstrated. Novel therapeutic strategies including vacuum-assisted wound-closure therapy and intravenous immunoglobulin have been described.

Summary

Necrotizing soft-tissue infection is a rare infection of the subcutaneous tissue and fascia that is often associated with sepsis and can progress rapidly with a possible fatal outcome. Although the cause is not yet understood fully, patients often have a prior history of a small, trivial trauma, wound, or scratch. Establishing the diagnosis can be the main challenge in treating patients, and knowledge of all available tools is key for early and accurate diagnosis.

Keywords

group A beta-hemolytic streptococci, myonecrosis, necrotizing fasciitis, necrotizing soft tissue infection

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Abbreviations

HBO	hyperbaric oxygen
IVIG	intravenous immunoglobulin
NSTI	necrotizing soft tissue infection

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Introduction

Necrotizing soft tissue infections (NSTIs) constitute a spectrum of disease processes characterized by fulminant, widespread necrosis of soft tissue, systemic toxicity, and high mortality. The terminology used to refer to NSTIs is extensive because of the absence of clear definitions and the use of classification systems based on a variety of criteria, including etiologic, microbiologic, anatomic, and clinical aspects. Clinically, a recommended classification is based on the spread of the infection into deeper regions (e.g., superficial versus deep soft tissue infections). Superficial infections (necrotizing cellulitis) are those confined to the cutis and subcutis, such as erysipelas. The second group, which is infection affecting fascia and muscle, includes necrotizing fasciitis and myonecrosis, both of which can be classified into either type I (polymicrobial) or type II (monomicrobial) NSTIs. Type I NSTIs include about 80% of such infections, whereas type II NSTIs comprise nearly all of the remainder. For practical purposes, the various diseases mentioned can be grouped together and discussed as one major disease process because of their similar clinical picture and principles of treatment.

Definition

Necrotizing infections have been recognized and reported for millennia, with the earliest reports dating back to Hippocrates in the fifth century BC. A Confederate Army surgeon during the US Civil War, Joseph Jones, referred to the condition as 'hospital gangrene'. In 1883, Fournier described necrotizing fasciitis of the perineal and genital region. A rapidly progressive soft tissue infection, caused by the synergistic action of a β-haemolytic group *Streptococcus* with or without *Staphylococcus*, was described in 1924 by Meleney. Wilson subsequently re-termed this observed phenomenon as necrotizing fasciitis in 1952.

There are approximately 500–1500 cases of NSTIs per year in the US [1]. The mortality rate is approximately 24–34%. A wide variety of prognostic factors or predictors of mortality have been identified. In a recent study of 350 patients from two tertiary care referral institutions, Anaya *et al.* [2••,3] created a score to categorize patients according to the risk of mortality. Parameters included in the score were age above 50 years; white blood cell (WBC) count over 40 000 cells/mm^3; hematocrit above 50%; heart rate over 110 beats/min; temperature above 36°C; and serum creatinine concentration above 1.5 mg/dl. Regarding its cause [4], NSTIs can be secondary to trauma,

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Figure 1 Myonecrosis of the abdominal wall in a 49-year-old patient after appendectomy for acute appendicitis

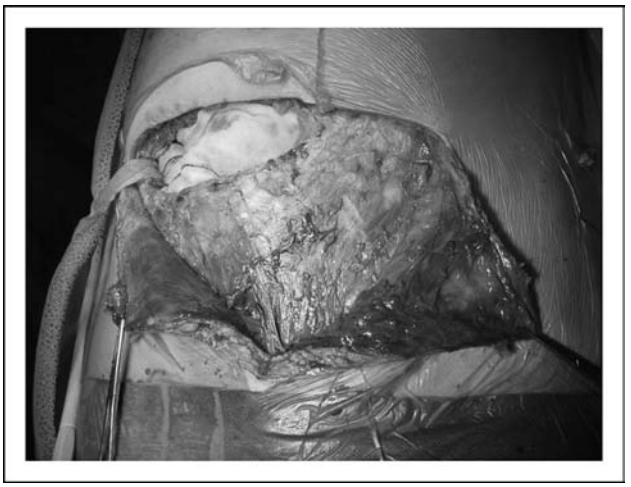

Table 1 Microbiology of necrotizing soft tissue infection

Class	Organism
Aerobic bacteria	
Gram-positive	Group A, β-hemolytic *Streptococcus*
	Group B *Streptococcus*
	Enterococcus
	Coagulase-negative *Staphylococcus*
	S. aureus
	Bacillus sp.
Gram-negative	*Escherichia coli*
	Pseudomonas aeruginosa
	Enterobacter cloacae
	Klebsiella spp.
	Proteus spp.
	Serratia spp.
	Acinetobacter calcoaceticus
	Citrobacter freundii
	Pasteurella multocida
Anaerobic bacteria	*Bacteroides* spp.
	Clostridium spp.
	Peptostreptococcus spp.
Fungi	*Candida* spp.
	Aspergillus spp.
	Rhizopus
Marine *Vibrio* spp.	*V. vulnificus*
	V. parahaemolyticus
	V. damsela
	V. alginolyticus

surgical site infections (Fig. 1), perianal or urogenital abscesses, or decubitus ulcers. In some cases, however, no primary cause can be found [5]. Patients who have preexisting conditions that increase susceptibility to infection seem to be at an increased risk of developing NSTIs; these conditions are as follows: advanced age; diabetes mellitus; alcoholism; peripheral vascular disease; chronic renal failure; heart disease; acquired immunodeficiency syndrome; cancer; nonsteroidal anti-inflammatory drugs; drug abuse, specifically of injection drugs; trauma; decubitus ulcer; perianal or urogenital abscess; surgical site infection; chronic skin infection; immune system impairment) [6]. Approximately one-half of the cases, however, occur in young and previously healthy patients [7,8]. The use of NSAIDs has been suggested by Kihiczak *et al.* [9••] to predispose to NSTI, and although the association is controversial, caution is recommended when using them in patients who may be infected. Varicella zoster virus infection, together with NSAID usage, may be predisposing factors for group A streptococcal NSTI (type II), but this is debated [10]. Only sparse case reports describe the rare association between NSTI and colorectal malignant disease [11]. All such cases are attributed to bowel perforation, resulting in NSTI over the perineal or abdominal region [12]. Isolated upper or lower limb presentations are exceedingly uncommon. Multilimb necrotizing infection is rarer still [13,14].

Microbiology

A single species of bacteria itself, or a polymicrobial infection may be responsible for NSTI (Table 1) [2••,3]. Two clinical subtypes exist. Type I is a mixed infection caused by aerobic and anaerobic bacteria, and occurs most commonly after surgical procedures and in patients with diabetes and peripheral vascular disease. Type II can occur in any patient group, and the culprit microbe is typically anaerobic *Streptococcus* with or without *Staphylococcus*. *Enterobacteriaceae* and *Bacteroides fragilis* may also be encountered. By contrast, group A beta-hemolytic streptococci (*S. pyogenes*) are most often associated with type II NSTI.

Group A streptococci, often referred to in the lay press as 'flesh-eating bacteria', are typically considered as extracellular pathogens but have been shown to survive intracellularly in macrophages during acute invasive infections [15]. This intracellular presence may have evolved as a mechanism to avoid antibiotic eradication, which may be corroborated by the finding that a high bacterial load is present even in tissue collected after prolonged intravenous antibiotic therapy. This new insight into the pathogenesis of streptococcal soft tissue infections highlights a need for alternative therapeutic strategies [16].

In 1935, Lancefield, an American microbiologist, first described a Gram-positive facultative anaerobic coccus that constitutes part of normal human skin, respiratory tract, and gastrointestinal tract flora as group G *Streptococcus* [17•]. Although implicated rarely in NSTI, its associated mortality could be comparable to that induced by *S. pyogenes*, suggesting that group G *Streptococcus* could represent a potentially life-threatening pathogen for all patients [4,11]. *Staphylococcus aureus* and other staphylococci are also known causes of NSTIs [14,18]. Saltwater-acquired NSTI occurs when a seemingly

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minor skin wound is infected with *Vibrio* spp. [13,19], usually *V. vulnificus*.

Clostridial myonecrosis or gas gangrene occurs most frequently in contaminated wounds following trauma or surgery. Some authors consider it to represent type III NSTI, whereas others include clostridial NSTIs among the type II infections. A wide variety of *Clostridium* spp. are pathogenic to human beings, the most common being *C. perfringens*. Spontaneous development of clostridial myonecrosis is described (most commonly produced by *C. septicum*), propagated mainly from the colon in patients with neoplasia and in poor health [4].

Pathophysiology

Necrotizing infection develops as pathogens proliferate within subcutaneous tissue along superficial and deep fascial planes [20]. Bacterial enzymes and toxins play a part in this process [21]. Bacterial factors believed to be important in NSTI include surface proteins and toxins. Surface proteins M-1 and M-3 increase the adhesion of streptococci to tissues and prevent phagocytosis by neutrophils [22]. Streptococcal pyrogenic exotoxins A, B, and C and streptococcal superantigen cause the release of cytokines [23••]. Indeed, exotoxins may bind to T-cell receptors and cause an overwhelming production of TNFα, IL-1, and IL-6, and set in motion a destructive process that may lead to toxic shock syndrome (in the case of Gram-positive pathogens), subsequent organ dysfunction, and death [24]. Necrotizing infection has been clearly associated with streptococcil [9••].

Understanding the pathophysiology of NSTI is important in discerning the clinical presentation. The rapid necrotizing process primarily affects the superficial fascia, after which the bacteria proliferate and invade secondarily the subcutaneous tissue and deep fascia while releasing toxic bacterial products. Skin involvement can develop in time due to thrombosis of the perforating vessels to the skin. As the disease progresses, extensive gangrene of skin, subcutaneous fat, fascia, and sometimes skeletal muscle occurs [14].

The rapid tissue destruction characteristic of both streptococcal and clostridial myonecrosis results from toxin-induced, platelet/neutrophil aggregate-mediated vascular occlusion. As infection progresses and greater quantities of toxins are produced and absorbed, local ischemia likely expands regionally until an entire tissue bed is destroyed. Systemically, microvascular occlusion may also contribute to the shock and organ dysfunction associated with these infections. Although the end result of platelet–neutrophil complex formation is the same in both group A streptococcal and clostridial NSTIs, the principal mechanisms are different. In the case of *C. perfringens*, the formation of large platelet–neutrophil complexes is mediated principally by the phospholipase C-induced activation of gpIIb/IIIa. This activation produces large platelet/neutrophil aggregates via both gpIIb/IIIa and P-selectin. In the case of *S. pyogenes*, toxins do not induce significant numbers of large platelet/neutrophil aggregates, which suggests that exotoxins do not directly activate gpIIb/IIIa. Furthermore, such secondary gpIIb/IIIa-mediated binding is likely enhanced by functional upregulation of the neutrophil adhesion molecule complex CD11b/CD18 [25].

Diagnostic tools

Establishing the diagnosis is not easy and it is probably the greatest challenge in managing these infections [1]. A delay in diagnosis leads to delayed surgical debridement, which leads to higher mortality [4]. It is for this reason that familiarity with the clinical characteristics, diagnostic tools, and principles of management is important when managing patients with necrotizing infection [26,27].

The most important discriminative information to be established in patients is the presence of a necrotizing component. The most common form affects the penis, scrotum, or perineum and is eponymously called Fournier gangrene, which generally occurs after a perianal infection or injury (and may affect females) [28]. A necrotizing infection of the abdominal wall is usually a postoperative complication of abdominal surgery, mostly due to extensive fecal contamination [29], but may occur from neglected or rapidly advancing NSTI of the perineum. A necrotizing infection of the extremity is most often the result of an injury (even a trivial one), or illicit drug use, although abdominal causes such as cholecystectomy, appendectomy, and femoral herniorrhaphy have also been described [14]. Symptoms may develop over a period of hours, but the process can also take several days. Initially, NSTI may be clinically indistinguishable from cellulitis, presenting only with pain (if out of proportion to physical findings, the clinician should be especially alert to the possibility of NSTI), tenderness, and warm skin. Once the infection progresses, more typical signs and symptoms include tense edema beyond the area of compromised skin, skin discoloration (ecchymosis), blisters/bullae, or crepitus or subcutaneous gas identified by an imaging study [11]. The findings of crepitus on palpation and soft tissue air on plain radiography are pathognomonic, although these signs are present in only 37 and 57%, respectively [2••]. The area affected may drain serosanguineous fluid. As the infection spreads along the fascial planes, painless, black, necrotic plaque-like ulcers may appear. With deep infection, vascular occlusion, ischemia, and tissue necrosis may occur. As a result, superficial nerves may be damaged, producing localized anesthesia.

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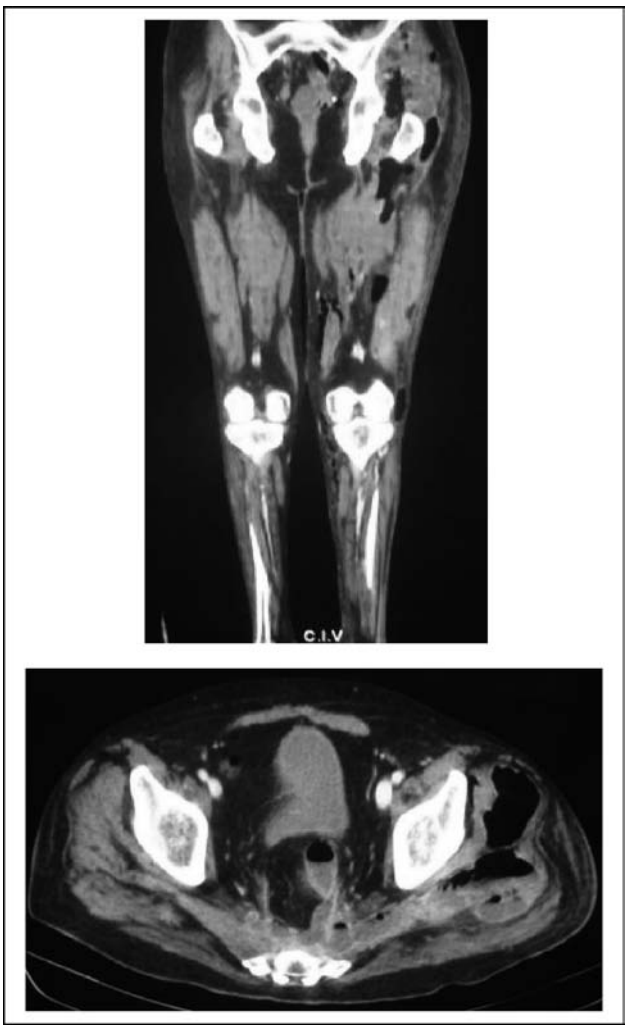
The classic presentation of myonecrosis is that of severe pain and underlying crepitus. Typically, pain is dysproportionate to physical examination findings, and is relieved minimally by medication. Initial physical examination of the site may be normal, with localized tense edema, pallor, and tenderness developing later. The extent of myonecrosis is often greater than the skin changes indicate. Systemic findings include diaphoresis, tachycardia disproportionate to temperature elevation, and extreme anxiety. Late complications include intravascular hemolysis, hemoglobinuria, hypotension, renal failure, and metabolic acidosis [12]. The disease progresses rapidly over the course of hours and is frequently fatal if not interdicted immediately by aggressive surgical debridement [18]. Clinical presentations of necrotizing soft tissue infection are as follows: pain; tenderness; warm skin; tense edema; ecchymosis; blisters/bullae; crepitus or subcutaneous gas; black necrotic plaque; fever; tachycardia; hypotension; neutropenia or neutrophilia; hyponatremia and shock.

The use of ultrasonography, computed tomography, and MRI can be helpful for patients with other sources of infection, particularly deep abscesses. Computed tomography may be more sensitive than plain radiography for defining subcutaneous air (Fig. 2), whereas MRI can define the extent of involvement of necrotizing infection. Furthermore, MRI may be valuable in guiding rapid surgical debridement. The sensitivity of MRI, however, exceeds its specificity [4,9••]. Regardless, imaging of any kind should never delay surgical debridement. The most crucial element in the evaluation is examination by a surgeon [14], including surgical exploration of suspected NSTI to confirm or refute the diagnosis. Rapid surgical debridement with deep incisional tissue biopsy and cultures for aerobic and anaerobic organisms are the gold standard of diagnosis of NSTI. Examination of a frozen section biopsy specimen from the compromised site, including deep fascia and possibly muscle, has been recommended as a means of achieving earlier diagnosis in patients [9••].

Upon histological examination, superficial epidermal hyaline necrosis with dermal and pannicular edema and hemorrhage may be noted in the initial phases of the process, but little or no deep tissue necrosis and no inflammatory cells or bacteria may be observed. Polymorphonuclear cell infiltration in deeper parts of the dermis, subcutaneous tissue and fascia are also observed in more advanced lesions. On Gram stain, bacteria may be seen in the fascia and dermis. Necrosis of all layers of tissue as well as eccrine glands and ducts may be present in more advanced cases [30].

Laboratory values may be helpful in differentiating NSTI from nonnecrotizing soft-tissue infections. WBC counts of more than 14 000 cells/mm^3, a serum sodium concentration less than 135 mEq/l, and a blood urea nitrogen concentration greater than 15 mg/dl may be associated with NSTI [3,9••].

Figure 2 Limb myonecrosis in a 45-year-old patient with perforated carcinoma of the left colon



Treatment

Definitive treatment involves early and complete debridement of the infected tissue, which controls the infection and allows for future recovery. Antibiotic therapy is a crucial adjunct. Hyperbaric oxygen (HBO) and intravenous immunoglobulin (IVIG) are possible adjuncts, although the efficacy of the former is unproven. Adequate organ support and close monitoring are crucial, particularly for the need for reoperation and additional debridement (Table 2) [9••].

The clinical diagnosis is often challenging and may not be confirmed until in the operating room [31]. During the

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Table 2 Treatment of necrotizing soft tissue infection

Treatment	Description
(1) Complete debridement of the infected or necrotic tissue	Occasionally, amputation of a limb may be necessary to obtain a margin of uninfected tissue or to control overwhelming toxicity.
(2) Antimicrobial therapy	Monotherapy agents Imipenem–cilastatin Meropenem Ertapenem Piperacillin/tazobactam Tigecycline Multidrug regimens Multidrug therapy regimens: high-dose penicillin or clindamycin plus a fluoroquinolone or an aminoglycoside Fungal infection Anfotericin B or fluconazole
(3) Hyperbaric oxygen therapy	
(4) Intravenous immunoglobulin	
(5) Physiologic support of organ function	

operation, a generous incision is performed and macroscopic findings of the disease are used to help guide the extent of debridement. The incision is extended as needed to allow for complete debridement of the infected or necrotic tissue. Amputation of a limb may occasionally be necessary if necrosis extends so proximally that a margin of healthy tissue may be difficult to achieve, or in the face of overwhelming toxicity. Operative findings of murky or 'dishwater' fluid in the wound, gray fascia, lack of bleeding fascia, and lack of resistance to digital exploration of normally adherent fascia are consistent with the diagnosis [32]. Debridement must remove all devitalized tissue, and frequent reoperation is needed to ensure the adequacy of debridement [33]. Closure of the wound has not been believed to be a viable option in the light of concern for any residual bacteria, and for poor wound healing. In the past, dressing changes and serial debridements would have been the only options for wound management, with slow granulation and possible eventual tissue flap or skin grafting [27]. The recent adoption of vacuum-assisted closure (VAC) has revolutionized open wound treatment [34••,35]. This mode of wound management has been well described for abdominal and lower extremity wounds and has more recently been described for the spine [15]

Broad-spectrum antimicrobial therapy should be administered empirically as soon as possible, and should cover Gram-positive, Gram-negative, and anaerobic organisms [2••]. Special consideration for group A *Streptococcus* and *Clostridium* spp. should be taken. Acceptable monotherapy regimens include imipenem-cilastatin, meropenem, ertapenem, piperacillin/tazobactam, and tigecycline. Multidrug regimens may include the addition of vancomycin, linezolid or daptomycin to a carbapenem or β-lactam/β-lactamase inhibitor combination if methicillin-resistant *S. aureus* is suspected [36], or a regimen that includes high-dose penicillin, high-dose clindamycin, and a fluoroquinolone or aminoglycoside for coverage of Gram-negative organisms. Clindamycin is highly recommended at the earliest possibility of group A streptococcal infection, as it is believed to inhibit both M-protein and exotoxin production, which may be crucial for controlling the inflammatory response. Gram-positive cocci may be treated with penicillin or clindamycin, as enterococci are seldom pathogenic in NSTI. Ampicillin and gentamicin represent alternatives for coverage of aerobic Gram-negative bacilli [37], but an aminoglycoside must be used with extreme caution in patients with hypovolemia, shock, or preexisting renal dysfunction. Metronidazole may be employed for antianaerobic coverage. Ampicillin-sulbactam lacks adequate coverage of *Pseudomonas* spp. and *Enterobacteriaceae* [38]. Special populations, such as immunocompromised children, those with an allergy to penicillin, and those that acquire infections in hospital, require specific antibacterial strategies. These usually involve broader antimicrobial coverage with increased Gram-negative (including antipseudomonal) and anaerobic coverage. In patients with a true allergy to penicillin, clindamycin and vancomycin play an important role in treating Gram-positive infections. Newer antibacterial agents, such as linezolid and quinupristin/dalfopristin, are increasingly being studied in children for the treatment of skin and soft tissue infections [31]. These agents hold promise for the future especially in the treatment of highly resistant, Gram-positive organisms such as methicillin-resistant *S. aureus* and vancomycin-resistant *S. aureus*. Antimicrobial administration should be continued until no further debridements are needed and the patient's physiology has improved [10], but no specific guidelines exist as to duration of therapy. The antibiotic regimen should be reassessed based on culture and sensitivity results. Prolonged courses of an arbitrary duration are not necessary and may predispose the patient to wound colonization with drug-resistant organisms [36,38].

The failure of modern medicine to improve mortality outcomes of NSTI is secondary to the destruction of the local microcirculation that is associated with these infections [39,40]. Because of the lack of antibiotic penetration, surgical debridement is the only effective treatment for the subcutaneous 'sequestrum'. Antibiotics alone may suppress the systemic sequela of the infection but will fail generally to address the underlying source [41,42], leading to the inevitable demise of the patient.

HBO therapy has been proposed for improving the outcome of NSTI [2••,9••]. Increased tissue oxygenation during HBO may prevent the spread of the offending

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organisms [43], but any therapeutic effect on morbidity and mortality in patients with NSTI is not established, except possibly for clostridial myonecrosis. Observational results from this strategy are contradictory, and no valid hypothesis-testing studies have been performed to elucidate the effect of HBO in patients with NSTI. HBO is not available at all institutions, and frequent transportation of patients may limit unacceptably the ability to perform close monitoring and timely debridement [44].

IVIG may be a useful adjunct treatment in type II group A streptococcal NSTI complicated by toxic shock syndrome, and in those with a high mortality risk (advanced age, hypotension, and bacteremia). The action of IVIG is believed to be the neutralization of superantigen activity and reduced plasma concentrations of TNFα and IL-6 [9••]. Kaul *et al.* [45] studied the survival of patients with streptococcal toxic shock syndrome given IVIG, and found that 30-day survival was 67% in patients receiving IVIG as compared to 34% in controls. A median dose of 2 g/kg of IVIG was employed in this study.

Finally, physiologic support, combined with close monitoring in an intensive care unit setting, is crucial. It is common to see patients with NSTI develop organ dysfunction, such as acute renal failure and acute respiratory distress syndrome, which require organ replacement therapies. Appropriate early nutritional support, delivered enterally if possible, helps reverse catabolism. Judicious control of glucose, as well as novel therapeutic approaches for severe sepsis or septic shock, should be considered to optimize the host response to infection.

Conclusion

Althought NSTIs are rare, they are life-threatening processes. The very young and very old are at especially high risk of an adverse outcome. Approximately 30% of individuals do not survive; delayed recognition, with consequent massive soft tissue loss and sepsis, remains a deadly pitfall in the management of NSTI. With a better understanding of the clinical manifestations and the potential use of various diagnostic adjuncts available for the assessment of equivocal cases of NSTI, a clear and logical approach to the diagnosis and treatment with early and complete debridement, broad-spectrum antibiotic therapy, and adequate organ support may result in improved outcomes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 469).

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