EXPERT REVIEWS

Management of necrotizing skin and soft tissue infections

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Although rare, necrotizing skin and soft tissue infections can be devastating infections that are difficult to diagnose and challenging to manage. Clinical presentation is often insidious, and a low index of suspicion is critical. Various diagnostic tools, such as scoring systems or imaging techniques, have been introduced, but none is convincingly superior to sound clinical judgment. Early diagnosis allows early adequate therapy that includes antibiotic therapy, critical care support, specific interventions such as intravenous immunoglobulin in selected patients and, most importantly, early source control. Empirical antibiotic therapy should cover a broad range of both Gram-negative and Gram-positive aerobic and anaerobic microorganisms, and clindamycin is recommended when group A *Streptococcus* is a suspected pathogen.

Keywords: antibiotic therapy • clindamycin • group A *Streptococcus* • intravenous immunoglobulin • necrotizing fasciitis • necrotizing skin and soft tissue infection • source control

Necrotizing skin and soft tissue infections (NSTIs) are rare, but potentially lethal, infections characterized by fulminant clinical course often with infection spreading rapidly along the fascial planes and leading to extensive necrosis of skin and associated structures. The exact incidence is not clear, but it is estimated that in the USA, the incidence of NSTI is approximately 500–1500 patients/year and is increasing [1]. NSTIs comprise only a small part of all skin and soft tissue infections (SSTIs) that cover a wide spectrum of clinical problems from cellulitis to NSTI [2]. Data from Taiwan show that approximately 9% of patients hospitalized with SSTI are admitted to the inrensive care unit, with most patients suffering from NSTIs and postoperative infections; NSTIs accounted for 7.3% of over 11,000 hospital admissions with SSTI [3]. Although SSTIs are frequent, most clinicians will only occasionally be confronted with NSTI; and this makes diagnosis by relatively inexperienced physicians difficult. As the clinical picture may be difficult to recognize and is often mistaken for less severe infection; this review will focus on diagnosing NSTI, differentiating these infections from non-NSTI, and finally, treatment strategies.

Classification of SSTIs

SSTIs cover a wide spectrum of clinical entities [4]. Several attempts have been made to classify SSTI [2,5,6], and although all serve some purpose, these are not really of use for management of the most severe infections. The US FDA has developed criteria to differentiate complicated infections from noncomplicated infections, where noncomplicated infections are infections that can be treated with incision alone and do not require antibiotic therapy; examples are typically superficial and mild infections such as furunculosis, cellulitis or simple cutaneous abscess. Complicated infections involve deeper structures such as fascia or muscle and are more extensive and severe from a clinical point of view; these also require oral or parenteral antibiotic therapy. Infected ulcer, burns or major abscess can be classified as complicated infections according to this classification. The purpose of this classification was to identify patients who should or should not be entered in clinical trials of antibiotic agents for SSTI. Overall, it has been reported that there are important shortcomings in the design of most studies on antibiotics in SSTIs, for example, only 30% of studies required both local and systemic symptoms at entry to the study, only a half reported comorbidities, and outcome reporting according to the need for surgery was rare [7]. Within the group of SSTI, the most relevant distinction is between non-necrotizing and necrotizing SSTIs, as NSTIs require an aggressive surgical approach, whereas non-necrotizing SSTIs do not. Establishing the

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diagnosis of NSTI is the most challenging part, and physicians taking care of these patients should be familiar with the clinical picture of NSTI and principles of early management.

The terminology of NSTI is based on the historical evolution of the reporting of and insights into these infections. NSTIs have were described in ancient Greece [8], but it was only in the 19th century that the clinical picture of SSTI with necrosis was described in combat victims and referred to as 'hospital gangrene' [9]. This was followed shortly thereafter by the description of perineal necrotizing infections by Jean Alfred Fournier in 1883. The term 'necrotizing fasciitis' was first used by Wilson in 1952 [8]. Later, NSTI emerged as a common denominator for conditions that involve necrosis of the skin and subcutaneous tissue including the fascia and/or muscle [10].

Classification of NSTIs

Different classification systems for NSTIs have been developed, which are either based on microbiology, extent or location.

Location

NSTIs can affect different parts of the body, and some of these clinical syndromes have been named after the physician who first reported the disease. Examples are Fournier's gangrene, which originates from the perineal area and is named after Jean Alfred Fournier, and cervical necrotizing fasciitis, among many others.

Extent of infection

NSTIs can affect the subcutaneous tissue, the fascia or muscle – or more frequently, the combination of all of these (necrotizing cellulitis, necrotizing fasciitis or myositis have been used in the literature) – clostridial cellulitis or myositis, if *Clostridium* is the cause, but again this is causing confusion rather than giving guidance for therapy. The authors strongly suggest not using this terminology, but coining all SSTIs with necrosis as NSTIs.

Microbiology

Depending on the microorganism involved, three different types of NSTIs have been described. Type I is a polymicrobial NSTI often with combinations of aerobic and anaerobic bacteria, rarely fungi, and is most frequent. Type II is a monomicrobial NSTI with group A *Streptococcus* (GAS) as, the predominant pathogen. Some authors have identified a third type of NSTI, type III where *Clostridium* species (with *Clostridium perfringens* isolated most frequently) cause the infection.

The challenge of classifying NSTIs has resulted in a confusing mix of 'different' clinical syndromes such as synergistic necrotizing cellulitis, Meleney's or bacterial synergistic gangrene [11], nonclostridial anaerobic cellulitis, clostridial cellulitis, hospital gangrene, phagedenic gangrene, streptococcal gangrene, acute dermal gangrene and fasciitis suppurativa, among others.

Unfortunately, this may lead clinicians to believe that NSTIs should be divided into different diseases, with differing management of each disease. The result is a semantic discussion regarding the disease classification that may lead to a delay in adequate therapy.

Pathophysiology

Some form of anatomical disruption of the skin integrity, which may no longer be identifiable at presentation, is usually the first event in the development of NSTI, and in most patients, an entry point can be found upon careful clinical examination [12]. Most often, a traumatic laceration, surgical incision or biopsy site, or perineal abscess, but also insect or animal bite, chronic ulcer for example, leg wounds in diabetics or injection site in intravenous drug users. However, in some patients (up to 20% in one study [13]), no entry point can be identified; the absence of an identifiable entry port does not exclude the diagnosis of NSTI. In some patients, hematogenous spread can also be observed, and may explain the development of necrotizing lesions distant from the initially affected body part.

In most patients, one or more underlying conditions or predisposing factors are present (Box 1). Among these, diabetes mellitus, smoking and alcohol abuse are most common, HIV, malignancy, cirrhosis and use of corticosteroid also appear to be associated with the development of NSTI [3,13–19]. These factors also seem to affect the outcome; a recent study found that diabetes mellitus and Child C liver cirrhosis were more frequently present in nonsurvivors [20]. Again, the absence of one of these conditions does not exclude the presence of NSTI.

Some studies have found NSAID to be associated with the development of NSTI [21]. This risk, however, does not seem to be substantiated; however, it is true that the use of NSAIDs may suppress the signs and symptoms and lead to a delay in diagnosis [22].

All NSTIs share pathological features, such as extensive tissue destruction, thrombosis of blood vessels (leading to tissue necrosis), overwhelming bacteria spreading along the fascia and variable infiltration of inflammatory cells in the affected areas [23].

Bacterial toxins and enzymes play an essential role in the spread of the disease and distant effects. This has been documented most extensively in GAS, where exotoxins inhibit phagocytosis by neutrophils, and cause a massive release of proinflammatory mediators that contributes to septic shock and multiple organ dysfunction syndrome (MODS) [23–25], often referred to as the streptococcal toxic shock syndrome (STSS).

The aforementioned processes result in local tissue destruction on the one hand, and systemic multiple organ failure in a considerable part of the patients on the other. Mortality rates in recent series vary from 10 to 40% and limb loss is around 20–25% depending on the type of patients included (Figure 1) [13,14,16–18,26–30].

Microbiology of NSTIs

NSTIs have been classified based on microbiological characteristics as discussed earlier. This classification is not helpful for clinical management purposes.

It is essential to know the expected pathogens of an infection when choosing empirical treatment. Most NSTIs are community acquired, but some may develop in surgical wounds or in hospitalized patients; as in other infections, this is an important

element as the spectrum of the antibiotic treatment should be adapted accordingly. Another important element is the source of the NTSI. Perineal NSTI develops mostly in patients with prior perineal abscess, in which a broad range of Gram-negative and Gram-positive aerobes and anaerobes should be targeted. Cervical necrotizing infections most often descend from dental or pharyngeal abscesses, in which the microbiology will reflect the oral flora.

In patients with comorbidities, previous antibiotic exposure may significantly alter the microbiology of NSTI, and a proper antibiotic history should be obtained.

NSTIs can be polymicrobial or monomicrobial, but most of the infections appear to be polymicrobial and the most feared pathogen, GAS, is only involved in a minority of infections [12]. In a landmark paper, McHenry *et al.* found that approximately two-thirds of NSTIs were polymicrobial, with mainly aerobic bacteria identified on culture, and with a balanced involvement of Gram-negative and Gram-positive pathogens [31]. Monomicrobial infections were mostly due to GAS, but in half of the monomicrobial infections, another bacterium was the sole pathogen.

When analyzing the involvement of different strains in NSTIs, *Streptococcus* and *Staphylococcus* species seem to be the most frequently isolated from these infections in most studies [12,18,31]. Other relevant pathogens include aerobic and anaerobic Gram-negative and anaerobic Gram-positive microorganisms. Box 2 lists the most commonly encountered pathogens. Fungi seem to be rarely involved in NSTI, and are found in less than 3% of patients [31].

The exact microbiological cause of NSTI is mostly identified by a *post-hoc* diagnosis, and empiric therapy should be broad spectrum, covering a wide range of Gram-negative and Gram-positive aerobe and anaerobe microorganisms in most patients (see following sections). The involvement of GAS or *Clostridium* cannot be predicted *per se* and definitive cultures are required to tailor antibiotic therapy (Table 1).

Box 1. Host comorbidities associated with necrotizing skin and soft tissue infection.

- Chronic liver disease
- Chronic kidney disease and/or renal replacement therapy
- Immunosuppression (e.g., transplantation)
- Steroid use
- Advanced age (>70 years)
- Intravenous drug use
- Alcoholism
- Diabetes mellitus
- Obesity
- Malnutrition
- Peripheral vascular disease
- Chronic skin lesions
- AIDS
- Cancer
- Congestive heart failure

Data taken from [3,13–19].

GAS

Streptococcus pyogenes, or GAS, has been linked to a number of severe infections, including STSS. NSTIs are probably the

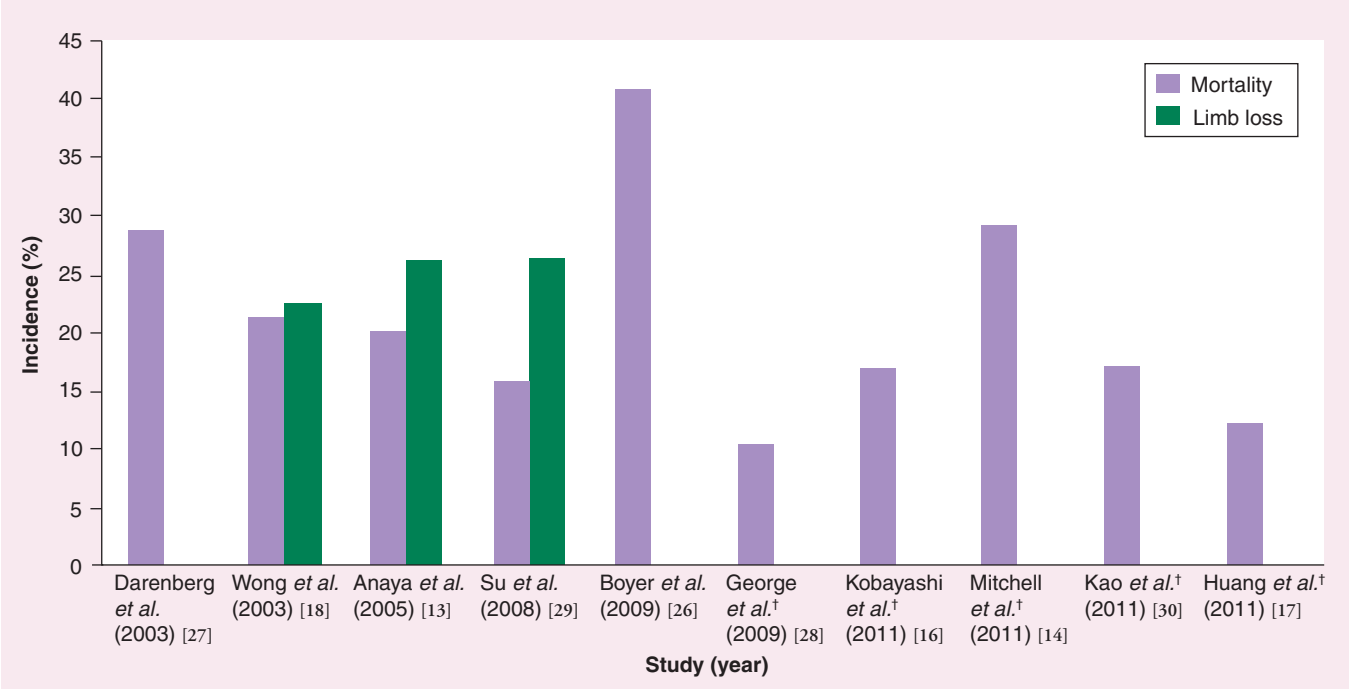

Figure 1. Reported outcomes of necrotizing skin and soft tissue infections in contemporary literature.
†Limb loss not reported.

Box 2. Commonly isolated pathogens in necrotizing skin and soft tissue infection.

Aerobic: Gram-positive
- *Staphylococcus aureus*
- Group A streptococci
- Enterococci
- Streptococci, other than Group A
- Coagulase-negative staphylococci

Aerobic: Gram-negative
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Enterobacter* spp.
- *Vibrio* spp.
- *Klebsiella* spp.
- *Proteus* spp.
- *Aeromonas* spp.
- *Serratia* spp.

Anaerobic
- *Clostridium* spp.
- Peptostreptococci
- *Bacteriodes* spp.

Data taken from [12,16–18,20,26,30,53].

most notorious diagnosis, but in a recent epidemiological survey from Europe, NSTI accounted for only approximately 8% of all severe GAS infections [32]. These GAS NSTIs occurred across all age groups and mortality was high. The pathogenicity of GAS is complex, and the interaction between host factors and microorganism is as important as the traits of GAS itself [23]. The bacterial load is often very large, and relates to the severity of the disease; GAS have multiple methods to evade the immune system, and can even be cultured after several days of antibiotic therapy, as they have been found to persist inside macrophages. Apart from this, GAS have the ability to induce an overwhelming inflammatory reaction, referred to as the STSS. This is mediated by M proteins that interact with fibrinogen and induce a massive release of proinflammatory mediators from the neutrophils, which leads to shock and acute lung injury when these mediators enter into the systemic circulation [23].

Table 1. Recommended empirical antibiotic therapy for necrotizing skin and soft tissue infection.

Antibiotic class	Antibiotic		Recommended dose
β-lactam plus β-lactamase inhibitor based	Amoxycillin:	clavulanic acid + clindamycin	1–2 g every 4–6 h 600–900 mg every 8 h
	Ticarcillin:	clavulanic acid + clindamycin	3 g every 4–6 h 600–900 mg every 8h
	Ampicillin:	sulbactam + clindamycin	1.5–3 g every 6–8 h 600–900 mg every 8 h
	Piperacillin:	tazobactam + clindamycin	3.375–4.5 g every 6 h 600–900 mg every 8 h
Carbapenem based	Imipenem + clindamycin		1 g every 6–8 h 600–900 mg every 8 h
	Ertapenem + clindamycin		1 g every 24 h 600–900 mg every 8 h
	Meropenem + clindamycin		1 g every 8 h 600–900 mg every 8 h

Antibiotic resistance in NSTI

Until recently, the problem of antibiotic resistance was not considered important in these infections. However, in the USA, there have been several worrisome reports of the involvement of community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in NSTI [33]. In most patients, MRSA was the sole microorganism, and it was susceptible to most commonly used drugs. The recovered isolates belonged to the same genotype and were Panton–Valentine leukocidin positive; survival was remarkably high at 100%. More recent reports have confirmed these findings and more specifically the role of Panton–Valentine leukocidin [34]. In a review of the published literature in extremity NSTI, MRSA accounted for 3.1% of the isolates [12]. Although currently there is not enough evidence to consider MRSA as a relevant risk in most NSTIs, risk factors for MRSA involvement should be studied. For now, it may be prudent to include MRSA in the empiric regiment for NSTI treatment when the probability of MRSA infection is high, for example, when isolated from other sites in the patient, in known colonization or in facilities where the incidence of MRSA infections is high.

Diagnosing NSTI

Early recognition is important as it is the first step towards adequate management of the patient. NSTIs are not frequent, and recognizing this devastating disease requires experience, as well as a high index of suspicion. Clinical evaluation by an experienced physician is crucial, but only if he/she has the necessary experience in diagnosing and treating this condition. When such an experienced physician is not available, immediate transfer to a higher level of care should be considered.

The first signs of NSTI are often confined to the skin and consist of erythema and edema; in this stage of the disease, it is notoriously difficult to differentiate NSTIs from less severe conditions such as cellulitis. Typically, the pain in and around the lesions experienced by the patient is severe and out of proportion to the clinical picture; this may serve as a first clue to the disease. An entry point for the infection may or may not be present. Rapid spread of the infection, even within 15- or 30-min time intervals, should alert clinicians. Patchy, deep red to purple discoloration of the skin, with or without blisters develops at a later stage and is diagnostic of NSTI. Crepitus may also be present, but is not required

for diagnosis. If left untreated, frank skin necrosis will occur, but the disease should not be left to develop until this stage to confirm the diagnosis of NSTI. Figure 2 shows a patient with advanced necrosis of skin, subcutaneous tissue and muscle. In fact, necrosis of the skin is the result of the fascial involvement that results in rapid progression along the fascial planes. Figure 3 lists the most frequent signs and symptoms over time; the category 'too late signs and symptoms' list signs and symptoms that should not be awaited when considering the diagnosis of NSTI.

Foul odor and 'dishwater-like fluid' draining from the affected areas are also often cited as clinical findings that point to NSTI. Although these are indeed indicative of NSTI, these cannot be used for diagnosis before surgery. At incision, these are typical findings in NSTI, and in cases where there was doubt about the diagnosis and surgical exploration was performed, they are diagnostic of NSTI and should prompt full surgical debridement.

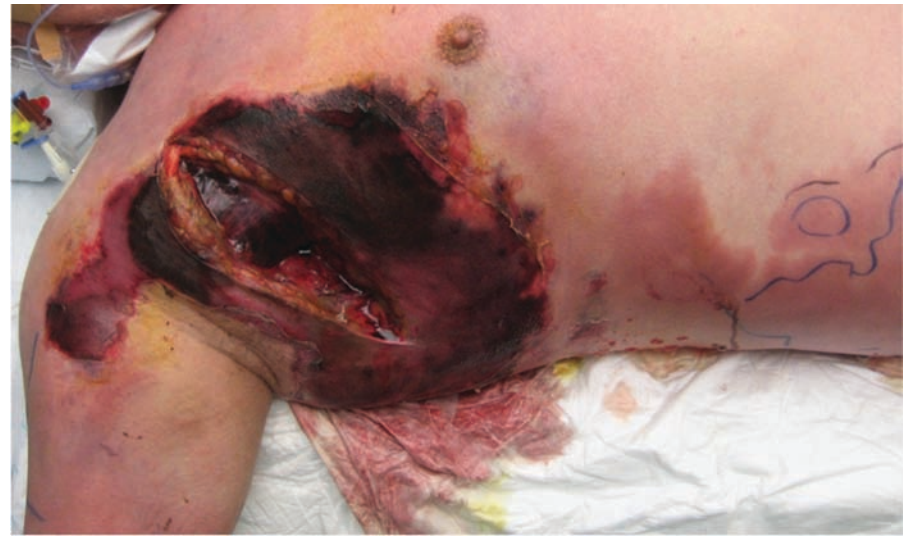

Figure 2. Patient with necrotizing skin and soft tissue infection after minor penetrating chest trauma. This patient displayed rapid progression of dermal necrosis of the skin with necrotic muscle apparent through an inadequate incision of the necrotic skin. Note the discoloration extending to the chest and upper arm.

Simultaneous with the development of skin lesions, organ dysfunction sets in and may develop at the same speed. Hypotension is typically the first sign, with other signs and symptoms of full-blown septic shock, such as encephalopathy and respiratory insufficiency, shortly thereafter. Cellulitis, skin abscesses or other non-NSTI rarely lead to septic shock. In NSTI, profound shock is poorly responsive to fluid resuscitation unless the source of the infection is urgently and adequately controlled and appropriate antibiotics are administered.

The challenge of diagnosing NSTI described earlier was well illustrated by Bisno *et al.* who described the course of 15 patients with GAS NSTI before the disease was recognized [35]. All patients had vague, flu-like symptoms, often with gastrointestinal symptoms. Remarkably, the physical findings in the patients at the first visit were limited and only a minority of patients had notable skin lesions at that stage; however, extreme pain, out of proportion with the findings, was found in almost all patients. Admission to a hospital took a median of 3 days after the first examination by a physician and mortality was higher than 50%.

Diagnostic adjuncts

A number of tools have been proposed to aid in the diagnosis of NSTI and, more importantly, the differentiation from less severe types of SSTIs. These include scoring systems, imaging techniques and more invasive strategies such as aspiration and biopsy.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has been developed specifically to discriminate between necrotizing and non-necrotizing SSTIs. It was derived retrospectively from a patient cohort, and is based on a number of laboratory parameters (C-reactive protein, white cell count, hemoglobin, sodium, creatitin and glucose) and can range from 0 to 13 [19]. In the original publication by Cheng *et al.*, the positive predictive value (PPV) was 0.92 and the negative predictive value (NPV) was 0.96 when the score was 6 or higher [20]. Only a few studies reported on the performance of the LRINEC score in other patient cohorts. The impressive performance of the score was not repeated in a smaller study where the PPV and NPV were 0.57 and 0.86, respectively [36]. Much depends on the timing when the score is calculated: patients with more advanced disease may have higher LRINEC scores. This was also suggested by

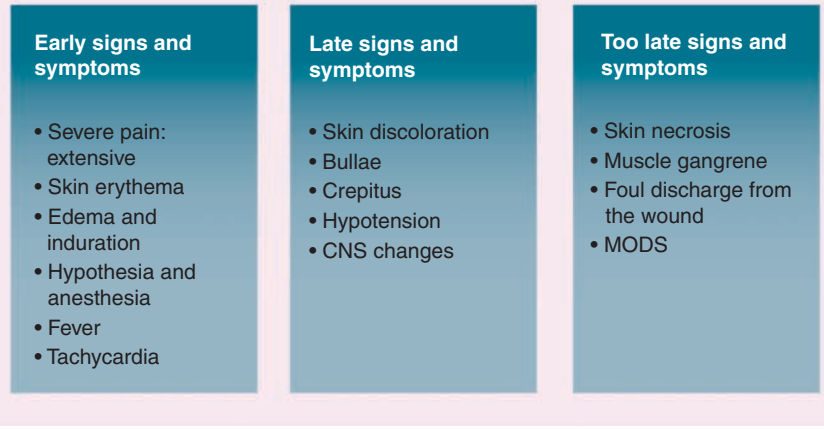

Figure 3. Signs and symptoms of necrotizing skin and soft tissue infection. MODS: Multiple organ dysfunction syndrome.

the observation that patients with higher LRINEC scores had a higher amputation and mortality rate in one study [29]; the performance of the LRINEC score to predict mortality was limited, with the area under the receiver operating characteristic curve of the LRINEC score to predict mortality only 0.61. The LRINEC score should always be combined with clinical clues or other tools for the early diagnosis.

Laboratory tests have also been suggested, with white blood cell (WBC) count of 14,000 or higher, sodium of <135 mmol/l or blood urea nitrogen level >15 mg/dl [37] as objective criteria for the diagnosis of NSTI; however, these have not been confirmed in large series. The same authors constructed a model using sodium and WBC count, which is probably most suited for excluding the diagnosis of NSTI [38]. When sodium is >135 mmol/l and WBC count <15,400, then the probability of NSTI is 1%.

Both the aforementioned parameters and the LRINEC score reflect the physiological derangement and organ dysfunction typically associated with severe infections rather than specific characteristics observed in NSTI. As MODS is a typically late finding, the role of these parameters in early diagnosis of NSTI is of limited value, although it may help less experienced clinicians to recognize NSTI.

Imaging techniques should be used cautiously in this setting. In textbooks, plain radiology is often cited in aiding the diagnosis and, indeed, the presence of gas in the subcutaneous tissue may be diagnostic of NSTI. It should be stressed that this sign is often not present, and moreover, this is a late sign of NSTI and the disease should preferably be diagnosed at earlier stages. Similarly, a CT scan may detect air at even earlier stages, and it can also detect inflammation. Zacharias *et al.* found that the presence of inflamed and necrotic tissue with or without gas or fluid collections across tissue planes was accurate in detecting NSTI; PPV was 76% and NPV 100% in a selected group of patients who did not undergo immediate surgery [39]. Recently, a scoring system was introduced that performed well in diagnosing NSTI. Based on the presence of the five criteria, fascial air, muscle/fascial edema, fluid tracking, lymphadenopathy and subcutaneous edema, a score can be calculated such that a higher score is highly suggestive of NSTI [40]. It should be added that this score relies mostly on the presence of gas, a sign that may only develop later in the course of the disease, and requires radiological expertise. Caution should be used when applying this limited experience in clinical practice; recently, Etkin *et al.* demonstrated that plain x-rays were positive in only 26% of patients and CT in 43%, and more importantly, imaging delayed surgery and was associated with an increase in mortality [Etkin Y, Personal Communication]. MRI has also been reported to differentiate NSTI from benign lesions [41]. However, the use of MRI should be carefully considered, as this inevitably leads to an even longer delay in diagnosis as MRI is not readily available in most hospitals; MRI may be challenging to obtain in instable patients, and experience among radiologists to diagnose necrosis from viable tissue may also impede rapid diagnosis. Ultrasound has also been used for NSTI diagnosis [42], but experience is currently too limited to consider this a valid option.

Biopsy with frozen section of affected areas has also been proposed as a diagnostic tool for NSTI [43,44]; frozen section necrosis, vascular thrombosis, microorganisms and WBC are present in NSTI patients. This method depends on the 24-h/7-day availability of a pathologist, which may be a limiting factor. Reported experience is limited and its performance compared with other diagnostic tools is unclear.

Gram stain of fluid aspiration from the lesions has no role in diagnosing NSTI. The presence of microorganisms as such is not indicative of necrotizing infection, although the presence of Gram-positive cocci may suggest involvement of GAS that may be typically involved in NSTI. Cultures should be obtained, but not used as a diagnostic tool, as it takes too much time for cultures to grow.

In summary, the diagnosis of NSTI should preferably be made on a clinical basis, as imaging (including CT scans and MRI) and biopsies have not been validated adequately for diagnosing NSTI, require a considerable level of expertise and often result in an undesirable delay in diagnosis. The authors advocate an approach where experienced physicians (surgeons, intensivists or infectious disease specialists) are called upon to clinically evaluate the patient based on a low level of suspicion. In the majority of patients, the diagnosis of NSTI will be confirmed or excluded; in equivocal cases, surgical exploration and probing of the affected areas should be considered. In this scenario, no time is lost with imaging or biopsies, and both surgical debridement and supportive therapy can be initiated early.

Management of soft tissue infections

The management of NSTI consists of three elements: antibiotic therapy, source control and specific treatment.

Source control

Source control consists of "all physical measures undertaken to eliminate a source of infection, to control ongoing contamination and to restore premorbid anatomy and function" [45], and is based on four different principles: drainage; debridement plus device removal; decompression; and restoration of anatomy and function. Source control may include nonsurgical procedures such as removal of infected prosthetic devices or percutaneous drainage for abscesses; in the context of NSTI, source control equals surgical debridement. Debridement is the removal of infected and necrotic tissues.

In NSTI, experience in surgical management is important. Owing to the relatively low incidence, most surgeons have only limited experience in deciding the extent of the debridement necessary. This often results in an underestimation of the problem, and a reluctance to intervene that may have catastrophic consequences.

Surgery for NSTI is demanding as repetitive surgery is often needed and subsequent reconstructive surgery is often challenging. Dedication from the surgery and operating room team in the initial phase is essential, as multiple debridement procedures – even within 24 h – may be necessary. This is most relevant when extensive lesions are present and surgeons are conservative in their approach. Patients who underwent surgery should be re-evaluated by the surgeon every few hours in order to detect progression of the necrosis.

Antibiotic therapy

Antibiotics have an obvious role in the management of NSTI. As the causative organism is not known upon diagnosis, a broad-spectrum antibiotic that covers aerobic and anaerobic Gram-positive and Gram-negative microorganisms should be administered. Depending on the local ecology, previous antimicrobial therapy and the circumstances of the infection and also coverage of resistant Gram-negative or Gram-positive bacteria may be indicated. After identification, empiric therapy can be tailored to the microbiology results, keeping in mind that often these infections are polymicrobial, and that anaerobic pathogens are often difficult to culture.

Clindamycin

When the involvement of GAS is suspected, the regimen should include clindamycin. Clindamycin is a protein synthesis inhibitor, and appears to have a specific role in the therapy of GAS [46]. First, it is not affected by inoculum size or the stage of growth of the bacteria that is most relevant, as the bacterial load in NSTI is high. Furthermore, clindamycin facilitates phagocytosis of GAS and suppresses toxin production. In general, a high-dose regimen of 900 mg three-times daily is recommended.

Specific treatment

Intravenous immunoglobulins

Intravenous immunoglobulins (IVIGs) also may have a role in the treatment of GAS infections. *In vitro* data demonstrated that IVIG contains antibodies that neutralize circulating streptococcal toxins that cause the STSS [47]. Beneficial effects were first reported in a Canadian observational study [48] and in a small randomized study from Scandinavia, MODS resolved more quickly in IVIG-treated patients [27]. On the basis of the available evidence, the authors reserve the use of IVIG for patients with documented GAS infections and MODS for 3–5 days or until MODS resolves; suggested dosing is 1 g/kg in the first 24 h, and half this dose in the following days.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) therapy has repeatedly been advocated as adjuvant therapy of NSTI. Multiple reports have been published, the majority single center analyses including ten or fewer patients, but no randomized studies have been performed. However, some studies claim improved outcomes when compared with national mortality rates [49], others found a trend towards a higher mortality [50]. Patient selection and lack of appropriate control groups make it impossible to draw any relevant conclusions. A recent study from Minneapolis (MN, USA) could not find any advantage in patients treated at an HBO center when compared with outcomes in a center in the same area without HBO [28]. As reported in a systematic review on this topic [51], other comparative studies that claim improved outcomes date from 15 to 30 years ago, which limits the relevance of their conclusions for the therapy of in NSTI in 2012.

The rationale seems to be the strongest in cases of clostridial infections, where HBO may reduce mortality and guide surgical treatment through better demarcation of necrotic tissue. In other types of NSTI, HBO should not be recommended, except for situations where resection of necrotic tissue is difficult such as periorbital infection or intercostal muscle involvement; HBO may not be easily accessible for all centers treating NSTI, and delaying surgery because of transfer to an HBO center is not justified in most patients.

Importance of early & aggressive management

The role of early, immediate fluid resuscitation upon recognition of hypotension is not discussed, whereas the role of early antibiotics has been intensely debated in the last few years with general agreement that antibiotics should be administered as soon as possible, that is, upon suspicion of the diagnosis of NSTI.

Several studies have demonstrated that delayed surgery increases mortality. Boyer *et al.* demonstrated that in septic shock patients, surgery postponed for more than 14 h after diagnosis increases the risk of mortality by a factor of 34 [26]. Recently, Kobayashi *et al.* found that patients operated on later than 12 h after admission required surgery more often and had more septic shock compared with patients who were operated on within that time frame [16]. Previous studies did not evaluate the timing of surgery in detail. Elliott *et al.* found a 27% increase in mortality for every day that surgery was delayed [52]. Similarly, Wong *et al.* found that postponing surgery for more than 24 h was related to increased mortality [18]; in this study, the timing of surgery was the only independent predictor of mortality after adjusting for age, gender, diabetes and hypotension on admission. Delay in surgical intervention is consistently associated with increased mortality, apart from other factors – mostly organ dysfunction at presentation and age; it is only the single risk factor for mortality that can be changed through early intervention.

Conclusion

NSTIs are difficult to diagnose and challenging to treat. Clinicians should have a high index of suspicion for NSTI in severely ill patients with skin lesions and expert advice should be sought immediately. Scoring systems and imaging are of limited use and should not defer initiation of appropriate therapy. Mainstays of management are early broad-spectrum antibiotic therapy and prompt surgical source control, but multiple procedures are often necessary.

Expert commentary

The management of NSTI remains challenging in many respects. Although overall survival may have improved in recent years through advances in critical care support and insights into the pathophysiology of GAS infections, further developments are currently hampered by the relatively low incidence of NSTI and low exposure even in large centers around the world. The failure to complete the prospective study on IVIG in GAS NSTI serves as an example for this, as does the lack of randomized controlled trials in this field. Most of the clinical research on which the insights in this review are based is retrospective and often single center experience. In addition, the proposed antibiotic treatment regimens are

based on the microbiology described in these series and experience from other severe infections rather than high-level evidence in which these regimens have been found effective. The same holds true for the use of clindamycin, which has a number of presumed advantages that are not supported by extensive clinical experience. Yet, in our opinion, the severity of NSTI, high amputation rate and mortality rate justify this prudent approach of combination broad-spectrum antibiotic therapy and use of IVIG when GAS is involved in patients with profound shock. A lot of attention has gone to early recognition of NSTI and the efforts to develop tools to achieve this goal should be commended; at the same time, these should not be used as a single tool and always combined with clinical judgment and careful follow-up. In recent years, multiple studies have confirmed that early surgery is the most important strategy in these patients; this is a very important achievement, and it is reassuring to see that in most studies, interval to surgery is becoming shorter than ever before.

Five-year view

NSTIs will continue to be one of the most challenging surgical infections in the next few years. Although insights in the pathophysiology are evolving rapidly, early diagnosis remains difficult and, therefore, is a research area of utmost importance. Technical advances in imaging techniques may facilitate early diagnosis in the next few years, and further improvements in scoring systems may also be expected. So far, biomarkers have not been studied intensively in NSTIs, but newer markers, such as procalcitonin, may aid in both early diagnosis and evaluation of the response to therapy. As other biomarkers, such as interleukins, may become more accessible in daily practice, these may also be of use in NSTI management.

As most physicians who see these patients at the first visit have limited experience, telemedicine may offer additional expertise at the bedside as high resolution images of suspected lesions may be readily transmitted to centers with higher exposure to NSTI.

As in other surgical fields, minimally invasive surgical strategies combined with anti-inflammatory strategies may be developed. Skin defects will become smaller, as surgeons can resect affected tissue in a more directed way, with intraoperative monitoring of tissue viability.

Although the incidence may be increasing, overall numbers treated at individual centers remain small. Collaborative studies appear to be the only way to rapidly increase knowledge of this much-dreaded infection.

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Key issues

- Necrotizing skin and soft tissue infections (NSTIs) are a rare, but potentially fatal condition that affect all age groups, often with associated underlying conditions, such as diabetes and a history of trauma or skin lesion.
- Proposed classification systems based on either location or microbiology are of little clinical use, as they do not affect any aspect of initial patient management.
- Diagnosis of NSTI remains one of the most important challenges, and clinical judgment and follow-up based on experience with NSTI is the key to early diagnosis.
- The microbiology of NSTI is diverse and most infections are polymicrobial; group A *Streptococcus* is an important pathogen but involved in <20–30% of patients.
- Diagnostic tools, such as CT scans and MRI, should be used cautiously, and therapy should not be delayed.
- Treatment of NSTI consists of early antibiotic therapy, emergent surgical source control by experienced surgeons and specific treatment, such as intravenous immunoglobulins, for selected patients.
- Time to source control is one of the sole modifiable risk factors for mortality, and should be a primary goal.
- Empirical antibiotic therapy for NSTI is broad-spectrum combination therapy, preferably β-lactam or carbapenem based, in combination with high-dose clindamycin.
- For group A *Streptococcus* infections with signs of streptococcal toxic shock syndrome, intravenous immunoglobulin can be considered.

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