Title page

Title: Necrotizing skin and soft tissue infections in the intensive care unit

Category: Narrative review

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Word count: abstract 215; manuscript 4012
Abstract

Background. Necrotizing skin and soft tissue infections (NSTI) are rare but potentially life-threatening and disabling infections that often require intensive care unit admission.

Objectives. To review all aspects of care for a critically ill patient with NSTI.

Sources. Literature search using Medline and Cochrane library, multidisciplinary panel of experts.

Content. The initial presentation of a patient with NSTI can be misleading, as features of severe systemic toxicity can obscure sometimes less impressive skin findings. The infection can spread rapidly, and delayed surgery worsens prognosis, hence there is a limited role for additional imaging in the critically ill patient. Also, the utility of clinical scores is contested. Prompt surgery with aggressive debridement of necrotic tissue is required for source control and allows for microbiological sampling. Also, prompt administration of broad-spectrum, antimicrobial therapy is warranted, with the addition of clindamycin for its effect on toxin production, both in empirical therapy, and in targeted therapy for monomicrobial group A streptococcal and clostridial NSTI. The role of immunoglobulins and hyperbaric oxygen therapy remains controversial.

Implications. Close collaboration between intensive care, surgery, microbiology and infectious diseases, and centralization of care is fundamental in the approach to the severely ill patient with NSTI. As many aspects of management of these rare infections are supported by low quality data only, multicentre trials are urgently needed.
Necrotizing skin and soft tissue infections (NSTI) refer to infections of the skin, subcutaneous tissue and superficial fascia, that are characterised by the development of necrosis in these structures. The term NSTI covers a range of infections that can occur in different anatomical locations and develop after the integrity of the skin (or mucosa) has been breached. NSTI are rare, but destructive and potentially lethal infections and patients often require admission to an intensive care unit (ICU).

NSTI are challenging because of a number of characteristics that distinguish them from other severe infections, including the ones reviewed in this issue of CMI. The diagnosis in the early phase of the disease is difficult as skin lesions may appear benign at first and hemodynamic instability can be absent. A high index of suspicion is required and diagnosis is often based on clinical clues that may trigger additional investigations, but their role is limited, notably in the most critically ill. NSTI can progress rapidly; the resulting tissue damage is often extensive, requiring surgical source control and reconstructive surgery in most patients and frequently leaving the patient with a permanent disability.

The management of these severe cases should prioritize timely diagnosis and intervention, with a central role for surgery and appropriate antibiotic therapy. All of this should be executed in a short time frame, so this requires swift decision making, and preferably an experienced multidisciplinary team to treat the patient.
Previous reviews have focused on either specific aspects of therapy or care, e.g., surgery, antibiotic therapy [1, 2] or ancillary treatments such as hyperbaric oxygen [3–5] or immunoglobulins [6]; a particular anatomical location [7–10], a specific pathogen [11–13], or they took a very broad perspective covering non-necrotizing infections as well [14–16].

In this narrative review, we want to focus on all aspects of care for these patients in the ICU, through the eyes of a multidisciplinary panel reflecting the approach required in severe infections in the ICU. This overview is based on an extensive literature search focusing on information published in the last years.

Methods

A literature search was performed on PubMed and the Cochrane Library on December 2nd, 2018 (see Figure 1 for PRISMA flow diagram). The following MeSH terms were used: “intensive care units”, “critical care”, “critical illness”, “fasciitis, necrotizing”, “Fournier gangrene”, “gas gangrene”, “soft tissue infections” and “skin diseases, infectious”. In addition, the following free text words were used: “intensive care unit”, “necrotizing fasciitis”, “gas gangrene”, “soft tissue infection”, “skin infection”, “cellulitis”, “myositis” and “necrotizing”. We applied filters for publications from 01/01/2004 onwards, written in English. Case reports were excluded, as were articles that did not involve critically ill patients with NSTI. We also searched the reference lists of relevant recent review articles [17, 18].

Epidemiology
NSTI are rare, with a population incidence of 4 per 100,000 per year [19–23], and account for a small proportion of ICU admissions, estimated at 0.2% in the UK [24] or 1.2% of all critically ill patients admitted with sepsis in the Netherlands [25]. However, because of the severity of illness, underlying comorbidities and intensity of postoperative wound care, ICU admission is frequently required [22, 23, 26–31]. A quarter to half of patients with NSTI develop septic shock [23, 29, 30, 32] and/or require mechanical ventilation [26, 29, 33] and a third exhibit acute kidney injury [30, 33, 34]. Organ failures tend to worsen in the first 24 hours of admission [34]. The duration of ICU stay typically ranges from 5 to 12 days [25, 29, 31, 32, 35–38].

The average age of NSTI patients is 50-60 years old [23, 26, 29, 31–35, 39–41], with a slight male predominance [22, 23, 26, 27, 29–37, 39–42]. Necrotizing fasciitis of the extremities is the most frequent clinical presentation [23, 27, 29, 31–34, 36, 37, 39, 41, 42], followed by perineal NSTI also known as Fournier’s gangrene [26, 31–36, 41, 42] (Table 1). Involvement of the trunk or head and neck region are less frequent [26, 27, 31, 33, 36, 39, 42]. Four to 12% of NSTI patients have a recurrent NSTI [26, 27, 31, 33]. Comorbidities associated with NSTI include diabetes mellitus in 22–59% [22, 23, 26, 27, 29–31, 33, 35–37, 39, 42] and obesity in 17–31% [26, 30, 35–37, 41, 42]. Other risk factors include cardiovascular (9–45%) or peripheral vascular disease (3–19%) [22, 23, 26, 30, 31, 33, 36, 39, 41, 42], intravenous drug use (2–80%) [27, 33, 36, 39], immunosuppression (4–30%) [23, 25, 30, 35, 36, 42] and chronic alcohol abuse (6–27%) [30, 33] (Table 1). Of note, up to a fourth of NSTI patients have no obvious predisposing factor [30, 36, 37, 39]. In 10–38% of NSTI patients, a local trauma is noted as the portal of entry; this can range from a minor skin abrasion or insect bite, to an operative injury or a blunt trauma. NSTI can also develop on the background of a chronic wound or dermatosis [29–31, 33, 36, 39]. Use of non-steroidal anti-inflammatory drugs (NSAIDs) is
regularly noted in the weeks prior to admission, potentially masking the clinical signs and symptoms of a developing NSTI; however, a causal relationship is not established [23, 30, 42, 43].

Table 1. Clinical pictures of NSTI (based on [17, 19, 26, 27, 29–50])

<table>
<thead>
<tr>
<th>Location of NSTI</th>
<th>Relative frequency*</th>
<th>Portal of entry</th>
<th>Main risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb (lower &gt; upper)</td>
<td>70%</td>
<td>Trauma</td>
<td>Age &gt; 60 years, Male gender, Immunosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic leg ulcer, Burns, Insect bites, IV drug use, Blunt trauma, Varicella</td>
<td>Diabetes, Obesity, Chronic lower limb ischemia</td>
</tr>
<tr>
<td>Perineal/genital (Fournier’s gangrene)</td>
<td>15%</td>
<td>Cutaneous Digestive Urinary/genital</td>
<td>Diabetes, Obesity</td>
</tr>
<tr>
<td>Cervical</td>
<td>&lt;5%</td>
<td>Tonsillar phlegmon Dental abscess Gland infection</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Thoraco-abdominal</td>
<td>&lt;5%</td>
<td>Post-operative</td>
<td>Diabetes, Obesity</td>
</tr>
<tr>
<td>Orbital</td>
<td>&lt;5%</td>
<td></td>
<td>Diabetes, Trauma</td>
</tr>
</tbody>
</table>

*The reported figures are estimates and may vary depending on local patient recruitment and case mix.

Patients with NSTI have considerable long-term functional disabilities. In one report, only half of them were able to return directly home while the others needed further hospitalization or transfer.
to an inpatient rehabilitation facility [26]. Importantly, ~10-20% of patients with limb NSTI will eventually require amputation [23, 27, 30, 33, 34, 36, 38, 42, 45].

About 20-30% of patients with NSTI die during their hospital stay [22, 24, 33, 36, 39, 40], though mortality may be lower depending on case mix [33, 34]. Risk factors for mortality are disease severity, reflected by severity of illness scores such as the APACHE II [33, 35, 41, 45], or hypotension and/or vasopressor need [23, 29, 36, 39]. Per unit increase in the APACHE II score, studies found a 16-18% increased odds of death [23, 29]. If a patient is hypotensive on admission, the mortality doubles [48]; while the odds ratio for mortality is 28.4 (95% CI 1.35–77.8) if vasopressors are required on admission to ICU [29]. Bacteraemia upon admission was also reported to be associated with mortality [29]. Other non-modifiable prognostic factors include age [22, 26, 29, 32, 36, 37, 40, 47, 50] and female gender [22, 48]. Diabetes is not consistently associated with mortality risk [21, 23, 32]. Other comorbidities such as cardiac [48], peripheral vascular [36] and chronic kidney [36] or liver disease [44] worsen prognosis. Potentially modifiable risk factors associated with NSTI mortality include the delay to surgical intervention [26, 46, 49], as well as the experience of the surgeon [33] and the case volume of the hospital [22].

Microbiology

Current knowledge about pathogens involved in NSTI is essentially based on data from retrospective cohort studies that present data based on culture dependent detection of microbes from blood and sterile site tissue cultures [30, 47, 48, 50–52]. Identification of etiological agents may assist infection control measures and antimicrobial therapy decision making and may offer prognostic information. Drug susceptibility tests are useful in fine-tuning of antimicrobial therapy
but, using the current technologies available in routine in bacteriology lab, they are available after at least 2 or 3 days which is detrimental based on the severity of NSTI in ICU patients [47, 51, 52]. NSTIs are often categorized according to causative organisms [17, 53]. Type I infections are polymicrobial with anaerobic, aerobic and facultative anaerobic bacteria acting synergistically. Differently, type II infections are monomicrobial. *Streptococcus pyogenes* (group A streptococcus; GAS) is the most frequent pathogen, followed by other beta-haemolytic streptococci such as *Streptococcus dysgalactiae* that is emerging [54–57]. In case of NSTI caused by GAS, close to 50% of the cases were found to be associated with streptococcal toxic shock syndrome (STSS) [58, 59]. In fact, due to the frequent association, soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene, is included in the consensus definition of STSS [60]. *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA), *Clostridium* species, *Vibrio vulnificus* and other gram-negative bacilli are uncommon causes of type II infection [61–63]. A myriad of bacterial species including MDR gram-negatives may be cultured from NSTI, even more so in immunocompromised patients [64, 65].

NSTIs can also be categorized according to the anatomical location of the infection (Table 1), and the microbiology differs according to the implicated site. Anogenital and abdominal infections are secondary to gastrointestinal or genitourinary infections that eventually spread along tissue planes. Essentially these are type I infections and pathogens are similar to those of intraabdominal and genitourinary infections [53]. Multi-drug resistant (MDR) organisms, e.g., ESBL-producing *Escherichia coli* or *Klebsiella* spp., or MRSA, are reportedly emerging in different parts of the world [61, 66, 67]. In Fournier’s gangrene the importance of anaerobic bacteria may have been underestimated [68].
Among deep neck space infections type I NSTI predominate [69]. The most important pathogens are viridans streptococci, staphylococci and gram-negative anaerobes such as *Bacteroides fragilis*, *Prevotella*, *Fusobacterium* and *Peptostreptococci* [69–71]. Clindamycin resistance is frequent among anaerobic bacteria [71], reaching 20 to 40% in the *Bacteroides fragilis* group in Europe [72]. Upper respiratory tract pathogens as *Streptococcus pyogenes* and *Haemophilus influenzae* may be encountered, whereas MDR pathogens are detected in a few cases [71]. There is risk of intrathoracic, prevertebral or intracranial spread.

In most cases NSTI of the limbs lower extremity infections predominate (Table 1). Type I infections are possibly more frequent [17], particularly in the lower limbs, whereas in type II infections GAS is the dominant cause [21, 30, 48, 73]. Even if GAS is isolated, in 30% of cases other micro-organisms are also found [74]. The risk of polymicrobial type I infections is increased in diabetes mellitus [75], including risk for infections with MDR organisms. Risk factors for MRSA involvement include intravenous drug abuse, diabetes mellitus and chronic liver disease [75, 76]. In subtropical areas *Vibrio vulnificus* is a pathogen causing NSTI after exposure to seawater or consumption of raw sea food. Major host risk factors are chronic liver disease and immunosuppression [61, 63, 77].

**Diagnosis**

**Clinical picture**

Early recognition of NSTI is a key step of patient management. Because cutaneous manifestations may be initially absent, the infection was shown to be misdiagnosed at first presentation in 71% of cases in a systematic review including 1463 patients [78], resulting in delayed diagnosis, antibiotic administration and surgery referral. Patients with NSTI typically present with signs of severe infection, including malaise, myalgia, diarrhoea and anorexia, which sometimes precede skin
lesions [17] (Table 2). Upon hospital admission, and as compared to patients having non-necrotizing skin and soft tissue infections (e.g., cellulitis), patients with NSTI are more likely to have sepsis or septic shock [79]. The clinical presentation of NSTI varies depending on the location (Table 1) and the course (Table 2) of the infection. Clinical findings were reviewed by Goh et al. after a systematic literature search that identified swelling (present in 81% of NSTI cases), pain/tenderness (79%), erythema (71%), warmth (44%), bullae (26%), skin necrosis (24%) (Figure 2), and crepitus (20%) as the most frequently encountered signs [78]. Fever was present in 40% of cases and hypotension in 21%, although the frequency of associated organ failures varies widely between studies, depending on the case mix, rising to 90% when only patients admitted to the ICU were included [25]. Because none of the previously mentioned signs provided a sufficient sensitivity when considered separately, approaches combining several clinical findings have been proposed and achieved better diagnostic yields than did each individual finding [80]. In atypical cases, involvement of dermatologists can aid in the differential diagnosis of NSTI from rare mimics such as pyoderma gangrenosum [81].

Table 2. Signs and symptoms of NSTI, according to the course of the disease.

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
<th>Very late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Purple discoloration</td>
<td>Frank necrosis</td>
</tr>
<tr>
<td>Pain</td>
<td>Haemorrhagic bullae</td>
<td>Dishwasher pus</td>
</tr>
<tr>
<td>Erythema/warmth</td>
<td>Crepitus</td>
<td>Hypoesthesia</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>Organ failures</td>
<td></td>
</tr>
</tbody>
</table>

Laboratory tests

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has been proposed as a diagnostic tool for distinguishing NSTI from other non-necrotizing skin and soft tissue infections,
based on the following laboratory tests: C-reactive protein, white blood cell count, haemoglobin, and serum sodium, creatinine and glucose levels. A score ≥6 was associated with a positive predictive value of 57 to 92% and a negative predictive value of 86 to 96% [82, 83] and associated with worse hospital outcomes [84]. External validity seems to be problematic however; Fernando et al. found that the score had poor sensitivity and concluded that it should not be used to rule out NSTI [85]. Due to its limitations, the LRINEC score has not been widely implemented. Other biomarkers may be elevated in patients with NSTI, including serum procalcitonin, creatine phosphokinase and lactate, but none of these have been shown to provide robust diagnostic yields in NSTI [86–88].

Imaging

For limb NSTI, standard x-rays show gas in the tissues in about 10-25% of cases and hence contribute little to the diagnosis [78, 89]. Computed tomography scans will most frequently show soft tissue swelling, which will not help discriminating between necrotizing and non-necrotizing cases. Magnetic resonance imaging (MRI) is the most effective method for diagnosing NSTI, showing thickening of the deep fasciae, with high signal on T2 images and contrast-enhanced T1 images [90]. Importantly, MRI should not be performed in patients with septic shock in order not to delay surgery. Unlike patients having limb NSTI, those with cervical, thoraco-abdominal and perineal NSTI (Figure 3) may require a computed tomography scan to explore the portal of entry of the infection (Table 1) together with its extension [91, 92].

When the clinical suspicion of NSTI is high and/or when patients present with signs of sepsis/septic shock, prompt surgical exploration is warranted in order to confirm the diagnosis of NSTI, assess the need for debridement/amputation and obtain tissue specimens for microbiological analyses.
Direct examination and Gram staining can aid in diagnosis and antimicrobial decision making [93]. Postoperatively, patients with septic shock should be admitted to a critical care area. A proposed algorithm for the management of patients with suspected NSTI is given in Figure 4.

**Patient transfer**

Given the incidence of NSTI many physicians and surgeons may only rarely encounter NSTI. Experience in diagnosing and treating patients (particularly the surgical debridement) may therefore be limited and a transfer to a specialized center may be considered. In a study from France [22], the volume of patients treated was linked to improved outcomes. The decision to transfer a patient to a specialized center should be based on the experience and availability of a surgeon, the extent and severity of the skin lesions as well as the delay that would be incurred by the transfer [94]. In many instances, the first debridement is done in the admitting hospital, and the patient is transferred to a specialized center afterwards.

**Surgery**

Surgery plays a crucial role in NSTI management, both in diagnosis and treatment. Obtaining a frozen section biopsy in unproven NSTI has been proposed in earlier publications but has been abandoned meanwhile due to low accuracy [15, 17]. Therefore, in uncertain cases, early surgical exploration in the operating theatre is recommended in recent guidelines and reviews in order to prevent a delay in the diagnosis and treatment of NSTI [17]. A deep incision provides crucial information about the local tissue conditions: a vivid and unchanged fascia excludes a NSTI. Typical intraoperative finding in progressive NSTI are colliquative necrosis of the fascia and the subcutaneous layer with muddy, dishwater-like fluid [17, 26, 46, 78] (Figure 5). Moreover, surgical exploration offers the opportunity to obtain samples for culture and Gram staining.
Once the diagnosis of NSTI has been established, initial aggressive debridement of all infected necrotic tissue is indicated (Figures 2 and 3); in critically ill patients, a relook within 24 h is recommended to ensure the adequacy of source control [14]. A major amputation is rarely necessary in NSTI, except for patients suffering from clostridial myonecrosis [52].

Several studies have addressed the timing of surgery in NSTI after admission to the hospital. Many studies are confounded by the fact that the time of admission does not correlate with the beginning of symptoms [95]. Nevertheless, a strong correlation between the timing of surgery and mortality was found. Patients who underwent surgery within 6-12 hours after admission had significant lower mortality rates than those who did not [46, 96, 97]. The optimal timeframe for intervention has not been established and different studies use different cut-offs. In patients with septic shock Boyer et al. found that time from diagnosis to surgical treatment of more than 14 h in patients was independently associated with hospital mortality (adjusted odds ratio 34.5, 95% CI 2.05–572, p= 0.007) [96].

After debridement and once the wound is stable, the subsequent use of negative pressure therapy allows reduction of wound surface, extraction of wound exudate and cell detritus as well as induction of granulation [98]. Moreover, it eases wound management and increases patient comfort in the ICU. In Fournier’s gangrene, a temporary diverting colostomy is helpful to reduce faecal contamination and control infection of large perianal wounds [99]. Adequate wound conditioning in NSTI is the prerequisite for secondary wound closure with plastic reconstructive techniques [100].
Throughout the treatment, a close cooperation between surgeons and intensivists is essential in order to achieve surgical source control as early as possible in the early stage, and to facilitate reconstructive surgery later [16, 17].

Antibiotics

There are no randomized clinical trials on empirical antimicrobial therapy in NSTI available, and data on optimal antibiotic treatment in NSTI are scarce [18]. Contemporary guidelines and recommendations offer pragmatic approaches as they are based on observational studies, experience in treatment of less severe infections, as well as experimental data. Antimicrobial therapy in NSTI aims to achieve the following goals: 1. adequate activity against gram-positive pathogens and Enterobacteriaceae or other gram-negative microbes carrying risk for multidrug resistance (MDR); 2. reduced toxin production in infections with Streptococcus pyogenes or Clostridium perfringens; and 3. anaerobic coverage necessary in all polymicrobial infections [15].

Clinical diversity may be huge in NSTI, but sepsis and septic shock are frequent. It is therefore particularly important to initiate broad-spectrum, bactericidal antimicrobial therapy without any delay upon diagnosis [14, 15]. Given the severity of illness and the lack of criteria that allow to discriminate mixed and GAS infection rapidly, a broad-spectrum antibiotic regimen should be selected, such as piperacillin-tazobactam, a carbapenem or a 3rd generation cephalosporin combined with metronidazole, always with the addition of clindamycin to limit potential toxin production. Combination therapy using clindamycin is also recommended in the directed antibiotic therapy for monomicrobial gram-positive infection with GAS or Clostridium species [15]. Depending on local epidemiology, extended coverage for MDR pathogens may be required.
When aetiology is identified and susceptibility tested, therapy can be adjusted. Type II infection caused by GAS is treated with penicillin plus clindamycin [15]. GAS is unequivocally sensitive to benzyl penicillin, but only clindamycin reliably maintains efficacy in infections with large amounts of bacteria in stationary growth phase [101, 102]. In addition, clindamycin diminishes streptococcal toxin production [103], an effect that was also demonstrated in an in vivo GAS NSTI murine model and proposed to contribute to less severe tissue pathology noted in clindamycin treated mice [104]. In two prospective observational studies of invasive GAS infections, including STSS and NSTI cases, clindamycin was found to be associated with a significantly improved survival [104–106]. Treatment options in less frequent aetiologies of monomicrobial NSTI are presented in Table 3.

Duration of therapy is not well defined, but typically it is continued until operative debridement has been completed and the patient is recovering, usually lasting around 7-10 days in total.
Table 3. Directed antibiotic therapy of causes of NSTI.

<table>
<thead>
<tr>
<th>Bacteria isolated</th>
<th>Antimicrobial agents</th>
<th>Adult recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymicrobial</td>
<td>Piperacillin/Tazobactam</td>
<td>4,5g every 6h</td>
</tr>
<tr>
<td>(Streptococci, S. aureus, E. coli, Bacteroides spp.)</td>
<td>Or Meropenem</td>
<td>1-2g every 8h</td>
</tr>
<tr>
<td></td>
<td>Or Ceftriaxone + Metronidazole</td>
<td>2g once daily + 0.5g every 8h</td>
</tr>
<tr>
<td></td>
<td>All with Clindamycin</td>
<td>600-900mg every 6-8h</td>
</tr>
<tr>
<td>Monomicrobial</td>
<td>Penicillin G</td>
<td>2-4 10^6 units every 4-6h</td>
</tr>
<tr>
<td>group A Streptococcus (S. pyogenes)</td>
<td>Or Ampicillin</td>
<td>1-2g every 4-6h</td>
</tr>
<tr>
<td>Clostridium spp.</td>
<td>All with Clindamycin</td>
<td>600-900mg every 8h</td>
</tr>
<tr>
<td>Aeromonas hydrophila</td>
<td>Doxycycline</td>
<td>100mg every 12h</td>
</tr>
<tr>
<td>Vibrio vulnificus</td>
<td>Plus Ciprofloxacin</td>
<td>500mg every 12h</td>
</tr>
<tr>
<td></td>
<td>Or Ceftriaxone</td>
<td>1-2g once daily</td>
</tr>
<tr>
<td>MRSA</td>
<td>Linezolid</td>
<td>1g every 12h, trough level adjustment (15-25 mcg/ml) or 20-25mg/kg bolus followed by 25-35mg/kg/24h in continuous infusion</td>
</tr>
<tr>
<td>ESBL-producing</td>
<td>Meropenem</td>
<td>1-2g every 8h</td>
</tr>
<tr>
<td>Enterobacterales (E. coli, K. pneumoniae)</td>
<td>Tigecyclin*</td>
<td>50-100 mg every 12h</td>
</tr>
</tbody>
</table>

Adapted from the 2014 Infectious Diseases Society of America guidelines (76). Antibiotic doses are for intravenous administration. ESBL = extended spectrum beta-lactamase. * Tigecyclin should not be used as monotherapy.

Intravenous immunoglobulins

Polyspecific intravenous immunoglobulin (IVIG) has been proposed as adjunctive therapy in severe infectious diseases because of its immunomodulatory functions and ability to opsonize bacteria and
neutralize bacterial toxins. The clinical value of IVIG in sepsis and NSTI remains to be demonstrated [107–109]. A recent meta-analysis of IVIG treatment of clindamycin-treated GAS toxic shock syndrome demonstrated a significant survival benefit [110]. The pooled data included 70 IVIG-treated and 95 non-treated STSS patients. IVIG-treatment was associated with a significant reduction in mortality from 33.7% to 15.7%. The INSTINCT randomized trial of IVIG in NSTI of all etiologies observed no apparent effect of IVIG on self-reported physical functioning and mortality [109]. Further studies are needed to evaluate if there is any value of adjunct IVIG in NSTI subgroups, particularly NSTI caused by GAS.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) has been proposed as an adjunctive therapy for patients with NSTI. HBOT increases tissue oxygen tension in infected necrotic wounds and might potentiate antibiotic efficacy [111]. As a matter of fact, in an international survey on NSTI management, one third of responding intensivists considered that HBOT was a reason for patient referral to another centre [112]. Observational studies have reported conflicting results [73, 113]; Devaney et al. recently reported on a cohort of 344 patients with NSTI, 275 of whom received HBOT, which was a protective factor for hospital mortality in multivariable logistic regression analysis [73]. However, a Cochrane review that aimed at assessing the evidence concerning the use of HBOT as an adjunctive treatment for patients with NSTI failed to identify any trial meeting the inclusion criteria and could thus not support or refute its effectiveness [3]. The latest guidelines of the Infectious Disease Society of America on NSTI management did not recommend HBOT due to the lack of evidence and because of the risk of delaying resuscitation and surgical debridement [15].

Research perspectives
Many aspects of the management are supported by clinical data with low to very low quality only.

High quality research is urgently needed in a number of areas (Table 4). Given the incidence of NSTI, international collaborative research is the only way to improve the care of these patients. On this note, a multicentre prospective observational study on NSTI (NCT01790698) [114], including both documentation of clinical and treatment variables as well as biobank collection was recently completed, and results are highly anticipated.

Table 4. Research agenda on severe NSTI.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Research question/aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology</td>
<td>How does the pathophysiology differ depending on causative pathogen and host susceptibility?</td>
</tr>
<tr>
<td></td>
<td>Define pathogenic mechanisms and/or host responses that can be used for patient stratification and tailored therapy in NSTI</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>What biomarkers can help in the diagnosis?</td>
</tr>
<tr>
<td></td>
<td>Define endotypes that would allow for studying precision medicine strategies</td>
</tr>
<tr>
<td></td>
<td>What is the role of rapid diagnostic techniques?</td>
</tr>
<tr>
<td>Treatment</td>
<td>Is there a role for IVIG in GAS NSTI?</td>
</tr>
<tr>
<td></td>
<td>What is the effect of HBOT?</td>
</tr>
<tr>
<td></td>
<td>Is combination therapy with clindamycin superior to monotherapy?</td>
</tr>
<tr>
<td></td>
<td>Is aggressive surgery superior to conservative surgery?</td>
</tr>
<tr>
<td></td>
<td>What is the appropriate duration of antibiotic therapy?</td>
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<td>Is there a benefit of negative pressure therapy?</td>
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<tr>
<td>Organizational</td>
<td>Do we need to centralize care for patients with NSTI?</td>
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<tr>
<td>Outcomes</td>
<td>What is the health-related quality of life after NSTI?</td>
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The pathophysiology of NSTI is incompletely understood, e.g., the role of the innate immune response to locally control these infections or on the other hand, mediate tissue pathology. Basic research in this field may help to find new targets for diagnostics and intervention, as well as provide critical insight to support patient stratification and personalized medicine in NSTI; GAS is an important pathogen and deserves particular attention.

Given the low number of patients with NSTI, organizational aspects of care such as concentrating the care for these patients in a limited number of experienced hospitals seems logical but has been investigated incompletely.

Even in the best circumstances delayed diagnosis is common and better tools such as biomarkers to diagnose and assess the risk of poor outcomes are a priority. Rapid diagnostic tools are under development and their role in NSTI could be very important. Molecular diagnostics represent important supplements, as they can detect relevant culture negative organisms [115, 116] and possibly shorten time to identification. There is a role for diagnostic microbiology [117] in development of novel therapies in NSTI.

While the role of early antibiotics and surgery is obvious, the role of IVIG, HBOT and clindamycin remains unclear. As for the surgical procedure itself, both the timing and extent of initial debridement require further study. Optimal duration of therapy is another area of uncertainty. Non-antibiotic therapies - e.g., targeting bacterial virulence factors - could offer new treatment opportunities.

The aftermath of NSTI should not be underestimated and continued high level care is important. Better-quality analysis of the impact of new strategies in reconstructive surgery such as negative
pressure therapy and optimized aftercare including psychological support and rehabilitation are also mandatory.

Conclusion

NSTI are life-threatening and disabling infections that remain a diagnostic and therapeutic challenge for clinicians. A multidisciplinary management involving not only intensivists, surgeons, microbiologists, infectious disease specialists, but also ICU nurses and physiotherapists is warranted. Early recognition of NSTI is a crucial step that should trigger the initiation of broad-spectrum antibiotics and aggressive surgical debridement. A major collaborative effort is required to design pragmatic studies aiming at assessing treatment strategies using patient-centred outcomes.
Figure captions

Figure 1. PRISMA flow diagram of literature search.

Reasons for exclusion of articles are given. “Not NSTI” indicates articles not involving patients with necrotizing skin and soft tissue infections; (*) “other” reasons for exclusion of screened titles were non-clinical research (n=7), palliative care setting (n=1), medicolegal focus (n=1), conference abstracts (n=3); (**) “other” reasons for exclusion of screened full text articles were non-clinical research (n=1), therapy coding (n=1) and mechanistic research about HBOT (n=1).

Figure 2. Clinical presentation before (left panels) and after (right panels) debridement in patients with lower limb NSTIs.

A) A 56-year-old male with right foot Streptococcus pyogenes (group A streptococcus; GAS) NSTI; the picture shows leg and foot swelling with skin necrosis anterior to the external malleolus and large bullae; an extensive debridement was performed; B) A 25-year-old female with bifocal GAS NSTI; the left foot is swollen and has a lilaceous appearance, and there is a concomitant involvement of the right internal malleolus; C) Type I NSTI (tissue specimen grew Staphylococcus aureus and Citrobacter koseri) of the right foot in a 54-year-old male; the picture typically depicts swelling, erythema and skin necrosis.

Figure 3. Clinical presentation of a patient with Fournier’s gangrene in a 74-year-old male with diabetes and paraplegia.

A) A picture taken upon hospital admission shows a stage IV sacral pressure ulcer together with scrotal skin necrosis; B) Transversal computed tomography scan slice depicting gas in the soft tissue and a collection between the sacral area and the scrotum; C) Post-operative aspect after drainage and right orchidectomy.
Figure 4. Algorithm for the approach to a patient with suspected NSTI.

Figure 5. Clinical findings during surgery in a 65-year-old female with posttraumatic necrotizing fasciitis. A) After primary incision. Note the typical landscape-like necrotic areas of the skin and soft tissue; B) After radical debridement. All necrotic tissue has been removed, the muscle tissue is vivid and not affected.

Transparency declaration

• Conflict of interest disclosure: JDW reports grants paid to his institution from Bayer, Pfizer, MSD, Grifols and Accelerate, outside the submitted work. The other authors have nothing to disclose.

• Funding: No external funding was received.

• Acknowledgments: None.

• Contribution: MP collected the data; all authors drafted the text and revised it critically.
References


**SUSPICION OF NSTI**
- Obtain microbiological samples (blood and skin cultures)
- Initiate broad-spectrum antibiotic treatment

**MULTIDISCIPLINARY MANAGEMENT** (Surgeon/Intensivist/Anesthesiologist)
- Consider ICU management if organ failures
- Consider surgical management as soon as possible

**EMERGENCY SURGERY PERFORMED** if
- Severe sepsis/septic shock
- Overt local signs of NSTI
  - Post-operative assessment
    - Consider second look surgery
    - Assess need for supplemental debridement
    - Adjust antibiotics based on microbiology
    - Plan wound care/Analgesia/Check tetanus vaccination status
    - Consider intravenous immunoglobulins if GAS

**NO EMERGENCY SURGERY PERFORMED** if
- No organ failure
- Low clinical suspicion of NSTI
  - Daily multidisciplinary assessment
    - Continue antibiotics
    - Imaging (e.g., MRI)
    - Dermatology consultation
  - Daily surgical evaluation