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Necrotizing Soft Tissue Infections: A Focused Review of Pathophysiology, Diagnosis, Operative Management, Antimicrobial Therapy, and Pediatrics

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Abstract

Background: Necrotizing fasciitis is a major health problem throughout the world. The purpose of this review is to assist providers with the care of these patients through a better understanding of the pathophysiology and management options.
Methods: This is a collaborative review of the literature between members of the Surgical Infection Society of North America and World Society of Emergency Surgery.
Results: Necrotizing fasciitis continues to be difficult to manage with the mainstay being early diagnosis and surgical intervention. Recognition of at-risk populations assists with the initiation of treatment, thereby impacting outcomes.
Conclusions: Although there are some additional treatment strategies available, surgical debridement and antimicrobial therapy are central to the successful eradication of the disease process.

Keywords: fasciitis; infection; necrotizing

This review is a collaboration between members of the Surgical Infection Society of North America (SIS) and the World Society of Emergency Surgery (WSES). Our purpose is to provide insights from throughout the world on the topic of necrotizing fasciitis (NF). The following is a review of the disease with focus on the pathophysiology, diagnosis, and treatment with a section specifically dedicated to the pediatric population. It is meant to assist providers who are faced with these challenging patients so that they may have a deeper understanding of this pathology and its management.

Pathophysiology

There are four specific characteristics associated with necrotizing soft tissue infection (NSTI) including presence of toxin-producing bacteria, local tissue destruction, fulminant progression of the inflammatory process, and early systemic toxicity resulting in sepsis, multi-organ dysfunction, septic shock, and death. Necrotizing infections may occur within any layer of skin and soft tissue—the dermal layer, subcutaneous tissue, fascia, or muscle. The majority of bacteria enter through a break in the skin barrier such as with bite wounds, small lacerations, trauma, or surgical procedure. Hematogenous spread of bacteria to the tissue is another mechanism, although less common. Not all contaminated wounds will progress to necrotizing infections. Local tissue environment plays a role in disease progression as seen in the case of contamination by spores of *Clostridium perfringens*. Here the anaerobic environment (caused by impairment of the blood supply resulting in tissue hypoxia) is necessary for maturation and proliferation of *Clostridium* strains [1].

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Characteristic local manifestation, as well as systemic manifestation, is related to the specific pathophysiologic mechanism, depending on the toxins and enzymes of involved bacteria [1–3]. Rapid bacterial spread is facilitated by protease activity of bacterial enzymes and toxins, causing damage of the extracellular matrix. Lack of fibrous attachments can lead to widespread infection and tissue destruction in some regions, such as the trunk and limbs. The inflammatory process usually begins in the deep tissue planes, often leaving the skin unaffected.

The lack of purulence is a hallmark of the histopathology of NSTI [1]. Absorbed bacterial toxins inhibit the influx of neutrophils from vessels while other mechanisms allow pathogens to escape phagocytosis by leukocytes (i.e., M-protein of *Streptococcus pyogenes*) [2]. In addition, toxin-induced intravascular platelet aggregates reduce the ability of leukocytes to cross the vascular endothelium into infected tissues, and polymorphonuclear neutrophils exhibit decreased function under hypoxic tissue conditions [1,2]. Clinically, marked swelling with edema and only mild erythema is observed in the site of inflammation.

The second basic characteristic is progressive necrosis of affected tissue. The necrosis may be directly mediated by bacterial toxins or indirectly because of vascular occlusion causing ischemia. Bacterial toxins are released into the blood stream and potently stimulate platelets, leukocytes, and endothelial cells resulting in the formation of occlusive intravascular aggregates [1,4]. The vascular perforators coursing through the fascia to supply the skin are thrombosed, resulting in critical skin ischemia. Blisters and bulla are caused by ischemia-induced necrolysis, and initially they are filled with clear fluid. Hemorrhagic bulla or blue-violet color of skin is a manifestation of dermal necrosis from irreversible local perfusion deficits. In the case of clostridial necrotizing infection, tissue destruction is associated with gas bubble formation. Superficial nerves are damaged, producing pain, which may manifest as hyper- or hypoesthesia [5].

Systemic manifestations of NSTIs are also related to toxin-mediated pathophysiologic mechanisms and include fever, hypotension, tachycardia, altered mental status, and signs of organ dysfunction. In principle, these mechanisms may involve both host and pathogen factors. Human genes that control release of cytokines and promote or inhibit the acute inflammatory response determine host-related factors. Microbial virulence factors include gram-positive and gram-negative bacterial products.

Bacterial superantigens (pyrogenic exotoxins) directly stimulate and non-specifically activate high numbers of T cells and macrophages to produce tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 [1,2]. The massive release of these cytokines produces the uncontrolled systemic inflammatory response that can lead to multi-system organ dysfunction and shock. Superantigens also activate complement, the bradykinin-kallikrein system, and the coagulation cascade. Other bacterial toxins may have direct effects on cardiac output, heart rate, and systemic vascular resistance [6]. Toxin-induced hemolysis can contribute to the development of acute renal failure because of hemoglobinuria [7].

The NSTIs comprise two distinct bacteriologic entities—polymicrobial infection (type I) and monomicrobial infection (type II) [8,9]. Polymicrobial infection is characterized by mixed aerobic-anaerobic populations, including at least one anaerobic species (most commonly *Bacteroides spp.*, *Clostridium spp.*, and *Peptostreptococcus spp.*) in combination with one or more aerobic species such as *Enterobacteriaceae* (e.g., *Escherichia coli, Enterobacter spp., Klebsiella spp., Proteus spp.*), streptococci, or staphylococci [10].

Monomicrobial infection is most commonly caused by *S. pyogenes* (group A streptococci, GAS) [11,12]. Other pathogens causing type II NSTI include *Staphylococcus aureus*, especially the USA300 clone, *Aeromonas hydrophila* in association with traumatic lesions in fresh water, and *Vibrio vulnificus* in association with seawater injuries [13–15]. *E. coli* and *K. pneumoniae* have both been described recently as causes of monomicrobial NF in East Asia and may represent therapeutic challenges because of multi-drug resistance [16,17].

Polymicrobial necrotizing infection

Polymicrobial necrotizing infection is the most common type of NSTI [10,11]. A shift of responsible bacterial spectrum toward monomicrobial infections with multi-drug-resistant bacteria has been observed in the last decade, however [12,18]. Pathophysiologic mechanisms of mixed aerobic-anaerobic infection are synergistic and more virulent than infections caused by each microbial species individually. Most polymicrobial infections are associated with preceding injuries, often resulting from only minor trauma. Polymicrobial NSTI occurs mainly in immunocompromised individuals, such as patients with diabetes mellitus or chronic renal failure [9,19].

Streptococcus pyogenes (GAS)

S. pyogenes has been identified as a major cause of monomicrobial necrotizing infection [11,12]. Streptococcal NF has a significant potential for aggressive local spread, as well as systemic toxicity including toxic shock syndrome. GAS has several virulence factors that are thought to play important roles in the pathogenesis of NSTIs, including M-proteins, hyaluronic acid capsules, adherence to vimentin, and pyrogenic exotoxins [2,20].

M protein is a filamentous protein anchored to the cell membrane that protects GAS against humoral immune surveillance and phagocytosis by polymorphonuclear leukocytes. Many M-protein types have been described; however, types 1 and 3 are the most common M-proteins related to necrotizing infection [19]. Hyaluronic acid capsule allows the bacteria to escape phagocytosis [2]. Vimentin is a host skeletal muscle protein upregulated on injured skeletal muscle, and GAS adheres to vimentin, a phenomenon that partially accounts for the increased incidence of GAS infections after muscle trauma.

Streptococcal pyrogenic exotoxins (type A, B, and C) belong to a group of proteins called superantigens. These pyrogenic toxins may stimulate and activate a much larger proportion of T cells and macrophages than conventional antigens activate in some individuals. Such stimulation of the host's immune cells is associated with production of both monokines (TNF α, IL-1, IL-6) and lymphokines (IL-2 and TNF β) [2,19]. The massive release of these cytokines contributes to shock, tissue destruction, and organ failure called streptococcal toxic shock syndrome. Superantigens also activate complement, the bradykinin-kallikrein system, and the coagulation cascade.

Staphylococcus aureus

S. aureus has been reported to be associated with NF mainly in polymicrobial infection; nevertheless, monomicrobial NF caused by *S. aureus* has been described as well [21,22]. Panton-Valentine leucocidin has been linked to severe infections like necrotizing pneumonia or deep abscesses in skin and soft tissue. The role of Panton-Valentine leucocidin in pathogenesis of NF has yet to be elucidated, however [3]. *S. aureus* may produce toxic shock syndrome toxin-1 that leads to toxic shock syndrome [3]. Toxic shock syndrome mediated by *S. aureus* was associated mainly with tampon use during menstruation; however, non-menstrual etiology including soft tissue infection has been described.

Clostridial necrotizing infection

Clostridium species are widespread in nature because of their ability to form spores. Necrotizing *Clostridium* infections are usually attributable to *C. perfringens, C. septicum, C. sordellii, C. histolyticum,* and *C. novyi* [1]. Some *Clostridium* species (*C. perfringens, C. histolyticum*, etc.) are the principal causes of trauma-associated necrotizing infections, whereas *C. septicum* may initiate infection spontaneously. Categories of *Clostridium*-related soft tissue infections include benign wound contamination, anaerobic cellulitis, NF, and life-threatening myonecrosis (i.e., gas gangrene).

Clostridial gas gangrene consists of progressive invasion and destruction of healthy muscle tissue and early systemic toxicity. The pathogenesis of gas gangrene is complex and can be considered in four separate stages—contamination and proliferation (stage 1), toxin production (stage 2), local and regional tissue destruction (stage 3), systemic toxicity including shock and organ failure (stage 4) [1]. If trauma compromises the blood supply, an anaerobic environment forms with tissue hypoxia and acidic pH providing an optimal condition for maturation of clostridial spores that were induced during injury. Clostridial micro-organisms begin to proliferate and produce toxins.

Alpha and theta toxins of *C. perfringens* have been implicated in the pathogenesis of gas gangrene. Alpha toxin is largely responsible for both the widespread tissue necrosis and the characteristic absence of tissue inflammatory response. Alpha toxin induces platelet aggregation and formation of occlusive thrombi that completely and irreversibly occlude vessels [1,4]. The major mechanism explaining the absence of polymorphonuclear leukocytes in tissue is sequestration within the adjacent vasculature [4]. Alpha and theta toxins are also cytotoxic to leukocytes; hence, these toxins likely destroy the small number of polymorphonuclear leukocytes that do migrate into tissue. Both toxins are absorbed systemically; they interact with leukocytes, platelets, and endothelial cells and induce release of cytokines (TNF α, IL-1, IL-6). Alpha toxin and theta toxins directly suppress myocardial contractility and may contribute to profound hypotension via a sudden reduction in cardiac output and decrease of systemic vascular resistance [1].

Pathogenic strains of *C. sordellii* produce up to seven exotoxins. Of these, lethal toxin and hemorrhagic toxin are regarded as the major virulence factors [23]. The *C. septicum* α toxin is a pore-forming hemolysin that induces rapid necrosis of cultured cells (without induction of apoptosis) by causing efflux of intracellular potassium and adenosine triphosphate depletion [24,25].

Diagnosis

Skin and soft tissues infections (SSTIs) are common causes of emergency department (ED) admission. The SSTIs are clinical entities with variable presentations ranging from mild and superficial such as impetigo to deeper and more severe such as NSTIs. At clinical examination, it can be difficult to distinguish a cellulitis or an abscess from a severe NSTI.

Necrotizing fasciitis is a subset of the aggressive NSTIs that cause necrosis of the muscle fascia and subcutaneous tissues. It can spread rapidly, causing infection of the fascia, peri-fascial planes, and cause secondary infection of the over- and underlying skin, soft tissue, and muscle. This infection typically travels along the fascial plane, which has a poor blood supply, leaving the overlying tissues unaffected initially, potentially delaying diagnosis and surgical intervention. Early diagnosis and appropriate surgical treatment decreases significant morbidity and death related to NF. The time from admission to surgical procedure is the most decisive factor for survival [26].

Clinical features

The most common risk factors for NF are diabetes mellitus (it can be found in 40%–60% of patients with any NF types), immunodeficiency diseases, illicit drug use, malnutrition, chronic renal failure, obesity, liver cirrhosis, chronic heart failure, alcohol abuse, systemic lupus erythematosus, Addison disease, peripheral vascular disease, and skin injuries [27]. The primary symptom that leads the patient to present to the ED is severe, excruciating pain resistant to medications. NF can occur with a trivial wound or often without any provocation. The infection is located commonly in the lower extremities, the perineum, and genital area (e.g., with Fournier gangrene), the abdominal wall, and in upper extremities. Classic physical examination findings include the presence of purulent secretions, erythema, swelling or induration, warmth, crepitus, cellulitis, pain, or tenderness.

Localized fluid collections such as carbuncles can be fluctuant. Cellulitis is a diffuse spreading infection of the dermis with erythematous, sometimes ill-defined borders, while erysipelas has a similar presentation to cellulitis but with a well-demarcated, raised border because of lymphatic congestion. Crepitus can be present, and it is suggestive of necrotizing tissues, usually caused by gas within tissues. The presence of bullae or ecchymotic changes to the skin and hyper/hypoesthesia also suggests NF.

Kim and colleagues [28] divided NF into three stages on the basis of the sequential presence of clinical features reported by Wong and Al [11]. In stage I (early stage), the overlying skin is warm, erythematous, and indurated, producing ''wooden skin.'' In stage II (intermediate stage), blisters and bullae form, and in stage III (late stage), the bullae become hemorrhagic, crepitus can be noted on physical examination, and skin necrosis, which can progress to overt gangrene, ensues. Involved areas in NF tend to be extremely painful in early stages and painless in more advanced stages. As local signs of NF can be minimal and clinical evolution can be fast and fatal, early diagnosis requires high clinical suspicion and the identification of systemic signs of toxicity including tachycardia, fever, hypotension, and tachypnea.

Medical decision making in the ED is often based on the presence or absence of fever. Presence of fever was found to

be the strongest predictor of need for hospitalization greater than 24 h, yet it is reported that fewer than 25% of patients with NSTI have a fever on presentation [29,30]. A prospective, observational study demonstrated fever in patients presenting to the ED with SSTI is uncommon (96/734 patients analyzed, 13.1%) in patients admitted for SSTI during the first 6 h of ED evaluation; area of erythema and leukocytosis are the only characteristics associated with fever. This association with fever negatively correlates with the severity of the infection (i.e., when the area of erythema was less than 9 cm^2, fever was unusual). Clinical features such as bullae, streaks, necrosis, and bone involvement on imaging, considered as signs of severe infections, were not associated with fever [31]. The strongest predictor of death in patients with SSTI is septic shock at ED admission [32].

Laboratory risk indicator for NF scoring

The Laboratory Risk Indicator for NF (LRINEC) is a scoring system introduced in 2004 to distinguish NF from other severe SSTI and to identify and classify patients with NF into different risk categories [33]. Six routinely performed laboratory tests were taken into consideration in this score: serum C-reactive protein (CRP) level, white blood cell (WBC) count, hemoglobin level, serum sodium level, serum creatinine level, and serum glucose level, as shown in Table 1. Several studies have assessed the utility of this score, and it has been proposed that the cutoff value for diagnosis of NF is 6, and the severity of the infection can be estimated as low (score ≤5), moderate (score 6–7), and severe (score ≥8) [34–36]. With a score of 8 or higher, there is a 75% risk of having NSTI (Table 2).

A recent systematic review and meta-analysis evaluated the clinical application of LRINEC scoring. Analysis of 16 studies with a total of 846 patients showed that the mean LRINEC score in patients with NF was 6.06. Two articles reported LRINEC scores in patients without NF with a mean 2.45. The authors concluded that LRINEC is a useful clinical determinant in the diagnosis and surgical treatment of patients with NF with a statistically positive correlation between LRINEC score and a true diagnosis of NF [37].

El-Menyar et al. [38] aimed to evaluate the prognostic value of LRINEC score in NF; they retrospectively analyzed 294 patients with hospital length of stay, septic shock, and hospital death as primary outcomes. Patients were divided into two groups: group LRINEC <6 and group LRINEC ≥6. Patients with a LRINEC ≥6 had a significantly greater hospital length of stay, septic shock, and death. The authors concluded that LRINEC scoring has a diagnostic role in NF and that it can identify high-risk patients. In contrast, other studies determined the LRINEC score to have low predictive value [39,40]. The LRINEC score can be misapplied easily; in fact, it was not designed to exclude NF in patients with a low-risk score, and case reports and small studies failed to replicate the high sensitivity and negative predictive value reported in the initial article [39–43].

Table 1. Laboratory Risk for Necrotizing Fasciitis Scoring

Variable	*Value*	*Score*
C reactive protein	<150 mg/L	0
	>150 mg/L	4
White blood cell count	<15 cells/mm^3	0
	15-25 cells/mm^3	1
	>25 cells/mm^3	2
Hemoglobin	>13.5 g/dL	0
	11-13.5 g/dL	1
	<11 g/dL	2
Sodium	≥ 135 mmol/L	0
	<135 mmol/L	2
Creatinine	≤1.6 mg/dL	0
	>1.6 mg/dL	2
Glucose level	≤180 mg/dL	0
	>180 mg/dL	1

Table 2. Necrotizing Fasciitis Patient Risk Categories according to Laboratory Risk for Necrotizing Fasciitis Scoring

Risk categories	*LRINEC scoring*	*Probability of NSTI (%)*
Low	<=5	<50
Intermediate	6-7	50-75
High	>=8	>75

LRINEC = Laboratory Risk for Necrotizing Fasciitis.

Burner et al. [44] and colleagues analyzed data about patients with NF evaluated in the ED of an urban, academic, tertiary care hospital to describe the sensitivity of the LRINEC score and examine the role of patient factors in the score's sensitivity. Among 266 patients discharged with a diagnosis of NF, the authors were only able to confirm the diagnosis, by chart review, in 167; it was only possible to calculate a LRINEC score in 80 patients because of the absence of an initial CRP value; a LRINEC score of 6 or greater had a sensitivity of 77%. Sensitivity analyses of missing data supported their finding of inadequate sensitivity to rule out NF. In subanalysis, NF patients with concurrent diabetes mellitus were more likely to be categorized accurately by the LRINEC score. Burner et al. concluded that the LRINEC score is not sufficiently sensitive to rule out NF. In clinical practice, CRP value is not routinely collected in the ED, which presents a barrier for the effective utilization of the LRINEC score as a predictive tool.

Neeki et al. [45] analyzed retrospective clinical data about 948 ED patients to assess the ability of the LRINEC score to differentiate cellulitis from NF. In the cohort with cellulitis, 10.7% had LRINEC scores in the moderate-to-high risk range for NF. The NF cohort (n = 135) only had CRP values available for 22 patients; LRINEC scores among the remaining 113 patients without CRP values included six patients with a score ≥8, while 19 patients had a LRINEC score ≤1, so a total of 47 patients (22 with CRP values, six with high LRINEC scores but no CRP, 19 with low LRINEC scores but no CRP) in the NF cohort were classified as low, moderate, or high risk for NF based on the LRINEC score. A majority of these 47 NF cohort patients (63.8%, 30/47) were classified as low risk (LRINEC score ≤5). These results suggest that in the ED setting, the LRINEC score may not be an accurate tool to determine NF risk stratification or to differentiate between cellulitis and NF

Hietbrink et al. [46] proposed a triple diagnostic strategy that included an incisional biopsy over the most suspected

area, a fresh frozen section and gram-staining to help with early recognition of NF and make the diagnosis in the early ambiguous stages of the infection. The authors provided an algorithm and retrospectively analyzed this strategy for 21 patients included in the study who presented with suspected NF and extensive comorbidities. The diagnosis was confirmed based on intra-operative macroscopic findings in 11 patients, and six of the 10 remaining patients had a change in treatment strategy because of histology or micro-biotic observations. Seventeen patients had proven NF, and two died from this disease. This approach emphasizes the importance of adequate algorithms and treatment protocols for all medical specialties that might encounter NF because clinical signs are often unrecognized or absent.

Imaging of NF

The diagnosis of NSTIs remains clinical primarily. Therefore, imaging should not delay emergency surgical treatment in patients with established NF. Imaging can be useful to map disease extent to aid in planning the surgical approach and margins and to exclude other processes. In patients whose conditions are severely toxic, treatment should not be delayed for the performance of imaging [47]. Plain radiographs, ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) may help the diagnosis of NF when uncertain [26,27]. Radiographic findings in the early stage of NF are similar to those of cellulitis and include increased soft-tissue opacity and thickness. Radiographs can often be normal until the infection and necrosis are advanced and manifest as soft-tissue emphysema tracking along fascial planes. Plain radiography is useful in cases of gas gangrene [47].

Point-of-care ultrasound (POCUS) has the advantage of rapid performance at bedside in critically ill patients who are unable to tolerate a CT or MRI, and it may be helpful in differentiating simple cellulitis from NF in the emergency setting [38]. The available literature demonstrates that the test is highly sensitive and specific (i.e., 88% sensitivity and 93% specificity) for NF on certain imaging criteria, such as soft tissue thickening, fascial fluid accumulation greater than 4 mm, and the presence of subcutaneous air [48]. In some cases involving non–gas-producing Group A streptococcal infections, US has been shown to help in the diagnosis of NF with negative findings on CT and MRI [49]. Because US can be highly operator-dependent, suitable teaching models should be available to train clinicians properly on how to best diagnose and recognize sonographic findings of NF [50]. By POCUS, subcutaneous air will show as shiny white dots in the fascial plane, while edema will show as hypoechoic areas; calcifications may mimic air on US, and the acoustic shadow can help clarify whether gas bubbles are truly present [51].

The most sensitive modality for soft-tissue gas detection is CT, and compared with plain radiography, CT is superior to evaluate the extent of tissue or osseous involvement, show an underlying, and potentially more remote, infectious source, and reveal serious complications such as vascular rupture complicating tissue necrosis. The CT characteristics correlate with pathologic findings of soft-tissue inflammation or liquefactive necrosis and thus may feature dermal thickening, increased soft-tissue attenuation, inflammatory fat stranding, and possible superficial or deep crescentic fluid or air in the subfascial planes [47]. The rapidity of CT compared with MRI may be advantageous for an emergent NF evaluation, but often patients at risk for NF have concurrent acute kidney injury precluding the administration of contrast [50].

An MRI is the preferred imaging platform for soft tissue infections, but its use is limited by acquisition time, potentially delaying rapid diagnosis of severe infections like NF. Detailed descriptions of MRI findings in NF are beyond the scope of this review, but can be found in the excellent review by Chaudhry et al. [47].

Carbonetti et al. [52] evaluated the diagnostic efficacy of contrast enhanced CT in the ED for diagnosis of NF and correlated radiologic findings with the LRINEC score. Two parameters were strongly associated with the diagnosis of NF: Involvement of the fascia and lack of fascial enhancement. The LRINEC score does not show strong association with the presence of fasciitis and can be high in other musculoskeletal infections. Final diagnosis of necrosis among the fascia is surgical. Presence of gas is not a specific sign of NF being present in other musculoskeletal infections. They concluded that in clinical practice, CT could be useful to discriminate NF from other musculoskeletal infections in emergency settings, when MRI, which is superior to CT in this discernment, could not be performed.

Operative Management

The management of NSTIs involves operative debridement in addition to antimicrobial therapy and physiologic support. A high index of suspicion should prompt early surgical consultation, because delays in diagnosis and time to surgical debridement are associated with higher mortality rates [11,53–58]. While the diagnosis is often obvious by the time surgical consultation is obtained, for equivocal cases, surgical exploration may be used to evaluate the tissue planes to avoid further delay [8,59]. A small skin incision made down to the fascia for evaluation of the separation from the surrounding tissues may aid the diagnosis [60]. Operative findings consistent with a NSTI include presence of gas, edema, purulence, dishwater drainage, necrotic tissue, thrombosed perforating vessels, and a dull gray fascia that separates easily from fat with blunt dissection [59,61].

Surgical debridement should encompass all clearly nonviable infected tissue and necrotic tissue including muscle, fascia and overlying skin. It often requires a wide debridement that involves large areas of tissue and potentially organs. Healthy tissue may need to be removed if there is extensive tissue involvement underneath, and the debridement should be taken back to healthy, bleeding tissue, because the goal is to create a well-vascularized bed. At the time of the initial debridement, tissue should be sent for culture, and the incision area should be left open, packed, and the patient should be taken to the intensive care unit for ongoing resuscitation. In addition, it is important to document the location and dimensions of the incision area and the existence of any undermining or tracts.

Rarely is one debridement adequate, and patients will likely need to be taken back to the operating room for reexploration after their hemodynamic values improve. This should occur within the first 24 h, and most patients will require on average 3–4 operative procedures [60]. Early redebridement is recommended because of increases in death

and complications with delaying the procedure [62]. If the clinical condition of the patient deteriorates or does not improve greatly before the planned re-exploration, the patient should be taken back to the operating room sooner because spreading infection and hypotension leads to progressive necrosis. During each subsequent exploration, all newly identified necrotic tissue should be debrided until a clean incision area is obtained.

While the traditional teaching for surgical debridement of NSTIs is wide debridement, these debridements can lead to large, difficult-to-treat complex incision areas. In addition, the areas can lead to disfigurement, immobility, and chronic pain with often only skin grafting as an option for reconstruction. Because of these complications, there have been techniques developed that employ a skin-sparing approach [63]. These techniques maintain maximal native tissue to improve reconstructive options and to minimize the surface area healing by secondary intention, and are based on the model of perforator blood vessels and permanent vessel enlargement known as the delay phenomenon [64–66]. The debridement includes only necrotic tissue, and the perfused skin beyond the margins of the necrotic tissue should be preserved [63]. Full-thickness skin flaps including subcutaneous tissue are raised with viable perforating vessels preserved if possible.

If exposure is inadequate, there are several adjunct techniques can be used including incision extension, counter incisions, and trap-door or hinge flaps [63]. One of the goals of using the skin sparing technique is to be able to close the spared skin primarily in a delayed fashion after the debridements are complete.

The NSTI of the perineal, peri-anal and peri-urethral tissue, otherwise known as Fournier gangrene, can also pose an operative challenge. Surgical debridement is the primary treatment, and careful examination of the patient under anesthesia should be performed to identify the cause of the disease and extent of the spread of infection [67]. If no perineal source can be found, an abdominal exploration should be considered [68,69].

If necrotic testicles are found during debridement, an intra-abdominal source should be suspected, because they are usually spared if necrosis only affects the subcutaneous tissue given their intra-abdominal vascular supply [68]. Debridement of muscle and deep fascia is usually not required, because rarely are these involved; however, debridement often results in exposure of the testes. Orchiectomy rarely is required unless there is testicular necrosis as seen with epididymo-orchitis or a scrotal abscess [70]. If the testes are exposed, they can be implanted temporarily into a medial thigh or lower subcutaneous pouch until healing or reconstruction are complete [71–75].

Fecal and urinary diversion may be necessary depending on the severity of the infection and extent of debridement. For cases with extensive anal sphincter damage or colonic or rectal perforation, diverting colostomy has been demonstrated to improve outcomes by decreasing the soilage and bacterial load in the perineal wound [76,77]. Diverting colostomy does not eliminate the necessity of multiple debridements, nor does it reduce the number of debridements [78]. If the incision bed can be kept clean with regular dressing changes and stool diverted using a fecal management system, colonic diversion may be avoided [60]. Urinary diversion with a supra-pubic catheter may be necessary if there is underlying urinary tract disease such as a known stricture with extravasation or urinary incontinence [70,79,80].

A NSTI of the extremities can be managed with serial debridements, but often requires amputation of the extremity. It can be performed as the initial operation in patients with profound shock, because it is usually a shorter procedure and patients may not tolerate a long operation. In addition, it requires less, if any, reconstructive procedures [81]. Independent risk factors for limb loss include shock on hospital admission, pre-existing heart disease, and clostridial infection [82]. The extent of the debridement required and the likelihood of a functional extremity should also be taken into consideration when the decision to perform amputation for source control is made [59]. Other indications include joint involvement, rapid progression to the torso, or destruction of the major nerves and blood vessels [61,83].

When the surgical debridement is no longer necessary, and the overall clinical condition of the patient has improved, ongoing incision management becomes increasingly important. Dressing changes can be performed at the bedside, as long as the patient can tolerate the procedure, often requiring high doses of pain medications. While certain centers use topical antiseptics such as sodium hypochlorite or mafenide for dressing changes in incisions with clinical signs of infection, it has not been established whether this is better than simple wet to dry dressing changes [59,60].

When the incision bed is clean, a negative pressure device or vacuum-assisted closure device (VAC) may be a possibility to help facilitate granulation. These VACs accelerate incision healing by removing excess fluid that leads to increased capillary circulation and inflow, reducing bacterial load at the incision base and encouraging growth of granulation tissue, vascularity, and epithelial migration [84,85]. This therapy has been shown to be effective in managing extremity areas from NSTIs, in addition to perineal areas [86–88]. Dressing changes are only performed every 2–3 days, therefore decreasing frequency, discomfort, and pain medication requirements. These devices also are useful in the reconstruction of incision areas by promoting the granulation-healing process and allowing elective planning of the definitive closure or reconstructive procedure [89,90].

When the incision area is clean, healing, and stabilized, definitive coverage or closure can be considered. Temporary skin substitutes such as porcine or cadaveric skin or artificial skin substitutes may be used with larger areas for immediate tissue coverage. These temporary skin substitutes can help decrease fluid and protein loss and minimize bacterial colonization of the incision bed [91,92]. The dermal skin substitutes play a role in optimizing the bed for eventual skin grafting.

Integra® is a bilayer matrix wound dressing with a silicone layer over a collagen fiber artificial dermis. The collagen replacement layer acts as a matrix for the patient's fibroblasts, macrophages, and endothelial cells to infiltrate, and this layer is replaced gradually by collagen and subsequent vascularization. After vascularization and engraftment, the silicone layer is removed, and an epidermal autograft is applied over the neodermis [93]. These skin grafts can be very thin, therefore decreasing the risk of scarring and promoting rapid donor site healing.

The most common type of coverage is split-thickness skin grafts; however, other reconstructive options include full-thickness skin grafts, delayed primary closure versus healing by secondary intention, tissue expansion and flap coverage, both pedicled and free flaps. Groin and perineal incision sites may be able to heal by delayed primary closure or secondary intention only if they are small with excess subcutaneous tissue and the lesions run parallel to the natural tissue planes [59]. For larger wounds, split-thickness skin grafts can be used; however, scar contracture can occur leading to an unsightly scar, the graft may not take on an uneven surface, and they are not as durable as a fasciocutaneous or myocutaneous flap [94,95].

Local versus distant flap selection is based on presence of infection, presence of vascular supply, defect depth, and other areas of damage that would preclude a local flap [96]. Free tissue transfer from remote sites with revascularization at the reconstructive site using micro-surgical techniques can be performed when local flaps are not available [97]. In cases where an extremity is amputated, a myofascial cutaneous skin flap can be preserved to allow for early pedicle flap coverage after surgical site control is achieved [60]. Tissue expansion and complex pedicled and free flaps should be undertaken in a multi-disciplinary fashion with plastic and reconstructive surgeons.

Antimicrobial Therapy

Empiric therapy (Table 3)

Empiric antimicrobial therapy must begin as soon as the diagnosis of NF is considered. Because clinical examination alone cannot differentiate between Type 1 and Type 2 NF, coverage initially should be broad, including gram-positive, gram-negative, and anaerobic organisms. Antimicrobials should include an anti-methicillin-resistant *S. aureus* (MRSA) agent, given the incidence of MRSA throughout the country.

Linezolid is preferred over vancomycin, given its association with improved outcomes in patients with MRSA SSTIs [98], as well as its anti-toxin effect and favorable safety profile, particularly because many of these patients already have acute kidney injury. Tedizolid is another oxazolidinone with antibacterial activity similar to linezolid, but there is less published clinical experience using this agent [99]. Daptomycin is a lipopeptide antibacterial drug with rapid bactericidal activity against MRSA in vitro; there are limited published data using this drug for MRSA-associated NSTIs. This drug is also rapidly bactericidal for other gram-positive etiologies of NF, such as beta hemolytic streptococci [100].

Ceftaroline is an advance generation cephalosporin that is active against MRSA, beta-hemolytic streptococci, and enteric gram-negative pathogens. This drug lacks activity against anaerobes, extended spectrum beta-lactamases (ESBL)- or AmpC-producing gram-negatives, and *Pseudomonas aeruginosa*, but this drug is non-inferior to vancomycin plus aztreonam in the management of complicated SSTIs [101]. There are no published data about the efficacy of ceftaroline for NF specifically, so caution is advised regarding the use of this agent empirically.

Other agents with activity against MRSA that have become available recently include the semi-synthetic glycopeptides telavancin, oritavancin, and dalbavancin. These agents have all been studied for the management of MRSA SSTIs and are all comparable in terms of efficacy, but telavancin is associated with a higher rate of adverse events compared with oritavancin or dalbavancin [102], and none of these agents have any published data for use in NF.

Delafloxacin is a new fluoroquinolone with activity against MRSA, other gram-positive bacteria associated with NF (beta-hemolytic streptococci), enteric gram-negative bacteria, anaerobes, and *P. aeruginosa*. This drug is approved for the management of acute bacterial skin and soft tissue infections, based on several phase III clinical trials that compared delafloxacin with vancomycin plus aztreonam [103]. None of these trials enrolled patients with NF, but this drug is attractive as a single agent that covers the bulk of pathogens associated with NF, has enhanced activity at acidic pH, and may be given as both an intravenous and oral agent. Further studies are needed to determine whether delafloxacin is comparable to older antibacterial regimens for NF (e.g., linezolid plus piperacillin-tazobactam).

Table 3. Empiric Antibacterial Agents for Necrotizing Soft Tissue Infections*

Recommended First-Line Agents (doses not adjusted for renal/hepatic function)
1. Linezolid 600 mg IV every 12 h PLUS piperacillin-tazobactam 4.5 gm IV every 6 h
2. Linezolid 600 mg IV every 12 h PLUS meropenem 1 gm IV every 8 h

Alternative agents for MRSA/gram-positive bacterial pathogens[1]
- Vancomycin: load 25 mg/kg IV, then 15 mg/kg IV every 8–12 h
- Tedizolid 200 mg IV every 24 h
- Daptomycin 6 mg/kg IV every 24 h
- Ceftaroline 600 mg IV every 12 h
- Telavancin 10 mg/kg IV every 24 h
- Dalbavancin 1500 mg IV as a single dose OR 1000 mg IV once, then 500 mg IV in 7 d
- Oritavancin 1200 mg IV as a single dose
- Delafloxacin 300 mg IV every 12 h
- Tigecycline 100 mg IV load on day 1, then 50 mg IV every 12 h
- Omadacycline 200 mg IV load on day 1, then 100 mg IV every 24 h

Alternative agents for gram-negative PLUS anaerobic bacterial pathogens[1]
- Delafloxacin 300 mg IV every 12 h
- Tigecycline 100 mg IV load on day 1, then 50 mg IV every 12 h
- Omadacycline 200 mg IV load on day 1, then 100 mg IV every 24 h

Agents that decrease protein toxin synthesis via ribosomal inhibition[2]
- Linezolid
- Tedizolid
- Clindamycin
- Tigecycline

IV = intravenous; MRSA = methicillin resistant *Staphylococcus aureus;*

*Includes only antibacterial agents with Food and Drug Administration-approved indication for skin/soft tissue infections.

[1]Published experience using these agents for NSTI varies from ''none'' to ''extensive''; there are no comparative trials that specifically address these agents for necrotizing fasciitis.

[2]These agents have published in vitro data supporting toxin synthesis inhibition.

Piperacillin-tazobactam provides completion coverage for enteric gram-negative bacteria and anaerobes that may be involved. Patients colonized with ESBL or AmpC-producing gram-negative pathogens should be treated empirically with a carbapenem such as meropenem or doripenem. While piperacillin-tazobactam may demonstrate in vitro activity against ESBL-producing organisms, a recently published clinical trial comparing clinical outcomes of bacteremia with ceftriaxone-resistant *E. coli* or *K. pneumoniae* for patients treated with piperacillin-tazobactam or meropenem clearly showed a survival benefit for those receiving meropenem [104].

Newer antibacterial agents with activity against multi-drug-resistant (MDR) gram-negative pathogens include ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, tigecycline, omadacycline, and eravacycline. The specific use of these agents as empiric therapies for NSTIs has not been studied, and these agents should be reserved for the tailored treatment of patients with MDR gram-negative pathogens who have limited therapeutic options.

All patients with NSTIs should receive an antibacterial agent that inhibits bacterial protein synthesis. Examples of these agents include linezolid, tedizolid, and clindamycin. For patients receiving linezolid (or tedizolid) as part of an empiric regimen, there is no need for an additional protein synthesis inhibitor. If other drugs are chosen for empiric gram-positive coverage, however, a ribosomal protein synthesis inhibitor should be added to the regimen to reduce bacterial protein toxin synthesis.

Duration of therapy for NF has never been studied formally nor is it commented on in many of the published guidelines [26,105,106]. Many experts in the Surgical Infection Society agree, however, that once source control is obtained and sepsis has resolved, further antimicrobial therapy is unnecessary.

Directed therapy

Ideally, micro-biologic laboratory testing of relevant patient samples will yield specific pathogens causing the NSTI. In these cases, antimicrobial therapy should be optimized for the involved organisms to reduce antibiotic-associated complications (e.g., allergic reactions, adverse drug events, colonization with MDR pathogens because of selective pressure, *Clostridioides difficile* infection) and improve clinical outcomes. This section details directed therapy for select pathogens involved in NF.

S. aureus. Agents active against MRSA have been discussed in the above section addressing empiric therapy. It is important to note that methicillin-sensitive *S. aureus* (MSSA) infections can be equally devastating, and continuation of a MRSA-active agent when MSSA has been isolated may not provide equivalent clinical outcomes. For example, vancomycin is associated with inferior clinical outcomes compared with nafcillin for the management of MSSA bacteremia [107]. Clinical trials comparing efficacy of cefazolin versus nafcillin or oxacillin have not found any significant differences among these beta-lactams for the management of MSSA bacteremia [108]; specific information regarding the relative efficacy of these agents for MSSA-associated NF are lacking.

Beta-hemolytic streptococci. The most common beta-hemolytic streptococcal species associated with NF is *S. pyogenes* (group A streptococcus, GAS), but other beta-hemolytic streptococci have been implicated uncommonly in NF as well. These bacteria remain susceptible to beta-lactam antibacterial agents, particularly penicillins and ceftriaxone; however, resistance to clindamycin has been documented [109]. The GAS infections are best managed with a combination of intravenous penicillin plus clindamycin. Group B streptococci (GBS) have also been described as NF pathogens, notably among infants, and generally remain susceptible to penicillin, Penicillin resistance has emerged, however, among GBS isolates via amino acid substitutions in penicillin binding protein 2x (PBP2x), leading to higher penicillin minimum inhibitory concentrations (MICs) [110]. Penicillin susceptibility testing should be performed before using penicillin alone for the definitive therapy of serious GBS infections, including NF.

Clostridial NSTI. *C. perfringens* is the prototypical clostridial pathogen in gas gangrene, a necrotizing infection that is associated with devitalized soft tissue wounds. Other important clostridia associated with soft tissue infections include *C. sordellii*, *C. histolyticum*, and *C. septicum*. This latter organism is associated with spontaneous gas gangrene among patients with gastrointestinal co-morbidities. Management of gas gangrene very much relies on surgical debridement of the devitalized tissues. Clostridial infections are characterized by the production of multiple protein toxins that damage host tissues and impair the innate immune response, so the inclusion of ribosomal protein synthesis inhibitors in antibacterial regimens for these infections is critical. The combination of a beta-lactam plus clindamycin will provide antibacterial coverage for the vast majority of clostridial soft tissue infections [105,109].

V. vulnificus. This halophilic gram-negative pathogen is associated with life threatening soft tissue infections, usually after exposure of an open site to brackish coastal water or shellfish. A history that includes these latter features should prompt rapid initiation of doxycycline and a third-generation cephalosporin [105].

Aeromonas species. *Aeromonas* species are ubiquitous, oxidase-positive, facultative anaerobic gram-negative bacilli found in many environmental sources, especially water that can cause a variety of severe human infections, including monomicrobial NF. Three species (*A. hydrophila, A. caviae, A. veronii*) account for >85% of human infections. *Aeromonas* NSTIs (NF, myonecrosis) are preceded commonly by traumatic injuries, especially in patients with underlying cancer or liver disease, and carry a high mortality rate in the 60%–75% range. Clinicians must maintain a high diagnostic suspicion for these organisms to include environmental exposures before presentation, recent leech therapy for wound healing, traumatic injuries from occupational or recreational activities, natural disasters, or animal bites.

Pathogenic *Aeromonas* species commonly are susceptible to carbapenems (meropenem, imipenem), third/fourth-generation cephalosporins, and piperacillin-tazobactam, so the recommended empiric gram-negative regimens already recommended in this review typically will kill these bacteria.

The major mechanism of antibiotic resistance utilized by this genus is expression of beta-lactamases, so antibacterial susceptibility testing is recommended highly to allow detection of potentially resistant isolates. Quinolones are highly active against aeromonads, but an important exception that should be highlighted are cases of *Aeromonas* infection arising from medicinal leech therapy; these patients commonly are given quinolone prophylaxis, and this can select for quinolone-resistant strains that result in infection [111].

Adjunct Therapy

In addition to surgical and antibacterial therapies, other modalities have been investigated to decrease the morbidity and death associated with NF. An extensive discussion of these therapies is beyond the scope of this review, but the reader is referred to two recent excellent summaries addressing novel adjunctive therapies for NF [61,112].

Special Populations

Pediatrics

The NSTIs are less common in children than in adults, with an annual incidence of approximately 0.08 per 100,000 children [113]. Several studies have suggested a slight increase in the incidence over the last 20 years [114–116]. The disease affects children of all ages, with incidence peaks correlating with the predisposing conditions in different age groups. Neonates, babies aged 1–2 years old, and younger teenagers are reported to each have an increased incidence [117].

Risk factors for NSTI in children have some distinctions from those in adults. Malnutrition, immunocompromise, and prematurity are cited to be predisposing factors; however, many cases occur in otherwise healthy children [118]. Trauma, either surgical or otherwise, is a known risk factor for NSTI in children. The most commonly reported skin traumas leading to NSTI are varicella skin lesions. Vaccine sites reportedly have also developed into NST [119]. Postoperative NSTI has been associated with all types of procedures, but there is a notable association with Fournier gangrene and herniorrhaphy, orchidopexy, and circumcision in young children [120]. Fournier gangrene has also been attributed to severe diaper rashes in infants. Neonates have a unique disease pattern, and neonatal NSTIs most commonly are caused by omphalitis. Infections such as balanitis, neonatal mastitis, reactions to hospital monitors, and necrotizing enterocolitis have also been associated with neonatal NSTI [121,122].

Given its rare occurrence, the overall mortality rate of pediatric NSTI has been hard to estimate. Studies in children suggest a significantly lower mortality rate in children than in adults—between 5.0%–25%, with a recent meta-analysis reporting an overall mortality rate of 15.4% [118,123–126].

Soft tissue infections can occur anywhere on the body but are more common on the trunk in children compared with adults. Most cases of truncal NSTI are seen in neonates and babies younger than a year old, with older children having an increased rate of extremity infections [117,118].

As in adults, there is often a delay in diagnosis of NSTI in children, and they often receive a diagnosis of cellulitis. The most common findings of NTSI in children are fever, tachycardia, erythema, tenderness, and pain [117,127]. The finding of ''pain out of proportion'' to physical findings, although described frequently in older patients, is often difficult to diagnose in children [127]. The erythema in children with NSTI is often described as having more induration compared with simple cellulitis [118]. Children with NSTI have also been described as more ''toxic'' appearing than those with cellulitis [114]. As the disease progresses, the skin can develop bullae and crepitus. As in adults, hypotension and mental status changes portend advanced infection.

Laboratory findings in children with NSTI are notoriously non-specific [114,117,121]. Anemia, likely because of hemolysis, is often reported, as is leukocytosis and leucopenia [118,121]. Thrombocytopenia may differentiate cellulitis from deeper soft tissue infections [114]. Although scoring systems have shown promise in adults, they have not been validated in children and are, therefore, of minimal utility [121].

There are no standard recommendations for obtaining imaging studies to diagnose NSTI in children. Plain x-ray rarely is useful in identifying soft tissue necrosis and is seldom part of the diagnostic algorithm. Frequently, US is used in the pediatric population because it lacks ionizing radiation and rarely requires sedation. Although it has demonstrated utility in differentiating drainable abscesses from simple cellulitis, US has not been used frequently to diagnose NSTI. Both CT scans and MRI have been utilized in the evaluation of children with concern for NSTI with varying success. The MRI has been shown to have a high false-positive rate and often requires anesthesia in young children [121]. CT may have a role in the diagnosis of NTSI in patients with head and neck infections [128].

The NTSIs can be classified according to the causative organisms. Type 1 is caused by a polymicrobial infection with an average of 4.4 organisms identified in culture [121]. These include *Streptococcus* spp., *Staphylococcus* spp., *Bacteroides* spp., *Pseudomonas* spp., *E. coli*, *K. pneumonia*e, and others. Type 2 NSTI is a monomicrobial infection caused by group A *Streptococcus* (GAS), sometimes in conjunction with *S. aureus* [121]. Although Type I classically has been thought to be most commonly encountered in children, more recent data suggest monomicrobial infection may be more common than previously described [117,127]. Specifically, community-acquired MRSA has been reported with increasing frequency [117].

With high clinical suspicion or once the diagnosis is made, admission to the neonatal or pediatric intensive care units with close monitoring, aggressive fluid hydration, and administration of broad-spectrum antibiotic agents are essential. In the absence of published evidence-based recommendations regarding antibiotic agents in NSTI, there is great variability in antibiotic choice [117]. For suspected GAS infections, combinations that include a penicillin or third generation cephalosporin are recommended most frequently, and the addition of clindamycin appears to be beneficial [117,121]. Those infections not suspected to be GAS require antibiotic agents targeting aerobes, anaerobes, and MRSA [121]. At the time of operation, cultures should be performed and antibiotic agents tailored to specific organisms.

As in adults, urgent extensive surgical debridement is the mainstay of tmanagement of NSTI in children [123]. Because of the difficulty in making the diagnosis, operation is often delayed, which has been associated with poorer outcomes.

Often, surgical exploration is diagnostic as well as therapeutic [121]. Once the diagnosis is made, serial debridements are often required to obtain clean, viable margins [121,123]. A small case series from a hospital in a resource-poor region described a more conservative approach with bedside, rather than operating room, debridements with acceptable results, but this approach has not been adopted widely [118,129].

Little data exist regarding optimal approach and timing for coverage of tissue defects after debridement, but reports of early and late split thickness skin grafts and primary or delayed skin closure have all had success. Negative-pressure surgical site therapy, although used with less frequency than in adults, has shown success in children [117]. Adjunct measures such as intravenous immunoglobulin or hyperbaric oxygen therapy have been described in children, but the data are scarce [117].

Conclusion

The NSTIs, including NF, continue to present a diagnostic and therapeutic challenge for clinicians. The core principles for the management of these infections have remained unchanged for the past 70 years: Rapid and repeated surgical debridement of dead and infected tissues, rapid initiation of broad-spectrum antibacterial agents that kill gram-positive, gram-negative, and anaerobic pathogens, inclusion of protein synthesis inhibitors with empiric antibacterial regimens, de-escalation of antibacterial therapies based on operative cultures, and cessation of these agents once the patient has been cured surgically. Further research in both the basic and clinical science arenas must address the challenges presented by these devastating infections to reduce morbidity and death for generations to come.

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