Necrotizing Fasciitis: Current Concepts and Review of the Literature

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Necrotizing soft-tissue infection (NSTI) was first described by Hippocrates circa 500 BC, when he wrote, "Many were attacked by the erysipelas all over the body when the exciting cause was a trivial accident . . . flesh, sinews, and bones fell away in large quantities . . . there were many deaths."[1] Despite many advances in our understanding of this disease and great improvements in medical care, the mortality associated with NSTI has not changed in the last 30 years and remains 25% to 35%.[2] Mortality is directly proportional to time to intervention.[3-6] In addition, prevalence of this disease is such that the average practitioner will see only one or two cases in his or her career. Physicians cannot be sufficiently familiar with NSTI to proceed rapidly with accurate diagnosis and the necessary management. The purpose of this article is to provide an evidence-based review of the microbiology, pathophysiology, diagnosis, and treatment of NSTI. Because there are no adequately powered, randomized, and blinded studies, the recommendations are based on retrospective and nonblinded study data available.

NSTI was described as "hospital gangrene" by British Naval surgeons in the 18th and 19th century. Dr Joseph Jones, a Confederate Army surgeon, was the first person to describe this disorder in a large group of patients in 1871, when he reported on 2,642 cases and found a mortality rate of 46%.[7] In 1883, the French physician, Jean Alfred Fournier, described a similar NSTI of the perineum in five male patients—a process that continues to bear his name. It is now described in both male and female patients. In the ensuing years, many other terms, such as *necrotizing erysipelas, streptococcal gangrene,* and *suppurative fasciitis,* have been also been used. Because the gas-forming organism, *Clostridium perfringens,* can be associated with this infection, it has also been referred to as "Clostridial gangrene" or "gas gangrene."

In 1951, Dr Wilson proposed the term *necrotizing fasciitis* to include both gas-forming and non−gas-forming necrotizing infection and stated that fascial necrosis is the sine qua non of this process.[8] More recently, the term *necrotizing soft tissue infection* has been advocated to encompass all forms of the disease process because necrotizing infection of all soft tissue involves a similar approach to diagnosis and treatment regardless anatomic location or depth of infection. This single, all-encompassing name, facilitates understanding and assurance of proper management.[9] It should be noted that mortality increases with the depth of the primary site of infection.

Incidence and classification

NSTI has an incidence of approximately 1,000 cases per year in the United States or 0.04 cases per 1,000 person-years.[10] The incidence of NSTI increased between 1980 and 2000, although the exact reason for this remains speculative.[11] Possible explanations include increased microbial virulence and resistance because of excessive use of antibiotics, better disease reporting, or both. Regardless, although it remains rare, NSTI is a highly lethal condition requiring early aggressive intervention for salvage.

NSTI can be classified based on anatomy, depth of infection, or microbial source of infection (Table 1). Although these classification systems are not clinically useful because they do not affect diagnosis or treatment, they are useful in providing a common language for research. In addition, as noted here, the depth of the primary site of infection correlates with mortality.

Microbiology and risk factor for disease

Three basic microbial subtypes of NSTI are described (Table 1). Type I infections are the most common form of disease and are polymicrobial in nature. Tissue isolates demonstrate an average of four different organisms in most wounds. Approximately 55% to 75% of all NSTI result from type I infection and the causative microbes are a combination of gram-positive cocci, gram-negative rods, and anaerobes.[4,6,12,13] Two recent, single-center retrospective studies have characterized the prevalence of these organisms in type I NSTI (Table 2).[2,9] Less commonly, the infection might be caused by a species of *bacteroides* or *clostridium*. Despite its historic prevalence, *C. perfringens* is now a rare cause of NSTI because of improvements in sanitation and hygiene. *Clostridia septicum,* a bacterium

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Abbreviations and Acronyms

HBO = hyperbaric delivery of 100% oxygen
MRSA = methicillin-resistant *Staphylococcus aureus*
NSTI = necrotizing soft-tissue infection
SC = subcutaneous

that is endogenous to the colon, is a very rare cause of NSTI in patients with perforated carcinoma of the colon.

Type I infections tend to occur in the perineal and trunk areas and are often diagnosed in immunocompromised patients, particularly diabetics and patients with peripheral vascular disease.[12] Other risk factors for this type of NSTI include obesity, chronic renal failure, HIV, alcohol abuse, abscess, IV drug use, blunt or penetrating trauma, insect bites, surgical incisions, indwelling catheters, chicken pox, vesicles, and (rarely) perforation of the gastrointestinal tract (eg, carcinoma or diverticulitis).[14-17] Despite the plethora of risk factors, there is no specific inciting event identified for 20% to 50% of patients.[2,6,13] In addition, the relative importance of each risk factor is unknown because studies evaluating this demonstrate wide variance between study populations and design.

Type II NSTI is a monomicrobial infection caused by group A *Streptococcus* (*Streptococcus pyogenes*) either alone or in association with *Staphylococcus aureus.* As such, type II NSTI is unique because it might be associated with toxic shock syndrome. In addition, in the last 5 years, there has been an increasing incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) soft-tissue infection reported, particularly in IV drug abusers, athletes, and institutionalized groups.[18-20] Today, MRSA is cultured in up to 40% of necrotic wounds. Additionally, group A streptococci can survive and replicate in macrophage, thereby escaping antibiotic therapy even in tissues that remain well-perfused and amenable to antibiotic penetration.[21,22]

Type II NSTI is far less common than type I infection and tends to occur in otherwise healthy, young, immunocompetent hosts. This infection is classically located on the extremities, although truncal involvement is well-reported. Frequently, there is a history of recent trauma to or operation on the area. IV drug abusers are at risk for either type I or type II NSTI.[23,24]

Although not universally agreed on, some sources classify necrotizing infection caused by *Vibrio vulnificus* as type III NSTI. This infection is acquired through a break in the skin and exposure to warm sea water and is most commonly found in coastal communities.[25] Aside from exposure to marine life, the single biggest risk factor for infection by this organism is moderate to severe liver disease, particularly chronic hepatitis B infection. Although this is the least common type of NSTI, it is associated with a fulminant course and must be recognized quickly by the surgeon to minimize the time to operative intervention. Multisystem organ failure will develop within 24 hours of infection and the disease is uniformly fatal if not promptly recognized and treated.

Table 1. Classification of Necrotizing Soft Tissue Infection

Classification factor	Comment
Anatomic location	Fournier's gangrene of perineum/scrotum
Depth of infection	Necrotizing adipositis (most common), fasciitis, myositis
Microbial cause	Type I: Polymicrobial (most common)
	Type II: Monomicrobial (*Staphylococcus, Streptococcus, Clostridia* sp)
	Type III: *Vibrio vulnificus**

*Classification of *Vibrio vulnificus* necrotizing infection as type III is not universally agreed on.

Pathophysiology

It is generally agreed that microbial invasion of the subcutaneous (SC) tissues occurs either through external trauma or direct spread from a perforated viscus (particularly colon, rectum, or anus) or urogenital organ. Bacteria then track SC, producing endo- and exotoxins that cause tissue ischemia, liquefactive necrosis, and often systemic illness.[11,26] Infection can spread as fast as 1 inch per hour with little overlying skin change.

Production of various exotoxins can enhance a particular microbe's virulence and accelerate progression of infection. The *Clostridium* species produce α-toxin, which cause extensive tissue necrosis and cardiovascular collapse. *Staphylococcus aureus* and Streptococci elaborate surface proteins M-1 and M-3, exotoxins A, B, C, streptolysin O, and superantigen. The M proteins increase the microbes' ability to adhere to tissue and escape phagocytosis. Toxins A and B damage endothelium, cause loss of microvascular integrity, and escape of plasma, resulting in tissue edema, and impaired blood flow at the capillary level. These toxins, along with streptolysin O, stimulate CD4 cells and macrophages to produce large bursts of tumor necrosis factors$-\alpha$, interleukin-1, and interleukin-6.[27,28] Systemic release of these cytokines produces the systemic inflammatory response syndrome and can progress to septic shock, multisystem organ dysfunction, and death. Tumor necrosis factor$-\alpha$ also causes additional injury to the vascular endothelium by stimulating neutrophil degranulation. Superantigens stimulate T cells directly, activating complement, the bradykinin-kallikrein system, and the coagulation cascade, thereby worsening small vessel thrombosis and tissue ischemia.[11] The final common pathway, tissue

Table 2. Common Microbial Causes of Type I Necrotizing Soft-Tissue Infection

Organism	Gram stain	Percent of isolates[9] (n = 162)	Percent of isolates[2] (n = 272)
Staphylococcus aureus	Gram-positive cocci	16	22
Streptococcus species	Gram-positive cocci	19	17
Klebsiella species	Gram-negative rod	10	
Escherichia coli	Gram-negative rod	7	
Gram-negative bacteria			18
Anaerobic bacteria		7	18

*Clostridia species (gram-positive rods) are a rare cause of necrotizing soft-tissue infection.

ischemia, impedes oxidative destruction of bacteria by polymorphonuclear cells and prevents adequate delivery of antibiotics.[26] Hence, surgical debridement is the mainstay therapy for NSTI, and antibiotic therapy alone is of little value.[29]

Although thrombosis of perforating vessels to the skin is the key feature in the pathophysiology of NSTI, the extent of infection is usually much larger than that suggested by skin findings alone because thrombosis of large numbers of dermal capillary beds must occur before skin changes suggestive of necrosis occur. Thrombosis is caused by the local hypercoagulable state, platelet-neutrophil plugging of vessels, and increased interstitial pressure together resulting in decreased capillary blood flow to end tissue. The inexperienced surgeon might not appreciate the seriousness or extent of infection based on examination of the skin alone.

Diagnosis

Decreasing mortality is directly correlated with establishing the diagnosis and instituting proper therapy (surgical and antimicrobial) quickly.[3-6] Because of its nonspecific findings, variable time course to fulminant disease, and relative rarity, a high index of suspicion must exist to expeditiously diagnose this disease process. Table 3 lists the common symptoms and signs associated with NSTI and Table 4 lists the differential diagnosis of this disorder.

Table 3. Symptoms/Signs Associated with Necrotizing Soft-Tissue Infection at the Time of Admission

Finding	Percent of patients[6] (n = 89)	Percent of patients[31] (n = 192)	Percent of patients[32] (n = 22)
Erythema	100	66	95
Pain or tenderness beyond margins of erythema	98	73	95
Swelling	92	75	86
Crepitus or skin necrosis	13	31	0
Induration	12	45	
Bullae	45	23	41
Fluctuance	11		
Fever	53	32	
Hypotension	18	11	

Table 4. Differential Diagnosis of Necrotizing Soft-Tissue Infection

Disorder	Characteristic
Cellulitis/adiposities (nonnecrotizing)	Erythematous, edematous, indurated tissue with normal appearing subcutaneous fat and fascia
Myonecrosis	Noninfectious inflammation/necrosis of muscle only
Lymphedema	Indurated, edematous extremity without systemic signs of infection
Noninfectious fasciitis (eosinophilic fasciitis)	Chronic disorder, diagnosed by biopsy, treated with steroids
Phlegmasia cerulea dolens	Edema of the entire affected extremity
Myxedema	Systemic manifestations of severe hypothyroidism

History and physical examination

Classic symptoms associated with NSTI are pain, anxiety, and diaphoresis, which worsen rapidly. The patient might be able to relate a history of trauma or a break in the skin within 48 hours before onset of symptoms, but only 10% to 40% of patients will present with this classic history.[4,6] As with other acute ischemia conditions (eg, mesenteric ischemia), the pain is usually out of proportion to physical examination findings, but some patients might have little to no pain. Later, the affected area can become insensate as additional tissue necrosis ensues.

Local erythema and swelling with pain are the most common signs of NSTI (Table 3). These findings are identical to those found in nonnecrotizing cellulitis, potentially making the distinction difficult. A retrospective single-center review showed that 35% of cases were initially misdiagnosed as simple cellulitis or severe, nonnecrotizing skin infection.[30] Another retrospective study of 89 patients during 5 years found that only 14% of patients with NSTI were admitted with the proper diagnosis—the remainder were initially diagnosed as cellulitis or simple abscess.[6] It is unclear if the admitting diagnosis was correct and the cellulitis progresses to a necrotizing infection. Regardless, NSTI developed in 86% of patients—a finding that highlights the need for a high index of suspicion with all skin and soft-tissue infections and abnormalities. Elliot and colleagues[31] and Wong and colleagues[6] found that the only signs that were present in >50% of patients were ery-

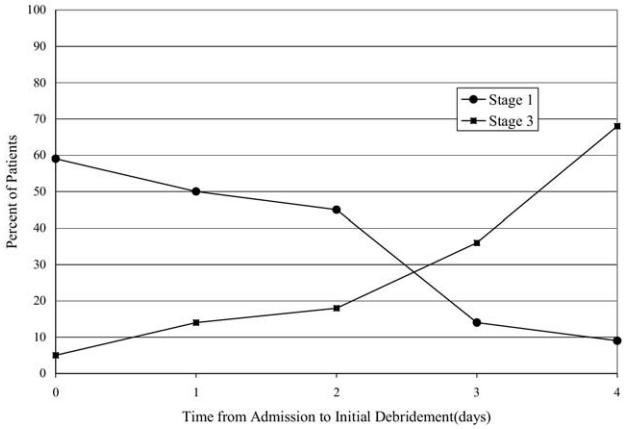

Figure 1. Stage 1 findings include tenderness to palpation beyond the rim of erythema, presence of erythema, and edema. Stage 3 findings include crepitus, skin anesthesia, and skin necrosis/discoloration.[32]

thema, tenderness, or edema beyond what appeared to be the confines of infection. This is in contradistinction to standard teaching, which stresses shock, fever, and mental status changes as frequent findings. The difference might be because most of the patients in both studies had an altered immune response stemming from their comorbidities (eg, diabetes, cancer, liver disease). Crepitus or skin necrosis, often taught to be the sine qua non of NSTI, was present in only 13% to 31% of patients. As noted previously, the skin might have a normal appearance in the early stages of disease because the infection tracks SC. Skin changes will become evident only with resulting skin ischemia, usually a late part of the disease. Wang and colleagues[32] retrospectively evaluated the evolving cutaneous manifestations of NSTI that was not treated surgically for at least 96 hours and described a staging system that correlates with progression of disease (Fig. 1). They described stage 1 (early) manifestations as erythema, tenderness, pain beyond the confines of erythema, and swelling; and stage 3 (late) manifestations as crepitus, skin anesthesia, and skin necrosis/discoloration. This staging system can be useful in following cases of suspected NSTI.

Fulminant NSTI, particularly from *Vibrio vulnificus,* is associated with cardiovascular collapse before extensive soft-tissue and skin changes manifest as it leads to a massive systemic inflammatory response without time for soft-tissue changes to occur. Cardiovascular collapse results from a substantial release of both bacteria-derived toxin and endogenous cytokines, and mandates immediate operative debridement once the patient is resuscitated.

Radiographic testing

Sometimes confirmatory radiographic studies are needed to determine if a patient has NSTI. Unfortunately, there

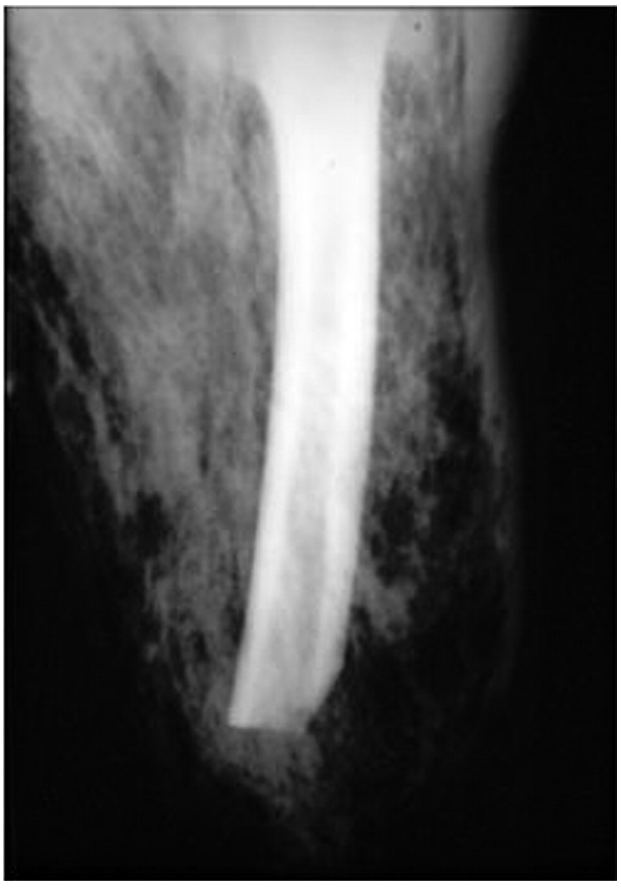

Figure 2. Plain x-ray showing diffuse subcutaneous emphysema.

are no adequately powered and well-designed studies comparing the various radiologic modalities. Overall, all radiographic modalities studied to date are limited by either low sensitivity to detect NSTI early or low specificity to diagnose it reliably.

Plain x-ray can reveal SC gas or soft-tissue swelling, but cannot show deeper fascial gas (Fig. 2). Although SC emphysema is a specific x-ray finding for NSTI, it is very insensitive and is present in a minority of patients. Lack of SC emphysema does not rule out NSTI, thereby making plain x-ray a poor screening study for this process.

CT scan is more sensitive because it can show inflammatory changes, such as fascial edema and thickening or abscesses, in addition to gas formation (Fig. 3).[33,34] A retrospective study of 20 patients found that fascial thickening on CT had 80% sensitivity for diagnosis of NSTI and that administration of IV contrast added little benefit.[33] Another study found that a constant but nonspecific finding on CT scan is thickening and increased enhancement (in instances when IV contrast is administered) of the effected tissue planes, but less frequent and more specific findings include gas or fluid collections.[35]

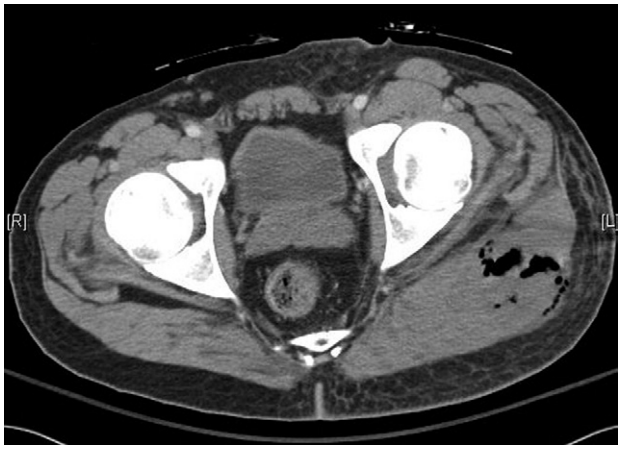

Figure 3. CT scan showing gas and fluid collection deep to the gluteus maximus muscle.

MRI has a sensitivity of 90% to 100%, but specificity of only 50% to 85% for detecting NSTI.[36,37] Characteristic findings include soft-tissue or fascial thickening on T_2-weighted images with enhancement after administration of contrast, but these findings can also be noted after trauma or other noninfectious cause for inflammation.[38] Findings that are more specific to NSTI include hyperintense signal on T_2-weighted images at the deep fascia and within muscles and peripheral enhancement on contrast-enhanced T_1-weighted images.[39] Use of MRI is often prohibitive in critically ill or unstable patients and frequently results in inappropriate delays to treatment, and CT is more expeditious and universally available.

Although ultrasonography is used to detect superficial abscesses, it is neither sufficiently sensitive nor specific for diagnosis of NSTI and should not be routinely used.[40]

Laboratory examination

Recently, scoring systems based on laboratory studies have been described to facilitate and expedite NSTI diagnosis. In a retrospective study, Wall and colleagues[41] found that patients with necrotizing infection had either a white blood cell count >15,400 cells/mm^3 or a sodium level <135 mmol/L on admission to the hospital. These values have a 80% positive and negative predictive value. Wong and colleagues[42] described a score that they call the "Laboratory Risk Indicator For Necrotizing Fasciitis" based on admission studies obtained in 89 patients with NSTI (Table 5). A score ≥6 has a positive predictive value or 92% and negative predictive value of 96% for NSTI. They also showed that the positive predictive value increases as the score increases and the probability of disease is >75% if the laboratory risk indicator for necrotizing fasciitis score is >7. To date, the laboratory risk indicator for necrotizing fasciitis score remains unvalidated in larger, prospective studies.

Table 5. Laboratory Risk Indicator for Necrotizing Fasciitis Score

Variable	Score
C-reactive protein	
<150	0
≥150	4
WBC (cells/mm^3)	
<15	0
15–25	1
>25	2
Hemoglobin (g/dL)	
>13.5	0
11–13.5	1
<11	2
Sodium (mmol/L)	
≥135	0
<135	2
Creatinine (mcg/L)	
≤141	0
>141	2
Glucose (mmol/L)	
≤10	0
>10	1

A sum ≥6 has a high correlation with necrotizing soft-tissue infection.

The gold standard modality for diagnosis of NSTI remains operative exploration. Operative findings that are consistent with necrotizing infection include "dishwater" or foul-smelling discharge, necrosis or lack of bleeding, and loss of the normal resistance of the fascia to finger dissection. Intraoperative biopsy with Gram stain can be used in equivocal cases, but is usually not needed, as intraoperative findings are often clear. There is no role for culturing blisters or skin surface because the infection tracts SC and surface manifestations reflect ischemic necrosis. When performed, intraoperative tissue biopsy should be obtained from the interface between live and dead tissue and must be reviewed by a pathologist who has experience with NSTI, otherwise its diagnostic yield diminishes.[43] Early in the disease process, the biopsy will show superficial epidermal hyaline necrosis, dermal edema, and polymorphonuclear infiltration into the dermis. Later on, inflammation and thrombosis of penetrating fascial vessels will be seen. In late stages, all tissue layers and SC ducts demonstrate variable levels of necrosis.[44]

Treatment

Successful treatment of NSTI requires coordination between the surgeon and intensivist. A discussion of the fundamentals of critical care needed to support these patients is beyond the context of this article and discussion is lim-

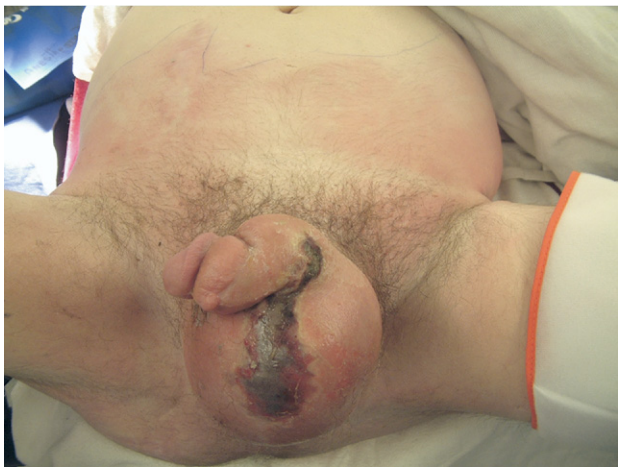

Figure 4. Rim of cellulitis marking confines of margins of resection.

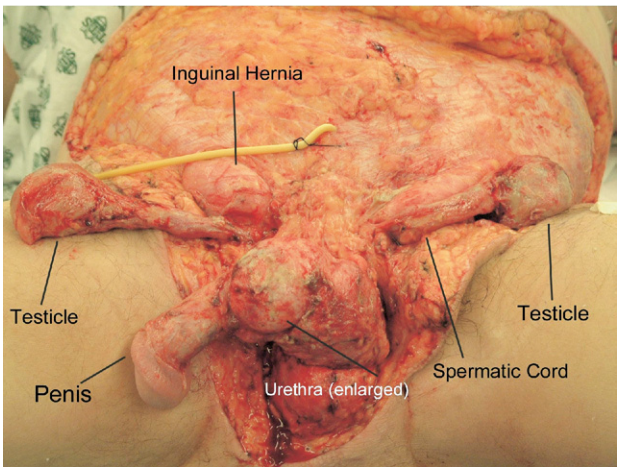

Figure 5. Extent of wound after serial debridements. Note the urethral diverticulum because of recurrent self-catherization.

ited to the other aspects of therapy: surgical debridement, antibiotic, hyperbaric oxygen, and IV γ-globulin (IVIg).

Surgical debridement

As stated already, the cornerstone of therapy for NSTI is surgical debridement. Numerous studies have shown that the most important determinant of mortality is timing and adequacy of initial debridement. Mok and colleagues[45] found that the relative risk of death was 7.5 times greater in cases that were not initially debrided adequately, and Wong and colleagues[6] reported a ninefold increase in mortality if the procedure was delayed >24 hours from the time of hospital admission. In a retrospective study, Bilton and colleagues[3] compared early, complete debridement with delayed, incomplete debridement and found that mortality increased from 4% to 38%. This was consistent with two previous studies that also showed dramatic increases in mortality with delay and inadequate operative intervention.[5,31]

Boundaries of the excision should be at least as wide as the rim of cellulitis, in cases where skin changes are evident (Fig. 4) and should be comprised of healthy, bleeding tissue regardless of the extent of debridement needed to obtain this goal. Intraoperatively, the boundaries often have to be extended because the area of SC infection and necrosis is usually much larger than appreciated on physical examination alone (Fig. 5). One study found that 33% of patients with NSTI of the extremity from IV drug use needed to have 5% of their body surface area resected.[23] Serial debridements are always needed because the infection is rarely eradicated after a single debridement. Optimally, an average of three debridements, spaced 12 to 36 hours apart, are needed to obtain control of gross infection.[6,23,31] At times, the extent and depth of debridement are massive, and on the extremities, it is not uncommon to find entire muscle groups involved. The surgeon must not be intimidated and carry out removal of all involved tissues and structures.

Amputation must be considered if the extent of infection includes a joint or the infection is rapidly spreading toward the torso despite aggressive attempts at surgical control. Amputation can also be necessary if the infection has rendered most muscle groups necrotic, thereby resulting in a useless extremity. Amputation might be needed in up to 20% of infections, particularly in IV drug users.[2,4]

Perineal, perianal, or scrotal infections require special consideration. A temporary, diverting colostomy should be considered in cases of perineal or perianal NSTI to facilitate wound hygiene, decrease the need for frequent dressing changes, and to protect the skin graft required for ultimate reconstruction. Surgical castration is rarely needed, even when infection involves the scrotum (Fig. 5). After scrotal resection, the testes are best treated by placing them in pockets in the medial aspect of the thighs. The testes can be kept in these pockets indefinitely.

There are little data on the optimal method of wound management after debridement. As with all infected wounds, the wound should be left open and treated with wet-to-dry dressings initially. Although not well-studied for NSTI, little benefit is gained from enzymatic debriding agents or caustic solutions, such as dilute sodium hypochlorite (bleach), iodine solutions (eg, Betadine), or antibiotic solutions. Vacuum-assisted closure devices have become a common method of treating large wounds once infection is controlled, although there are no well-designed studies evaluating their role in patients with NSTI. Preliminary studies suggest that this therapy results in enhanced granulation and reduction in wound surface area compared with wet-to-dry dressing changes.[46,47] Vacuum-assisted closure dressings can also decrease the time required for

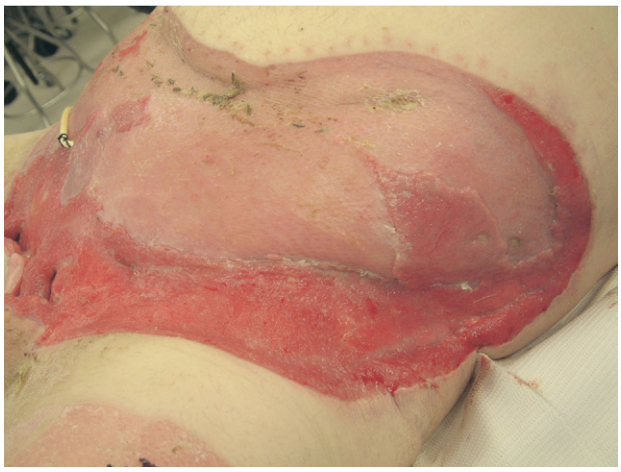

Figure 6. Wound closure using staged split-thickness skin grafting.

wound care approximately fourfold,[46] thereby facilitating both inpatient and outpatient nursing care.

Skin grafting is most commonly needed in large wounds once the wound is clean and granulating well (Fig. 6). Once the infection is under control and the wound does not require additional debridement, patients with extensive loss of muscle or exposed bone can require full-thickness, free, or rotational flaps for proper coverage.

IV antibiotic

Antibiotic therapy has an important role in ameliorating systemic sepsis and bacterial spread. Medications are unable to penetrate infected necrotic tissue because of the thrombogenic nature of the process and aggressive surgical debridement remains the first priority as noted here.[26,29] Historically, an empiric regimen using high-dose penicillin and clindamycin was recommended to cover gram-positive and anaerobic organisms. This particular combination was also shown to be synergistic against *clostridia* species. A third agent was used for additional empiric coverage of gram-negative organisms.

Today, the recommended initial antibiotic regimen has changed because of the emergence of resistant microbes and relative decrease in the incidence of clostridial infection. Vancomycin, linezolid, daptomycin, or quinupristin/dalfopristin are recommended for empiric coverage of gram-positive organisms because of concern for MRSA infection, especially in IV drug users.[18-20] The incidence of clindamycin-resistant MRSA prohibits use of this drug alone for coverage of gram-positive organisms in severe infections. Clindamycin remains a useful agent because it covers anaerobic organisms well and inhibits M protein and exotoxin synthesis by group A *Streptococcus*. Quinolones offer excellent soft-tissue penetration and can be used to cover gram-negative organisms. Duration of antibiotic therapy has not been studied, but most experts suggest continuation of therapy until no additional surgical debridement is needed and the patient is no longer manifesting signs of systemic inflammation. This generally results in at least a 10- to 14-day course.

IV immune globulin therapy

IV immune globulin is a concentrated pooled product containing primarily immunoglobulin G isotypes derived from human donors. It has not been FDA approved for treatment of NSTI and its use and efficacy remain controversial. Use of this agent is based on the theoretical mechanism that it can bind staphylococcal- and streptococcal-derived exotoxin, thereby limiting the systemic cytokine surge associated with systemic inflammatory response syndrome.[48,49] This possible benefit has been corroborated in some clinical trials but, to date, all studies are either underpowered or nonrandomized.[50-52] If used, IV immune globulin should be restricted to critically ill patients with either staphylococcal or streptococcal NSTI.[53,54] Suggested dosing for this agent varies from 200 to 2,000 mg/kg/day for 1 to 5 days, and its cost is $50 to $80 per gram.

Hyperbaric oxygen therapy

Hyperbaric delivery of 100% oxygen (HBO) at two to three times atmospheric pressure results in arterial oxygen tension as high as 2,000 mmHg and tissue oxygen tension of 300 mmHg. This contrasts with arterial oxygen tension of 300 mmHg and tissue oxygen tension of 75 mmHg noted with normobaric inhalation of 100% oxygen. Despite many theoretical uses, its role in NSTI remains controversial and unproved.[55]

Use of HBO therapy in NSTI is based on animal and human studies showing that hyperbaric conditions inhibit infection (especially anaerobic)[56] and exotoxin elaboration by *clostridia*.[57-59] It has been shown to augment the oxidative burst and killing ability of leukocytes[60] and can enhance efficacy of antibiotics by increasing local oxygen tension in tissue.[58,61,62] These effects can, in turn, result in a reduced need for surgical debridement and improved morbidity, mortality, or both, in patients with NSTI.[63-65] Animal studies have shown mortality reductions with HBO in clostridial NSTI.[66]

All clinical studies on use of HBO for NSTI have been underpowered, retrospective, poorly controlled, or nonrandomized. The few controlled clinical studies published to date have yielded conflicting results on HBO-related morbidity or mortality benefit.[63,67-69] It is possible that if a mortality benefit exists, it applies mainly to patients with clostridial infection, but, as noted previously, this subgroup constitutes the minority of patients with NSTI. Unfortunately, the weakness of these studies precludes a meta-analysis to resolve these contradictory findings and a firm

Table 6. Variables Associated with Mortality in Necrotizing Soft Tissue Infection[2,4,13,31,41]

Timing to operative intervention*
Age older than 60 years
Number of comorbidities
Diabetes mellitus
Shock on admission
Acute renal failure
Coagulopathy or acidosis on admission
Clostridial or group A streptococcal infection
Vibrio vulnificus infection
Admission white blood cell count > 30 cells/mm^3
Admission serum creatinine > 2 mg/dL.

*Only variable that has been shown to be predictive of survival in all studies.

recommendation on the use of HBO cannot be made until better designed studies are conducted.

The surgeon must take into account the patient's overall physiologic status when deciding whether or not to use HBO as an adjunct to surgical debridement and antibiotics. Transport of the patient out of the ICU and restricting acute care in a pressurized chamber greatly limit urgent or emergent intervention, and the risk-to-benefit ratio of this therapy must be considered. When used, HBO is usually administered at 2 to 3 atmosphere pressure for 30 to 90 minutes with three to four treatments daily. There is no consensus on the end point of therapy. As with antibiotic therapy, many surgeons stop HBO therapy when no additional surgical debridement is needed and the patient is not manifesting signs of systemic inflammation/sepsis. Others might continue therapy until there is evidence of robust wound granulation, because HBO can enhance wound healing.[70]

Morbidity and mortality

As stressed previously, the most important determinant of mortality in patients with NSTI is time to operative intervention.[3-6] Other factors can also impact on mortality (Table 6), although no consensus has been reached on the importance of each factor. In a multivariate regression analysis of 166 patients, Anaya and colleagues[2] found that admission white blood cell count >30,000 cells/mm^3, admission serum creatinine >2 mg/dL, clostridial infection, and coronary artery disease are independent predictors of mortality with an odds ratio of death of 3 to 4 for each variable.[2] Of note, time to operative intervention was not assessed and was not included in the multivariate model.

Patients not succumbing to NSTI have very high morbidity and require a prolonged recovery period. Elliot and colleagues[31] found 82% morbidity in a review of 198 patients. Noted complications included other nosocomial infection (76%), ventilator-dependent respiratory failure and adult respiratory distress syndrome (29%), acute renal failure (32%), seizure (5%), stroke (4%), cardiac arrest (3%), and heart failure (2%). Anaya and colleagues[2] noted an amputation rate of 15% overall and 26% in patients with primary extremity infection, but infection from IV drug abuse developed in 30% of patients in this study. Another study found a similar incidence of amputation (18%) in patients with NSTI from a variety of causes.[4]

In conclusion, necrotizing soft-tissue infection is a highly lethal uncommon disease, but presents at least once or twice in most surgeons' career. High-risk patient populations do exist, but healthy young patients are also susceptible. A high index of suspicion, coupled with appropriate resuscitation and operation are needed to ensure timely intervention. No factors other than rapid widespread operative debridement and appropriate antibiotics have an effect on the very high mortality. Even with adequate care, patients frequently suffer substantial morbidity and require reconstruction and rehabilitation.

Future research efforts are needed to monitor ongoing changes in microbiologic cause and to enhance imaging and diagnostic techniques to improve the ability to detect and treat this disease in its earliest stages. To date, there remains a paucity of well-designed trials comparing various imaging and diagnostic modalities. In addition, clinical studies are needed to determine which current or future adjunctive treatments can additionally impact mortality and morbidity.

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