Current diagnosis and management of necrotizing soft tissue infections: What you need to know

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ABSTRACT: Necrotizing soft tissue infections are rare bacterial infections of the skin and soft tissues with a high morbidity and mortality rate, requiring prompt diagnosis and surgical intervention. These represent a spectrum of disease resulting in tissue necrosis that is rapidly progressive; however, they remain a diagnostic challenge because the average surgeon or emergency medicine provider may only see one or two over the course of their career. Diagnosis is largely clinical and based on subtle physical examination findings, physiologic instability, and laboratory derangements. Aids to diagnosis such as scoring systems and cross-sectional imaging may be used; however, the findings are not specific, so management should not be based on these alone. The most common cause of necrotizing soft tissue infection is polymicrobial infection; however, specific bacteria such as clostridial species, group A streptococcal, methicillin resistant *Staphylococcus aureus*, and aquatic bacteria may also be causative. Initial management includes broad spectrum antibiotics, fluid resuscitation for severe sepsis, and early aggressive surgical debridement. Often, these patients require multiple operative debridement to achieve source control, and a low threshold for repeat debridement should be maintained because these infections can progress rapidly. Once source control is achieved, patients may be left with extensive wounds requiring multidisciplinary care and wound management. Necrotizing infections have long been viewed based on mortality outcomes alone because of their rarity and severity. Over recent years, more reports have shown a decrease in the mortality rates from those previously reported, allowing for a focus on methods to improve morbidity of these infections. (*J Trauma Acute Care Surg.* 2024;97: 678–686. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Bacterial infection; necrotizing fasciitis; necrotizing soft tissue infection.

Necrotizing soft tissue infections (NSTIs) are rare bacterial infections of the skin and soft tissues with a high morbidity and mortality rate, requiring prompt diagnosis and surgical intervention.[1] These represent a spectrum of disease resulting in tissue necrosis that is rapidly progressive; however, they remain a diagnostic challenge because of variety of presentation and rarity of the condition.[2] The diagnostic challenge is due to the involvement of deeper tissue layers, with systematic toxicity and pain out of proportion to examination, at least early, when there are little to no skin findings.[3] Surgeons must maintain a high index of suspicion for an NSTI because survival depends on expedient treatment with broad spectrum antibiotics, and early surgical debridement and transfer to a tertiary care facility are keys to survival.[4–6] The timing to debridement is an independent predictor of survival, but this hinges on the diagnostic accuracy, which remains overall poor with some reports of up to 85% of patients misdiagnosed on initial presentation.[7]

EPIDEMIOLOGY

The incidence of NSTI appears to be increasing. Previous estimates in the United States suggested the rate to be 4 per 100,000 persons/year; however, a study published in 2020 reported 8.7 to 10 per 100,000/year.[8–11] One possible explanation for the increased incidence is a greater awareness of the disease process and better early recognition. The mortality rate remains high but recently has been decreasing and is reported around 10% to 20% with a wide range across series.[12–14] Importantly, for survivors, there is a high rate of morbidity with 15% requiring amputations[3] and up to 30% having mild to severe functional limitations.[15]

DIAGNOSIS

The diagnosis for NSTI remains largely clinical. Using a combination of history, physical examination findings, and laboratory data, a clinician should maintain a high level of suspicion. A history of obesity, diabetes mellitus, peripheral vascular disease, and immunosuppression all confer an increased risk of these infections. In addition, these infections are more commonly seen in injection drug use or with deep traumatic wounds. Any anatomical site can be involved, but the most common sites are perineal, anorectal, foot, or lower extremities.[16]

Early presentations may have findings consistent with simple cellulitis with mild erythema or skin discoloration due to the subtle deeper changes that have not yet manifested. Delay in diagnosis and treatment by as few as 6 to 12 hours has been associated with increased mortality, which is relevant because misdiagnosis is extremely common: up to 75% in some series.[17,18] The classic clinical signs and symptoms are rarely all present especially in early disease. Crepitus or gas in the soft tissues, while specific, is only present in approximately 10% of patients.[19] More often, the presenting symptoms are nonspecific: fever, pain, induration, and edema. Pain out of proportion to examination is a more specific finding that may assist in differentiation of NSTI from cellulitis.[20] Skin findings such as bullae, skin ecchymosis preceding skin necrosis, and cutaneous anesthesia are indicative of NSTI; however, they usually present later in the course and in the minority of cases with reports ranging from 7% to 44% (Fig. 1).[1,21] Imaging may be used as an adjunct in diagnosis. Presence of gas on plain x-ray is reported around half the time 47.9%, and computed tomography is superior with gas seen 70.3% of the time; however, absence of radiologic findings cannot be reliably used to rule out an NSTI.[22]

Laboratory evaluation has also been used to improve the diagnostic accuracy of NSTI. Elevated white blood cell (WBC) count, hyponatremia, elevated C-reactive protein, and signs of acute kidney injury are all used in diagnosis. Multiple scoring systems have been developed to assist with the difficult diagnostic challenge presented by NSTI. Arguably, the best known is the Laboratory Risk Indicator for Necrotizing Fasciitis score, which includes WBC, creatinine, sodium, hemoglobin, glucose, and C-reactive protein (Table 1).[23] Many subsequent studies on its utility have shown that, for high risk (score, ≥6) and very high risk (≥8), sensitivity and specificity range widely from 42.3% to 92% and 63% to 78%, respectively.[24–26] With the clear limitations, the Laboratory Risk Indicator for Necrotizing

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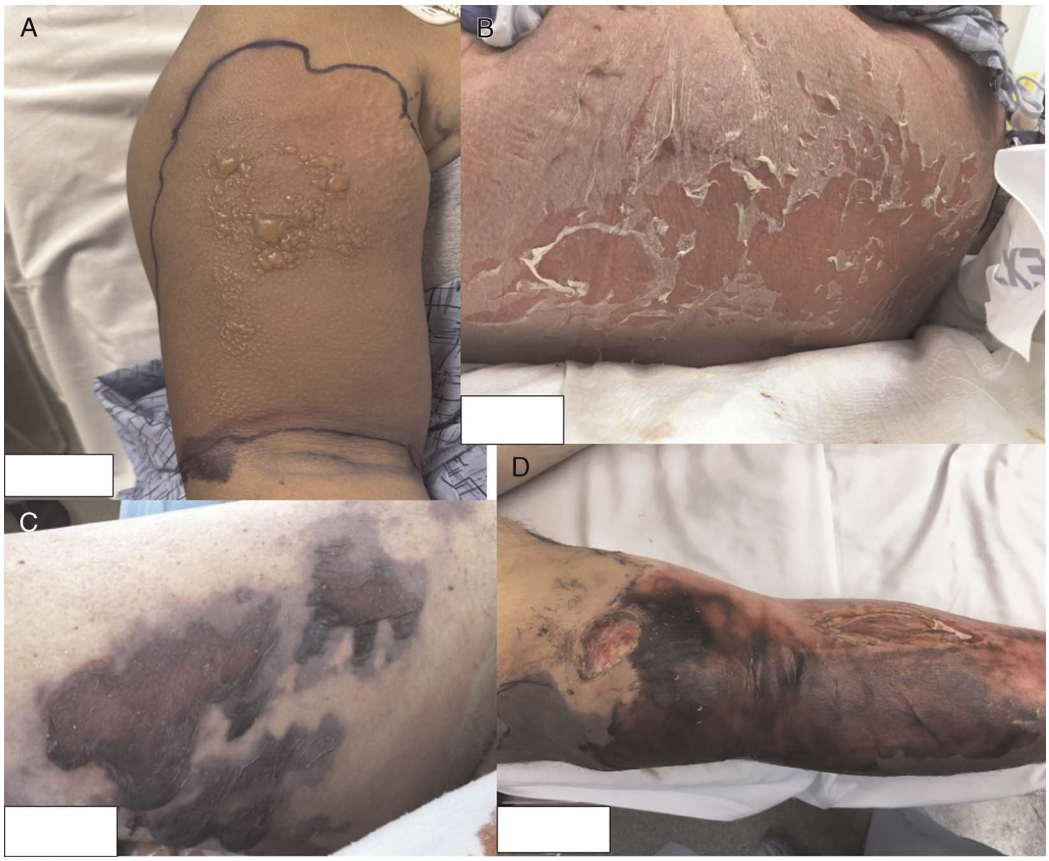

Figure 1. Skin changes classic for NSTI including (*A*) bullae, (*B*) hemorrhagic bullae, (*C*) skin sloughing, and (*D*) hemorrhagic necrosis.

Fasciitis score can be used to increase suspicion of NSTI, but clinical decisions should not be based on this score alone (Table 2).

TABLE 1. Laboratory Risk Indicator for Necrotizing Fasciitis Score

Variable		Unit	Score
C-reactive protein		mg/dL	
	<15		0
	≥15		4
WBC		per mm^3	
	<15,000		0
	15,000–25,000		1
	>25,000		2
Hemoglobin		g/dL	
	>13.5		0
	11.0–13.5		1
	<11.0		2
Na		mmol/L	
	≥135		0
	<135		2
Creatinine		mg/dL	
	≤1.6		0
	>1.6		2
Glucose		mg/dL	
	≤180		0
	>180		1

MICROBIOLOGY

Historically, NSTI has been classified into types based on their microbiology with type I being polymicrobial, type II being monomicrobial, and type III arising from an aquatic bacterium.[1]

Many of these infections are polymicrobial close to 50% in some series with five or more bacteria isolated from wound cultures.[27,28] These include gram-positive cocci, gram-negative rods, and anerobic bacteria and are frequently associated with preceding wounds or abscesses.[1,14]

Clostridial Infections

Clostridial infections are a rare subtype of NSTI but deserve special mention, as they portend rapid increased mortality and limb loss.[29] The most common isolate for clostridial infections is *Clostridium perfringens* followed by *Clostridium sordelli* seen in women after childbirth and injection with black tar heroin.[30] These bacteria produce α toxin (phospholipase C) and θ toxin (perfringolysin), which leads to microvascular thrombosis and hemolysis. α Toxin also has antagonistic effects on cardiac myocardial contractility, which can hasten cardiovascular collapse.[14] Clostridial infections classically present with very high WBC counts, and a WBC count of >40K on admission is associated with a poor prognosis.[29] Surgical and imaging findings may include gas gangrene or myonecrosis, a condition in which there is rapid progression of tissue destruction and production of foul-smelling gas that is usually fatal. On imaging, there will be extensive gas throughout the muscle bellies more

TABLE 2. Diagnostic Criteria for NSTI

Risk Factors	Signs and Symptoms	Radiographic Diagnosis	Surgical Confirmation
• Intravenous drug use* • Diabetes • Obesity • Peripheral vascular disease • Immunosuppression	• WBC >20,000 • Thin, gray drainage • Marked induration • Edema of entire limb • Hyponatremia (sodium <135) • Skin blistering/sloughing • Skin necrosis • Crepitus or soft tissue gas on x-ray • Pain out of proportion to skin findings • Septic physiology (tachycardia, hypotension, high fluid requirements)	X-ray: • Soft tissue swelling • Gas in soft tissues* CT scan: • Soft tissue edema • Thrombosis of superficial vessels • Gas tracking along fascial planes* • Lack of soft tissue enhancement • Fluid collections within muscle or fascial planes	Multiple cutaneous incisions should be made over concerning areas with any of the following: • Murky, gray, "dishwater" drainage • Purulence • Thrombosed vessels • Edematous, pale appearing fat • Easy separation of fascial planes • Necrotic, noncontractile, pale muscle

*Absence does not exclude NSTI.
CT, computed tomography.

so than in other kinds of infection.[30] Myonecrosis is a result of the toxin produced by these bacteria leading to extensive muscle destruction.

Group A β-Hemolytic streptococcus

There is a rising incidence of streptococcal infections, comprising approximately one third of reported infections.[16,31] These infections are associated with massive cytokine release and a profound toxic shock syndrome (TSS) and can also lead to myonecrosis.[25] This TSS is due to expression of exotoxin specifically in group A streptococcus species, which leads to circulatory collapse along with widespread thrombosis.[32]

Methicillin-Resistant *Staphylococcal Aureus*

The second most common cause of a monomicrobial NSTI is methicillin resistant *Staphylococcus aureus* (MRSA). This is an important implication because proper coverage for this pathogen is not always seen in antibiotic regimens. Emergence of this pathogen as a causative agent for NSTI is linked to a mutation of the Panton-Valetine leukocidin gene, which has been associated with tissue invasion and necrosis in multiple anatomic sites.[33] These isolates are more commonly seen in community-acquired MRSA infections and have prevalence as high as 20% reported in some series.[34,35]

Vibrio vulnificans and *Aeromonas hydrophilia*

The final causative agent in monomicrobial infections is aquatic bacteria endemic to certain regions including *Vibrio* and *Aeromonas* species. Presentation is similar, but important history components include exposure to seawater or raw seafood, *V. vulnificans*, or fresh and brackish waters, *A. hydrophilia*.[36] There are similar predisposing factors for these bacteria; however, there is a strong association with *Vibrio* infections and alcoholic cirrhosis.[37] Initial management with aggressive surgical debridement is the same as for other types of necrotizing infections (Fig. 2). Although cases are rare, high mortality rates are reported for both species up to 20% to 30% usually within the first 48 hours.[36,37]

MANAGEMENT

The fundamental management of NSTI is prompt diagnosis, broad spectrum antibiotics, volume resuscitation, and rapid operative exploration. Wound cultures should be sent from the operating room to help guide antibiotic coverage postoperatively.[38]

Antibiotics

If there is concern for NSTI, broad spectrum antibiotics covering gram positives including MRSA, gram negatives, and anaerobic bacteria should be started promptly. In addition, because of the toxin forming nature of the monomicrobial infections, there should be adequate toxin coverage in the antibiotic choice.[39,40] A regimen consisting of piperacillin-tazobactam, a carbapenem or a third-generation cephalosporin combined with metronidazole, with the addition of high-dose clindamycin (1,200 mg intravenous, every 6 hours) or linezolid should be used to quell toxin production.[39] The decision around high-dose clindamycin or linezolid should be guided by local bacterial resistance patterns specifically because of emerging rates of clindamycin resistance in group A streptococcal infections. Rates of clindamycin resistance as high as 31% have been reported in some series.[41] MRSA coverage with vancomycin or linezolid is important given its prevalence in the community (Table 3).[14] Once initiated, broad spectrum antibiotics should be continued until culture data are available, which may be absent in up to one third of cases, and surgical debridement is completed.[15] The antibiotic regimen should include doxycycline with ceftriaxone and cefotaxime or ciprofloxacin, for *V. vulnificans* and *A. hydrophilia*, respectively.[32]

Once the patient is improving, antibiotics may be narrowed based on the culture results. The duration of antibiotic coverage after debridement is completed remains controversial. If the patient is bacteremic, treatment for the isolated organism should continue based on blood culture data. For those without bacteremia, after surgical debridement is complete and systemic symptoms have improved, antibiotic duration is largely at the discretion of the provider with studies ranging from 5 to 16 days.[32,42–44]

Operative Debridement

Prompt, aggressive surgical debridement is the lynchpin for survival in NSTI. Delays from admission to initial debridement are associated with increased mortality. Initial debridement should be done as soon as possible from the time of presentation; however, it should absolutely be accomplished within 6 to 12 hours of presentation because of increased morbidity with

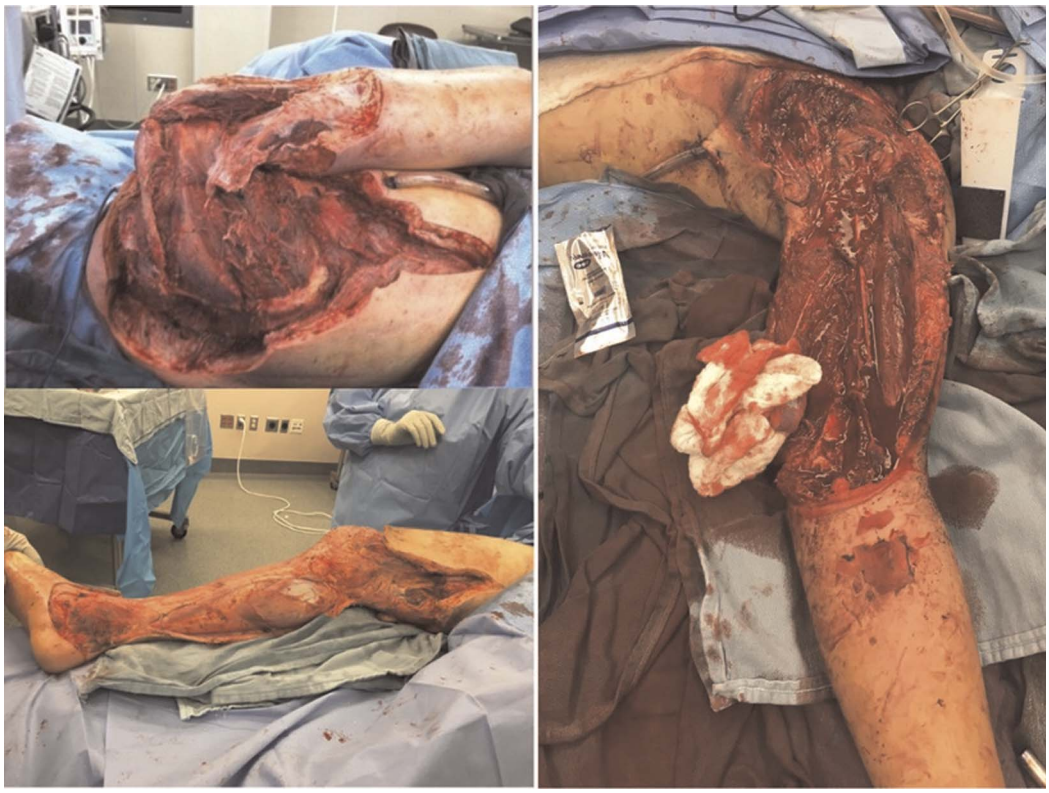

Figure 2. Examples of the extensive debridement required for NSTI.

delays.[4,45] The extent of debridement required depends on the layers and extent of tissue involved. The fascial must be exposed and completely explored, opening all layers to examine muscle for color, viability, and contractility and removing any tissue that appears necrotic or ischemic during the first operation.[44] All necrotic tissue should be debrided, all fluid collections drained, and all deep tissues evaluated.[46] Signs of adequate debridement include bleeding at skin edges, no visible thrombosed vessels,

TABLE 3. Common Antibiotic Regimens for Management of NSTI

Antibiotic	Indication	Coverage	Notes
Vancomycin	Empiric MRSA	Gram-positive cocci *Enterococcus* MRSA	Narrow coverage, should not be given in isolation
Piperacillin-tazobactam	Empiric Pseudomonal coverage	Enterococcus Gram-positive cocci Gram-negative rods *Pseudomonas* Anaerobes	Weak gram-positive coverage, no toxin protection
Linezolid	Empiric MRSA Toxin production	Gram-positive cocci *Enterococcus* MRSA Group A streptococcus toxin *Clostridium* toxin	Risk of serotonin syndrome with multiple drug interactions (methadone, fentanyl, selective serotonin re-uptake inhibitor, and serotonin and norepinephrine reuptake inhibitor)
Clindamycin	Toxin production	*Clostridium* toxin Group A streptococcus toxin	Rising levels of resistance in group A streptococcus infections
Penicillin	*Clostridium* infection Group A streptococcus infection	Gram-positive cocci	
Ceftriaxone	Negative cultures No culture data *Escherichia coli* *Klebsiella*	Gram-positive cocci Gram-negative rods	Should be combined with stronger gram-positive agent in the absence of tissue or fluid culture
Metronidazole	Anaerobes	Anaerobes	
Fluconazole	Fungal infection	*Candida* species	Consider adding for *Candida* isolates from operative cultures for high-risk patients

facial planes that do not separate easily with tension, and viable appearing fascia and muscle. Because the infection is primarily of the deep tissues, the initial skin incision does not need to encompass all areas of cellulitis, thus sparing the skin to decrease morbidity postoperatively.[47] The latter can be difficult to distinguish because of extensive tissue edema.[14]

A special consideration should be paid in cases of Fournier's gangrene or necrotizing infection of the perineum, labia, or scrotum. Early consultation with urology is recommended for assistance with debridement to avoid damage to urologic structures. If these infections include the perineum, often there will be a significant amount of debridement required around the rectum and anus.[48] The site and anatomy of these wounds create real wound care challenges because of frequent soiling of dressings and contamination. Adjuncts to wound care such as fecal management systems or negative pressure wound therapy may provide adequate protection of the wounds, but if unable to keep the wound free of fecal contamination, colonic diversion may be required.[49]

Necrotizing soft tissue infections carry a risk of rapid progression, but the optimal timing of a second look is not well established,[50] although most surgeons recommend return to the operating room within 24 hours.[28] The average number of serial debridements is 3 to 4; however, a low threshold should be maintained to reevaluate the wound in the operating room if there is any concern for progression.[43] For patients with perineal disease, a diversion procedure may be required to facilitate wound care and healing, although this does not have to be a routine procedure because many patients can be managed with local wound care. Wounds should be dressed to facilitate frequent bedside assessments to determine if another debridement is needed. Gauze soaked with saline or dilute hypochlorite bleach solution should be used as initial dressing materials. Negative pressure wound therapy should be avoided in the acute phase because of the need for frequent inspection of the wound.

Adjuvant Therapies

There have been several adjuvant therapies for NSTI described without definitive data to support their use. Hyperbaric oxygen therapy is a treatment modality during which a patient is placed into a high-pressure chamber and exposed to oxygen at two to three times the atmospheric pressure with the aim of improving tissue oxygenation and facilitating bacterial killing.[1] There are no sufficient data to recommend its use for critically ill NSTI patients.[51,52] Intravenous immunoglobulin has been suggested as a treatment modality for its effects on staphylococcal TSS via toxin binding. There is conflicting evidence on the benefit of intravenous immunoglobulin in group A streptococcal infections, so it is not currently recommended.[53,54] Recent randomized trials of a novel peptide (AB103/Relticimod) demonstrated improved resolution of organ dysfunction and more favorable discharge status but no difference in mortality.[55,56] However, this drug has not received Food and Drug Administration approval and so is not commercially available.

POSTOPERATIVE CARE AND OUTCOMES

After initial debridement, the patient should be admitted to a monitored setting for ongoing resuscitation and close observation. These patients are at high risk of complications related to their critical illness including ventilator-associated pneumonia, acute kidney injury, and cardiac complications. Earlier development of end-organ dysfunction and persistent organ dysfunction are associated with increased morbidity and mortality.[57] Baseline patient characteristics and preexisting comorbidities contribute to overall morbidity. While there have been some conflicting reports of which patient factors portend a worse outcome, older age, poor renal function, liver disease, heart failure, peripheral vascular disease, cancer or other immunosuppression, and intravenous drug use have been associated with increased morbidity and mortality in NSTI patients.[5] A mortality risk calculator has been recently developed showing good predictive value based on age, prehospital functional status, need for dialysis, American Society of Anesthesiologists class 4, emergency operation, thrombocytopenia, and septic shock.[58] Clostridial infections have been shown to be independent predictors of mortality and higher rates of amputation. A major morbidity concern surrounding these infections involves extremity amputation. Lower extremity amputation is reported in approximately 25% of patients.[29,59]

WOUND CARE AND PAIN CONTROL

After successful debridement and management of sepsis, patients are often left with large complex wounds creating care challenges. Multidisciplinary care including wound care and plastic surgery or burn surgery for assistance with complex wound management is essential for long-term management of these patients. The goals are to keep the wound clean, monitor for progression of infection, and avoid desiccation of structures such as tendons, bones, or cartilage. Documentation of the extent of the wound including areas of tracking with the addition of frequent updated wound care photos can assist with wound care coordination.[1] Pain control during this process has a great influence on appropriate wound care and dressing changes. Many of the wounds created after extensive debridement can be likened to burn wounds in the amount of total body area involved, so multimodal pain control should be judiciously used to promote the best wound care possible. Once infection is definitively cleared, negative pressure wound therapy can assist with vascularization of the wound and pain control by removing the need for daily dressing changes. As much as possible, dressings should be applied to allow for early mobilization to prevent all the known complications of bedrest, similar to burn patients. Optimal management of these wounds may be facilitated by transfer to a burn center or tertiary care center with experience in complex wound management and reconstruction.[60,61]

LONG-TERM OUTCOMES

Necrotizing infections have long been viewed based on mortality outcomes alone because of their rarity and severity. Over recent years, more reports have shown a decrease in the mortality rates from those previously reported, allowing for a focus on methods to improve morbidity of these infections. Patients having to undergo amputation have higher rates of functional disability and discharge to skilled nursing facility compared with those with limb salvage.[13] Cancer patients with NSTI have overall higher mortality rates and a much higher rate of disposition to an skilled nursing facility.[62] The posttreatment

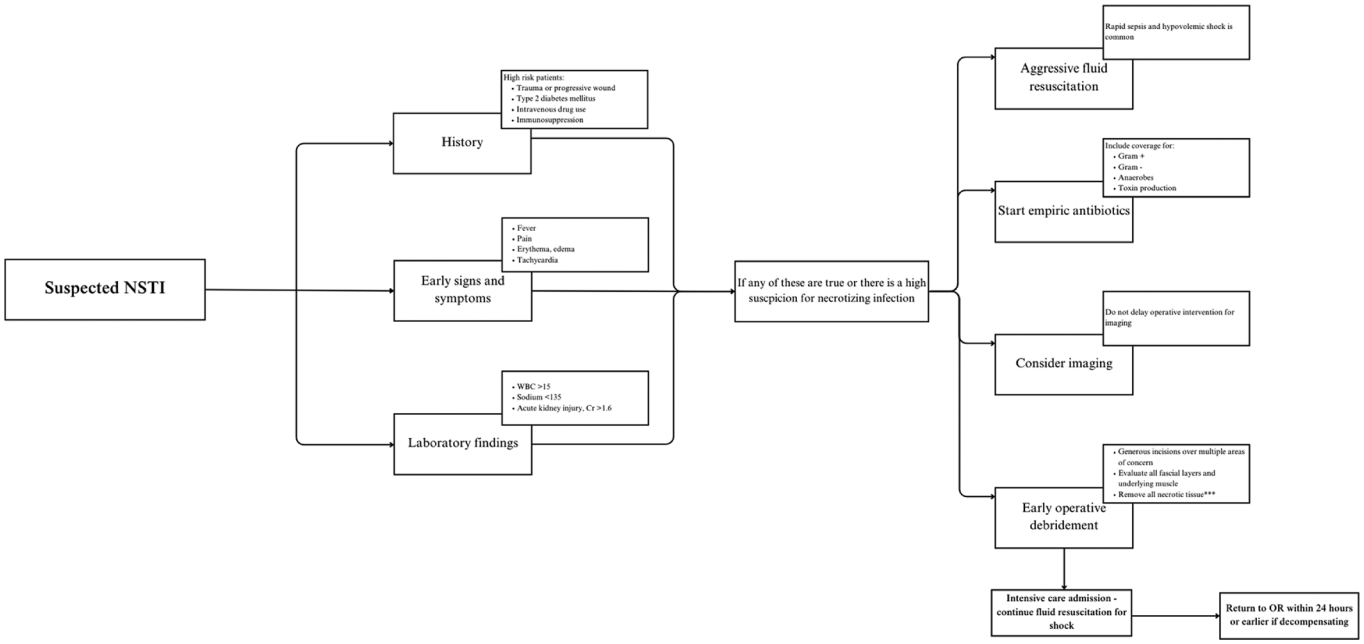

Figure 3. Take home points for NSTIs.

care of these patients is extensive, and factors beyond disposition at discharge must also be considered. Long-term effects on quality of life and ability to return to work because of functional limitations are just a few of the factors that need to be addressed at the time of discharge. Many outcomes that are important to patients, that is, altered physical functioning, pain, and the effect of the experience on the survivor's relationships, are harder to quantify but are prevalent and have long-lasting implications for these patients.[63]

As the understanding of this disease process improves, the concept of expedient care at a high-volume center portends better overall outcomes. Because NSTI remains a rare entity, there are only a few centers with enough volume to develop expertise and have the appropriate resources to care for these complex patients. As such, many of these patients are transferred for a higher level of care, but in multiple reports, transfer has been shown to be an independent risk factor for increase mortality perhaps due to delays in the initial debridement.[13,64] In addition, there is a high rate of readmission after NSTI treatment, up to 25% to 30%, and often to the nonindex hospitals, which is associated with increased mortality.[65] The reason for this mortality increase is multifaceted, as the patients requiring transfer are often sicker and the centers they present to do not have the infrastructure to adequately care for them. That leads to worse outcomes for underrepresented minorities and rural populations presenting with NSTI.[66]

CONCLUSION

Necrotizing soft tissue infections represent a spectrum of severe infections that present diagnostic and treatment challenges. Early diagnosis is paramount for survival, and a high index of clinical suspicion should be held for any soft tissue infection. Broad spectrum antibiotics should be started at the time of presentation and narrowed based on culture data as available. After initial debridement, multidisciplinary care for these complex wounds or transfer to a center with the infrastructure and expertise to manage these complex patients may improve outcomes (Fig. 3).

AUTHORSHIP

E.K.B. contributed in the literature search, study design, data collection, data analysis, writing, and critical revision. E.M.B. contributed in the study design, data analysis, and critical revision.

DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D740).

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