Evaluation and Management of Necrotizing Soft Tissue Infections

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KEYWORDS

• Necrotizing fasciitis • Soft tissue infection • Sepsis • Gangrene

KEY POINTS

- Necrotizing soft tissue infections (NSTI) are generally severe and rapidly progressive and accompanied by sepsis, multisystem organ failure, and often death.
- Rapid recognition and early surgical intervention form the mainstay of management of NSTIs. Most cases require more than 1 debridement. Imaging can facilitate diagnosis and the decision to operate should not delay treatment in unequivocal cases; direct exploration remains the gold standard for diagnosis.
- Initial surgical debridement should be promptly performed, preferably at the presenting hospital when adequate surgical infrastructure and personnel exist. Transfer of the patient to a referral center may be necessary for definitive surgical and complex wound care.
- Broad-spectrum empiric antibiotics directed at the likely organisms are essential early in the treatment course but do not substitute surgical management. Antibiotic therapy should be subsequently tailored to the etiologic agent. In cases of documented NSTI due to group A *Streptococcus*, clindamycin should be administered in addition to penicillin.
- There are insufficient data to warrant routine use of adjuvant hyperbaric oxygen. Adjuvant intravenous immunoglobulin is an expensive intervention that is not likely to improve survival or physical quality of life and is best reserved for use on a case-by-case basis.

INTRODUCTION

Necrotizing soft tissue infections (NSTIs) are rapidly progressive skin and soft tissue infections that cause widespread tissue necrosis and are associated with systemic illness.[1] The term NSTI has been increasingly used in lieu of the term necrotizing fasciitis, originally coined by BL Wilson[2] in 1952 to encompass cases in which necrosis

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extends beyond the fascia and can involve the muscle, skin, and surrounding tissues. The incidence and prevalence of NSTIs varies by season, location, and patient population. It is known from the active surveillance operations of the Centers for Disease Control and Prevention that the incidence of NSTI due to invasive group A streptococcal (GAS) infections in the United States is 0.4 per 100,000.[3] The estimated incidence of all-cause NSTI remains less clear due to wide variability in reporting practices. Despite advances in the care, mortality from NSTI has remained relatively high at 25% to 30% for the past 30 years, and has only recently seen a decrease to just over 20%.[4–8] Case fatality rates remain highest when NSTI is accompanied by shock and/or host factors such as advanced age, comorbidities, or immunocompromised state.[1]

Necrotizing soft tissue infections can be classified based on microbiology, location, or depth of tissue involvement. Giuliano and colleagues[9] originally described 2 distinct microbiologic profiles in NSTI; however, the classification system has evolved over time with the recognition of additional pathogen classes (**Table 1**). Type 1 is the most common infection seen, and describes polymicrobial infections, often including anaerobes. Type 2 infections are monomicrobial and typically involve GAS or, less commonly, *Staphylococcus aureus*. Monomicrobial NSTI can also be caused by *Clostridium* spp and, rarely, by *Vibrio vulnificus* (from exposure to warm coastal seawater or consumption of raw oysters; classified by some as type III), *Aeromonas hydrophila* (from exposure to leech therapy or traumatic lesions in fresh water),[10] and fungi (classified by some as type IV) such as *Apophysomyces* spp. Certain monomicrobial causes have presented as local outbreaks (eg, community-associated methicillin-resistant *Staphylococcus aureus* [MRSA] in Los Angeles)[11] or exhibited geographic clustering (eg, *Klebsiella pneumoniae* among diabetic patients with NSTI in Taiwan).[12] Terminology varies by anatomic site as well. Fournier gangrene is used to describe NSTIs of the perineum, which is generally polymicrobial. Diabetic foot infections are polymicrobial and associated with an anaerobic milieu and compromised microvasculature and can sometimes progress to a necrotizing pattern. Finally, the depth of necrosis can also help classify NSTI, with necrotizing cellulitis describing an infection involving the dermis and subcutaneous tissue, necrotizing fasciitis involving the fascia, and pyomyositis or myonecrosis describing involvement of the muscle fascicle without necessarily having overlying skin infections.

PATHOPHYSIOLOGY

The vicious cycle of fulminant infection, toxin production, cytokine activation, microthrombosis and ischemia, and tissue dysfunction and death, and, in turn, greater dissemination of infection is central to the rapidly progressive necrosis seen in NSTI and differentiates it from that of uncomplicated skin and soft tissue infections (**Fig. 1**).[13] Inoculation may be related to trauma or surgery; injured skeletal muscle cells have demonstrated greater adherence to bacteria.[14] The pathogen first spreads in the tissue, releasing a variety of toxins. In the case of GAS and *S aureus*, these are exotoxins.[15] Toxins mediate an inflammatory change in the walls of the microvasculature that facilitates microvascular thrombosis. Pyrogenic exotoxins act as superantigens that bind to antigen-presenting cells and cause rapid proliferation of T cells, and, in turn, production of cytokines that perpetrate shock and multiorgan failure. This is the mechanism for development of toxic shock syndrome (TSS), which is seen with up to half of the NSTI cases due to GAS[16] and can also be seen in cases due to *S aureus*. All the clinical criteria of TSS, including macular rash and desquamation of palms and soles, are not always present, making TSS difficult to distinguish from septic shock by the bedside; the latter can be associated with all causes of NSTI.

Table 1
Microbiologic classification of necrotizing soft tissue infections

Types of Necrotizing Fasciitis	Cause	Organisms	Clinical Progress	Mortality
Type I (70%–80% of cases)	Polymicrobial or synergistic, often bowel flora–derived	Mixed anaerobes and aerobes	More indolent, better prognosis, easier to recognize	Variable, depends on underlying comorbidities
Type II (20%–30% of cases)	Often monomicrobial-, skin-, or respiratory-derived	Usually A β-hemolytic *Streptococcus* (GAS), occasionally *S aureus*	Aggressive, presentation easily missed	>30%, depends on associated myositis
Type III (more common in Asia)	Gram-negative, often marine-related organisms	*Vibrio* spp	Seafood ingestion or water contamination in wounds	30%–40%
Type IV (Fungal)	Trauma-associated	*Candida* spp, immunocompromised patients *Zygomycetes* in immunocompetent patients	Aggressive with rapid extension, especially if immunocompromised	>50%, higher if immunocompromised

Adapted from Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. J Hosp Infect 2010;75:249–57.

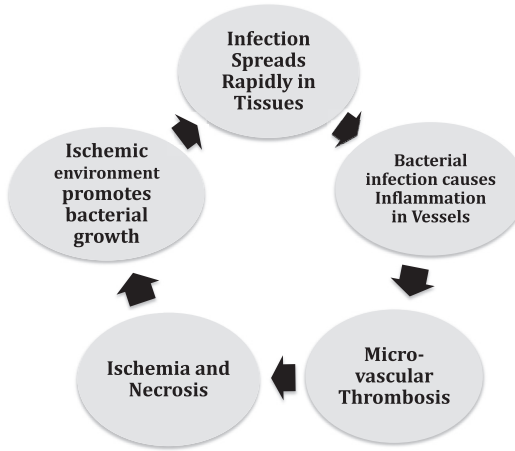

Fig. 1. Vicious cycle of necrotizing soft tissue infection.

Antibiotics penetrate dead and dying tissue poorly and such organism-laden dead tissue represents a perpetual source of infection, underscoring the need for emergent surgical source control in NSTI.

DIAGNOSIS

Clinical Assessment

Nothing replaces early recognition and immediate initiation of treatment of NSTI, which are key to a favorable outcome. Most cases exhibit swelling and erythema but the most consistent finding is pain that is out of proportion to examination findings.[17] However, it can often be difficult to discern a necrotizing process from a simple cellulitis. Patients with NSTI may often present with systemic illness and encephalopathy alone. A thorough examination is valuable when history cannot be easily elicited. Suspicion should be very high in patients with a soft tissue infection who rapidly deteriorate with organ system failure.[18] Additional skin examination findings that should lead to a high index of suspicion include bullae, skin ecchymosis, skin necrosis, and edema outside of the area of erythema, as well as, sometimes, cutaneous anesthesia.[19]

Laboratory Values and Scoring Systems

Laboratory values and imaging have little to add to diagnosis when clinical suspicion of NSTI is high enough to warrant treatment. However, clinical features alone might be poorly sensitive for making a diagnosis of NSTI in equivocal cases. Additionally, the disease is rare enough that some practitioners may have limited experience with these severe infections and supplemental diagnostic assistance may be desirable to those less familiar with NSTI.[20] Notably, laboratory findings of leukocytosis and hyponatremia have been shown to improve sensitivity from clinical examination alone.[21] An admission lactate greater than 6 mmol/L and a serum sodium less than 135 mEq/L have been shown to be independent predictors of in-hospital mortality in those presenting with NSTI.[22] In 2004, Wong and colleagues[23] developed the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. White blood cell count, hemoglobin, sodium, glucose, serum creatinine, and serum C-reactive protein are used to score for the likelihood of necrotizing fasciitis. In the original publication, a score of

equal to or greater than 6 yielded a positive predictive value of 92% and negative predictive value of 96%, displaying promise for predicting severity of skin and soft tissue infection among patients presenting to emergency care. Although retrospective validation of this scoring system has been attempted in small case-series,[24,25] a recent multicenter prospective evaluation of the LRINEC score has lessened the excitement around this predictive tool; a cut-off of greater or less than 6 in NSTI patients failed to discriminate between those with and without high cytokine levels, septic shock, and death.[26] Furthermore, the LRINEC score can be artificially elevated in other musculoskeletal infections. The Fournier's Gangrene Risk Index, although shown to be a predictor of outcome in retrospective studies, has not shown to be any better than the age-adjusted Charlson comorbidity index and remains of research interest alone.[27] As such, these scoring systems should not be solely relied on for diagnosing or excluding NSTI.

Imaging

Gas in the soft tissues on plain, portable radiographs, when seen, can aid in the diagnosis of NSTI in patients who are too unstable to travel for more advanced radiographic studies (**Fig. 2**). However, for those patients able to undergo computed tomography (CT) scan or MRI, both have been shown to be useful adjuncts for diagnosis when the diagnosis is not certain on clinical evaluation. A CT scan with contrast that demonstrates lack of enhancement of the fascia, along with involvement of the fascia in the infectious process, is more specific for NSTI than air or edema alone (**Fig. 3**).[28] In the case of MRI, imaging finding consistent with a diagnosis of NSTI includes greater thick signal intensity on T2-weighted images and focal nonenhancing

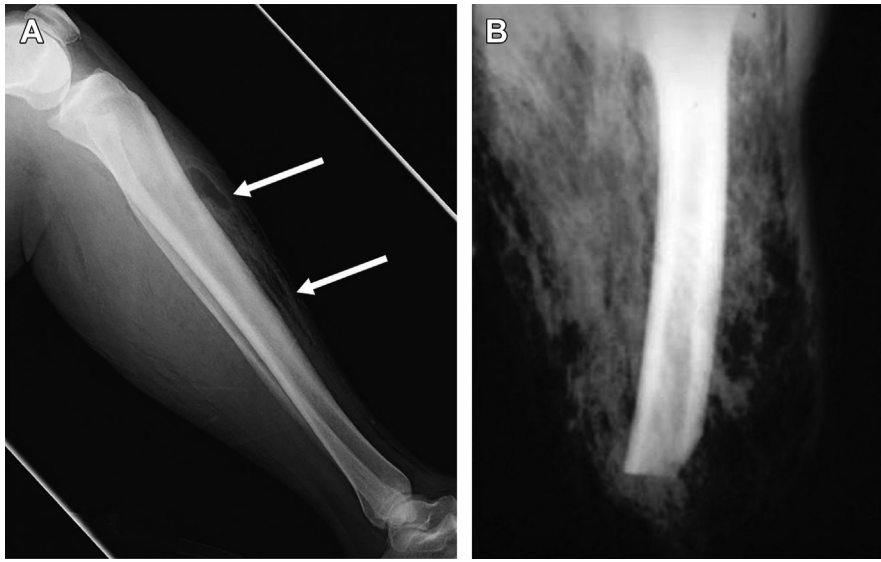

Fig. 2. (*A*) Evidence of GAS tracking (*arrows*) on the fascia on radiograph in a patient with NSTI involving the leg. (*B*) Subcutaneous emphysema on radiograph in a patient with NSTI of the thigh. ([*A*] *Data from* Chaudhry A, Baker K, Gould E, et al. Necrotizing fasciitis and it's mimics: what radiologists need to know. AJR 2015;204:128–39; and [*B*] *From* Sarani B, Strong M, Pascual J, et al. Necrotizing fasciitis: current concepts and review of the literature. JACS 2009;208(2):282; with permission.)

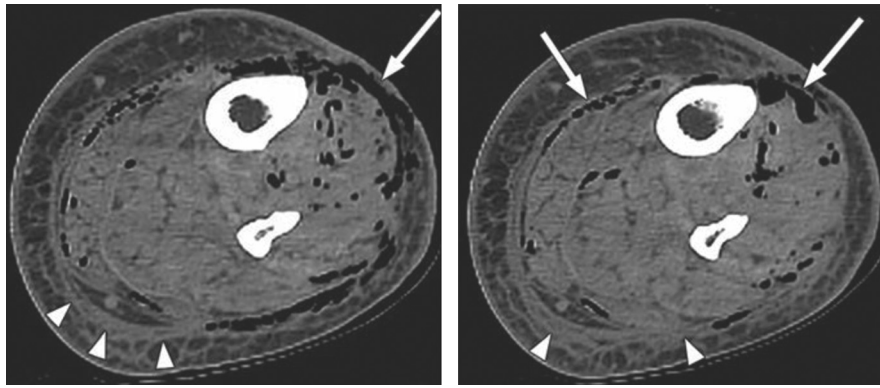

Fig. 3. Two Axial CT Images of the left lower extremity of a patient with necrotizing soft tissue infection, demonstrating edema in the soft tissues (*arrowheads*) and air tracking along the fascial planes (*arrows*). (*From* Chaudhry A, Baker K, Gould E, et al. Necrotizing fasciitis and it's mimics: what radiologists need to know. AJR 2015;204:133; with permission.)

areas of abnormal signal intensity in the deep fascia (**Fig. 4**). This is useful in distinguishing a necrotizing infection from a non-necrotizing infection in the case of non-diagnostic CT and plain radiograph findings, such as soft tissue swelling.[29] However, MRI can be overly sensitive as well as time consuming; it can certainly delay necessary surgical management and should be used with caution. Ultrasound can identify soft tissue abscesses in NSTI. The rapidity and portability of point-of-care ultrasound in the emergency room is attractive in principle but evidence is currently limited to sporadic reports and additional data are needed before it can be thought of as a mainstream diagnostic modality for NSTI.[30]

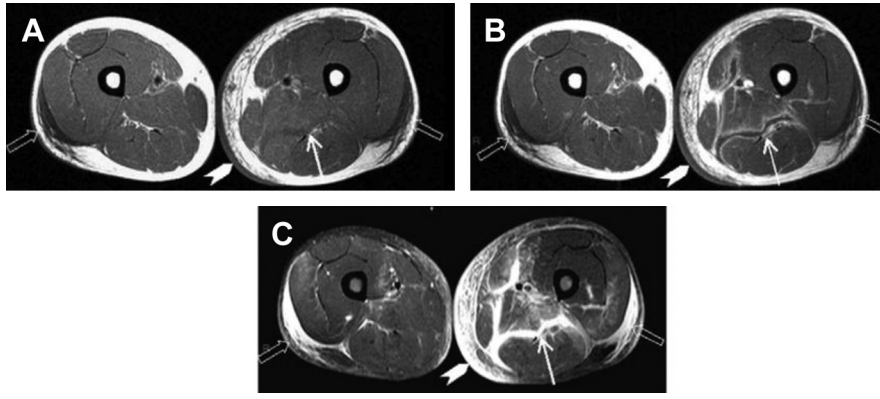

Fig. 4. MRI findings for a patient with necrotizing fasciitis and myositis: axial sections of the left thigh demonstrating increased soft tissue enhancement and gas in the soft tissues. T1 images (*A*) before and (*B*) after contrast injection where thick white arrows show thickening of skin and subcutaneous fat infiltration and with (*C*) Short TI Inversion Recovery (STIR) sequence where thin white arrows show thickening of the deep intermuscular fasciae and hollow arrows show stasis edema. (*Reproduced from* Malghem J, Lecouvet FE, Omoumi P, et al. Necrotizing fasciitis: contribution and limitations of diagnostic imaging. Joint Bone Spine 2013;80(2):146–54; with permission. Copyright © 2013.)

Bedside Exploration and Biopsy

The definitive diagnosis of NSTI is made surgically. A large number of equivocal cases exist in which additional evidence might be needed before the patient is taken for surgery. In such cases, before any formal operation, surgeons can assist in the bedside diagnosis of NSTI by performing a local exploration of the area under local anesthetic. Alternately, surgeons may proceed to the operating room where additional debridement can be immediately performed if NSTI is diagnosed on local exploration. In this case, a small incision is made over the area of maximal suspicion and the overlying soft tissue is divided. The fascia is examined locally for signs of necrosis: dishwater brown fluid or positive finger sign in which a finger inserted along the fascial planes easily dissects the overlying tissue without resistance.[31] Similarly, the underlying muscle tissue can be examined intraoperatively for evidence of necrosis. Electrocautery may be used in anesthetized patients without systemic paralytic therapy in place to demonstrate muscle fiber nonreactivity, which indicates tissue death. High organism density and worse clinics outcome have been suggested; albeit on univariate analyses alone.[1] Use of biopsy for frozen section analysis might aid in unequivocal cases; however, Infectious Disease Society of America (IDSA) guidelines caution against undue reliance due to potential false negatives from sampling error.[32,33]

TREATMENT

Any patient with evidence of septic shock should be treated in the critical care setting. The intensivist should maintain a high clinical suspicion and heighten the level of urgency among members of the care team at the point of initial patient contact so that all aspects of workup and treatment are expedited wherever possible. Once the diagnosis of NSTI is suspected, early consultation with a surgeon is warranted. Even in institutions with immediate surgical capabilities, however, a period of time will be spent evaluating the patient and preparing transport to the operating room, during which delivery of antibiotic therapy and supportive critical care must be expedited. In the case of a patient with systemic illness and shock, resuscitation is performed in a similar manner as is done for septic shock and initial management occurs simultaneous to the search for pathogen and source.

Antibiotic Therapy

Early and aggressive use of antibiotic therapy is essential and should be performed concomitant to the patient undergoing surgical evaluation and treatment. Blood cultures, and if possible, deep tissue, abscess, and/or operative cultures must be obtained promptly because these will help tailor antibiotic therapy. Antibiotic therapy for necrotizing infections in particular has not been studied in randomized controlled trials. Data for antibiotic treatment are extrapolated from proposed therapy for nonnecrotizing complicated skin and soft tissue infections.

Initial empirical therapy should encompass a broad-spectrum coverage of polymicrobial infections because about half of these infections will be polymicrobial in nature.[33] This should include a MRSA-active agent, such as vancomycin, daptomycin, linezolid, or ceftaroline, as well as a broad-spectrum agent against gram-negative pathogens, such as piperacillin-tazobactam, ampicillin-sulbactam, ticarcillin-clavulanate, extended-spectrum cephalosporins, or carbapenems. If the selected regimen lacks anaerobic activity, an agent such as metronidazole or clindamycin must be added. More recently, a German study has suggested tigecycline as a possible single-agent therapy in patients previously colonized with resistant bacteria, such as patients who have been recently hospitalized or institutionalized[34]; however,

such practice must be guided by local epidemiologic patterns. Similarly, empirical use of fluoroquinolones and ceftriaxone in areas with high prevalence of resistance to these agents among gram-negative bacteria must be avoided. Empirical antifungal therapy is not essential but an appropriate antifungal agent may be added on visual evidence on stains or growth in blood or operative cultures of fungal elements such as *Candida* or *Mucorales* spp.

Animal models have demonstrated greater efficacy with the clindamycin (a lincosamide antibiotic that works by inhibition of ribosomal translocation) compared with β-lactams in GAS infection; these findings were corroborated in 2 small retrospective cohort studies.[35,36] Notably, clindamycin may have multiple advantages over β-lactams, including an effect that is independent of inoculum size or infection stage, as well as potential antitoxin properties. In TSS, clindamycin is thought to mitigate the severity of shock by decreasing toxin production.[37] Although macrolide resistance in GAS remains low in the United States, it tends to be relatively higher among invasive strains of GAS; consequently, penicillins being universally active against GAS could offer coverage in clindamycin-resistant infections. Hence, the Surgical Infection Society and IDSA guidelines both strongly recommend combination therapy with penicillin and clindamycin in NSTI (with or without TSS) due to GAS.[33,38,39] Because the causative pathogen is not usually known up front, it is reasonable to add clindamycin to the empirical regimen for suspected NSTI. Like clindamycin, linezolid is also a protein synthesis inhibitor with potential toxin-inhibiting properties (particularly in the case of *S aureus* infection); however, no clinical studies to date have evaluated the clinical impact of this property of linezolid in NSTI.

After the organisms have been identified in the microbiology laboratory, therapy can usually be tailored further. The absence of growth of MRSA in cultures demonstrates a high negative predictive value and can facilitate discontinuation of the MRSA-active agent. For known or suspected *Vibrio* spp, NSTIs, doxycycline plus a third-generation cephalosporin is recommended, and combination therapy is key when a cell wall–inhibiting agent is used.[40] For known or suspected *Aeromonas* infections, doxycycline is recommended in combination with ciprofloxacin for community-acquired infections or cefepime for leech therapy–acquired infections, which have been reported to be resistant to ciprofloxacin.[41]

No clinical trials have evaluated duration of therapy in NSTI. Guidelines suggest continuation of appropriate antibiotics for a minimum of 48 to 72 hours after resolution of fever and other systemic signs of infection, as well as hemodynamic stabilization. Please refer to IDSA practice guidelines for skin and soft tissue infections for additional details on antibiotic therapy for NSTI.[33]

Surgical Intervention

Although antibiotic therapy, resuscitation and critical care evaluation are necessary in the treatment of patients presenting with NSTIs, the mainstay of therapy remains surgical treatment. **Fig. 5** shows a proposed management pathway in NSTI. Multiple large studies cite the need for early and aggressive debridement in NSTIs, and claim it as the single most important treatment intervention for this disease process, although no randomized controlled trial has studied the timing or extent of surgical therapy or clearly defined an adequate debridement.[42–45] Delay in the identification or early surgical management of these infections clearly increases mortality.[45] In addition, recent data suggest that delay not only increases mortality but, in survivors, also increases the number of subsequent operations needed to control the infection.[46] Increased number of operations may increase the total tissue loss from the disease process because more tissue is removed with each operation and, therefore, limit functional recovery because more muscle and, possibly, critical structures such as nerves are

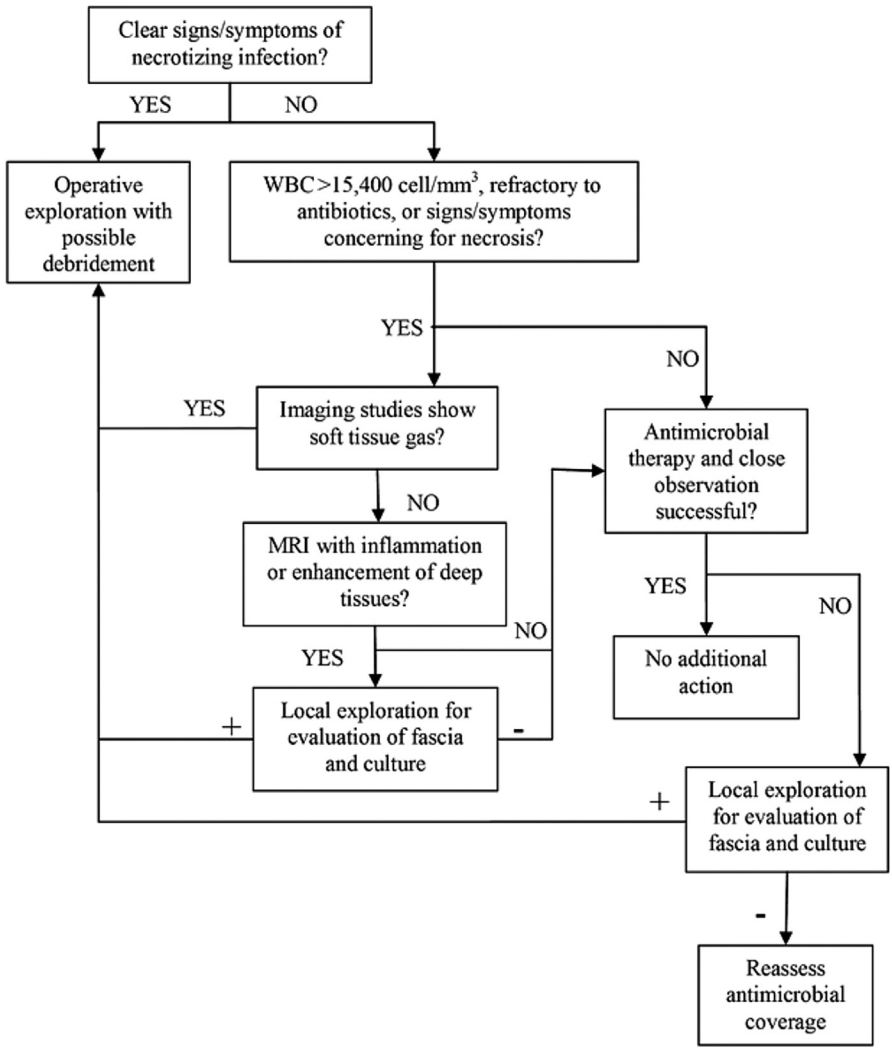

Fig. 5. Management pathway in NSTI. WBC, white blood cell. (*From* Burnham JP, Kriby JP, Kollef MH. Diagnosis and management of skin and soft tissue infections in the intensive care unit: a review. Intensive Care Med 2016:42:1904; with permission.)

sacrificed. There is also associated increased cost with each subsequent operation. Early identification and aggressive treatment, therefore, remains critical in the treatment of these infections.[47] Time to surgical debridement has been demonstrated as an independent predictor of improved outcome in large studies.[18,42] In another study, the presence of a 24-hour in-house emergency general surgical team provided both the expertise and expeditious treatment needed to reduce time to operation and improve mortality.[48] Although this was an isolated single-center experience, it underscores the importance of early surgical evaluation and advocates for widespread emergency surgical capability or early transfer to a facility with these capabilities.

Despite being a mainstay of therapy for this infection, no study has defined what an adequate debridement is, although typical training dictates that all necrotic tissue

should be removed. Debridement, therefore, remains at the discretion of the operating surgeon.[43] Many studies refer to aggressive debridement without objectively quantifying the term. It is, however, well demonstrated that wounds should be frequently re-evaluated, typically with re-exploration in the operating room within 24 to 48 hours of the initial debridement procedure. The return to the operating room is intended for re-evaluation of the wound, debridement of any further necrotic tissue, confirming the absence of progression, and to facilitate dressing changes. The average number of debridement procedures is 3 to 4 before further dressing changes are performed at the bedside.[18,42,46]

In the case of wide or disfiguring debridements, involvement of additional teams, including urology for perineal wounds or wounds involving the penis or scrotum, plastic surgery for complex reconstruction or muscle flap reconstruction, or orthopedics for bony involvement, may be necessary. In the case of perineal wounds, it may be necessary to divert the fecal stream away from the area of contamination with a loop colostomy.[49] Amputations may be necessary in the case of diabetic foot infections or larger scale debridements of entire muscle compartments, resulting in a nonfunctioning limb. Reconstruction with rotational flaps or skin graft techniques may be necessary and warrant early intervention and comanagement with plastic surgery. Widespread use of vacuum-assisted closure devices provides consistent and easy nursing care, suctioning of soft tissue edema, and promoting granulation tissue.[50] Newer vacuum-assisted closure products are accompanied by continuous wound irrigation, which may be beneficial in wounds from debridement of NSTI.[51] Negative pressure dressings can provide dermatotraction to limit the wound size and facilitate closure.[52] In the case of complex and repeated reconstructive surgeries, rehabilitation, physical therapy, or occupational therapy may be necessary and treatment courses can be significantly life-altering and prolonged.

The impact of early transfer versus on-site initial debridement in NSTI has not been systematically investigated in a clinical trial and, as such, is difficult to decipher retrospectively. Initial resuscitation, initial debridement (when available), and control of the infectious process must be prioritized at the presenting hospital. Often, however, the decision of when to operate and when to transfer is complex and must be made carefully, taking into account clinical severity and institutional capabilities. Institutional factors that might prompt transfer include the lack of an intensive care unit; the lack of availability of advanced services, such as continuous renal replacement therapy, large volume blood transfusion, or on-call surgical staff; and the need for complex reconstruction techniques that may not be available at certain hospitals.

Adjuvant Therapies

The 2 most common adjunctive medical treatments discussed for NSTIs include intravenous immune globulin and hyperbaric oxygen. Intravenous immunoglobulin has been suggested as a treatment of superantigen-mediated TSS due to streptococcal[53] or staphylococcal necrotizing fasciitis.[54] The proposed mechanism of action is that IVIG binds and inactivates circulating superantigens, thereby blunting the superantigen-mediated cytokine cascade. Initial retrospective studies demonstrated some promise but a randomized controlled trial on the subject was terminated early and lacked sufficient power to detect a survival benefit.[55] A subsequent pediatric study also demonstrated no benefit of IVIG therapy.[56] Additionally, the cost associated with the treatment is high. In 2016, Kadri and colleagues[57] reported findings of a propensity-matched analysis of administrative data from 130 US hospitals evaluating the role of adjunctive IVIG in NSTI and validated administrative data algorithms against clinical data from 4 hospitals. There was no clinical benefit to IVIG therapy

observed, regardless of timing of treatment. Also, not surprisingly, IVIG was found to be used rather sporadically at 4%. In 2017, the Immunoglobulin G for Patients with Necrotizing Soft Tissue Infection (INSTINCT) study, a Danish multicenter randomized controlled trial also evaluating the adjunctive potential of 3 days of IVIG therapy in NSTI found no benefit of the same on physical functioning or survival at 6-months.[58] Plasmapheresis, in principle, could remove circulating inflammatory mediators and potentially decrease the host's intrinsic inflammatory response, lessening the severity of vasodilatory shock. However, the data supporting this strategy remain anecdotal.[59]

Hyperbaric oxygen has been proposed as an adjunctive therapy after surgical debridement for NSTI.[60] The fascia is known to be a relatively hypoxic environment owing to its tenuous blood supply when compared with surrounding muscle or skin. By increasing plasma dissolved oxygen concentration, hyperbaric oxygen is believed to potentially enhance oxygen delivery to hypoxic tissues surrounding areas of necrosis, directly killing anaerobic bacteria and improving leukocyte activity.[61] This proposed mechanism has led to a series of retrospective studies, with some showing decreased mortality and others showing no effect.[60,62] These studies are not compelling to recommend hyperbaric therapy. Furthermore, the greatest barrier to practical use of this modality in NSTI is the limited number of centers nationwide with hyperbaric chambers where critically ill patients can be adequately monitored. In summary, despite theoretic benefits, no prospective literature exists to support use as adjuvant therapy and society guidelines to do not recommend routine use in these infections.[17]

SUMMARY

In summary, NSTI remains a disease with high morbidity and mortality, despite improvements in care. In the past several decades, understanding of this disease process has improved such that it is known that early diagnosis, along with rapid aggressive treatment with broad spectrum antimicrobial treatment and wide surgical debridement, are necessary to effectively treat this disease process. Adjunctive therapies have been explored and found to be largely ineffective and are not routinely recommended. More recently, differences in the timing of antibiotic therapy administration has been observed between high-volume and low-volume centers for the treatment of necrotizing fasciitis, and suggests that differences in care may exist between centers with high-volume care of this disease.[1] If indeed, patients must be identified early, treated expeditiously, and supported with the best available critical care, then perhaps further advances in the care of this disease will be less about finding a better treatment modality. It may be that improving the systems that bring patients to the attention and care of appropriate clinicians will be the intervention that moves the needle on the burden of this disease.

REFERENCES

1. Faraklas I, Yang D, Eggerstedt M, et al. A multi-center review of care patterns and outcomes in necrotizing soft tissue infections. Surg Infect (Larchmt) 2016;17(6):773–8.
2. Wilson B. Necrotizing fasciitis. Am Surg 1952;18:416–31.
3. Nelson GE, Pondo T, Toews KA, et al. Epidemiology of invasive group A streptococcal infections in the United States, 2005-2012. Clin Infect Dis 2016;63(4):478–86.
4. Yilmazlar T, Ozturk E, Alsoy A, et al. Necrotizing soft tissue infections: APACHE II score, dissemination, and survival. World J Surg 2007;31:1858–62.
5. Miller AT, Saadai P, Greenstein A, et al. Postprocedural necrotizing fasciitis: A 10-year retrospective review. Am Surg 2008;74:405–9.

6. Lee TC, Carrick MM, Scott BG, et al. Incidence and clinical characteristics of methicillin-resistant *Staphylococcus aureus* necrotizing fasciitis in a large urban hospital. Am J Surg 2007;194:809–12.
7. Hefny AF, Eid HO, Al Hussona M, et al. Necrotizing fasciitis: a challenging diagnosis. Eur J Emerg Med 2007;14:50–2.
8. Childers BJ, Potyondy LD, Nachreiner R, et al. Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. Am Surg 2002;68:109–16.
9. Giuliano A, Lewis F, Hadley K, et al. Bacteriology of necrotizing fasciitis. Am J Surg 1977;134:52–7.
10. Sartor C, Limouzin-Perotti F, Legré R, et al. Nosocomial infections with *Aeromonas hydrophila* from leeches. Clin Infect Dis 2002;35(1):E1–5.
11. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. N Engl J Med 2005;352(14):1445–53.
12. Cheng NC, Yu YC, Tai HC, et al. Recent trend of necrotizing fasciitis in Taiwan: focus on monomicrobial *Klebsiella pneumonia* necrotizing fasciitis. Clin Infect Dis 2012;55(7):930–9.
13. Anaya DA, McMahon K, Nathens AB, et al. Predictors of mortality and limb loss in necrotizing soft tissue infections. Arch Surg 2005;140(2):151–7.
14. Bryant AE, Bayer CR, Huntinton JD, et al. Group A streptococcal myonecrosis: increased vimentin expression after skeletal-muscle injury mediates the binding of *Streptococcus pyogenes*. J Infect Dis 2006;193(12):1685–92.
15. Bohach GA, Fast DJ, Nelson RD, et al. Staphylococcal and streptococcal pyrogenic toxins involved in toxic shock syndrome and related illnesses. Crit Rev Microbiol 1990;17:251–72.
16. Darenberg J, Luca-Harari B, Jasir A, et al. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. Clin Infect Dis 2007;45(4):450–8.
17. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005;41:1373–406.
18. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. Ann Surg 1996;224:672–83.
19. Wall DB, de Virgilio C, Black S, et al. Objective criteria may assist in distinguishing necrotizing fasciitis from nonnecrotizing soft tissue infection. Am J Surg 2000;179:17–21.
20. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 2007;44:705–10.
21. Chan T, Yaghoubian A, Rosing D, et al. Low sensitivity of physical examination findings in necrotizing soft tissue infection is improved with laboratory values: a prospective study. Am J Surg 2008;196(6):926–30.
22. Yaghoubian A, de Virgilio C, Dauphine C, et al. Use of admission serum lactate and sodium levels to predict mortality in necrotizing soft-tissue infections. Arch Surg 2007;142(9):840–6.
23. Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 2004;32(7):1535–41.
24. Kincius M, Telksnys T, Trumbeckas D, et al. Evaluation of LRINEC scale feasibility for predicting outcomes of Fournier gangrene. Surg Infect (Larchmt) 2016;17(4):448–53.

25. Chao WN, Tsai SJ, Tsai CF, et al. The laboratory risk indicator for necrotizing fasciitis score for discernment of necrotizing fasciitis originated from *Vibrio vulnificus* infections. J Trauma Acute Care Surg 2012;73(6):1576–82.
26. Hansen MB, Rasmussen LS, Svensson M, et al. Association between cytokine response, the LRINEC score and outcome in patients with necrotizing soft tissue infection: a multicentre, prospective study. Sci Rep 2017;7:42179.
27. Roghmann F, von Bodman C, Loppenberg B, et al. Is there a need for the Fournier's gangrene severity index? Comparison of scoring systems for outcome prediction in patients with Fournier's gangrene. BJU Int 2012;110(9):1359–65.
28. Carbonetti F, Cremona A, Carusi V, et al. The role of contrast enhanced computed tomography in the diagnosis of necrotizing fasciitis and comparison with the laboratory risk indicator for necrotizing fasciitis (LRINEC). Radiol Med 2016;121(2):106–21.
29. Kim KT, Kim YJ, Won Lee J, et al. Can necrotizing infectious fasciitis be differentiated from nonnecrotizing infectious fasciitis with MR imaging? Radiology 2011;259(3):816–24.
30. Kehrl T. Point-of-care ultrasound diagnosis of necrotizing fasciitis missed by computed tomography and magnetic resonance imaging. J Emerg Med 2014;47(2):172–5.
31. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. Chest 1996;110:219–29.
32. Hietbrink F, Bode LG, Riddez L, et al. Triple diagnostics for early detection of ambivalent necrotizing fasciitis. World J Emerg Surg 2016;11:51.
33. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:147–59.
34. Eckmann C, Heizmann W, Bodmann KF, et al. Tigecycline in the treatment of necrotizing soft tissue infections due to multiresistant bacteria. Surg Infect (Larchmt) 2015;16:618–25.
35. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. Pedatr Infect Dis J 1999;18(12):1096–100.
36. Mulla ZD, Leaverton PE, Wiersma ST. Invasive group A Streptococcal infections in Florida. South Med J 2003;96(10):968–73.
37. Bernardo K, Pakulat N, Fleer S, et al. Subinhibitory concentrations of linezolid reduce *Staphylococcus aureus* virulence factor expression. Antimicrob Agents Chemother 2004;48:546–55.
38. Gemmell CG, Ford CW. Virulence factor expression by gram-positive cocci exposed to subinhibitory concentrations of linezolid. J Antimicrob Chemother 2002;50:665–72.
39. May AK, Stafford RE, Bulger EM, et al, Surgical Infection Society. Treatment of complicated skin and soft tissue infections. Surg Infect (Larchmt) 2009;10(5):467–99.
40. Zanetti S, Spanu T, Deriu A, et al. In vitro susceptibility of *Vibrio* spp. isolated from the environment. Int J Antimicrob Agents 2001;17:407–9.
41. Aravena-Román M, Inglis TJ, Henderson B, et al. Antimicrobial susceptibilities of *Aeromonas* strains isolated from clinical and environmental sources to 26 antimicrobial agents. Antimicrob Agents Chemother 2012;56(2):1110–2.
42. McHenry CR, Piotrowski JJ, Petrinic D, et al. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 1995;221:558–63.

43. Sudarsky LA, Laschinger JC, Coppa GF, et al. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg 1987;206:661–5.
44. Tillou A, St Hill CR, Brown C, et al. Necrotizing soft tissue infections: improved outcomes with modern care. Am Surg 2004;70:841–4.
45. Bilton BD, Zibari GB, McMillan RW, et al. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. Am Surg 1998;64:397–400.
46. Kobayashi L, Konstantinidis A, Shackelford S, et al. Necrotizing soft tissue infections: delayed surgical treatment is associated with increased number of surgical debridements and morbidity. J Trauma 2011;71(5):1400–5.
47. Sartelli M, Malangoni MA, May AK, et al. World Society of Emergency Surgery (WSES) guidelines for the management of skin and soft tissue infections. World J Emerg Surg 2014;9:57.
48. Gunter OL, Guillamondegui OD, May AK, et al. Outcome of necrotizing skin and soft tissue infections. Surg Infect 2008;9:443–50.
49. Kilic A, Aksoy Y, Kilic L. Fournier's gangrene: etiology, treatment, and complications. Ann Plast Surg 2001;47:523–7.
50. Czymek R, Schmidt A, Eckmann C, et al. Fournier's gangrene: vacuum-assisted closure versus conventional dressings. Am J Surg 2009;197:168–76.
51. Kiyokawa K, Takahashi N, Rikimaru H, et al. New continuous negative-pressure and irrigation treatment for infected wounds and intractable ulcers. Plast Reconstr Surg 2007;120(5):1257–65.
52. Lee JY, Jung H, Kwon H, et al. Extended negative pressure wound therapy-assisted dermatotraction for the closure of large open fasciotomy wounds in necrotizing faciitis patients. World J Emerg Surg 2014;9:29–39.
53. Linnér A, Darenberg J, Sjölin J, et al. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis 2014;59(6):851–7.
54. Darenberg J, Söderquist B, Normark BH, et al. Differences in potency of intravenous polyspecific immunoglobulin G against streptococcal and staphylococcal superantigens: implications for therapy of toxic shock syndrome. Clin Infect Dis 2004;38(6):836–42.
55. Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2003;37:333–40.
56. Shah SS, Hall M, Srivastava R, et al. Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. Clin Infect Dis 2009;49:1369–76.
57. Kadri SS, Swihart BJ, Bonne SL, et al. Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: a propensity-score matched analysis from 130 US hospitals. Clin Infect Dis 2016;64(7):877–85.
58. Madsen MB, Hjortrup PB, Hansen MB, et al. Immunoglobulin G for patients with necrotizing soft tissue infection (INSTINCT): a randomized, blinded, placebo-controlled trial. Intensive Care Med 2017. [Epub ahead of print].
59. Kyles DM, Baltimore J. Adjunctive use of plasmapheresis and intravenous immunoglobulin therapy in sepsis: A case report. Am J Crit Care 2005;14:109–12.
60. Shupak A, Shoshani O, Goldenberg I, et al. Necrotizing fasciitis: An indication for hyperbaric oxygenation therapy? Surgery 1995;118:873–8.

61. Jallali N, Withey S, Butler PE. Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. Am J Surg 2005;189:462–6.
62. Riseman JA, Zamboni WA, Curtis A, et al. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery 1990; 108:847–50.