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Evaluation and Management of Necrotizing Soft Tissue Infections

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Introduction

Necrotizing soft tissue infections (NSTI) 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 increasing used in lieu of the term “necrotizing fasciitis”, originally coined by BL Wilson in 1952, to encompass cases where necrosis extends beyond the fascia and can involve the muscle, skin and surrounding tissues[2]. The incidence and prevalence of NSTI varies by season, location and patient population. We know from the active surveillance operations of the CDC 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 25–30% for the past thirty years, and has only recently seen a decrease to just over 20%[4,5,6,7,8]. 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 on the basis of microbiology, location or depth of tissue involvement. Guiliano et al 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)[9]. Type 1 is the most common infection seen, and describes polymicrobial infections, often including anerobes, 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 vulnificans* (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] as well as fungi (classified by some as Type IV) such as *Apohyphomyces* spp. Certain monomicrobial etiologies have presented as local outbreaks (e.g. community-associated MRSA in Los Angeles)[11] or exhibited geographic clustering (e.g. *Klebsiella pneumoniae* among diabetic patients with NSTI in Taiwan)[12]. Terminology varies by anatomic site as well; Fournier's 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, 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 (Figure 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 *Staphylococcus 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 *Staphylococcus aureus*. All the clinical criteria of TSS including macular rash and desquamation of palms and soles are not always present, often making TSS difficult to distinguish from septic shock by the bedside; the latter can be associated with all etiologies of NSTI. 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 for NSTI, which are key to a favorable outcome. The majority of cases exhibit swelling and erythema, but the most consistent finding is pain that is out of proportion to exam 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 exam 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 exam findings that should lead to a high index of suspicion include bullae, skin

ecchymosis, skin necrosis, and edema outside of the area of erythema, and 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 exam alone[21]. An admission lactate >6 mmol/L and a serum sodium <135 mEq/L have been shown to be independent predictors of in-hospital mortality in those presenting with NSTI[22]. In 2004, Wong et al developed the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. This score uses white blood cell (WBC) count, hemoglobin, sodium, glucose, serum creatinine and serum c-reactive protein to develop a scoring system for the likelihood of necrotizing fasciitis[23]. In the original publication, a score of ≥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 ≥ or <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 Co-morbidity Index and remains of research interest alone[27]. As such, these scoring systems should not be solely relied upon for diagnosing or exluding 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 (Figure 2). However, for those patients able to undergo 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 (Figure 3)[28]. In the case of MRI, imaging finding consistent with a diagnosis of NSTI include greater thick signal intensity on T2-weighted images and focal nonenhancing areas of abnormal signal intensity in the deep fascia (Figure 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].

Bedside exploration and biopsy

The definitive diagnosis of NSTI is made surgically. A large number of equivocal cases exist where additional evidence might be needed before the patient is taken for surgery. In such cases, prior to any formal operation, surgeons can assist in the bedside diagnosis of NSTI by performing a local exploration of the area in question at the bedside 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, and 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, IDSA guidelines caution against undue reliance on the same 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 aspect of work up 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 patients 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 where possible, deep tissue, abscess and/or operative cultures must be obtained promptly as 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 is extrapolated from proposed therapy for non-necrotizing complicated skin and soft tissue infections.

Initial empiric therapy should encompass broad-spectrum coverage of polymicrobial infections, as 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, ticarcilin-clavulanate, extended-spectrum cephalosporins

or carbapenems. If the selected regimen lacks anerobic activity, an agent such as metronidazole or clindamycin must be added. More recently, a German study has suggested tigecycline as 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, empiric use of fluoroquinolones and ceftriaxone in areas with high prevalence of resistance to these agents among gram-negative bacteria must be avoided. Empiric antifungal therapy is not essential, but an appropriate antifungal agent may be added upon 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 tranlocation–compared to β-lactams in GAS infection; these findings were corroborated in two 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 toxic shock syndrome (TSS), clindamycin is thought to mitigate the severity of shock by decreasing toxin production[37]. Although macrolide resistance in GAS remains low in the US, 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 Infectious Disease Society of America (IDSA) guidelines both strongly recommend combination therapy with penicillin and clindamycin in NSTI (with or without TSS) due to GAS[38,39, 33]. Since the causative pathogen is not usually known upfront, it is reasonable to add clindamycin to the empiric 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 organism(s) have been identified in the microbiology lab, 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 48–72 h 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

While antibiotic therapy, resuscitation and critical care evaluation are necessary in the treatment of patients presenting with NSTIs, the mainstay of therapy remains surgical treatment (refer to Figure 5 for 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[42,43,44,45]. Delay in the identification or early surgical management of these infections clearly increases mortality[46]. In addition, recent data suggests that delay not only increases mortality, but in survivors, also increases the number of subsequent operations needed to control the infection[47]. Increased number of operations may increase the total tissue loss from the disease process, as more tissue is removed with each operation, and therefore limit functional recovery as more muscle and possibly critical structures such as nerves, are 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[48]. Time to surgical debridement has been demonstrated as an independent predictor of improved outcome in large studies[49,50]. 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[51]. While 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 reevaluated, typically with re-exploration in the operating room within 24–48 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 3–4 before further dressing changes are performed at the bedside[47,49,50].

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[52]. 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 co-management with plastic surgery. Widespread use of vacuum-assisted closure devices is generally used to provide consistent and easy nursing care, suctioning of soft tissue edema, and promoting granulation tissue[53]. Newer vacuum assisted closure products are accompanied by

continuous wound irrigation, which may be beneficial in wounds from debridement of NSTI[54]. Negative pressure dressings can provide dermotraction to limit the wound size and facilitate closure[55]. 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 *vs* 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 decion 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, lack of availability of advanced services such as continuous renal replacement therapy, large volume blood transfusion or on-call surgical staff and need for complex reconstruction techniques that may not be available at certain hospitals.

Adjuvant therapies

The two most common adjunctive medical treatments discussed for NSTIs include intravenous immune globulin and hyperbaric oxygen. Intravenous immunoglobulin has been suggested as a treatment for superantigen-mediated toxic shock syndrome due to streptococcal[56] or staphylococcal NF[57]. 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 control trial on the subject was terminated early and lacked sufficient power to detect a survival benefit[58]. A subsequent pediatric study also demonstrated no benefit of IVIG therapy[59]. Additionally, the cost associated with the treatment is high. In 2016, Kadri et al 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[60]. Also, not surprisingly, IVIG was found to be used rather sporadically at 4%. In 2017, the 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[61]. 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 remains anecdotal[62].

Hyperbaric oxygen has been proposed as an adjunctive therapy after surgical debridement for NSTI[63]. The fascia is known to be a relatively hypoxic environment owing to its tenuous blood supply when compared to 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[64]. This proposed mechanism has led to a series of retrospective studies, with some showing decreased mortality and others showing no effect[65,66]. 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 theoretical benefits, no prospective literature exists to support its use as adjuvant therapy and society guidelines to do not recommend it's routine use in these infections[17].

Summary/Discussion

In summary, NSTI remains a disease with high morbidity and mortality, despite improvements in care. In the past several decades, our understanding of this disease process has improved such that we know 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 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[67]. 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.

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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 one debridement. Imaging can facilitate diagnosis and the decision to operate but 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 is 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 is 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 quality of life and is best reserved for use on a case-by-case basis.

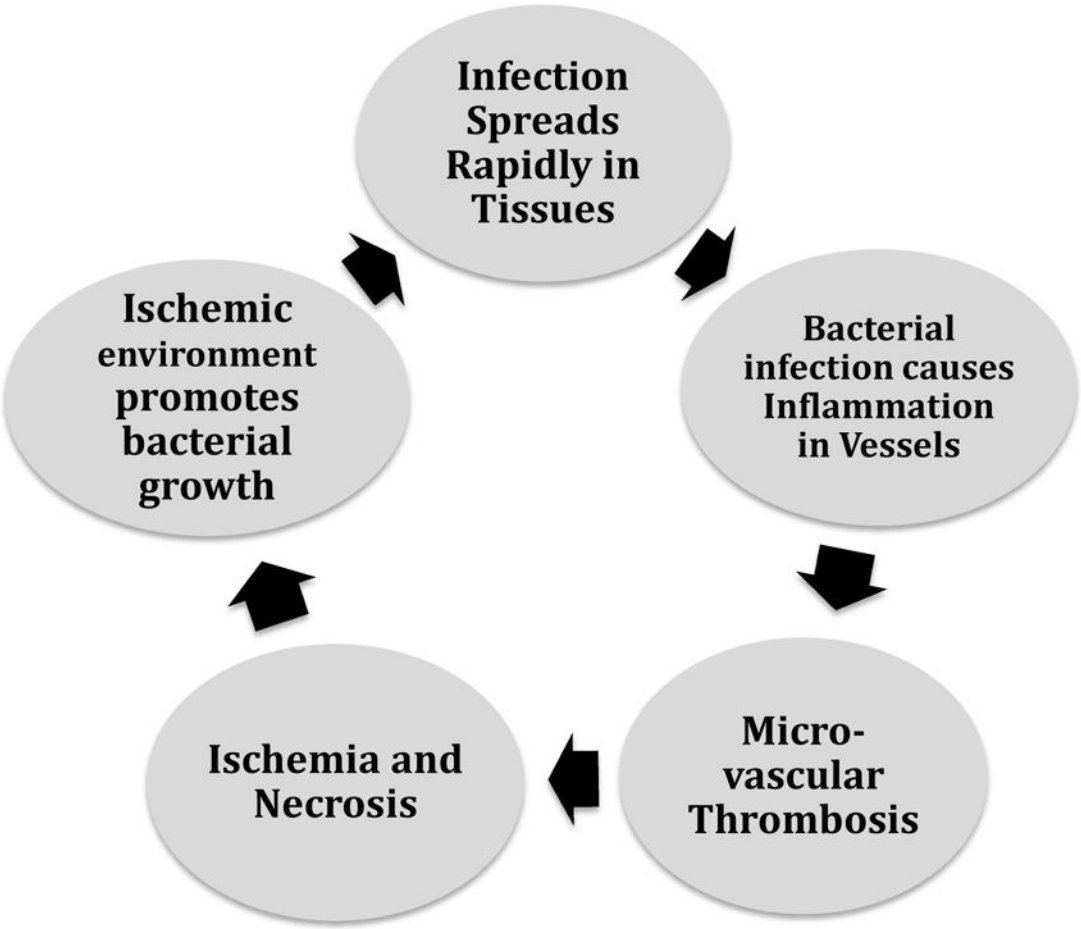
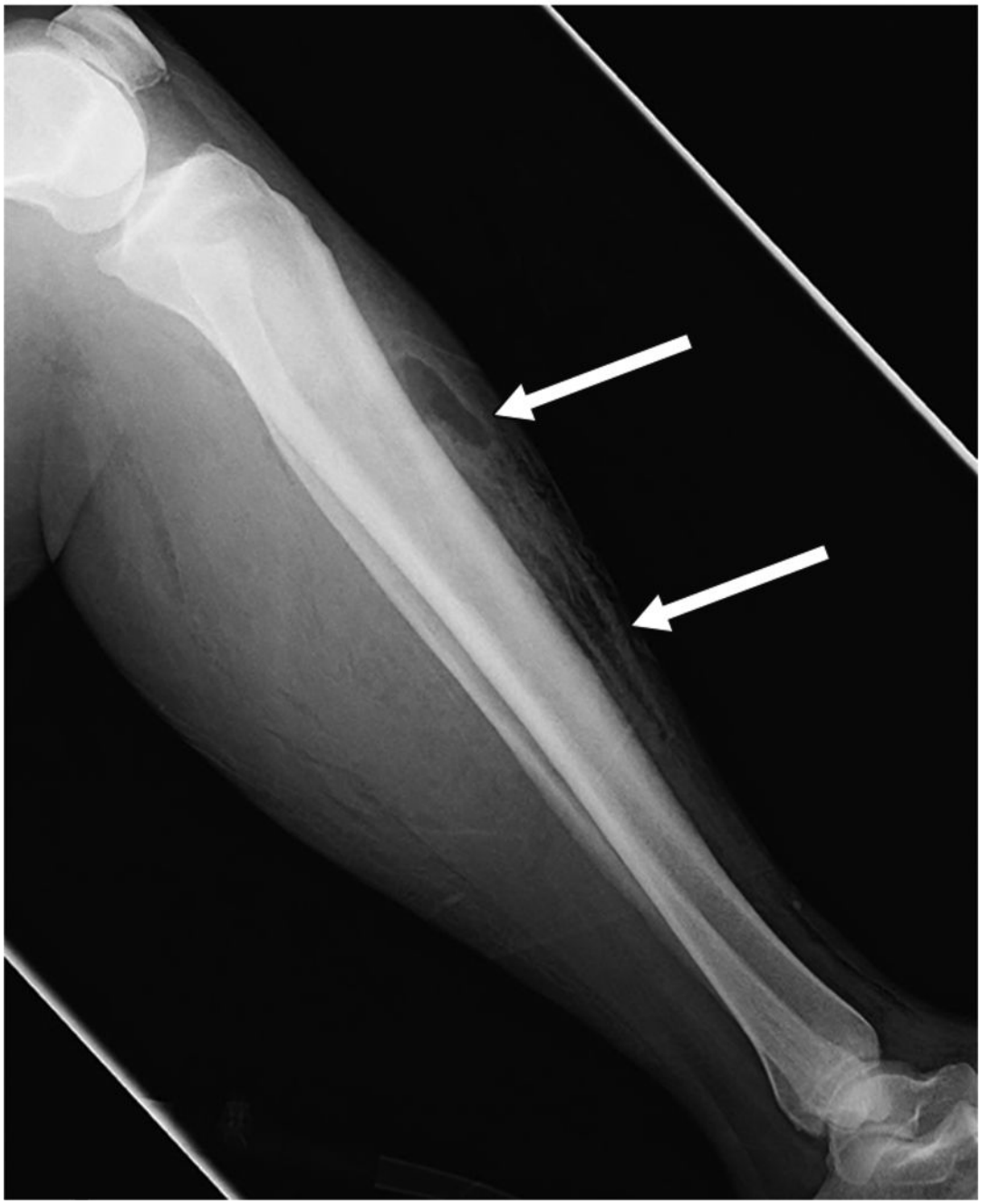


Figure 1.
Vicious cycle of necrotizing soft tissue infection

a



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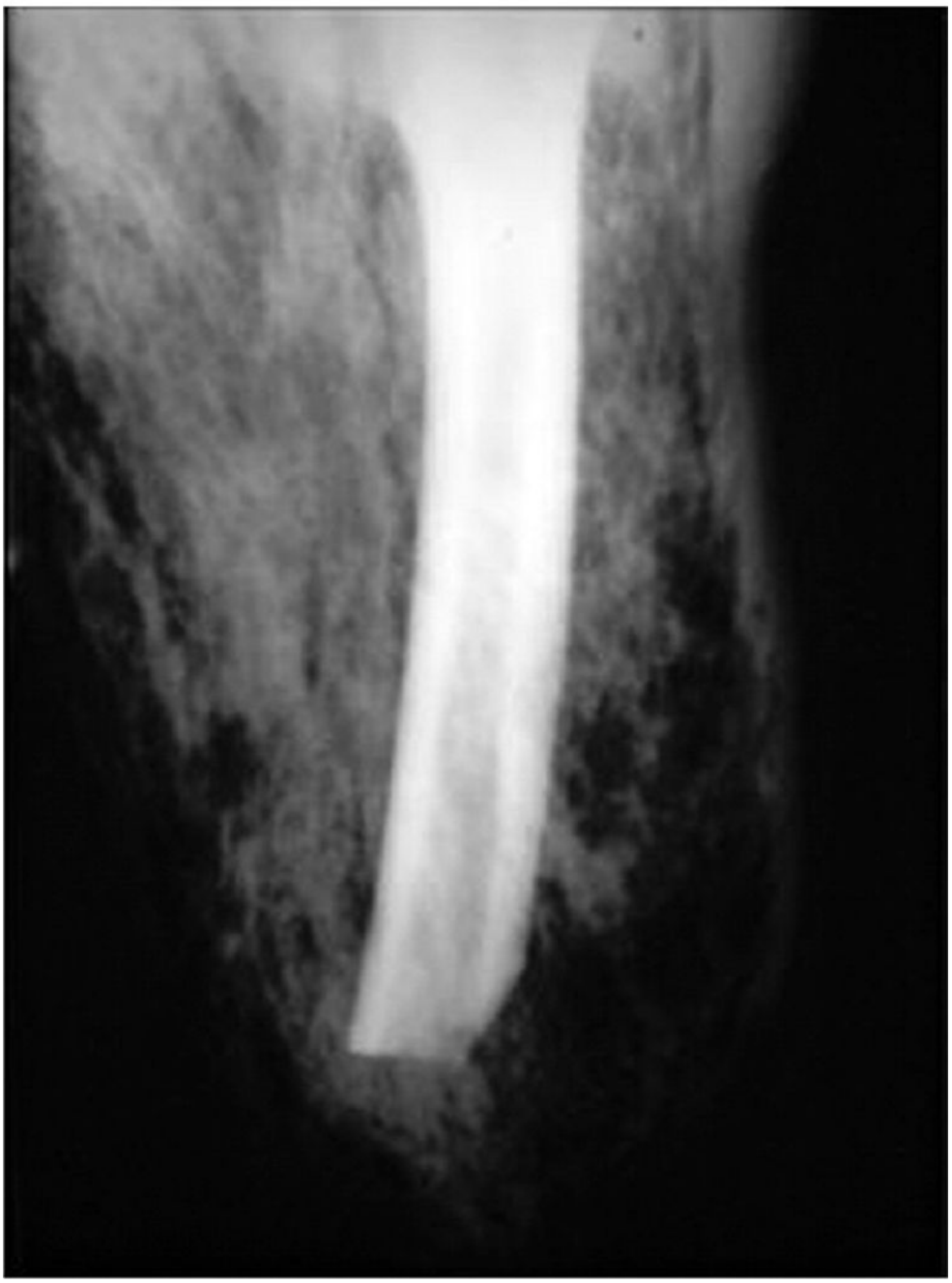

Figure 2.

a Evidence of Gas tracking on the fascia on X ray in a patients with NSTI involving the leg. [Used with permission]: Chaudhry A, Baker K, Gould E, Gupta R. Necrotizing Fasciitis and it's mimics: What Radiologists need to know. AJR 2015; 204: 128–139.

b Subcutaneous emphysema on X ray in a patient with NSTI of the thigh. [Used with permission] from Sarani B, Strong M, Pascual J, Schwab CW. Necrotizing Fasciitis: Current Concepts and Review of the Literature. JACS 2009; 208(2): 279–288.

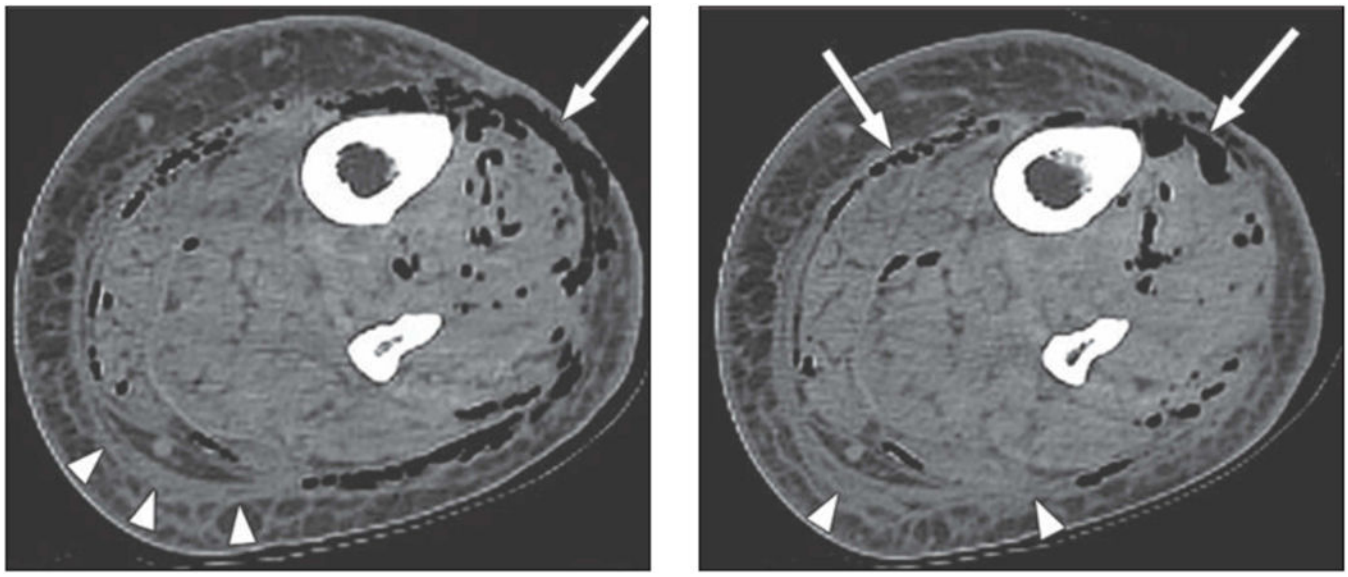

Figure 3.
CT scan of a patient with necrotizing soft tissue infection, demonstrating edema in the soft tissues and air tracking along the fascia planes. [Used with permission] : Chaudhry A, Baker K, Gould E, Gupta R. Necrotizing Fasciitis and it's mimics: What Radiologists need to know. AJR 2015; 204: 128–139.

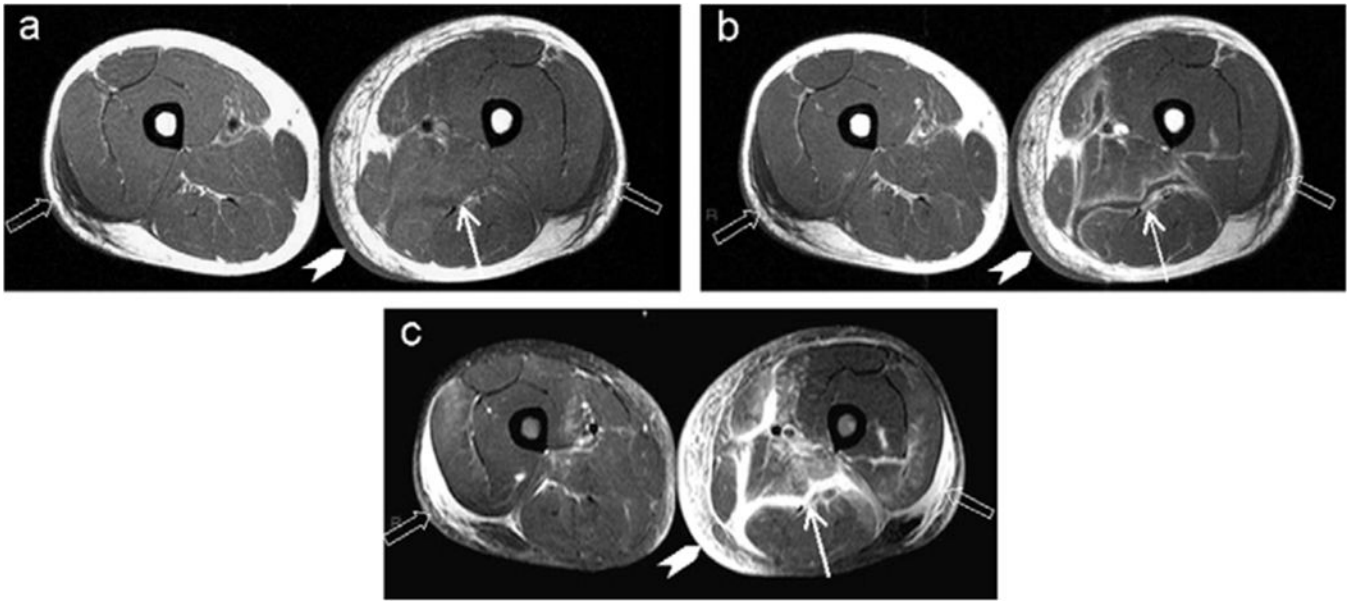

Figure 4.
MRI findings for a patient with necrotizing fasciitis and myositis, demonstrating increased T2-weighted soft tissue enhancement and gas in the soft tissues. [Used with permission:]

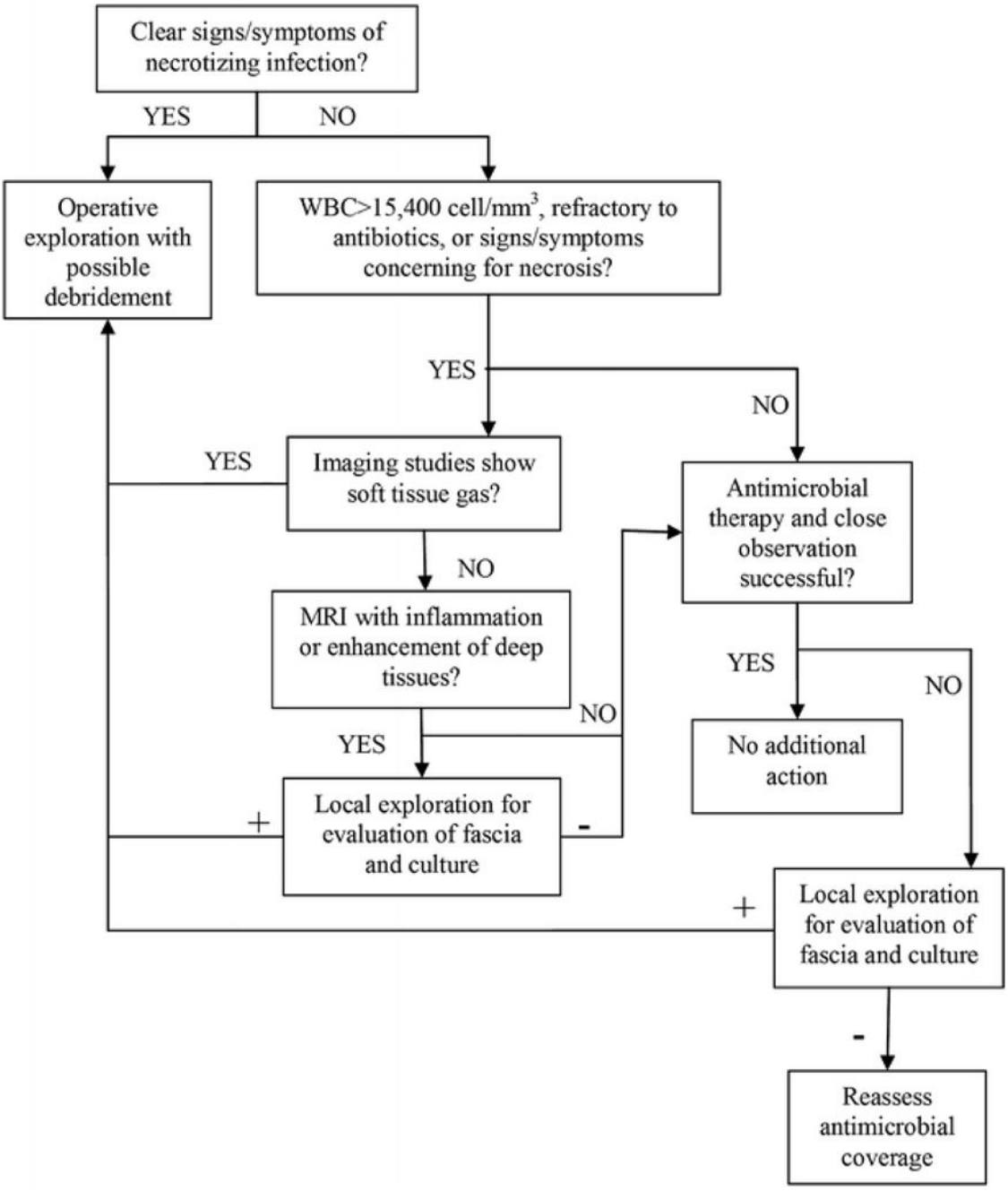

Figure 5.

Management pathway in NSTI. [Used with permission]. Original source: Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect* 2010;75:249–57.

Table 1

Microbiologic classification of necrotizing soft tissue infections

Types of NF	Etiology	Organism(s)	Clinical Progress	Mortality
Type I (70–80% of cases)	Polymicrobial/ 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.