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Necrotizing Soft Tissue Infections in the Vasculopathic Patient: Review of Literature

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Background: Necrotizing soft tissue infection is a surgical emergency associated with high mortality. Its presence in patients with risk factors for peripheral arterial disease such as diabetes mellitus is consistently associated with significantly poorer outcomes. Though it has been over a century since it was initially described in the literature, mortality rates remain high and treatment regimens are not standardized.

Materials and methods: PubMed and Cochrane databases were searched for articles pertaining to necrotizing soft tissue infections. Articles were screened for relevance with the intent to compare outcomes in prospective studies of patients with diabetes mellitus or peripheral arterial disease. Patient demographics, clinical findings, mortality, rates of amputation, and morbidity were intended to be compared.

Results: 857 articles were identified, 165 duplicates were removed, and 6 prospective trials were identified for inclusion. Due to significant paucity of data, patient heterogeneity, and lack of standardization for surgical management, a descriptive review of the literature in relation to necrotizing soft tissue infections was pursued, with a focus on high-risk patients with peripheral arterial disease or diabetes mellitus.

Conclusions: Early aggressive surgical intervention or major amputation may reduce mortality at the cost of increased disability and poorer quality of life in the long term, and may be appropriate in vasculopaths with poorly controlled diabetes and rapidly progressive fulminant infection. However, there is a deficiency in high-level evidence supporting surgical decision-making in this setting, with no standardized protocols for amputation. Future research will be needed to clarify the patient population who would benefit from radical amputation versus intention for limb salvage.

Key words: Necrotizing soft tissue infection – Diabetes mellitus – Peripheral arterial disease – Vasculopathy – Amputation – Necrotizing fasciitis

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Necrotizing soft tissue infections (NSTIs) are a spectrum of severe infection characterized by tissue necrosis and systemic toxicity with associated high morbidity and mortality rates.[1] Its existence has been recorded since the time of Hippocrates in the 5th century B.C.,[2] and was first studied in modern literature in 1924 by Meleney.[3] Despite advances in modern medicine and surgery, the mortality rate of NSTIs is high, with up to 21.9% reported in a recent systematic review.[1] Management of this condition is not well standardized, and diagnosis remains challenging especially in certain populations such as the immunocompromised, diabetics, and those with peripheral arterial disease.[4] Not surprisingly, it is these same groups who have been consistently plagued with higher mortality and incidence of major amputations.[1] This paper will review the basic pathophysiology of this condition, summarize current research and management guidelines, as well as explore avenues for future endeavors focusing on patients with peripheral arterial disease and diabetes mellitus.

Definitions

With the first recorded case dating back to Hippocrates in the 5th century B.C., NSTIs comprise a spectrum of rare life-threatening infections characterized by rapidly spreading necrosis of skin, subcutaneous tissue, fascia, and or underlying muscle, usually accompanied by rapid development of systemic toxicity. It is often preceded by some degree of trauma or result from hematogenous dissemination of pathogenic microorganisms,[1,4] and is associated with chronic conditions including diabetes mellitus, renal impairment, alcohol abuse, and immunocompromised states.[4,5]

Vasculopathy is commonly referred to as diseases affecting blood vessels including degenerative, inflammatory, metabolic, and other disorders.[6] For the purposes of this review, we have limited our scope to peripheral arterial disease secondary to atherosclerosis, which is a commonly identified risk factor associated with NSTIs, as well as a poor prognostic indicator for major amputation and mortality.[1]

Epidemiology

NSTI is a relatively rare condition with global annual incidence of approximately 0.4 cases per 100,000 patients.[1,7–9] There is a slight male preponderance with a male:female ratio of 1.4:1, with a mean age of 56.3 years.[10] Rare pediatric cases have occasionally been studied.[11,12] The lower extremities are the most commonly affected sites,[10] although NSTIs of the hands and upper limbs certainly occur.[13,14] NSTIs of the abdomen and perineum occur less frequently.[1] The condition is often preceded by trauma, with scald burns,[15] stab wounds,[16] or iatrogenic surgical sites[17,18] all being reported in the literature. The degree of trauma may be trivial in nature,[19,20] or significant with subsequent massive microbial contamination.[21,22] In a minority of cases, spontaneous occurrence of NSTI without the presence of identifiable risk factors also can occur.[23]

NSTI appears to more commonly affect individuals with significant chronic health issues.[24] Most common comorbidities include diabetes mellitus,[4,25–28] immunocompromise,[29–31] peripheral arterial disease,[30,32] obesity,[28,33] chronic liver disease,[7,34,35] malignancy,[32,36,37] and organ transplantation.[38–40] Otherwise healthy individuals developing NSTIs triggered by elective medical procedures,[41] medication injections or vaccinations,[42,43] or minimal trauma[20] have also been reported.

Although NSTIs most frequently afflict middle-aged to elderly individuals with a number of comorbid conditions, rare cases in the pediatric population have also been reported in the literature.[12,44,45] Extremely rare pediatric cases with hereditary sensory and autonomic neuropathy[46] and congenital syndromes characterized by insensitivity to pain[47] have been described, but the vast majority of cases are in otherwise healthy children.

Classification

NSTIs may be classified based on microbiology as polymicrobial or Type I accounting for the large majority of cases, monomicrobial or Type II comprising one-third of cases, with the rest involving Gram-negative marine species or Type III, and fungal or Type IV.[7–9] The most common organism isolated in Type II infections is Group A beta-hemolytic streptococci.[4,7,48] Diabetes is highly associated with polymicrobial infections.[49,50]

Pathophysiology

NSTI is usually preceded by localized trauma or other pathologic condition allowing microbial access to superficial fascia,[48,51] although the etiology may be idiopathic in more than one-third of cases.[52] In the extremities or trunk where fibrous attachments between subcutaneous tissues and fasciae that may potentially limit the spread of infection are lacking, microbes readily invade and propagate along fascial planes. Bacterial proliferation and expression of enzymes such as hyaluronidase and lipase lead to liquefactive necrosis of the superficial fascia.[4,32] Bacterial endotoxins and exotoxins elicit cytokine release that sustains a significant inflammatory response.[52] Spread of infection along fascial planes causes thrombosis of penetrating vessels and skin ischemia.[32] Initial cutaneous manifestations may be nonspecific and relatively unremarkable with erythema, edema, warmth, and tenderness. Progressive ischemia causes epidermal necrolysis characterized by blistering and bullous eruption. Crepitus may be present due to gas-forming bacteria. The skin eventually exhibits ulceration, necrosis, and gangrene.[4] Extensive inflammatory response often results in septic shock, multi-organ failure, and eventually death.[52] An exception to skin breach can occur in the perineum as well as head and neck regions. In the special case of Fournier's gangrene, NSTI can be initiated by a breach of the lower gastrointestinal or urethral mucosa.[53] In the neck, NSTI can be due to oropharyngeal mucosa breach or associated with dental instrumentation.[54]

Prognosis

NSTI is associated with high morbidity and mortality. Despite aggressive surgical and multidisciplinary management, overall mortality has been estimated to be approximately 20%.[1,8] There is also consensus on the significant morbidity with large retrospective studies reporting mean length of hospital stay of 28 days, with a large standard deviation observed.[26] Clinical factors including advanced age, significant renal impairment, poor white blood cell response, low hemoglobin, and delay to surgical intervention have all been associated with increased mortality in various studies.[25,33,55,56]

Methods

In April 2019, 2 authors independently searched PubMed and Cochrane databases for articles pertaining to NSTIs using the same MESH term (Appendix A). All articles were screened for relevance to NSTI with the intent to compare mortality rates in prospective studies of patients with a diagnosis of diabetes mellitus or peripheral arterial disease. Intervention was intended to be early amputation (less than 3 days from presentation) versus limb salvage. Patient demographics, clinical findings, mortality, and morbidity outcomes were intended to be compared.

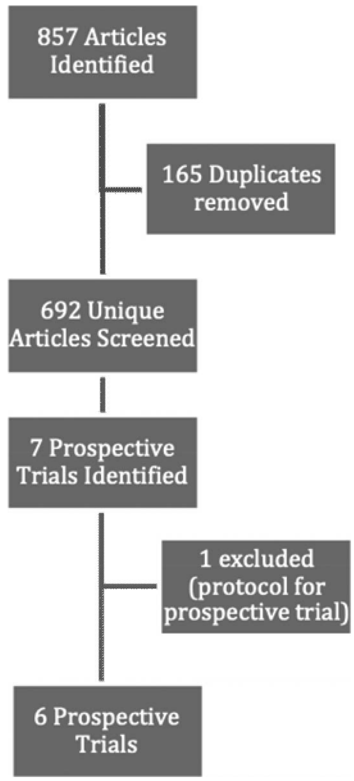

Fig. 1 Summary of study selection.

Results

A total of 857 articles were identified, 165 duplicates were removed, and all abstracts were screened for relevance. Further, 7 prospective trials were identified for inclusion. Just 1 study was excluded as it was a protocol for a prospective trial leaving 6 prospective studies with a Cohen's kappa of 1 (Fig. 1). A list of all prospective studies is included in Table 1.

Of the 6 relevant prospective studies, only 2 exclusively studied NSTIs, with the largest dataset focusing on the biochemical markers relevant to NSTIs. The other 4 studies had a combined total of 80 patients with NSTI within their patient population. No study focused on NSTI in those with diabetes mellitus or peripheral arterial disease. None of the 6 prospective trials specified the intervention undertaken for patients with a diagnosis of peripheral arterial disease or diabetes mellitus.

Table 1 Summary of prospective studies

Author	Year	Total N	Percentage of diabetics or PAD	Gender (% male)	Mean Age	Treatment	Key outcomes
Bahebeck[89]	2010	56	100% were diabetic	68% $N = 38$	70 (range 51–86)	Debridements or minor amputation VS major amputation	Mortality of 9% overall; 48% required major amputation
Aziz[27]	2011	100	100% were diabetic	51% $N = 51$	60 (range 21–91)	Conservative management VS debridements or minor amputation VS major amputation	Peripheral arterial disease, low hemoglobin and high white cell count increased risk of limb loss
Espandar[60]	2011	24	29% were diabetic, 4% had diagnosis of peripheral arterial disease	75% $N = 18$	50 (SD 16.1)	Repeated debridements VS major amputation	Mortality of 21% overall; diabetes increased gangrene and limb loss; hyponatremia and hyperkalemia predicted severe infection
Hansen[52]	2017	294; 135 in Studies I & II, 159 in Study 3	Not specified	Not specified	Not specified	Debridements VS major amputation	Pentraxin-3 is significantly greater in those needing amputation and is a marker of disease severity and mortality
Sirikurnpiboon[63]	2017	164 total; 61 patients had necrotizing fasciitis; 103 had cellulitis	33% of necrotizing fasciitis group were diabetic, 19% of cellulitis group were diabetic	50% $N = 82$ overall; 57% $N = 35$ for necrotizing fasciitis; 46% $N = 47$ for cellulitis	55 (SD 18) overall; 56 (SD 18) for necrotizing fasciitis; 55 (SD 18) for cellulitis	Medical management VS debridements VS major amputation	LRINEC score > 4 is a reasonable predictor of necrotizing fasciitis as opposed to cellulitis in those with symptom duration > 8 hours; diabetes mellitus predisposed one to develop necrotizing fasciitis compared to cellulitis
Sharma[49]	2018	322	24% were diabetic	65% $N = 209$	54 among diabetics, 37 among non-diabetics	Single drainage VS repeat drainage VS amputation	Diabetes predisposes to necrotizing fasciitis, causes deeper and more proximal infections and increases need for repeat drainage and amputation

PAD, peripheral arterial disease.

Due to significant paucity of data, heterogeneity in patient population, and a lack of standardization for surgical decision-making, a decision was made to pursue a descriptive review of the literature.

Discussion

Timely diagnosis remains difficult

The gold standard for definitive diagnosis of NSTIs remains tissue biopsy performed during surgical exploration and debridement.[57] Tissue integrity and depth of infection can be determined intraoperatively, with findings of "dishwater" pus, gray necrotic fasciae, lack of resistance to blunt dissection of the superficial fascia, myonecrosis, and lack of bleeding on fascial dissection indicative of necrotizing infection.[1,4] Some have described a bedside finger test for diagnosis involving a deep incision down to deep fascia under local anesthesia. This is followed by probing with a finger, with a positive result being lack of resistance to finger dissection, release of "dishwater" pus, and lack of bleeding.[58]

Despite this, clinical judgment remains the most paramount aspect of initial assessment and diagnosis as the prompt recognition and treatment of NSTIs are vital in reducing morbidity and mortality.[59] Thorough clinical examination for sources of sepsis and a low threshold of suspicion for this condition are essential.[5,60] Erythema, warmth, edema, woody induration, pain, and fever may be early signs and can be nonspecific.[51,60] Pain out of proportion and a toxic appearance may be the only distinguishing features at an early stage.[4,8,32] Bullae, skin necrosis, crepitus, fluctuance, purulence, and systemic manifestations with tachycardia, hypotension, and shock may occur later.[1,7] Subcutaneous emphysema may be appreciated on plain radiographs in one-third of patients,[7] but it may not reveal specific findings until the necrotizing process is quite advanced.[51] Magnetic resonance imaging findings may include thickening of subcutaneous tissues, fluid collections, and high signal intensity in deep fascia in T2-weighted images; but its specificity may be low.[51] Adjunctive imaging may potentially delay surgical intervention; therefore, a thorough physical examination is often more important in reaching the correct diagnosis.[51]

Early diagnosis may be complicated by paucity of cutaneous findings.[55] Vague and wide-ranging complaints including skin lesions, subjective fevers, changes in mentation, and gastrointestinal symptoms.[10] There also may be overlapping signs with other clinical entities, such as cellulitis, further complicating the picture.[4] Failure to respond to initial antibiotic therapy, systemic toxicity with altered mentation, bullous lesions, and the presence of skin necrosis may help distinguish between simple cellulitis and more sinister NSTIs.[61] Accurate diagnosis in early stages is even more challenging in patients with diabetes mellitus.[50,60] Diabetic patients tend to present more atypically with less tenderness or hypotension, leading to greater rates of misdiagnosis.[50] Delay to diagnosis also tends to be greater in diabetic patients, with a longer time to surgical intervention and greater lengths of hospitalization.[50,60]

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) has been developed as a scoring system to facilitate diagnosis. It incorporates white blood cell count, hemoglobin, C-reactive protein, sodium, glucose, and creatinine for score computation.[5,60] Scores of ≥ 8, ≥ 6, and ≤ 5 are categorized as high, intermediate, and low risk of NSTIs, respectively.[62] A recent prospective study showed that among patients with duration of symptoms >8 hours, a cutoff score of >4 was reasonably effective in distinguishing necrotizing fasciitis from simple cellulitis, with sensitivity of $\sim$85% and specificity of $\sim$75%.[63] Narasimhan *et al* demonstrated that LRINEC is a robust and easily performed adjunct to aid clinical diagnosis of necrotizing fasciitis.[64] Another retrospective analysis of patients argued that LRINEC is a useful tool for risk stratification and prognostication.[65] Some retrospective studies have found correlations between the score and risk of amputation or mortality,[66,67] whereas other retrospective analyses have not demonstrated an association between LRINEC score and clinically meaningful outcomes.[8,68–70] Hence, clinical acumen and judgment are of critical importance regardless of the score;[52,71] a low LRINEC score should not prevent prompt surgical intervention in the presence of clinical suspicion.[8] LRINEC scoring has been found to be more sensitive among diabetic patients for diagnosing NSTIs, but can be less specific as hyperglycemia and accompanying renal impairment may produce a falsely elevated result.[50] LRINEC hence should be used with extra caution when diagnosing necrotizing fasciitis in diabetic patients.[50]

Diabetes mellitus and peripheral arterial disease are major risk factors

Diabetes mellitus is a disorder of insulin secretion or action and increases susceptibility to various infections through its detrimental effects on neutrophil function, T-cell response, and humoral immunity.[72] Hyperglycemia induces bacterial overgrowth[73] while it simultaneously impairs recruitment, chemotaxis, and phagocytic function of polymorphonuclear cells, and promotes their apoptosis.[74] Production of pro-inflammatory cytokines such as interleukin-1 and interleukin-6 by mononuclear cells in response to foreign antigens such as lipopolysaccharides is also reduced. The complement system is important in mediating opsonization and phagocytosis of microorganisms, as well as activating B lymphocytes and promoting production of immunoglobulins. Diabetes mellitus has been associated with C4 deficiency, possibly secondary to polymorphonuclear cell dysfunction and blunted cytokine response.[75] In addition, glycation of immunoglobulins occurs in diabetes mellitus and may also impair humoral immunity.[74] Secondary complications such as diabetic neuropathy and microangiopathy impair tissue healing and increase skin breakdown, thereby providing a port of entry for bacteria and further increasing infection risk.[76] Decreased production of neuropeptides such as substance P and nerve growth factor that normally promote recruitment and chemotaxis of immune cells may contribute to poor wound healing in diabetic neuropathy.[77]

Diabetes mellitus is the predominant comorbid medical condition among patients with NSTIs.[1,4,48] A prospective study has found that rates of gangrene, limb loss, and amputation in necrotizing fasciitis are significantly greater among those with comorbid diabetes mellitus, and hence suggests that a lower threshold of amputation would be appropriate in this subset of patients.[60] Similarly, Khamnuan *et al* conducted a large-scale retrospective study of patients with necrotizing fasciitis and found that diabetes mellitus is a significant predictive factor for amputation and limb loss.[73] In addition, Cheng *et al* and Leiblein *et al* had also shown through their retrospective studies that diabetes mellitus is associated with a much higher risk of amputation.[8,78] On the contrary, some other retrospective studies have not been able to demonstrate that diabetes mellitus dramatically increased rates of amputation or mortality in NSTIs.[26,79,80]

Peripheral arterial disease refers to occlusive arterial disease to the limbs, causing inadequate blood flow usually due to underlying atherosclerosis. It may progress from intermittent claudication to critical ischemia. Diabetes mellitus contributes to peripheral arterial disease by significantly accelerating atherosclerosis via various mechanisms in large and smaller caliber vessels.[76] Due to reduced blood flow and thickening of capillary membranes from increased resting pro-inflammatory cytokines and vascular inflammation, influx of immune cells, nutrients, and oxygen to the site of infection are diminished in the presence of concomitant peripheral arterial disease, thereby sabotaging host defense and wound healing.[76] A retrospective study has identified peripheral arterial disease as a significant risk factor for mortality in necrotizing fasciitis, and argued that patients with this comorbidity would benefit from early and primary amputation.[81]

These aforementioned mechanisms are thought to result in the clinical manifestation that those with concurrent peripheral arterial disease and diabetes mellitus are faced with a high risk of failure from medical and surgical management of NSTIs.[4,8,51,60,73] Antibiotic use in diabetics is associated with the requirement for longer durations of therapy and higher incidence of treatment failure.[73] The sole recent systematic review of trials in NSTIs has shown an underlying diagnosis of diabetes mellitus or peripheral arterial disease to be associated with a higher risk of mortality and major amputation.[1] These mechanisms again are multifactorial but are primarily believed to be driven by poor macrovascular and microvascular circulation for healing and impaired response to infection and wound healing.[76]

Although there are review articles and guidelines on diabetic wound management in the literature,[82,83] the authors of this paper are unaware of well-defined evidence-based guidelines on the management of NSTIs specific to patients with diabetes mellitus or peripheral arterial disease. Future studies focusing on this unique high-risk subgroup of individuals developing NSTIs should be sought to better delineate management.

Time to surgical intervention is critical

Although clinical measures including timely broad-spectrum antibiotic therapy, resuscitation, and intensive care review are critical, surgical intervention remains the mainstay of care for patients presenting with NSTIs.[84] Despite being frequently used in the literature, the exact definitions of "adequate debridement" or "aggressive surgical intervention" are not clearly characterized; although conventional practice would mandate resection of all devitalized or nonviable tissues.[84] Hence, the exact degree of debridement would ultimately remain the decision of the surgeon.[33] Frequent evaluation of the wound followed by repeated surgical exploration and debridement to assess disease progression and ensure removal of all necrotic tissue are essential to optimize outcomes.[1,7,8] The average number of surgical debridements reported in the literature is 3 to 4.[85,86] Early wound closure is associated with risk of residual bacteria and hence the wound is left open to dressing changes and eventual skin grafting post-infection clearance.[1]

Multiple studies have suggested that delays in operative intervention usually increase mortality and worsen outcomes.[15,29,55,81] Time to surgery has been shown to be an independent predictor of better outcomes in large studies.[85,87] In addition to greater mortality, delay to surgical intervention also increases the number of repeat explorations required, amount of total tissue loss, degree of long-term functional disability, and overall financial cost.[86,88] Interestingly, some retrospective studies have not demonstrated a statistically significant difference in mortality or length of stay between early and delayed (>12 hours) surgical intervention, possibly due to arbitrary definition of delayed surgical intervention in relation to disease severity and small sample size.[7] In addition, some retrospective studies have proposed a reduction in mortality in unstable patients presenting with *Vibrio* necrotizing fasciitis receiving a conservative temporizing incision under regional anesthesia followed by definitive debridement compared to initial aggressive debridement under general anesthesia.[35] However, the applicability of this result to patients with necrotizing fasciitis secondary to other organisms without septic shock on presentation is yet to be determined.[35]

Early amputation versus debridement in limb NSTIs

Surgical management of extremity NSTIs involves debridement and or amputation. In the lower limbs, below-knee or above-knee amputations that involve the tibia or more proximal tissues are regarded as major amputations, whereas those involving the only the foot are minor.[27,89] Patients who have only undergone debridements, incision and drainage, or minor amputation are usually classified as having had successful limb salvage.[27] Amputation can be primary when performed within 3 days of admission, or late when it is executed beyond that time frame.[81]

Overall, approximately 20% of patients with necrotizing fasciitis undergo major amputation or incur limb loss,[1] although this figure is higher in developing countries.[89] Various studies have attempted to delineate clinical or biochemical factors associated with higher mortality and argued the need for early amputation in these high-risk groups. Espandar *et al* highlighted in their prospective study that biochemical markers including hyponatremia, hyperkalemia, and increased band cells to indicate life-threatening necrotizing fasciitis, and hence lower threshold to consider amputation.[60] Large retrospective studies have demonstrated that the presence of hemorrhagic bullae, peripheral arterial disease, LRINEC score of greater than 8, and bacteremia are all independent significant risk factors for increasing mortality and that early primary amputation should be pursued in these groups.[81] Similarly, Schwartz *et al* illustrated in their retrospective study that increased arterial lactate and reduced serum sodium to be significant predictors of amputation and mortality.[90] Elevated creatinine and presence of hypotension have also been linked to severe infection and increased mortality.[91] Another study on *Vibrio* necrotizing fasciitis has established a significant association between severe hypoalbuminemia and mortality and major amputation, and found increased alanine transaminase, aspartate transaminase, and creatine kinase in patients who had amputation or died from the infection, arguing that these could be used as biomarkers of muscle damage and to help determine the optimal time for amputation.[71] In addition, elevated pentraxin-3 but not procalcitonin or C-reactive protein has been recently identified as a potential biomarker that correlates significantly with mortality and amputation.[52] In contrast, procalcitonin was found to be significantly greater in patients eventually requiring a below-knee or above-knee amputation compared to more distal amputations.[92]

Patients requiring amputation are almost 4 times as likely to have comorbid diabetes mellitus than those who do not, and also command a much higher mortality rate, close to 50%.[7] Diabetes mellitus often increases the diagnostic difficulty and has been shown to increase the chance of limb amputation.[8,49,60] Diabetes mellitus tends to cause atypical presentation, leading to greater rates of misdiagnosis, increased delays to surgery, higher risk of limb loss, and longer duration of hospitalization.[50] Diabetes mellitus is also associated with more proximal and deeper infections, as well as increased need for re-operation; the latter appearing to be only associated with inpatient glycemic control but not baseline control or HbA1c.[49]

A review article of necrotizing fasciitis has recommended pursuit of early amputation as opposed to serial debridements aiming at limb salvage in cases of significant cardiorespiratory disease and poorly controlled diabetes that would confer increased anesthetic risk from multiple operations, peripheral arterial disease, shock, and rapidly progressive infection.[4] Bahebeck *et al* had demonstrated in their prospective study that amputation may reduce mortality in severe diabetic foot infections.[89] Similarly, another prospective study on diabetic foot infections including necrotizing fasciitis has found a strong correlation between reduced ankle-brachial index (<0.8) and older age (>60 years) with limb loss or amputation. Biochemical markers including raised white blood cell count, high C-reactive protein, reduced hemoglobin, and elevated creatinine are also shown to be significant predictors of limb loss in diabetic foot infections and hence may signal severe disease.[27] Similarly, a retrospective study identified diabetes mellitus, soft tissue necrosis and gangrene, and elevated serum creatinine on admission to be significant independent predictors of amputation.[73] Nevertheless, another retrospective study by Lauerman *et al* at a high volume center has found no association between amputation and mortality, implying that aggressive use of limb salvage may not be at the expense of worse outcomes.[93] However, this may be due to the fact that it was a single-institution retrospective study with a limited patient sample size, and did not specifically review high-risk groups such as diabetics or vasculopaths. Interestingly, a retrospective study on *Vibrio* necrotizing fasciitis patients with septic shock proposed an alternative treatment regimen with conservative incision under regional anesthesia to decompress tissues, improve perfusion, and provide drainage followed by definitive debridement 24 hours later, and has demonstrated better mortality from this regimen than primary aggressive debridement or amputation.[35] As a result, they argue given poor 5-year survival data among patients undergoing major amputation often around 30% to 40%, it may be more prudent to pursue conservative incision for patient stabilization followed by definitive debridement, both from a mortality and from a limb salvage perspective.[35]

The literature generally supports that patients with shock, rapidly progressive infection, vasculopathy with poorly controlled diabetes, and concurrent chronic medical conditions conferring a high anesthetic risk may benefit from amputation compared to limb salvage, and the optimal treatment pathway needs to be individualized to each patient.[4] It is reasonable that those without evidence of shock or are responsive to inotropic support and resuscitation, and are previously in good health may trial limb salvage therapy initially.[4] A multidisciplinary approach involving comprehensive evaluation of clinical factors, and discussion with patient and family regarding the risks and benefits of different forms of surgical management are likely to lead to best outcomes. Case reports in the literature where various surgical and medical teams were involved early in patient management have been shown to contribute to higher rates of limb salvage, as well as reduce overall morbidity and mortality.[94]

Amputation is not without risk and carries morbidity that should be considered. There is paucity of long-term data in patients with NSTIs who have undergone major amputation. The best available evidence for outcomes associated with amputations comes from a prospective study by Eneroth *et al*, who described a 6-month mortality of one-third of 177 patients with peripheral arterial occlusive disease.[95] The authors recognize that studies such as this may not be generalizable to patients who underwent major amputation for NSTIs, but it is clear that from a rehabilitation perspective, research shows worse rehabilitative and functional outcomes for above-knee amputation compared to below-knee amputation.[96]

The management of head and neck, thoracoabdominal, and perineal NSTIs is outside of the scope of this review but follows similar principles of timely multidisciplinary surgical, medical, and intensive care interventions.

Medical and adjunctive treatment of NSTIs

A multidisciplinary approach is critical for optimizing outcomes in NSTIs.[7,89] In NSTIs, prompt diagnosis, appropriate antibiotic therapy, and early surgical intervention are essential in maximizing survival and limb salvage.[4,81,91,97] Blood transfusion, dialysis, inotropic support, and intensive care unit admission are frequently required to treat complications.[8,48] Data on diabetics and patients with peripheral arterial disease remain sparse but an analysis of 122 patients presenting to the emergency department in an urban California hospital showed a median time from presentation to administration of antibiotics in necrotizing fasciitis was 200 minutes.[91] Given that there is well-supported data for time-dependent increased mortality with increasing time to administration of antibiotics in sepsis, it can be inferred that delays to antibiotic treatment of NSTIs may have similar consequences.[98] A mean administration time of 200 minutes represents a significant delay and further highlights the importance of early accurate diagnosis.[91] Antibiotic therapy should be guided by the likely responsible organisms and local patterns of susceptibility, but in general, empirical broad-spectrum antibiotics should be given to cover Gram-positive cocci, Gram-negative rods, and anaerobic species.[1,4,29,97]

A number of adjunctive therapies have been trialed with variable success including negative pressure dressings, hyperbaric oxygen, muscle flaps, skin grafting, and other advanced wound dressing technologies.[99] Some of these will be discussed in the following section on reconstructive considerations. Evidence for these therapies is not robust, and is lacking especially for diabetics and those with peripheral arterial disease. Nevertheless, in the realm of negative pressure therapy, a small retrospective study of 11 patients with NSTIs shows some promise.[59] Baharestani *et al* demonstrated continuous negative pressure wound therapy until reconstructive wound closure post-limb-preserving debriding surgery had high success rates in wound closure and patient survival.[59] Various dressings have been trialed with a recent report of success with the use of Nanoflex powder, which the authors found reduced exudate production and acted as a platform to deliver analgesics, antibiotics, and angiogenic agents.[100]

Level III evidence exists for the use of hyperbaric oxygen in NSTIs.[32,101] There has been promise shown by Escobar *et al*, and Wilkinson *et al* in this area with retrospective cohort studies demonstrating significant improvement on short and long-term survival as well as rates of limb salvage compared to the standard treatment regimen with as much as an odds ratio of 8.9 of survival to hospital discharge.[32,101] However, other studies have not corroborated this result and have argued that hyperbaric oxygen therapy may delay surgical intervention and worsen outcomes.[4] Studies that have not illustrated benefit of hyperbaric oxygen in reducing mortality or amputation attributed this to low sample size and the retrospective nature of most similar studies.[102] Intravenous immunoglobulin has also been shown by some to reduce mortality in necrotizing fasciitis, possibly via neutralizing superantigen activity of Group A streptococci, thereby ameliorating cytokine release.[4] Intravenous immunoglobulin may reduce mortality associated with streptococcal toxic shock syndrome, but its benefit has not been generalizable to all patients.[4]

Reconstructive considerations

The initial surgical management for sepsis control should not compromise adequate excision margins for reconstructive purposes, and serial debridements may be necessary before reconstructive considerations.[103] This is because NSTI is a rapidly progressive infection that often requires multiple debridements to ensure thorough excision of necrotic tissue, which remains as a nidus of infection if left in situ.[1] Reconstructive considerations should occur as soon as the patient is hemodynamically stable and sepsis control has been achieved.[103] Modalities for wound coverage include primary closure, secondary closure, or complex reconstructions that may involve free flap transfer.[99]

Although small wound areas may heal spontaneously via epithelialization, major wounds may require application of skin grafts to promote adequate closure of healthy healing tissue.[104] Skin substitutes such as Integra and skin grafts also can be used, which offers coverage of wounds, promotion of wound healing, and reduction of risk of infection.[99,105]

Vacuum-assisted closure (VAC) therapy has been demonstrated to be effective in managing nonhealing wounds in a systematic review of NSTI wounds.[1] The caveat is that some clinicians have recommended against the use of VAC until anaerobic infection has been excluded and wound has been cleaned by thorough repeated debridements.[8] Hyperbaric oxygen has also shown some promise.[32] Hyperbaric oxygen therapy places patients in environments with increased ambient pressure while inhaling 100% oxygen, thereby increasing oxygenation of arterial blood, promoting bacteriostasis of anaerobic species, and also improving neutrophil function.[4,32,102] Once infection is cleared, hyperbaric oxygen may also promote angiogenesis and collagen lay-down, thereby facilitating wound closure.[32]

In more complex wounds, free flap reconstruction is also an option.[103] Modern free flap reconstruction offers the ability to facilitate defect repair with a combination of cutaneous, fasciocutaneous, muscle-only, myofasciocutaneous, and or bony transfer from local or distant sites to defects but may be limited by the defect's vascular perfusion.[103,106] However, a recent retrospective study by Lauerman *et al* on 124 patients in a high-volume center has not found additional mortality benefit with use of advanced wound management techniques beyond skin grafting or secondary intention healing.[93]

Nevertheless, isolated case reports, such as one by Yuen *et al*, describe successful limb salvage of necrotizing fasciitis affecting the hand that requires multiple soft tissue debridements that subsequently repaired with rectus muscle flap and delayed skin grafting, with successful preservation of hand tendons and limb function.[14]

There have certainly been myriad case reports citing limb salvage in various complex patients including those with immunosuppression.[37,39,40] Although the reproducibility of these case reports is yet to be verified in larger prospective trials, it remains a tantalizing option in cases where limb preservation is appropriate.

Conclusion

NSTIs represent a surgical emergency where prompt serial debridements are recommended for the best outcomes. Although radical surgical intervention and amputations may reduce mortality in select patients, it may also come with the caveat of increased disability and poorer quality of life in the long term; hence, there is yet no standardized clinical protocol in relation to amputation. Nonetheless, radical surgical measures including major amputation should be considered in those with poor underlying comorbid states such as diabetes mellitus presenting with septic shock. Future research will be needed to clarify the patient population who would benefit from radical amputation versus intention for limb salvage.

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APPENDIX A: PubMed MESH Search Terms

("Fasciitis, Necrotizing"[Mesh] OR "necrotizing fasciitis" OR "necrotising fasciitis" OR "necrotising soft tissue infection*" OR "necrotizing soft tissue infection*" OR Myonecrosis OR ("Necrosis"[Mesh] AND limb)) AND (("Amputation"[Mesh] OR amput*[TIAB] OR) AND ("Limb Salvage"[Mesh] OR "limb salvage" OR limb salvag* OR surgery[tiab] OR surgical[tiab])) AND (English[lang])

((("Limb Salvage"[Mesh] OR "limb salvage" OR limb salvag* OR limb saving[tiab] OR limb preservat*[tiab]))) AND ((((("Amputation"[Mesh] OR amput*[TIAB])))) AND ((((("Necrosis"[Mesh] AND limb)))) OR (("Fasciitis, Necrotizing"[Mesh] OR "necrotizing fasciitis" OR "necrotising fasciitis" OR "necrotising soft tissue infection*" OR "necrotizing soft tissue infection*" OR Myonecrosis))))