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Necrotizing Soft Tissue Infections, Rare but Deadly - Know What You Do - Act Timely!

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ABSTRACT

Necrotizing soft tissue infections (NSTIs) are a rare yet highly lethal group of infections presenting as a surgical emergency. Although clinical course is characterized by rapidly progressive tissue necrosis, diagnosis may be delayed due to vague signs and symptoms upon initial presentation. Hence, it is of utmost importance that clinicians are able to make a timely diagnosis in order for the patients to receive appropriate therapy the soonest possible. In this review, we summarize basic epidemiologic and microbiological features of NSTIs, as well as current diagnostic modalities and principles of medical and surgical treatment in this special group of patients.

Keywords

Necrotizing soft tissue infections, Surgical debridement, Antibiotics, VAC.

Introduction

A rather rare but at the same time highly lethal group of infections characterized by necrosis of skin, subcutaneous tissue and superficial fascia of any anatomical region are commonly referred to as necrotizing soft tissue infections (NSTIs) [1]. In 1952, Wilson et al. [2] were the first to introduce the term Necrotizing Fasciitis (NF), which is nowadays considered synonymous of this type of infections, since the fascial layer involvement seems to be the most consistent feature of this clinical entity. Despite our better understanding of NSTIs pathophysiology and the advances in therapy over the last decades, the mortality of this disease is admiringly high, with most studies reporting a mortality rate ranging between 20% and 50% [3,4]. Nowadays, it is commonly accepted that one of the major reasons for the steadily high mortality of NSTIs is the failure of timely diagnosis and management due to lack specific signs and symptoms early in their course [5,6] and this is why physicians should always be alert and keep a high level of suspicion not to miss a diagnosis. This narrative review is going to focus on the basic features of NSTIs, the diagnostic tools in use as well as the main the current therapeutic approach in this group of patients.

Epidemiology

Necrotizing soft tissue infections are quite uncommon with an annual incidence ranging between 0,3 and 15 patients per 100,000 populations according to several studies [1,7-11]. According to a national ICU audit conducted in 2008 [12], only 0.2% of the ICU admissions in the UK hospitals would be attributed to NSTIs complications, which is lower than the 1.2% of total ICU admissions in Dutch hospitals [13]. Most of the patients diagnosed with NSTIs are between 50 and 60 years old [11,14-23] while several studies report that this type of infection is slightly more common among males [10,11,14-23]. As regards the anatomical location of infection, the extremities hold the first place in terms of frequency [11,15-20,23] followed by the perineal region (Fournier's gangrene) [14,16-20,23] and the torso-neck-head region [14,16,18,21]. Interestingly, an obvious portal of entry in the form of local trauma would be recognized in no more than 38% of patients [15,16,18,21] (Figure 1). Although up to 25% of the patients lack any obvious predisposing factor [21,24-26], the role of diabetes mellitus [10,11,14-16,20-24] and obesity [14,20,22,24] as major risk factors is fairly well established. Other

worth mentioning risk factors include cardiovascular disease [10,11,14,16,18,21,23], alcohol abuse (PEET 30, 33) and IV drug use [18,21,25] as well as immunosuppression of any kind [11,13,20,24,25].

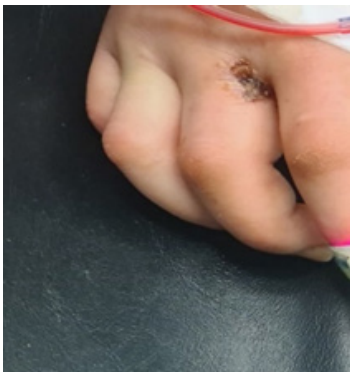

Figure 1: A 27-year-old patient with NF of right thoracic wall. Portal of entry in 2nd interdigital cleft of right hand.

Factors which are commonly associated with increased in-hospital mortality in this group of patients include disease severity as assessed by scores such as the APACHE II [18,20,23], presence of bacteremia [15] or hemodynamic instability [11,15,21,25] upon admission, female gender [10,27] and increased age [10,14,15,17,25]. Pre-existing cardiovascular [27], liver [28] or kidney [25] disease are also associated with worse prognosis. On the other hand, low experience of the surgeon [18] as well as a delay in adequate surgical debridement and use of appropriate antibiotics [16,29,30] are modifiable risk factors interfering with mortality.

Microbiology

Taking into consideration the causative pathogenic microorganisms, NSTIs are further classified as type I-IV [1,31-34]. Type I infections are considered to be the most common (70-90% of all NSTIs) and they are polymicrobial in origin [31]. Such infections are caused by the synergistic action of aerobic, anaerobic and facultative anaerobic bacteria fueling a vicious circle of bacterial colonization and tissue necrosis following inflammatory response [35]. For an infection to fall under this category, at least two pathogenic microorganisms should be present. On the other hand, type II infections are monomicrobial in origin, most commonly caused by group A Streptococcus (GAS) and less commonly by beta-hemolytic Streptococci and Staphylococcus aureus [24,25,35,36]. Interestingly, several authors report that up to 50% of the cases caused by GAS were closely associated to the presence of streptococcal toxic shock syndrome (STSS) [37,38]. Type III infections are mainly caused by Clostridium species, several gram-negative bacteria and Vibrio species, which are quite often associated with severe manifestations and worse prognosis [39,40]. Finally, type IV infections are fungal in origin (mainly Candida species and zymomycetes) [34].

Diagnosis

Although most of the patients with NSTIs will present with symptoms and signs indicative of infection, the actual findings could be nothing more than a localized edema and erythema [7]. This is why clinicians should be always alert and capable of timely distinguishing a case of a simple cellulitis from a necrotizing infection that could turn out to be lethal should there be a delay in its management [41,42]. Unfortunately, the distinction between cellulitis and NSTIs based solely on clinical findings may be really hardsince many NSTIs initially present with vague symptoms [41]. Moreover, several factors like previous NSAIDs intake or preexisting diabetic neuropathy could mask a disproportionate to clinical findings cresendo-like pain, which is considered to be a typical sign of NSTIs [43-45]. Patients with comorbidities presenting with NSTIs caused by organisms releasing exotoxins will most of the time, but not always, present with signs of severe sepsis, such as severe hypotension, mental status impairment and lactic acidosis [46]. In the specific case of gas-producing microorganisms, crepitus could be evident upon palpation, while blisters and bullae could be found in advanced stages of the disease. While those signs could help clinicians differentiate NSTIs from benign conditions, they certainly lack the appropriate level of diagnostic sensitivity, which means that the absence of such overt signs and symptoms does not necessarily rule out an NSTI diagnosis [43,44,47] (Figure 2).

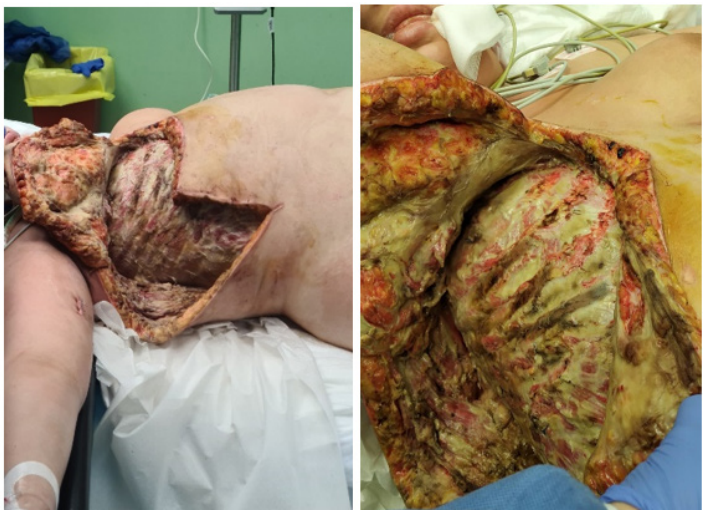

Figure 2: Initial incision over right anterior axillary line, Wound with necrotic tissue remnants.

Unfortunately, so far no lab test has been proven to be sensitive and specific enough to diagnose NSTIs [48]. As with any kind of infection, several inflammatory markers can be used to assess the severity of patients diagnosed with NS. An elevated neutrophil count often accompanied by anemia and thrombopenia seem to be a standard finding in NSTI patients. More specifically, Wall et al. developed a model according to which a WBC value higher than 15,4 x 10^9 /L and serum sodium lower than 135 mmol/L upon admission could diagnose NF with 90% sensitivity but only 76% specificity [49]. Additionally, Park et al. reported that decreased hemoglobin along with elevated glucose, creatinine and CRP levels were higher predictive of a higher amputation risk among patients with NISTs [50].

Back in 2004, Wong et al. developed a model known as LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) with an aim to be used by clinicians as a screening tool for diagnosing necrotizing fasciitis. This specific tool used the hemoglobin, total white blood cell count, creatinine, glucose, sodium and CRP values and according to the authors a score of 6 or higher was associated with a positive predictive value ranging between 57% and 92%, while the negative predictive value was found to be 86%-96% [51]. In 2008 Su et al. conducted a multicenter retrospective study aiming to establish a possible association between LRINEC score, need for surgical management, LOS (lenght of hospitalization) and finally mortality [52]. According to them, patients with a score ≥6 were reported to have statistically significant higher rates of mortality and limb amputation. Similarly, in 2018, Narasimhan et al. published the results of a single center study, according to which, LRINEC score should be definitely considered as a useful tool for early diagnosis of necrotizing fasciitis with an area under the ROC curve (AUC) equal to 0.925 [53]. In 2009 Holland et al. [54] published their 4-year experience of their institution, suggesting that a score ≥5 rather than ≥6 would markedly increase the NPV (negative predictive value) of the test should a biopsy result of the inflamed tissue come back negative.

On the other hand there is a no negligible volume of studies questioning the role of LRINEC as a diagnostic tool. In 2017, Nekki et al. [55] conducted a retrospective study based on the experience of a level II trauma center over a period of 10 years. The authors included patients with cellulitis and patients with necrotizing fasciitis and subsequently stratified them according to risk based on LRINEC score. According to them, the high rate of false positive and false negative could not justify the safe use of LRINEC score in the emergency setting. Similarly, Al-Hindawi et al. [56] retrospectively evaluated the applicability of LRINEC score in a UK population the inappropriately low sensitivity and the high false negative rate would not justify its use as a screening tool in this specific population. Finally, Foo et al. [57] tested LRINEC score in a special group comprising of patients suffering from hematological malignancies. The authors reported that although the outcome of necrotizing fasciitis was not worse when compared to immunocompetent patients, the score is not sensitive enough to be used in this special subgroup of population.

More recently, procalcitonin has been introduced as an inflammation marker to be used in daily clinical practice. Kishino et al. [58] were among the first to evaluate the performance of procalcitonin levels as a tool that could help differentiate NF from other less severe soft tissue infections. According to them, this specific biomarker could not only serve as a useful diagnostic tool but also predict the risk of upcoming septic shock and death, with that being the reason why several studies nowadays support the measurement of procalcitonin levels along with other common biomarkers upon admission to the hospital [59-61]. In 2016, a Danish prospective study [62] examined the predictive role of several biomarkers and concluded that ficolin-2 levels (part of lectin complement pathway) was associated with both short-term and long-term mortality and that a high ficolin-2 level upon admission was indicative of a chance of survival during the first 28 days equal to 94%. Similarly, another study [63] showed that a multifunctional molecule known as Pentraxin-3 (PTX3) could also serve as a predictive biomarker in patients with NSTIs, since it was found to be significantly higher in patients on septic shock and it could also predict risk of amputation, need for hemodialysis and mortality. As expected, several studies have been designed in order to assess the performance of different imaging modalities in the diagnosis of NSTIs. Starting with conventional radiography, experience has shown that it has little to no contribution in the diagnostic process since it is found to detect presence of gas among tissues in only 10-25% of patients [64,65]. On the other hand, point-of-care ultrasound (POCUS) apart from outperforming conventional radiography in terms of gas visualization [66,67] seems to be a good alternative, taking into consideration that it is not only convenient and quick to perform on the ward [68], but suitable for those individuals who could not undergo a CT or MRI for various reasons [69,70]. Studies report that while ultrasonography has indeed a high specificity when used in the context of NSTIs (up to 93%), the disproportionately low sensitivity should definitely alert clinicians not to miss a highly morbid diagnosis just by relying solely on US findings [71,72]. As far as computed tomography (CT) is concerned, several studies report a sensitivity up to 90% and specificity up to 93% as a tool to diagnose NSTIs [73-77]. It is generally considered useful in planning the appropriate surgical intervention by giving information on the extent of the disease, while IV contrast use should be considered when possible in order to further characterize the soft tissue [74,75]. Finally, the MRI with contrast seems to be an excellent alternative with high performance in characterizing soft tissues [67] and certainly more helpful than CT when it comes to accurately defining the true extent of infection [78,79], with a sensitivity up to 100% and specificity up to 86% in diagnosing NSTIs [65,80]. Nevertheless, it is considered highly unsuitable for use in the emergency setting, since besides being very costly and time-consuming, it certainly for the patient to be clinically stable [80].

Therapeutic Approach

Surgical Treatment

As expected, the most important intervention in cases of NSTI is an extensive surgical debridement, aiming at removal of all damaged and necrotic tissue to prevent further spread of the infection as much as possible [41,81]. Interestingly, according to Sarani et al. [82], for each hour of delay in operative management there is a high probability that the infection spreads locally up to an inch, thus putting the patient in danger of serious local and systemating complications. Although the exact mechanisms for this quick spread are poorly understood, it has been hypothesized that it is mainly due to the fact that at some time the extreme virulence of exotoxins produced prevails over the patient's defense mechanisms [82,83]. There are several studies reporting that a timely surgical management does not only offer a better chance of survival, but is also associated with a lower number of operations needed and lower risk of septic shock during the course of the disease [84,85]. Back in 2018, Gelbard et al., conducted a meta-analysis of six studies and according to their findings, among those

patients operated ≥12hrs the mortality was two times higher when compared to patients operated within the first 12hrs (26% vs 13%) [86]. A more recent meta-analysis by Nawijn et al. [87] yielded similar results as the previous study (mortality 19% vs 34%) and showed that although achieving a surgical debridement within the first 12hrs is of utmost importance, the mortality rate among patients operated within the first 6hrs was statistically significant lower (19% vs 32%). Interestingly, whether the patients received surgical treatment within 6hrs or 12hrs played no significant role in the amputation rate for those individuals with an NSTI localized on one of their limbs. The authors also suggest that ideally the first operation should last no more than 90min, treating those individuals as severely compromised trauma patients and implementing a damage control strategy [88]. Generally, a second look operation is recommended, especially in critical ill patients, in order for the surgeon to confirm the adequacy of source control [81]. Thereafter, Stevens et al. [42] suggest that the patients should be led to the operating theater on a daily basis until surgeons confirm that only healthy tissue is left behind, with the average number of operations needed being equal to 3.5 according to Chawla et al. [89].

Another important aspect that all involved surgeons should have in mind, is the extent to which the skin should be removed during the debridement procedures. Although so far there is no official consensus of the superiority or inferiority of a skin-sparing approach, there are authors suggesting that it could be an option when treating patients with NSTIs. Based on pathophysiology, it seems that in most cases the infection spreads across fascial planes with only secondary involvement of the skin due to perforating branches occlusion [41,90,91]. Under these circumstances, an extensive debridement of deep tissues with only necrotic skin removal seems to be a reasonable option, since it contributes to the minimization of postoperative scar thus improving quality of life among the survivors [44,92-96]. Nevertheless, we should bare in mind that there are types of NSTIs (eg: necrotizing cellulitis, gas gangrene) with infection affecting mainly the skin or spreading evenly in all layers, in which case a skin-sparing approach would be unsuitable (Figure 3).

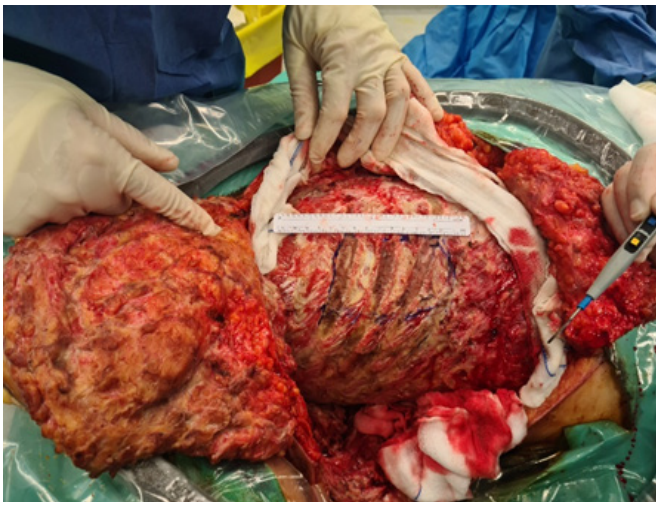

Figure 3: Extensive surgical debridement.

As far as wound management following surgical intervention is concerned, the implementation of Negative Pressure Wound Therapy (NPWT) has received a lot of attention lately [97]. As described by several studies, the most important advantages of VAC systems usage are the reduction of local edema, bacterial colonization and wound size along with a simultaneous increase in local blood supply [98,99]. It has been also proven to be useful in preserving as much healthy subcutaneous tissue as possible, thus facilitating reconstructive operations later in a later stage [100-103]. According to meta-analysis published by Zhang et al. [97], the use of VAC in the context of NSTIs could decrease mortality by almost 27% when compared to conventional gauze dressing, without substantially affecting the rate of complications, the length of hospitalization and the number of debriding operations needed. With regard to the hypothetical risk of increased local bleeding after application of a VAC system, no such complication has been recorded [104,105]. Finally, according to the findings of a large multicenter study published back in 2017, the authors suggested usage of VAC only in complex cases of NSTIs since it is not only more expensive than conventional dressing but it was also not found to decrease length of hospitalization (p=0.2**)** [46] [Figure 4].

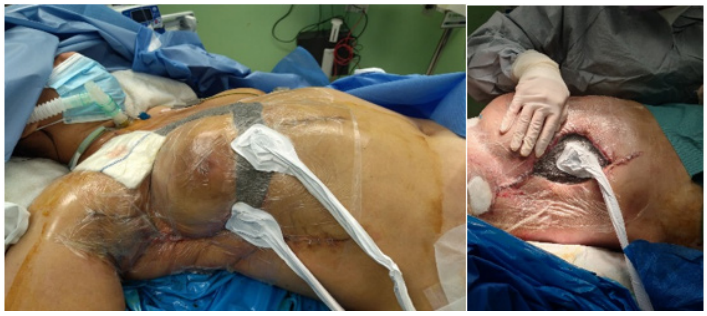

Figure 4: VAC device in place.

Antibiotic Management

So far, our knowledge on the appropriate antibiotic treatment in NSTIs relies on expert consensus, since we lack ground evidence coming from prospective and controlled studies. As a rule, broad-spectrum antibiotics covering both gram positive and negative bacteria as well as anaerobic microorganisms should be commenced as soon as possible in patients suspected to have an NSTI [42,81]. A recommended empiric antibiotic regimen would include vancomycin or linezolid to cover for MRSA along with a carbapenem or combination of a beta-lactam with beta-lactamase inhibitor (eg: piperacillin-tazobactam) [106]. In the above group of antibiotics, we should also think of adding clindamycin mainly as an effective modulator of cytokine production and major suppressor of exotoxin production [107,108]. Should a patient have severe hypersensitivity in carbapenems or beta lactams, we can replace those antibiotics with a fluoroquinolone along with metronidazole for anaerobic coverage [42]. In the rare case we suspect contamination with Vibrio vulnificus or Aeromonas hydrophila due to documented marine exposure or exposure to seafood, we should add doxycycline to the initial regimen [106]. Moreover, in individuals at risk for fungal infections we should add an antifungal agent (eg: fluconazole, amphotericin

B) [109,110]. As expected, once the causative agent has been identified and susceptibility tests have been run, an adjustment of previous therapy should be done. Finally, as far as proper duration of antibiotic therapy is concerned, the lack of consensus has led to a great deal of heterogeneity in daily practice [111], with some authors suggesting continuation of treatment for 2-3 days after the last operation [42] and others endosing continuation of antibiotics for at least 5 days following resolution of signs and symptoms [82].

Adjunct Therapies

Over the last decades, several studies have examined the role of hyperbaric oxygen therapy (HBOT) as an adjunct treatment in patients diagnosed with NSTIs. This type of therapy most probably acts via achievement of arterial hyperoxia, which in turn results in vasoconstiction, bacteriostasis, reduced adherence of white blood cells and finally reduction of edema [112]. More specifically, hyperoxic vasoconstriction is found to improve local edema while in parallel maintaining adequate oxygen levels in peripheral tissues [113,114]. What is more, the increased oxygen tension in capillaries reduce neutrophilic adhesion thus preventing microvascular plugging [115,116], while reactive oxygen species are not also considered to be bacteriostatic but also promote the action of some antibiotics [117-119]. For patients with NSTIs, initial studies reported a decrease in number of operations needed and a decrease in overall mortality following HBOT [120,121], Nevertheless, according to two subsequent systematic reviews published in 2013 and 2015, the lack of ground evidence in this subgroup of patients could not justify the use of HBOT as adjunct treatment [122,123]. This recommendation is also given by the Infectious Disease Society of America [42], while the World Society of Emergency Surgery recommends the use of HBOT when available [81] (Figure 5).

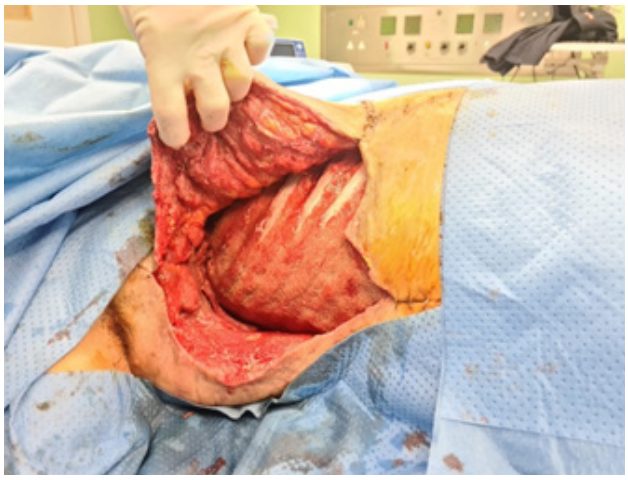

Figure 5: Wound healing with abundant granulation tissue present.

Another possible adjunct therapy for NSTIs would be the administration of intravenous immunoglobulin (IVIG). Immunoglobulin besides reducing the levels of TNFa and IL6, can also enhance opsonization and neutralization of exotoxins [124]. Although initial studies on IVIG turned out to be inconclusive [125-127], subsequent studies support its administration, especially in the context of a necrotizing infection coexisting with steptococcal toxic shock syndrome (STSS). More specifically, back in 2018, a meta-analysis on patients with STSS showed that the administration of IVIG could significantly decrease 30-day mortality from 33.7% to 15.7% [128]. Similarly, in 2020 Bruun et al., based on the results of a multicenter prospective study, reported that NSTIs caused by group A Streptococcus would have a better 90-day mortality rate if treated with IVIG [129]. On the other hand, the INSTICT randomised study, comprising of patients with NSTIs regardless of etiology, failed to show a substantial benefit of IVIG administration on mortality rates [125]. Having all the above in mind, we can easily understand that more carefully designed randomized trials are needed in order to prove any benefit of IVIG in patients with NSTIs. Finally, it would be remiss of us not to mention scientist's efforts on developing novel targeted therapies to be added in our armamentarium against NSTIs. More specifically, back in 2020, Bulger et al. [130] published the results of a large multicenter study on the efficacy of a relatively new immune modulator known as Reltecimod. According to the authors, this synthetic peptide which acts by blocking T-helper cells activation by several pathogenic bacteria through the CD28 receptor pathway, has been shown to promising results regarding the resolution of organ dysfunction to be seen in severe necrotizing soft tissue infections. To date, this novel agent awaits FDA approval.

Conclusion

Necrotizing soft tissue infections, although rare, are still associated with significantly high morbidity and mortality. Nonspecific signs and symptoms at initial presentation increase the difficulty of diagnosis, which means that clinicians should be properly trained and preserve a high level of suspicion not to miss a diagnosis. Unfortunately, current laboratory tests lack appropriate specificity and screening tools like LRINEC score have not gained wide acceptance. As far as imaging modalities are concerned, they could assist in the differential diagnosis process, but in no case should they be the reason to delay a prompt therapeutic intervention. While a lot of steps have been taken towards finding the most common causative microorganisms and defining a proper antibiotic therapy for that condition, more well-designed studies will be needed in order to establish commonly accepted guidelines. Upon recognition of a necrotizing infection, apart from early administration of broad-spectrum antibiotics, it is of utmost importance that the patient receives an aggressive surgical debridement the soonest possible, since it is widely accepted that "time is fascia" and any delay is associated with worse outcomes and higher mortality. Finally, adjunct treatments like hyperbaric oxygen and IVIG have already been studied but they have not yet been proven to be so beneficial as to become part of the standard of care for patients with NSTIs.

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