Necrotizing Soft Tissue Infections

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KEYWORDS

• Necrotizing soft tissue infection • Cellulitis • Necrotizing fasciitis
• Toxic shock syndrome • Gangrene • Sepsis

KEY POINTS

- Necrotizing soft tissue infections are life threatening infections, which require a high index of suspicion to diagnose appropriately.
- The microbiology can be predicted based on risk factors, which can assist in appropriate choice of antimicrobial therapy.
- Emergent surgical assessment and debridement to control the source of infection remains the mainstay of therapy.
- Further research is necessary to improve early detection of necrotizing soft tissue infections.

INTRODUCTION

Necrotizing soft tissue infections (NSTI) represent a heterogenous group of infections with a common final pathway resulting in tissue necrosis. NSTI are also associated with varying degrees of systemic illness including varying degrees of sepsis, organ failure, and high levels of mortality. These infections were originally termed *necrotizing fasciitis* but NSTI represents a more comprehensive grouping of infections, as many cases extend beyond the skin, subcutaneous tissue, and fascia into deep musculature.[1] NSTI can occur in individuals with no medical history or in immunocompromised individuals, as well as in post-surgical patients. The range of skin or mucosal breakdown, which can predispose to an NSTI, includes minor barrier breaches (such as tears, lacerations, sports injuries, or arthropod bites), routine obstetric and gynecologic procedures, major traumatic injuries, and prior minor skin infections including cellulitis, furuncles/carbuncles, or skin abscesses.

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Abbreviations	
CT	computed tomography
GAS	group A Streptococcus
HBO	hyperbaric oxygen therapy
IDSA	Infectious Disease Society of America
IVIG	intravenous immunoglobulin
LRINEC	Laboratory Risk Indicator for Necrotizing Fasciitis
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
NSTI	Necrotizing soft tissue infection
TSS	Toxic shock syndrome

Various classification schemes have been created in the description of NSTI. Microbiologic characteristics, underlying risk factors, location, and depth of tissue involvement can provide useful frameworks for understanding individual disease processes.[2] Specific incidence data for many types of NSTI are difficult to determine precisely due to high variability in reporting practices to local, national, and international authorities, but overall NSTI appear to be increasing.[3] Despite advances in care, NSTI are still associated with high morbidity and mortality, underscoring a need for expedient diagnosis, aggressive surgical intervention, and prompt administration of antimicrobial therapy. The epidemiology, microbiology, pathophysiology, clinical presentation, diagnostic approaches, and treatment options will be reviewed in this article.

EPIDEMIOLOGY

The exact number of NSTI which occur can be difficult to estimate owing to a lack of required reporting to public health services or government agencies in some countries across the globe. Unclear or ambiguous nomenclature regarding specific infection types also hampers identification and accurate data collection. Additionally, many studies rely on electronic medical records and the International Classification of Diseases system to attempt to evaluate the incidence of NSTI, introducing bias due to misdiagnosis or carrying forward inaccurate diagnoses.[4,5] A more robust system of monitoring would facilitate more detailed analyses of antimicrobial resistance patterns, emerging infectious agents causing NSTI, and the effects of climate change.[6]

Most of the available data regarding the epidemiology of NSTI are related to *Streptococcus pyogenes* (group A Streptococcus, GAS) surveillance. Several countries track invasive GAS infections including the United States,[7] France,[8] Netherlands,[9] Australia,[10] and Canada[11] among others. The incidence for invasive NSTI appears to vary depending on geographic area with an incidence from 0.2 to 6.9 per 100,000 person-years, reaching a peak of 15.5 per 100,000 person-years in Thailand.[12] Prospective population-based studies place the incidence at somewhere between 3 and 4 per 100,000 person-years.[13] Overall, NSTI remains relatively rare when compared to non-necrotizing cellulitis.[2]

Pharyngitis remains the most common infection associated with GAS, and uncomplicated soft tissue infection remains the most common presentation of invasive GAS infection. Necrotizing infection comprises only about 10% of invasive GAS infections.[7] The incidence of NSTI and invasive GAS tends to increase in seasons where GAS pharyngitis is more common, specifically during influenza season in winter months and scarlet fever season in spring months.[14,15] There is also increased incidence of NSTI among different groups of people within a country or geographic area, such as the 5 to 10 times elevated incidence of GAS among indigenous populations or within tropical countries.[16]

CLASSIFICATION AND MICROBIOLOGY

NSTI can be classified based on the microbiology of the infection, as well as the presence or absence of gas in tissues, either intra-operatively or radiographically. Anatomic overlap can sometimes occur, especially between necrotizing fasciitis and necrotizing myositis, which occasionally involve both skeletal muscle and fascia.[17] Necrotizing cellulitis is usually more distinct, involving only various layers of the skin and subcutaneous tissue, but sparing fascia and skeletal muscles. Many terms have been used to describe various etiologies of NSTI including hospital gangrene, Ludwig's angina, Fournier's gangrene, and Meleney's gangrene among others. The general public is often subjected to articles containing headlines such misleading terms as *Flesh Eating Bacteria*, further complicating matters.

Necrotizing fasciitis refers to infections of the deep soft tissues causing fascia and subcutaneous fat necrosis. Owing to the relatively poor blood supply of the fascia, these infections can rapidly progress. Skeletal muscle's blood supply is comparatively rich compared to fascia, and sparing of muscle can occur with these infections.[18] The categories of necrotizing fasciitis can be divided into polymicrobial (Type I) and monomicrobial infections (Type II, III, and IV). Polymicrobial infections tend to involve multiple different aerobic and anaerobic organisms, but commonalities do exist.

Type I infections are usually seen among elderly patients or those with underlying significant co-morbid conditions such as diabetes mellitus, fistulas or hemorrhoids, or recent surgical procedures (especially those involving the urogenital or alimentary tracts). Gas is usually found in affected tissues either radiographically or intraoperatively and can be difficult to distinguish from gas gangrene. Mixed aerobic and anaerobic organisms are typically recovered from cultures, including many of the common organisms isolated in Type II infections. When an NSTI is present, clinical signs and symptoms of sepsis are common such as leukocytosis, acidosis, and hemodynamic compromise.

Type II infections are usually monomicrobial and the associated pathogens depend on the underlying risk factors of the patient. *S. pyogenes* is among the most common isolated organisms, followed by *Staphylococcus aureus* and *Clostridium* spp. Other rare causes of monomicrobial infections have also been reported including *Escherichia coli*, *Bacteroides fragilis*, and many others. Type III and Type IV infections have also been described in the literature, but their acceptance as distinct entities is controversial. Most sources place Type III into monomicrobial infections with *Aeromonas hydrophila* and *Vibrio vulnificus* and are associated with exposure to fresh or saltwater.[19] Type IV refers to monomicrobial infections with fungi such as *Apohyphomyces* spp.[20] and *Candida* spp., which are typically seen among patients with significant underlying immunocompromised states.[21] This classification scheme as described is not universally accepted, and further refinement is necessary to reconcile many of the inconsistencies, which exist in this framework.

PATHOGENESIS AND RISK FACTORS

NSTI development depends on a number of factors, which allow exposure to the specific pathogens and, in some cases, on underlying co-morbid risk factors, which increase the likelihood of an exposure leading to an invasive infection. A vicious cycle of infection, toxin production, cytokine activation, microthrombosis and tissue ischemia, physiological dysfunction, and, eventually, death differentiates it from uncomplicated skin and soft tissue infections.[1]

S. pyogenes, being the most common microbial etiology of NSTI, has had its pathophysiology best defined. It gains entry to deep tissues via superficial cuts and

disruptions of the epidermis layer after infections such as varicella zoster virus, arthropod bites, lacerations or recent surgeries, or penetrating trauma. It can also occur spontaneously in some cases. The bacteria establish a local nidus of infection, replicates, and toxin production begins, especially of exotoxins. The M protein is a major virulence factor, eliciting a type-specific host immune response.[22] GAS superantigens are also important factors helping to induce systemic toxicity.[23]

In cases of Clostridial myonecrosis (gas gangrene), a deep penetrating injury allows for inoculation of areas with potentially less blood supply and eventually a nidus of infection develops. Less frequently, this can occur spontaneously as well. Eventually, the compromised blood supply facilitates an anaerobic environment where spore germination occurs and bacterial proliferation results.[24] Other predisposing conditions to Clostridial sepsis include bowel and biliary tract surgeries, gynecologic and obstetric surgical procedures, retained placenta, intrauterine fetal demise, and indwelling central venous catheters. *C. septicum* is often associated with nontraumatic gas gangrene, whereas *C. perfringens* is most often associated with penetrating gas gangrene.[25] *C. sordellii* myonecrosis and sepsis occurs most often in women of childbearing age, especially after recent childbirth, gynecologic procedure, or abortion.[26] Injection drug use history has also been associated with various *Clostridium* spp. infections. For a schema to assist in determining a likely microbiologic diagnosis, see **Fig. 1**.

CLINICAL PRESENTATION

Obtaining a thorough history is paramount to determining the risk of an NSTI in a patient. History obtained about recent surgical procedures, relevant medical history, or important environmental exposures can provide vital clues about potential inciting

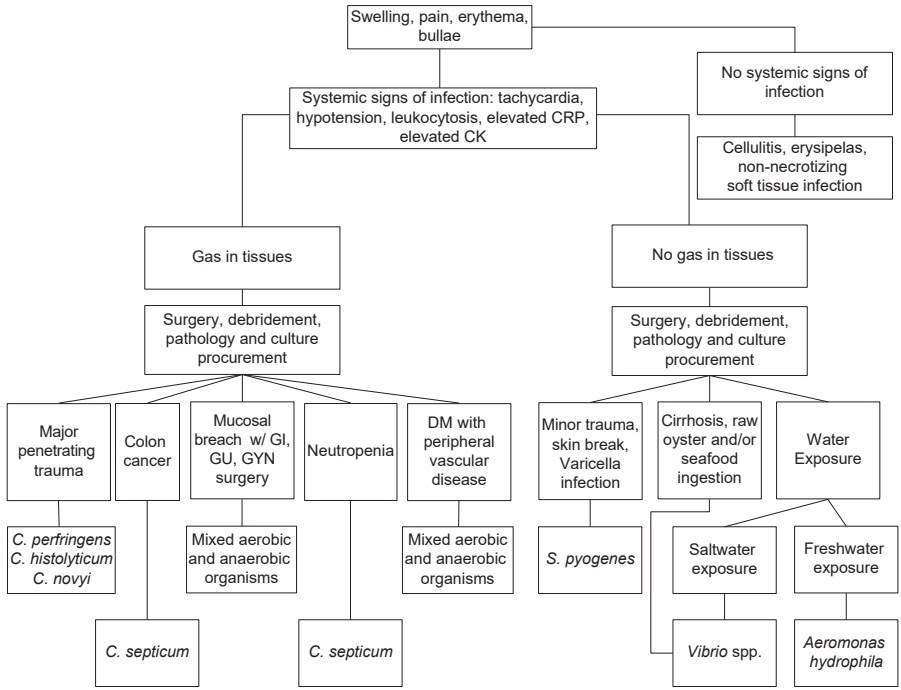

Fig. 1. Diagnostic pathway for evaluating the likely microbiologic etiology of necrotizing soft tissue infections. CK, creatine kinase; CRP, C-reactive protein.

organisms requiring different types of antimicrobial coverage. If the patient is unable to provide history due to hemodynamic compromise, encephalopathy, or is on mechanical ventilation, collateral history from other sources should be obtained to assist in making the diagnosis.

The clinical manifestations of NSTI can be challenging to recognize owing to the rapidly progressive nature of the infection and subtle clinical clues, which require a discerning eye to spot. NSTI can involve any or all layers of the epidermis, dermis, subcutaneous tissues, fascia, and muscle, and clinical manifestations can reflect the involvement of each layer. The majority of cases present with erythema and edema of the affected area, and a telltale sign is when a patient describes severe pain that is out of proportion to examination of the affected area.[27] Anesthesia or sensory changes to areas of the skin may be the first clinical sign of an NSTI developing, and may precede any skin changes suggestive of an active infection.[28] The presence of bullae, skin ecchymoses, skin necrosis, and edema outside of the area of erythema should prompt high consideration for NSTI.

DIAGNOSIS

As a result of the difficulties in diagnosing NSTI early, various scoring systems have been developed in an attempt to improve rapid detection of cases. One of the earliest scoring systems developed was the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. Wong and colleagues developed a score using white blood cell count, hemoglobin, sodium, glucose, serum creatinine, and serum C-reactive protein to determine a likelihood ratio of whether an NSTI was present.[29] Studies assessing the LRINEC score in clinical practice have demonstrated variable sensitivity profiles, and it should not be routinely used to rule in or rule out an NSTI.[30–32] The LRINEC score can also be artificially elevated in other musculoskeletal infections.

Intraoperative findings can help to provide definitive diagnosis of an NSTI. Surgical exploration should never be delayed while awaiting laboratory or imaging results if the diagnosis of NSTI is being considered. While obvious evidence of tissue necrosis and hemodynamic instability make exploration in the operating theater a necessity, equivocal cases can sometimes be explored at the bedside using only local or regional anesthesia. Alternatively, a surgeon may elect to proceed straight to the operating room where a small pilot incision is made to assess for muscle or fascial necrosis and the presence of *dishwater* brown fluid or a *positive finger sign* in which a finger inserted along fascial planes easily dissects tissue without encountering resistance.[33]

Imaging findings in NSTI depend upon the type of NSTI present, as well as the microbiology of the infection. Generally speaking, soft tissue swelling can be noted on radiographs, computed tomographic (CT) scans, or MRI scans in cases of GAS infection, whereas patients with gas gangrene or type I necrotizing fasciitis will show gas in the tissues. A study of contrast-enhanced CT imaging in patients with documented necrotizing fasciitis showed the absence of fascial enhancement was highly specific for necrotizing fasciitis.[34] In equivocal clinical cases, MRI is probably the most effective method to diagnosing NSTI. These changes on imaging are demonstrated as fascial thickening $\geq$3 mm and enhanced signal on fat-suppressed T2-weighted sequences.[35,36] It must continue to be emphasized; however, that prompt surgical exploration should never await imaging studies if there is high enough concern for an NSTI.

MEDICAL TREATMENT OF NECROTIZING SOFT TISSUE INFECTION

Rapid administration of appropriate antimicrobial therapy is essential in the treatment of NSTI. The choice of antimicrobial depends upon the suspected diagnosis, as well

as the severity of illness, but sole administration of antimicrobial therapy without surgical debridement is associated with excessive mortality rates, with some studies approaching 100%.[37] Blood cultures should be obtained from patients prior to the administration of antibiotics, and if possible, deep surgical wound cultures should also be obtained to aid in the optimal choice of therapy.

The specific choice of antimicrobial therapy in NSTI has not been studied in randomized controlled trials, and data from cellulitis and non-necrotizing soft tissue infections are used to guide initial choice of therapy. Because many infections are polymicrobial in nature, coverage for methicillin-resistant *S. aureus* (MRSA), *S. pyogenes*, anaerobic gram positive rods such as *Clostridium* sp., and gram negative organisms should be included in the regimen.[27] Vancomycin, daptomycin, ceftaroline, and linezolid are all considerations for an MRSA-active agent, while gram negative agents such as piperacillin-tazobactam, ampicillin-sulbactam, ticarcillin-clavulanate, extended-spectrum cephalosporins such as ceftriaxone or cefepime, or carbapenems such as imipenem-cilastin, meropenem, or ertapenem should be considered. Prolonged infusions of β-lactams are recommended when possible to maximize the time above minimum inhibitory concentration (MIC) for various pathogens, especially when those pathogens demonstrate a higher MIC.[38] If an antimicrobial with high protein binding is chosen such as ceftriaxone or ertapenem, some consideration should be given to more frequent dosing in patients with severe hypoalbuminemia, especially if they are critically ill.[39] Patients with exposure to specific pathogens such as *Vibrio vulnificus* in marine environments or *Aeromonas hydrophila* in freshwater environments should be placed on regimens with activity against those pathogens. There have also been reports of other *Vibrio* species (along with *V. vulnificus*) causing NSTI after natural disasters, such as the outbreak of *Vibrio parahaemolyticus* NSTI, which occurred after Hurricane Katrina.[40] There are also isolated reports of other pathogenic *Vibrio* species causing NSTI including *Vibrio alginolyticus*[41] and *Photobacterium damsela* (previously *Vibrio damsela*).[42] Empiric antifungal therapy is generally not required unless there is concern for an exposure to a particular fungus of concern. See **Table 1** for additional information regarding specific antimicrobial regimens for each organism.

Additional therapy with antimicrobials targeting toxin-producing organisms is usually recommended when clinical suspicion is high that such an organism is involved in the infection. Many times, the microbiologic diagnosis has not been established at the time of therapy initiation, and thus empiric therapy is added until cultures return. Clindamycin is the best studied antimicrobial with anti-toxin activity, and the Surgical Infection Society and Infectious Disease Society of America (IDSA) both recommend combination therapy with penicillin therapy in NSTI (with or without Toxic Shock Syndrome, TSS) with GAS.[27,47] A retrospective study of patients admitted from 2000 to 2015 at 233 US hospitals showed a mortality benefit when patients were given clindamycin therapy in addition to beta-lactam antimicrobials.[48] However, of significant concern is the increasing number of clindamycin-resistant GAS strains recovered from clinical cultures.[49] A recent study showed clindamycin resistance in the infecting isolate to be associated with an 86% increase in the risk of amputation (RR 1.86; 95% CI: 1.1–3.16).[50] Additionally, clindamycin remains an antimicrobial with significant *Clostridium difficile* infection rates, further complicating clinical recovery after an NSTI. Clindamycin's future role as an antimicrobial adjunct is uncertain in the face of changing susceptibility patterns and potential alternative regimens.

There are emerging data on another class of antimicrobials, which inhibit bacterial protein synthesis and which may play a role as an adjunctive drug in the treatment of toxin-producing organisms and TSS: the oxazolidinones. The first member of the

Table 1
Pearls and pitfalls in antimicrobial therapy for necrotizing soft tissue infections

Causative Organism	Explanation
Streptococcus pyogenes	• Universally susceptible to beta-lactams; vancomycin is an alternative. • Trimethoprim-sulfamethoxazole may be an option for uncomplicated infections but no data in NSTI.[43] • Fluoroquinolones and doxycycline should be avoided due to clinical failures and high rates of resistance. • Resistance rates to macrolide antimicrobials is on the rise.[44]
Staphylococcus aureus	• Linezolid has activity against both MSSA and MRSA, in addition to suppressing toxin-associated illness. • Beta-lactams such as nafcillin, oxacillin, or cefazolin are the preferred treatment for MSSA infections, but clinical failures with cefazolin in bacteremic patients have been reported due to the inoculum effect.[43]
Clostridium spp.	• Good activity of penicillin, metronidazole, some second and third generation cephalosporins. • Linezolid and clindamycin retain good anti-toxin activity against most *Clostridium* spp. • Aminoglycosides and sulfonamides have poor activity, and should be avoided.
Vibrio spp.	• Fluoroquinolones, ceftriaxone, cefotaxime, and tetracyclines have excellent activity. • Retrospective data suggest combination therapy with a beta-lactam and tetracycline or a fluoroquinolone and tetracycline associated with lower mortality compared to beta-lactam therapy alone.[45]
Aeromonas hydrophila	• Fluoroquinolones have excellent activity, along with aminoglycosides, carbapenems, and tetracyclines. • Many strains harbor various Ambler A, B, C, and D beta-lactamases, reducing susceptibility to many beta lactams.[46]

class to be marketed, linezolid, has recently been considered as an alternative to clindamycin. Linezolid offers an enticing option, with less risk for *C. difficile* infection, rapid reduction in GAS exotoxin A has been observed in vitro when linezolid is used.[51] However, clinical experience with linezolid is limited, and are mostly limited to case reports.[52,53] A single center retrospective study showed no difference between clindamycin versus linezolid in mortality (11.5% vs 7.7%, $P = .22$) and resolution of infection (92.3% vs 88.5%, $P = 1.0$).[54] Linezolid also provides an attractive empiric option for treatment of MRSA and is more reliably active against MRSA than clindamycin. Unfortunately, there is no available large head-to-head prospective comparison of linezolid and clindamycin, and additional data will be necessary to fully parse out the utility of linezolid and other oxazolidinones in the treatment of toxin-mediated NSTI. An excellent review of the data comparing clindamycin and linezolid, presented as a friendly debate, is available.[55]

Duration of therapy is not well-established in the management of NSTI. No specific clinical trial data exist, and guidelines on the subject are available for more information. Forty-eight to 72 hours of therapy after resolution of fever and other systemic signs of infection are probably sufficient. A prospective study of 151 patients showed no differences in treatment failure or mortality rates after a change in practice occurred in 2018.[56] The duration of therapy can also be affected by the presence or absence of

concomitant bacteremia, especially in the case of *S. aureus,* which is often treated with 2 to 6+ weeks of parenteral antimicrobial therapy.

Antimicrobial resistance is a global threat to the field of modern medicine, and appropriate treatment of NSTI is also at risk. A recent Lancet article suggested that if no mitigation measures are implemented, approximately 1.9 million people will die annually from antimicrobial resistant infections.[57] While much of the risk is attributed to drug-resistant strains of gram negative bacteria, there are also concerns regarding drug resistance among gram positive bacteria such as *S. aureus* and GAS. Of significant concern is the novel isolation of clinical GAS strains with missense mutations in the *pbp2x* gene, conferring significantly increased MICs for ampicillin and representing a pathway toward developing beta-lactam resistance.[58] MRSA remains a significant driver of increased hospital length-of-stay and increased hospital and health care costs.[59]

SURGICAL MANAGEMENT OF NECROTIZING SOFT TISSUE INFECTION

Aggressive surgical interventions remain a cornerstone in the approach to management of NSTIs. Determining the extent of infection, obtaining microbiologic specimens for gram's staining and culture, and assessing the need for debridement or amputation all contribute to the need for surgical exploration. Multiple large studies have demonstrated the importance of surgical intervention in the treatment of NSTI, though no randomized controlled trial has studied the timing of intervention or extent of therapy.[60–62] Prompt recognition is essential, and debridement which occurs at the initial receiving facility have been shown to decrease morbidity and improve overall patient survival.[63] In order to achieve optimal outcomes, interfacility transfers may be necessary to facilitate patient access to appropriate specialist care, depending on the extent of intervention that is required.[64]

The extent to which tissue debridement should occur has not been defined, and *adequate debridement* depends on the surgeon's direct visualization of tissue in the operating room. The average number of debridements necessary to fully control the infection is around 3 to 4 before further wound care can be performed at the bedside without necessitating formal operative intervention.[65,66] The anatomic site of infection can also necessitate the intervention of surgical specialists including urologists, otolaryngologists, orthopedic surgeons, and others. If a reconstructive technique with a rotational tissue flap or skin graft is necessary, plastic surgery assistance may be required. Amputations may be necessary depending on the extent of devitalized tissue.

Wound management is extremely important in ensuring good cosmetic and functional outcomes in cases of NSTI. Negative pressure dressings can limit the size of wounds by providing traction to the overlying skin and speed closure.[67] Vacuum-assisted closure devices help to promote granulation tissue formation, minimize soft tissue edema, and aid bedside nursing care, and remain a mainstay in the long-term management of wounds after operative debridements have ceased.[68]

ADJUVANT THERAPIES

Additional therapies are sometimes recommended beyond appropriate antimicrobials and surgical interventions. The most common of these are intravenous immunoglobulin (IVIG) and hyperbaric oxygen therapy (HBO). IVIG is thought to be effective in mitigating toxin-mediated shock syndromes caused by streptococcal or staphylococcal NF by binding to and inactivating circulating superantigens and blunting the resulting cytokine storm.[69,70] Hyperbaric oxygen is a proposed adjuvant method of therapy

after surgical debridement for NSTI is complete. It is hypothesized to increase plasma dissolved oxygen concentration, enhancing oxygen delivery to hypoxic tissues, improving leukocyte activity, and directly killing obligate anaerobic bacteria.[71]

The data regarding IVIG in patients with NSTI are mixed, with many studies suffering from serious statistical or methodological flaws, and agreement among physicians regarding the use of IVIG is lacking. Initial retrospective studies showed promise for IVIG, but additional data demonstrated little, if any benefit to its routine use in patients. A well-controlled study from 2017 by Kadri and colleagues assessed the use of IVIG across 130 US hospitals with no clinically significant benefit being found, regardless of the timing of IVIG.[72] Other studies evaluating IVIG were limited due to small sample size,[73] NSTI incidence differences between study groups,[70] and low mortality rates in the group that did not receive IVIG.[74] However, a 2018 meta-analysis of patients with streptococcal TSS showed a significant reduction in 30-day mortality (33.7–15.7%) among patients treated with clindamycin and IVIG.[75] Additionally, a 2021 prospective observational study from 5 centers in Northern Europe found an association of IVIG use with reduction in 90-day mortality.[76] Further prospective trial data will be required to fully determine the utility of IVIG in the treatment of patients with NSTI.

HBO is another potential adjuvant therapy for use in facilitating wound healing after completion of surgical debridement. Data are contradictory, with a 2003 systematic review of 57 studies between 1998 and 2001 not demonstrating any significant benefit. The authors noted that most studies were of poor quality with inadequate or improper controls and with highly variable study populations.[77] In contrast, a retrospective nationwide study of 45,912 inpatients in the United States from 1988 to 2009 had a statistically significant lower risk of dying (OR 0.49, 95% CI 0.29–0.83), though HBO was also associated with higher hospitalization costs and longer length-of-stay.[78] Smaller observational studies have also been contradictory, with some demonstrating lower mortality rates and fewer necessary debridements[79,80] but others demonstrating increased costs, morbidity, and mortality.[81] The use of HBO is also somewhat limited by its requirement for specialized equipment and facilities. Patients who would be transferred for HBO treatment may actually do worse if the transfer process itself delays proper surgical assessment, debridement, or administration of appropriate antimicrobial therapy.[78,82] Thus, the utility of HBO may be limited to few cases in which its applicability for limb salvage may be required, but it is not generally recommended for all cases of NSTI.

OUTCOMES

Outcomes for NSTI remain highly dependent on expedient surgical intervention and debridement of vitalized tissue, as well as prompt administration of adequate antimicrobial therapy. Wounds acquired from NSTI can be challenging to manage and often require plastic surgical intervention, as well as skilled nursing wound care to optimize patient outcomes. Retrospective data support the use of a vacuum-assisted wound closure device to improve wound closure times, decrease hospital length-of-stay, and potentially improve overall survival.[83] A long-awaited randomized clinical trial is due to have results available sometime in 2025 (NCT05071443). Timing of skin graft placement, if necessary, is also controversial.

Mortality for NSTI remains high, though specific numbers remain difficult to accurately report due to inconsistencies in International Classification of Diseases (ICD) code use and high rates of misclassification. It is also difficult to fully determine due to the rarity of the condition, with some sample sizes ranging from n = 7 to n = 198.[84] This study found a mortality rate of 23.5% with a wide range of 6% to 64%.

In the United States, NSTI accounted for 4.8 deaths per 1,000,000 person-years, with no significant change between 2003 and 2013.[85] Many studies have been published assessing risk factors for mortality in NSTI, with advanced age, immunocompromised status, shock, multi-organ failure, and in some cases, the microbiologic characteristics being identified as risks.[86,87]

PREVENTION AND INFECTION CONTROL

The role of postexposure prophylaxis in preventing instances of NSTI is unclear at this time, and the best available data focus on the prevention of GAS-related NSTI. Household contacts of invasive GAS have a much higher risk of invasive GAS by up to 2000-fold.[88] There have been cases reported of nosocomial transmission of necrotizing fasciitis.[89] If patients have significant risk factors such as marked immunocompromising condition (ie, organ transplantation, untreated HIV infection, undergoing cytotoxic chemotherapy, etc) or recent surgical procedure, it may be reasonable to offer post-exposure prophylaxis to patients. Most data suggest use of a beta-lactam such as penicillin or amoxicillin orally for 10 days.[90] Contacts of patients with invasive GAS infections who have been in close proximity for more than 20 hours are recommended to receive post-exposure prophylaxis.[91]

While there is no currently available vaccination available for preventing NSTI, it is an enticing target from a public health perspective in preventing both GAS pharyngitis, as well as GAS-related NSTI due to the large burden of disease globally. There are currently 8 products in development, 4 of which target M-protein and 4 of which target non-M-protein antigens. An excellent review article discussing the history of GAS vaccination development is available, and the reader is referred there for a more detailed review.[92]

When patients are admitted to the hospital with NSTI, infection control guidance suggests that, in addition to standard precautions, patients should be placed on contact precautions, plus droplet precautions for the first 24 hours of appropriate antimicrobial therapy if invasive GAS disease (NSTI) is suspected. After the first 24 hours for GAS infections, standard precautions alone can be resumed. Droplet precautions are not necessary for *S. aureus*, whether methicillin-susceptible or methicillin-resistant, but most hospitals utilize contact precautions for MRSA for the duration of the hospital stay.[93] There is no specific guidance for other pathogens, which cause NSTI, so standard precautions are usually recommended.

SUMMARY AND DISCUSSION

In summary, necrotizing soft tissue infections remain life-threatening infections necessitating early recognition, aggressive surgical intervention, and rapid administration of appropriate antimicrobial therapy. The incidence of necrotizing soft tissue infections is difficult to measure accurately as a result of insufficient or non-existent monitoring programs, as well as inconsistent verbiage and classification systems. Clinical diagnosis remains challenging in many cases, and lack of access to appropriate surgical expertise can compromise patient care and risk life and limb for the patient. Emergent surgical exploration and debridement remains the cornerstone of management along with administration of appropriate antimicrobials. Anti-toxin therapies serve as important adjuvants to care, while other treatments such as IVIM and HBO therapy are more controversial. Morbidity and mortality for necrotizing soft tissue infections remains high despite extensive advances in medical care, highlighting the importance of investment into the detection, diagnosis, and management of these infections.

CLINICS CARE POINTS

- Necrotizing soft tissue infections are life threatening infections, which require a high index of suspicion to diagnose appropriately.
- The microbiology can be predicted based on risk factors, which can assist in appropriate choice of antimicrobial therapy.
- Emergent surgical assessment and debridement to control the source of infection remains the mainstay of therapy.
- Further research is necessary to improve early detection of necrotizing soft tissue infections.

DISCLOSURES

The authors have nothing to disclose.

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