NECROTIZING SOFT-TISSUE INFECTIONS (NSTIs): A REVIEW ARTICLE
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ABSTRACT: Necrotizing Soft-Tissue Infections (NSTI) are a dreaded form of infections of the layers within the soft tissue compartment (dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle) that are associated with necrotizing changes and systemic toxicity. These spread rapidly and carry high mortality (16%-24%). These infections can present with trivial features like small ulcers or mild cellulitis. Gram staining is important for empirical treatment and specific treatment starts after culture and sensitivity of the toxic fluid according to the organisms isolated. Even after the advancements of antibiotics, adequate surgical debridement remains the mainstay in limiting the spread of the infection. Novel therapeutic management like hyperbaric oxygen, Intravenous immunoglobulin have been developed but with limited success. Various prognostic scoring systems are present to predict the morbidity and mortality associated with these infections which help to identify high-risk patients who may benefit from the new therapeutic strategies. Care for patients with NSTIs requires an approach with expertise from critical care, surgery, reconstructive surgery, and rehabilitation specialists.

KEYWORDS: Necrotizing Soft Tissue Infections, Infection, Sepsis, Debridement.
MESHTERMS: Infection, Sepsis.

INTRODUCTION: Necrotizing soft-tissue infections (NSTIs) are defined as infections of any of the layers within the soft tissue compartment (dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle) that are associated with necrotizing changes and systemic toxicity. First described by Jones in 1871, they were initially termed as “hospital gangrene.” In 1951, Wilson coined the term “necrotizing fasciitis” to encompass some of these infections.¹ The use of the term “necrotizing soft-tissue infections” has been emphasized to include all the necrotizing infections and accentuate a targeted approach for diagnostic and treatment strategies.

CLASSIFICATION: NSTIs can be classified according to depth of tissue involvement, severity of infection, or microbiology. The Food and Drug Administration classifies infections of skin and soft tissues as either complicated or uncomplicated.² Necrotizing infections are categorized into three types according to the microbes involved.

Type I Infections: Type I infections are the most common type of NSTI and are responsible for 80% or more of infections. On average, four or more organisms are isolated from Type I infections, and usually include a mix of aerobic and anaerobic bacteria. The most common aerobic species isolated from these infections are streptococci, however, staphylococci, enterococci, and the family of Gram-negative rods are also found. Bacteroides species are the most common anaerobes involved and are found in more than half of cases, while peptostreptococci are isolated from approximately one-third of patients.³,⁴
The involvement of multiple organisms in Type I infections is likely due to the presence of multiple pathogenic organisms at the nidus of infection and also may represent an underlying failure of the host immune system. Diabetes mellitus, obesity, peripheral vascular disease, chronic kidney disease, and alcohol abuse are commonly found in this group of patients.

Several Type I infections are named based on their anatomical location. Fournier’s gangrene is a necrotizing infection involving the perineum or genital areas. Ludwig’s angina is a polymicrobial infection involving the submandibular space that can extend into the fascial planes of the neck and mediastinum and is also known as cervical necrotizing fasciitis. Most of the cases have an odontogenic etiology. Similarly Meleneey’s gangrene is supposed to be usually of abdominal wall after an abdominal surgery.

**Type II Infections:** Type II infections were originally thought to be caused only by beta-hemolytic streptococcal species. These infections account for 10% to 15% of NSTIs. Staphylococcus aureus, especially methicillin-resistant species, is increasingly associated with Type II NSTIs, either as a single isolate or in conjunction with streptococci. Typically, these infections originate from an apparent minor injury that provides a portal of entry for the bacteria or creates an environment where hematogenously transported bacteria can thrive. These infections have been associated with non-steroidal anti-inflammatory drug use also.

**Type III Infections:** Clostridial myonecrosis is the prototypical Type III infection. Clostridia are ubiquitous, Gram-positive, anaerobic, spore-forming bacilli found in soil. They are not strict anaerobes, but nonetheless need to be inoculated deeply into tissues in an environment of low oxygen tension to be pathogenic. These infections typically occur as a result of a deeply penetrating wound or a crush injury that is accompanied by local devascularization.

Clostridial myonecrosis has also been reported following intestinal surgery, black tar heroin injection (skin popping), and in association with obstetrical complications, such as retained placenta, prolonged rupture of membranes, and spontaneous abortion. Clostridium perfringens is the most common pathogen of this species. Spontaneous clostridial myonecrosis also can be due to C. septicum and occurs in association with a gastrointestinal or hematogenous malignancy in 80% of patients. In contrast to patients with traumatic myonecrosis, those with spontaneous infections are often immunosuppressed or have a malignancy.

Type III infections are highlighted by rapid progression, which can measure up to 2 cm/hour. This feature is related to an impressively muted host response and an elaborate set of bacterial toxins. The theta-toxin has phospholipase C activity and is lytic to many cell lines, including red blood cells, myocytes, fibroblasts, platelets, and leukocytes.

Several water-borne bacterial infections can cause NSTI and are not readily classified by the above-mentioned system. Necrotizing infections following exposure to a water-borne agent are almost always attributable to either Vibrio vulnificus or Aeromon ashydrophilia. Vibrio is a Gram-negative bacterium that occurs in marine and estuarial environments. The majority of infections related to Vibrio occur after handling sea food, often during a recreational water activity. Most patients who develop these infections have underlying liver disease, such as alcoholic cirrhosis, chronic hepatitis, or hemochromatosis.
Virulence is related to a toxin that produces a reactive oxygen species. Aeromonas hydrophilia, formerly considered part of the Vibrio family, is a Gram-negative bacillus that is primarily a fresh water organism. Infections can occur in immunocompetent hosts, as demonstrated by the high rates of wound isolates after the 2004 Indian Ocean tsunami.11

Rarely, NSTI can be due to fungi. The three most common human pathogens are Rhizopus, Mucor, and Rhizomucor. Rhino-orbital-cerebral and cutaneous involvement typifies these unusual NSTIs. Mucormycete spores are ubiquitous and can migrate to susceptible soft tissues by inhalation or ingestion, or can be directly inoculated into wounds.12

Conditions predisposing to these infections include diabetes mellitus, hematologic malignancies, organ transplantation, steroid use, acquired immunodeficiency syndrome, treatment with desferoxamine, and iron overload. Rhizopus contains a ketone reductase, which allows the fungus to grow in the glucose-rich, acidic environment frequently found in patients with diabetic ketoacidosis.

**Risk Factors:** Several risk factors have been described like Age greater than 50 years, Atherosclerosis, Burns, Cancer or other immunocompromised state, Chronic alcoholism, Corticosteroid use, Diabetes mellitus, Hypoalbuminemia, Intravenous drug abuse, malnutrition, Obesity, Occult diverticulitis, Peripheral vascular disease, Postoperative infection and Trauma.13

**Clinical Features:** NIs may present as mild cellulitis or a small ulcer. Events predisposing patients to soft tissue NIs include mild trauma, insect bites, drug reactions, illicit drug injections, perianal abscesses, major traumas, and surgical procedures. The most frequent spontaneous site of the infectious gangrenes is in the perineum, but the extremities are the most common sites of involvement. The frequent association of soft tissue NIs with underlying risk factors is diagnostically helpful; however, these skin and soft tissue NIs do occur in healthy individuals as much as 30% of the time.13

There is no clinical evidence of skin death initially in NI. Severe pain and systemic symptoms that occur out of proportion to the local infection characterize clostridial infections. As the clostridial infection progresses, the skin may develop a bronze color, followed by hemorrhagic bullae, then dermal gangrene, and finally crepitus. Clostridial exotoxins produce extensive tissue necrosis, with minimal hyperemia, fibrin formation, or neutrophil infiltration seen within the affected tissue. Nonclostridial infections are most likely to be associated with erythema, pain, and swelling but frequently are initially identical to simple cellulitis.

Failure to respond to antibiotics, rapid progression, or evolving systemic signs of infection are significant clues that NI may be present. The patient generally appears ill and has a rapid pulse and significant temperature elevation. Sometimes, unique finding of necrotizing fasciitis is numbness of the involved area that is probably due to infarction of the cutaneous nerves located in necrotic subcutaneous fascia and soft tissue.14 Some patients with necrotizing fasciitis may present with localized pain of the involved site, and the overlying skin is erythematous, hot, and edematous.

An apparent superficial cellulitis that fails to respond to standard therapy must raise suspicion of a more extensive underlying subcutaneous infection. Moderate to severe pain of the skin of an infected area is characteristic of group A streptococcal infections that develop into streptococcal gangrene. Excruciating pain is a significant clinical symptom of clostridial myonecrosis.
**Diagnosis:** The most important discriminative information to be established in patients with soft-tissue infection is the presence of a necrotizing component. This will confirm NSTI, and by definition, will identify patients that require surgical debridement. A high index of suspicion is necessary to diagnose NI. Patients with injection drug use and chronic debilitating co morbidities (e.g., diabetes mellitus, immune suppression, and obesity) should be evaluated to confirm or rule out NSTI.

Clinical characteristics, on the other hand, can help to raise the index of suspicion for NSTI. Initial signs and symptoms usually include swelling, erythema, pain, and tachycardia, and once the infection progresses, more typical signs and symptoms can be observed, including tense edema outside the area of compromised skin, pain disproportionate to appearance, skin discoloration (ecchymosis), blisters/bullae and necrosis, and crepitus and/or subcutaneous gas.

Systemic findings include fever, tachycardia, hypotension, and shock. It is important to emphasize that, although these findings are typical and fairly specific for NSTI, their sensitivity is low, and they are present in only 10%–40% of patients with NSTI.

**Diagnostic Tools:** The various investigations useful are hematological investigations as Complete Haemogram, Biochemical investigations as renal function tests, liver function tests, C Reactive Protein etc; Imaging studies as X ray, Computed tomography, Magnetic resonance imaging with intravenous gadolinium contrast medium; microscopic examination especially of pus, incised tissue biopsy with frozen section evaluation; Gram’s stain and microbiologic culture of tissue and exudates. Further, Fine-needle or large-bore needle aspiration with Gram’s stain and culture of aspirate may be helpful.

Wall et al (2000) performed a retrospective study and compared a set of admission variables of patients with NSTI and patients with non-necrotizing soft-tissue infection and found that having a WBC count >15, 400 cells/mm$^3$ or a serum sodium level <135 mmol/L was associated with NSTI and that a combination of both increased the likelihood of NSTI. It proved to be a very sensitive tool, with a negative predictive value (NPV) of 99%, but not very specific, with a positive predictive value (PPV) of only 26%.$^{15}$ Wong et al. (2004) created a score (laboratory risk indicator for necrotizing fasciitis score- LRINEC) to discriminate between NSTI and non-necrotizing soft-tissue infection.$^{16}$ The total score had a range of 0–13, and patients were categorized according to the risk of NSTI among 3 groups. After internal validation, Wong and colleagues showed that, for intermediate and high-risk patients (score>16), the score had a PPV of 92% and a NPV of 96%. This constitutes a great tool for both confirming and discarding NSTI and has the advantage that it is based on laboratory variables that are easily available.

**Imaging Studies:** Plain Radiography can only help to identify subcutaneous gas. This is a very specific finding, but it is not very sensitive in patients with NSTI. Computed tomographic (CT) scans provide an accurate picture of the presence and the extent of abnormal soft tissue gas dissecting along fascial planes, which is almost always diagnostic of necrotizing fasciitis. Other suspicious findings evident on rapid helical CT include fascial stranding, and asymmetric thickening of fascial planes.$^{20}$ Magnetic resonance imaging (MRI) with gadolinium contrast enhancement can accurately determine the presence of necrosis of fascia and the extent of the infectious and necrotic process. Unfortunately, the time required to obtain an MRI scan in an unstable patient with sepsis may be excessive and life-threatening.$^{17,18}$
Macrosopic and microscopic Tools: Examination of a frozen section biopsy specimen from the compromised site that includes deep fascia and possibly muscle has been recommended as a means to achieve earlier diagnosis of NSTI in patients.\textsuperscript{19,20} A bedside frozen tissue section biopsy is an expedient method to establish the diagnosis on the basis of typical histologic changes of subcutaneous necrosis, polymorphonuclear cell infiltration, fibrinous vascular thrombosis with necrosis, microorganisms within the destroyed fascia and dermis.\textsuperscript{20}

Biopsy can also identify fungi in the tissue and fungal invasion with thrombosis of blood vessels. Tissue biopsy with Gram's stain of the exudate may also reveal the characteristic finding of clostridia organisms, which appear as Gram-positive rods with blunt ends resembling boxcars. Fine-needle or large-bore needle aspiration is another method by which to establish the diagnosis and direct antimicrobial therapy.

Inability to obtain fluid, however, is non-diagnostic and does not rule out NI. Tense edema of an extremity should be evaluated by measuring muscle compartment pressure. Easy passage of a probe along a plane between the subcutaneous tissue and deep muscle is suggestive of necrotizing fasciitis.

It is preferable to explore the compromised area during an operation and certain findings give a strong suspicion of NSTI. These findings include gray necrotic tissue, lack of bleeding, thrombosed vessels, “dishwater” pus, noncontracting muscle, and a positive “finger test” result, which is characterized by lack of resistance to finger dissection in normally adherent tissues.

Microbiology: The majority of NIs resulting in necrotizing fasciitis consists of a mixture of beta-hemolytic streptococci (90%), anaerobic Gram-positive cocci, aerobic Gram-negative bacilli, and Bacteroides species. A single organism, with the unusual exception of Group A beta-hemolytic streptococci (GAS), rarely causes an infection resulting in necrotizing fasciitis. Necrotizing fasciitis occurs when a mixed variety of organisms—aerobic and anaerobic—in invade the subcutaneous tissue and fascia in a synergistic fashion.

Bacterial synergistic gangrene is primarily a subcutaneous gangrenous infection caused by the same organisms as those that cause necrotizing fasciitis, but there is no involvement of any fascial tissue. Classically, cultures yield the combination of a microaerophilic nonhemolytic streptococcus in the spreading periphery of the lesion and Staphylococcus aureus found in the zone of gangrene. Streptococci can be accompanied by a variety of other organisms, such as Proteus, Enterobacter, Pseudomonas, and Clostridium species.

The clinical course of bacterial synergistic gangrene is frequently slow but initially should be treated as an infectious gangrene until the lack of fascial involvement is recognized. Streptococcal gangrene is caused only by toxigenic strains of GAS. Acute streptococcal gangrene is usually a rapidly advancing gangrenous infection associated with severe toxic symptoms (eg, streptococcal toxic shock syndrome).

Clostridial and mycotic infections must be considered in any initial evaluation of skin and soft tissue NIs, despite their relatively rare occurrence. Clostridial infections should be suspected when necrotic muscle is found during debridement of an infectious gangrene with severe systemic toxicity associated with clinical central nervous system manifestations. Patients with malignancies are particularly prone to NIs caused by Clostridium septicum.
NIs can be caused by marine vibrio species, but cases are rare and usually are associated with chronic liver disease and immune-compromised states. Mucormycosis (ie, Zygomycetes infection) can produce an aggressive gangrenous infection because of its ability to invade directly and thrombose blood vessels, which results in infarction of tissue.

**Treatment:** The treatment for NSTI involves the following principles: source control, antimicrobial therapy, support, and monitoring. Source control is of utmost importance in NSTI. Early and complete debridement is essential for the treatment of NSTI along with appropriate broad-spectrum antibiotic coverage, combined with adequate organ support and close monitoring. Care for patients with necrotizing soft tissue infection requires a team approach with expertise from critical care, surgery, reconstructive surgery, and rehabilitation specialists.

**Initial Treatment of necrotizing Infection:** Under the preliminary guidance of Gram-stained smears while aerobic and anaerobic tissue and blood cultures are in progress, a triple regimen of IV antibiotic coverage is appropriate to cover the diverse and varied causative bacteria:

- Penicillin or ampicillin for clostridia, streptococci, and Peptostreptococcus.
- Clindamycin/metronidazole for anaerobes, Bacteroidesfragilis, Fusobacterium, and Peptostreptococcus. Clindamycin may be useful for treating GAS in patients with the toxic streptococcus syndrome because it inhibits toxin production.
- Aminoglycoside for Enterobacteriaceae (ie, Gram-negative organisms). Gentamicin has a synergistic effect with penicillin against streptococci.

Imipenem and meropenem, by virtue of their high beta-lactamase resistance, wide-spectrum efficacy, and inhibition of endotoxin release from aerobic (ie, Gram-negative) bacilli, may be the initial agents of choice for treatment of the frequent polymicrobial infections that result in necrosis or skin and soft tissue. Postoperative antibiotic coverage is adjusted on the basis of microbiologic testing results from cultures of tissue and blood. The most common organisms not adequately covered by initial antibiotic therapy are enterococci.

Tetanus prophylaxis with absorbed tetanus toxoid and passive immune coverage with tetanus hyperimmune globulin are indicated in the management of all high-risk wounds, because tetanus is an occasional complication of necrotizing lesions of any infectious gangrene. Patients with mucormycosis and progressive necrotizing lesions are at high risk of death. Once invasive mucormycosis has been demonstrated, treatment with amphotericin B or liposomal formulations for patients with renal dysfunction must be started promptly.

Clostridial infections may initially be recognized at the time of surgery by the identification of necrotic muscle. Complete debridement of all necrotic tissue must be performed in NIs during the initial operative procedure. Amputation of an extremity should be considered early in the treatment of clostridial gangrenous infections as it may be lifesaving. High-dose IV penicillin should be administered; clindamycin or metronidazole is substituted for patients with penicillin allergy.

Whenever NSTI has been confirmed surgical debridement is indicated. Debridement of the necrotic tissue should be undertaken as soon as possible. When comparing earlier and complete with delayed or incomplete debridement, mortality always has been significantly lower with the most
aggressive strategy. During the operation, a generous incision is performed and macroscopic findings of the disease are used to help guide the extent of the debridement.

If needed, the incision is extended to allow for complete debridement of the infected or necrotic tissue. Occasionally, amputation of a limb is necessary to achieve this goal. Healthy, viable, bleeding tissue should be present at the edges of the excision site, and aggressive resuscitation should accompany the perioperative period.

Once the initial debridement has been done, management in an intensive care unit is recommended, and scheduled debridements at intervals of 6–48 h should be performed until no further necrosis or infected tissue is seen. Close monitoring of the physiology of the patient, as well as serial WBC counts, should be performed every 6–12 h. Any additional physiologic derangement or increase in the WBC count at a time earlier than planned re-debridement should prompt more frequent reoperations.

Patients with NSTI may develop organ failure, such as acute renal failure and acute respiratory distress syndrome, which require supportive care. Appropriate early nutritional support helps control the catabolic response of these patients. Aggressive fluid resuscitation and blood component therapy is often required during the perioperative period. Judicious control of glucose, as well as novel therapeutic approaches for severe sepsis or septic shock, should be considered to optimize the host response to infection.

Hyperbaric oxygen has been advocated by different groups that argue for a decreased number of debridements and decreased mortality. A typical treatment protocol involves HBO, given aggressively after the first surgical debridement. Three treatment sessions, in a multi place chamber at 3 atmosphere absolute (ATA), 100% oxygen for 90 minutes each, can be given in the first 24 hours.

From the second day, twice daily treatments can ensue until granulation is obtained to a total of 10-15 treatments. Hyperbaric oxygen is not available at all institutions, and transportation of patients at least 3 times per day may become unsafe and may limit the ability to perform close monitoring and timely debridements.

Intravenous immune globulin has also been used in the treatment of NSTI, particularly if the NSTI is associated with group A streptococcal infection. These studies are also controversial and difficult to compare, given the small number of patients and the different methodologies used.

**Prognosis:** Mortality rates in patients of NSTI have been reported between 16%–24% in various series. A wide number of prognostic factors or predictors of mortality have been identified. Various scores have been created recently to stratify and predict the mortality associated with NSTI.

Anaya et al. (2009) created a score to categorize patients according to the risk of mortality which included age >50 years; WBC count >40,000 cells/cu mm; hematocrit >50%; heart rate >110 beats/min; temperature <36°C; and creatinine level >1.5 mg/dl. Patients were categorized in 3 groups, according to the risk of mortality. Tools like this should help to identify high-risk patients who may benefit from novel therapeutic strategies or for selection of patients for future trials.

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