Necrotizing Soft-Tissue Infection: Diagnosis and Management

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Necrotizing soft-tissue infections (NSTIs) are highly lethal. They are frequent enough that general and specialty physicians will likely have to be involved with the management of at least 1 patient with NSTI during their practice, but they are infrequent enough that familiarity with the disease will seldom be achieved. Establishing the diagnosis of NSTI can be the main challenge in treating patients with NSTI, and knowledge of all available tools is key for early and accurate diagnosis. The laboratory risk indicator for necrotizing fasciitis score can be helpful for distinguishing between cases of cellulitis, which should respond to medical management alone, and NSTI, which requires operative debridement in addition to antimicrobial therapy. Imaging studies are less helpful. The mainstay of treatment is early and complete surgical debridement, combined with antimicrobial therapy, close monitoring, and physiologic support. Novel therapeutic strategies, including hyperbaric oxygen and intravenous immunoglobulin, have been described, but their effect is controversial. Identification of patients at high risk of mortality is essential for selection of patients that may benefit from future novel treatments and for development and comparison of future trials.

Necrotizing soft-tissue infections (NSTIs) are infrequent but highly lethal infections. They can be 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. NSTIs are typically not associated with abscesses, although they can originate from an untreated or inadequately drained abscess. These infections were first described by Jones [1] in 1871 and at the time were termed “hospital gangrene.” Since then, multiple descriptions of NSTI have been published, and a wide number of terms, definitions, and classifications have been used [2–5]. In 1951, Wilson [6] coined the term “necrotizing fasciitis” to encompass some of these infections. However, still today, different terms are used to define and classify NSTIs, leading to confusion when referring to infections that have common pathophysiological and clinical characteristics and, most importantly, share a common management strategy [5]. We encourage the use of the term “necrotizing soft-tissue infections” to encompass all of these necrotizing infections and advocate an approach to all of them that uses the same principles for diagnostic and treatment strategies. This will allow for earlier diagnosis and expedited treatment, which are essential for improving outcomes and decreasing mortality in patients with NSTI.

The incidence of NSTI in the United States is estimated to be 500–1500 cases per year. A recent study that established the incidence of soft-tissue infection, using insurance databases from various states in the United States, determined the incidence of NSTI to be 0.04 cases per 1000 person-years [7]. Despite the relatively low incidence of NSTI, it is our observation that NSTIs occur often enough that surgeons, family physicians, internists, infectious diseases specialists, and others will encounter at least 1 patient with NSTI during their practice. Establishing the diagnosis of NSTI is probably the greatest challenge in managing these infections. Delay of diagnosis leads to delayed surgical debridement, which leads to higher mortality. It is for this reason that familiarity with the clinical characteristics, diagnostic tools, and principles of management is important when treating patients with NSTI.

The purpose of this article is to review the different tools available for diagnosis of NSTI early in its course. We will also review some of the treatment principles for all NSTIs and the
prognostic factors that can help identify high-risk patients who may benefit from additional therapeutic interventions.

**DIAGNOSIS**

Establishing the diagnosis of NSTI is not easy. The use of different terms to define different kinds of NSTI and the attempt to diagnose each of these is even more difficult and purposeless. 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. The first and most important tool for early diagnosis of NSTI is to have a high index of suspicion. Unfortunately, true risk factors for NSTI have not been identified. However, some conditions appear to be more commonly associated with NSTI and are worth considering when dealing with any kind of soft-tissue infection. These include injection drug use and chronic debilitating comorbidities (e.g., diabetes mellitus, immune suppression, and obesity) [8–10]. Patients that have any of these characteristics and present with soft-tissue infection should be evaluated to confirm or rule out NSTI. Other than injection drug use, the precipitating factor of NSTI does not appear helpful for establishing the likelihood of NSTI versus nonnecrotizing soft-tissue infection. In fact, most large published series show that, in ≥20% of patients with NSTI, the etiology is unknown, and the patients are considered to have idiopathic NSTI [11–13]. We have also observed that cases of NSTI without a recognized precipitating factor are more likely to be caused by group A streptococcal infection. More recently, NSTI without a recognized precipitating factor has also been identified with community-acquired methicillin-resistant staphylococcal infection [14].

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 [15, 16]. Also, the progression of these signs and symptoms is usually relatively fast, particularly if group A Streptococcus or Clostridium species are involved; however, in selected cases, NSTI can progress in a more insidious manner, which makes the diagnosis even more difficult to establish.

**DIAGNOSTIC TOOLS**

There are a wide variety of diagnostic tools that have been described and tested to diagnose NSTI more accurately and expeditiously. Even in the most experienced hands, clinical findings are not accurate enough for diagnosis, and both clinical clues and diagnostic tools should be used in combination to help make an early diagnosis [17].

**Laboratory findings.** Two studies have been reported to help discriminate between necrotizing and nonnecrotizing infections. In the first, Wall et al. [8] performed a retrospective study and compared a set of admission variables of patients with NSTI and patients with nonnecrotizing soft-tissue infection. After univariate and multivariate analysis, they found that having a WBC count >15,400 cells/mm³ or a serum sodium level <135 mmol/L was associated with NSTI and that a combination of both increased the likelihood of NSTI [8]. Wall and colleagues’ method 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%. In conclusion, Wall and colleagues’ method is a good tool to rule out NSTI, but it is not as good for confirming its presence.

More recently, Wong et al. [9] created a score (laboratory risk indicator for necrotizing fasciitis score) to discriminate between NSTI and nonnecrotizing soft-tissue infection. They compared a set of laboratory variables between patients with and without NSTI and identified 6 independent variables as-

<table>
<thead>
<tr>
<th>Value</th>
<th>LRINEC score, points</th>
</tr>
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<tbody>
<tr>
<td>C-reactive protein, mg/L</td>
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</tr>
<tr>
<td>&lt;150</td>
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</tr>
<tr>
<td>&gt;150</td>
<td>4</td>
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<tr>
<td>WBC count, cells/mm³</td>
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</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
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<td>1</td>
</tr>
<tr>
<td>&gt;25</td>
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<tr>
<td>Hemoglobin level, g/dL</td>
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<tr>
<td>&gt;13.5</td>
<td>0</td>
</tr>
<tr>
<td>11–13.5</td>
<td>1</td>
</tr>
<tr>
<td>&lt;11</td>
<td>2</td>
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<tr>
<td>Sodium level, mmol/L</td>
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<tr>
<td>&gt;135</td>
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<tr>
<td>&lt;135</td>
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<td>&gt;180</td>
<td>1</td>
</tr>
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</table>
Intermediate 6–7 50–75
termediate and high-risk patients (score, internal validation, Wong and colleagues showed that, for inc
soring to the risk of NSTI among 3 groups (table 2). After
nternal validation, Wong and colleagues showed that, for in-
termediate and high-risk patients (score, >6), 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 widely available
difficult across different institutions. Wong and colleagues’ method is
useful, however, only in the context of a diagnosed or strongly
spected severe soft-tissue infection.

Imaging studies. Plain radiography, ultrasonography, CT, and MRI have all been used to help diagnose NSTI. 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. CT has the additional advantage to identify other
causes of infection, particularly deep abscesses. There have been studies with ultrasonography, CT, and MRI, which try to iden-
tify specific findings present in patients with NSTI [18–23].
Most of these findings have shown that increased thickness of the
fascial layer with or without enhancement can be associated with
NSTI. The primary limitation of these studies is that they
tend to compare the involved site (usually a limb) with the
contralateral or uninvolved limb, rather than comparing it with a
nonnecrotizing soft-tissue infection. The studies show similar
results as clinical findings: high sensitivity but low specificity.
Additional studies with better methodology need to be per-
formed; however, the use of ultrasonography, CT, and MRI can be helpful for patients with other sources of infection and for
those for whom additional anatomic information may be
valuable.

Macroscopic and microscopic tools. Examination of a fro-
zened section biopsy specimen from the compromised site that includes
deep fascia and possibly muscle has been recom-
mended as a means to achieve earlier diagnosis of NSTI in
patients. Two studies evaluating this method also showed de-
creased mortality with historical comparisons, although this is
probably related to the fact that an earlier diagnosis can be
accomplished if clinicians are suspicious enough to perform
the biopsy [24, 25]. In our practice, we prefer to explore the
compromised area during an operation, rather than examine
a frozen biopsy specimen. We have found that frozen biopsy
is not very practical, because it requires availability and ex-
perience from the pathologists, and we are usually able to ex-
ploring the site and identify macroscopic findings consistent with
NSTI during an operation. 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. Once NSTI is confirmed, the incision
is extended, and additional debridement is performed. It is our
principle and recommendation to perform exploration of the
involved area through an operation whenever there is doubt
and likelihood for NSTI.

MICROBIOLOGY

No specific combination of bacterial species is either diagnostic
of NSTI or found in all cases. A wide spectrum of organisms
are commonly recovered (table 3). In a relatively recent series,
approximately two-thirds of cases were polymicrobial, and one-
third were monomicrobial, with the great majority of mono-
microbial cases being a result of gram-positive cocci.

TREATMENT

The treatment for NSTI involves the principles of treatment
for any kind of surgical infection: source control, antimicrobial
therapy, support, and monitoring. NSTIs, however, are excellent
examples of the important role of source control [26]. History

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of cases</th>
</tr>
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<tbody>
<tr>
<td>Streptococcus species a</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>26</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>17</td>
</tr>
<tr>
<td>Enterococci</td>
<td>14</td>
</tr>
<tr>
<td>Acinetobacter baumanii</td>
<td>13</td>
</tr>
<tr>
<td>Eschericia coli</td>
<td>12</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
<td>10</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>6</td>
</tr>
<tr>
<td>Proteus species</td>
<td>6</td>
</tr>
<tr>
<td>Bacteroides species</td>
<td>6</td>
</tr>
<tr>
<td>Fungi (Candida species)</td>
<td>5</td>
</tr>
<tr>
<td>Peptostreptococcus species</td>
<td>4</td>
</tr>
<tr>
<td>Clostridium species</td>
<td>2</td>
</tr>
<tr>
<td>Other b</td>
<td>10</td>
</tr>
</tbody>
</table>

NOTE: Data are adapted from [16].

a Includes Chryseobacterium species (1 case), Meningosepticum species
b Includes Propionibacterium species (2), Morganella morgagni (1), Veillonella species
(1), Bacillus species (1), Aeromonas species (1), Burkholderia pseudomallei (1), and Vibrio vulnificus (1).
has shown that when treatment is only based on antimicrobial therapy and support, mortality approaches 100%. It is clear that early and complete debridement is essential for the treatment of NSTI. Concomitantly, appropriate broad-spectrum antibiotic coverage, combined with adequate organ support and close monitoring, helps patients during the acute phase of the disease, but it is only the complete debridement of infected tissue that controls the infection and allows for future recovery.

Antimicrobial therapy is an adjunct to source control for the treatment of NSTI. Broad-spectrum antimicrobial therapy should be started early to include coverage for gram-positive, gram-negative, and anaerobic organisms. Special consideration for group A Streptococcus and Clostridium species should be taken. Acceptable regimens include monotherapy agents, such as imipenem, meropenem, ertapenem, piperacillin/tazobactam, and tigecycline. Multidrug regimens have also been described, including triple-drug therapy regimens, such as high-dose penicillin, high-dose clindamycin, and a fluoroquinolone or an aminoglycoside for coverage of gram-negative organisms. Vancomycin, daptomycin, or linezolid should be included in the regimen until methicillin-resistant staphylococcal infection has been excluded. The use of protein synthesis inhibitors, such as clindamycin, may help by inhibiting toxin production, which can be crucial for controlling the inflammatory response in patients with NSTI, particularly in those with clostridial and streptococcal infections [27]. Antimicrobial administration should be continued until no further debridements are needed and the patient’s physiology has improved. Prolonged courses of an arbitrary duration are not necessary and may predispose the patient to wound colonization with drug-resistant organisms.

Whenever NSTI has been confirmed surgical debridement is indicated. Some researchers also advocate surgery as a means for diagnosis in patients for whom clinical and laboratory findings are still not conclusive and for whom the diagnosis of NSTI is still possible. Debridement of the necrotic tissue should be undertaken as soon as possible. Other researchers have clearly shown the impact of early and complete debridement on final outcome in patients with NSTI [15, 28, 29]. When comparing earlier and complete with delayed or incomplete debridements, 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 and is encouraged if that is the case. 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 redebridement should prompt more frequent reoperations.

Finally, physiologic support, combined with close monitoring in an intensive care unit setting, is encouraged. It is not uncommon to see patients with NSTI develop organ failure, such as acute renal failure and acute respiratory distress syndrome, which require replacement therapies. Appropriate early nutritional support, delivered enterally if possible, 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.

A series of experimental therapies have been reported in select groups of patients with NSTI. Hyperbaric oxygen has been advocated by different groups that argue for a decreased number of debridements and decreased mortality [30, 31]. Results from this strategy are contradictory, and no real epidemiologically based studies have been performed to elucidate the effect of hyperbaric oxygen in patients with NSTI. Certainly, hyperbaric oxygen therapy should not jeopardize standard therapy for NSTI—specifically, adequate and timely debridements. 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. According to the Canadian experience, it seems reasonable to use intravenous immune globulin in patients with group A streptococcal infection who have developed streptococcal toxic shock syndrome and in those with a high mortality risk (advanced age, hypotension, and bacteremia) [32]. In determining how to apply more novel therapies for patients with NSTI, it is paramount to select groups of patients who may have a higher risk of mortality and in whom the risk-benefit assessment of these therapies may favor their use.

Since the first description by Jones [1], mortality in patients with NSTI remains high. He reported a mortality rate of 46%, and a recent pooled analysis determined it to be ∼34% [15]. More recent series have reported mortality rates with a range...
of 16%–24%—a rate that, although lower than the rate 100 years ago, still accounts for high mortality associated with NSTI.

A wide number of prognostic factors or predictors of mortality have been identified. However, these are not universal and vary from series to series. In a recent study that included 350 patients with NSTI from 2 tertiary care referral institutions, Anaya et al. [12] created a score to categorize patients according to the risk of mortality. Variables included in the score included were age, >50 years; WBC count, >40,000 cells/mm³; hematocrit, >50%; heart rate, >110 beats/min; temperature, >36°C; and creatinine level, >1.5 mg/dL. Patients could be categorized in 3 groups, according to the risk of mortality (unpublished data). 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.

SUMMARY

NSTIs are relatively infrequent but highly lethal infections. They encompass a wide variety of soft-tissue infections associated with necrosis that share the same diagnostic and treatment principles. Establishing the diagnosis of NSTI is one of the biggest challenges in treating patients with NSTI. Accuracy increases with familiarity of clinical findings and knowledge of laboratory, imaging, and macroscopic and microscopic findings, all combined with a high index of suspicion. Surgical debridement is the primary means of treating NSTIs, and antimicrobial therapy and physiologic monitoring and support constitute adjuvant therapies. Scores that identify high-risk patients serve to guide novel therapeutic strategies and to identify patients for future trials.

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