Necrotizing Soft-Tissue Infections: Clinical Guidelines

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RECOMMENDATIONS

Standards

1. Prompt and aggressive surgical debridement is mandatory for the treatment of necrotizing soft-tissue infections (NSTIs); in particular, necrotizing fasciitis is a surgical emergency.
2. Broad-spectrum empiric antibiotics should be started immediately and should include coverage of both Gram-positive and Gram-negative organisms.

Guidelines

1. Hyperbaric oxygen (HBO) may have beneficial effects when used postoperatively in NSTIs.
2. High white blood cell counts and low serum sodium levels may help to clarify the diagnosis of NSTIs.
3. Supplemental enteral nutrition is usually necessary for patients with NSTIs. Indirect calorimetry may be useful in more accurately determining basal energy expenditure.

Options

1. Clindamycin should be considered in initial coverage for its effects on exotoxin production in group A beta-hemolytic *Streptococcus* (GAS) infections.
2. Vacuum-assisted closure devices may be helpful in secondary wound management after debridement of NSTIs.
3. Empiric vancomycin may be warranted during pending culture results to cover for the increasing incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in NSTIs.

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OVERVIEW

Purpose

The purpose of these guidelines is to examine existing data regarding the diagnosis and treatment of NSTIs and to provide an evidence-based and reasoned approach to the care of patients with NSTI.

Users

These guidelines target both physicians involved in the initial diagnosis and management of NSTI and specialists involved in the definitive treatment—including debridement and coverage procedures—of patients with NSTI.

Clinical Problem

NSTIs are rare but potentially fatal infections involving the skin, subcutaneous tissues, and muscle. Because of accompanying systemic illness and profound inflammatory response, these patients are typically critically ill and have prolonged intensive care unit stays. In addition, these patients have large, complex wounds and are often treated in specialized treatment centers such as burn units.[1,2]

PROCESS

A PubMed literature search was performed for topics relating to NSTIs including pathology, genetics, diagnosis, treatment options, outcomes, antibiotic therapy, plasma exchange, burn centers, HBO, wound coverage, and nutrition. References were classified as Class I evidence (prospective, randomized, controlled trials); as Class II evidence (prospective or retrospective studies based on clearly reliable data); as Class III evidence (clinical series, comparative studies, case reviews or reports); or as Technology Assessment (a study that examined the utility/reliability of a particular technology).

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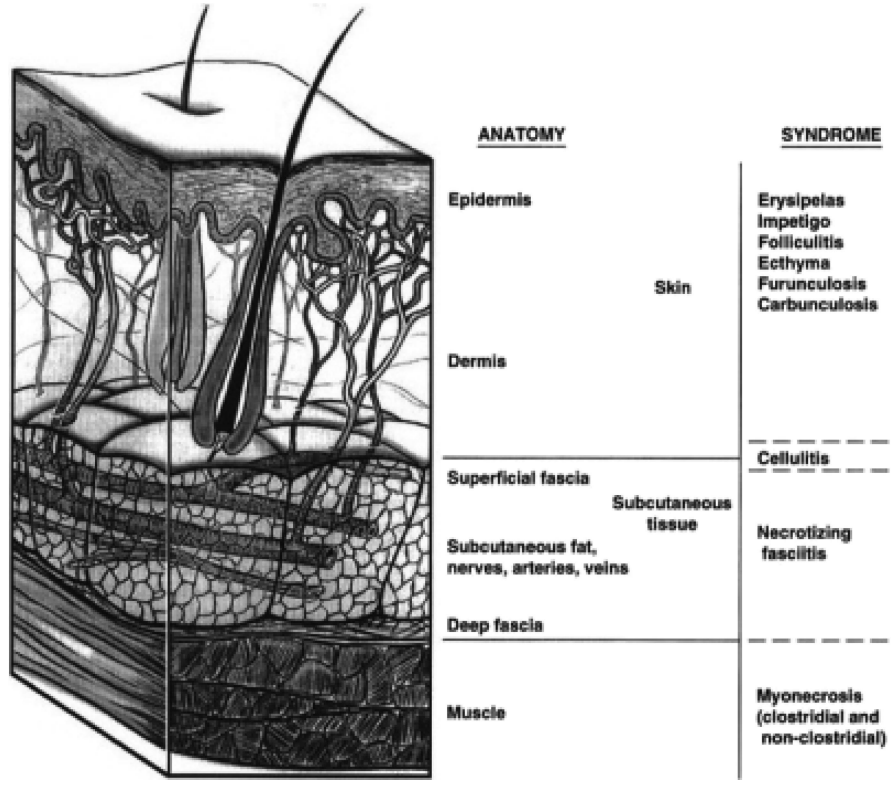
SCIENTIFIC FOUNDATION

The term NSTI is now commonly used to describe similar disease processes such as necrotizing fasciitis, Fournier's gangrene, Meleney's synergistic gangrene, and clostridial myonecrosis. Necrotizing fasciitis typically does not cause myonecrosis, but it can invade the deep fascia and muscle (Table 1). These invasive infections were classically thought to result from GAS pathogens, but it is clear that many are polymicrobial in nature.[3] This has led to the classifying of necrotizing fasciitis into two groups, with type 1 being polymicrobial and encompassing about 80% cases, and type 2 being GAS and making up approximately 20% of cases. The Centers for Disease Control and Prevention's Active Bacterial Core Surveillance program studied invasive GAS infections over a 4-year period and found that the incidence was 3.5 cases per 100,000 persons. Mortality of necrotizing fasciitis was 24% in their study population.[4] Others have reported mortality rates as high as 40% for intensive care unit patients with NSTI[5] and a 10-fold increase in risk of mortality if there is concurrent toxic shock syndrome.[6] Hospital costs can be a major burden, with mean costs reported from $60,000 to $115,000 in data from 2001 to 2004.[7,8] Patients with NSTI are often treated at facilities with burn centers for their complex wound management and critical care issues,[1,2] but it has been difficult to show any mortality benefit at burn centers because of variations in severity of NSTI treated at different institutions.[8]

The most common risk factor for development of NSTI is diabetes mellitus, with as many as 56% of patients having diabetes in one large series.[9] Other comorbidities that are common in patients with NSTI include obesity and hypertension.[3] Reported causative factors of these infections are numerous and include abcesses, traumatic, and surgical wounds,[10] intravenous drug abuse, decubitus ulcers, burns and perforated viscus, liposuction, infected arteriovenous grafts, and invasive cancer. As many as half of these patients may not be able to identify a previous lesion at the site of the NSTI[3,9] (Table 2). Causative organisms are numerous and often may be polymicrobial (Table 3).

Clinical findings may include swelling, pain, fever, erythema, induration, crepitus, skin sloughing or blistering, and purulent discharge. Later signs may include tachycardia, mental status changes, hypoten-

Table 1. Depth of Involvement With Varying Necrotizing Soft-tissue Infections



http://intmedweb.wfubmc.edu/grand_rounds/1998/necrotizing_fasciitis.html.

Table 2. Risk Factors for Development of NSTI

Preexisting Conditions
Immunosupression
Diabetes
Alcoholism
Peripheral vascular disease
Intravenous drug use
Hypertension
Corticosteroids
HIV
Age >50 yr
GI malignancy
Malnutrition
Major trauma
Surgery
Perforated viscus
Chronic liver disease
Chronic renal insufficiency
Obesity
Events preceding NSTI
Varicella with bacterial superinfection
Fractures
Liposuction
Seawater, seafood
Surgery
Spider bite
Childbirth, C section
Burns

NSTI, necrotizing soft-tissue infection; *GI*, gastrointestinal; *HIV*, human immunodeficiency virus.

sion, and weakness. Any anatomic site may be affected and multiple areas may be involved.[11] Cutaneous findings may be minimal, or they may progress to bulla formation and then to full-thickness necrosis. Erythema can be mistaken for cellulitis, but it will progress to purplish or blue color areas with bullae or vesicles draining a thin foul-smelling discharge. Patients with an elevated temperature, an elevated white blood cell count, and pain out of proportion to the clinical findings are especially concerning. Waiting for late manifestations to make the diagnosis can lead to gangrene, coagulopathy, systemic shock, and death.

Because the clinical picture may not always be straightforward, other diagnostic adjuncts have been proposed. Soft-tissue emphysema can be a sign of NSTI, but only half of patients with NSTI will have gas on plain x-ray studies.[9] Computed tomography, ultrasound, and magnetic resonance imaging scanning may reveal deep fascial thickening or enhancement and may better show fluid and gas in the soft tissue.[12] Waiting for further radiologic studies may delay proper therapy, so cases with a high degree of clinical suspicion should not be delayed from surgery to wait for radiologic study results.

The search for more rapid and reliable methods of diagnosing NSTI has led to the development of clinical scoring systems. A white blood cell count greater than 15.4×10^9/L combined with serum sodium less than 135 mmol/L had a sensitivity of 90% and specificity of 76% in one study.[13] Especially, high white blood cell counts may be a sign of clostridial infection, which is an independent predictor for both limb loss and mortality.[14] The Laboratory Risk Indicator for Necrotizing Fasciitis model uses C-reactive protein, white blood cell count, hemoglobin, sodium, creatinine, and glucose to create a scoring system with a positive predictive value of 92.0% and negative predictive value of 96.0% (Table 4).[15] A model using sodium and lactate has shown a high sensitivity but low specificity.[16] The Acute Physiology and Chronic Health Evaluation II score is not specific to NSTI but is an accurate predictor of mortality in this disease

Table 3. Causative Organisms in NSTI

Group A beta-hemolytic *Streptococcus* (p*yogenes*)
Anaerobes—*Bacteroides, Clostridium, Peptostreptococcus*
Group B *Streptococcus*, other *Streptococcus, Pneumococcus*
Staphylococcus aureus, including community-acquired MRSA
Vibrio specis (water, seafood)
Klebsiella pneumoniae, *Escherichia coli, Pseudomonas, Serratia*
Aeromonas hydrophilia (water)

NSTI, necrotizing soft-tissue infection; *MRSA*, methicillin-resistant *Staphylococcus aureus.*

Table 4. The LRINEC Scoring System

Variable	Values	Score
C-reactive protein	<150 mg/L	0
	≥150 mg/L	4
White blood cell count	<15 per mm^2	0
	15–25 per mm^2	1
	>25 per mm^2	2
Hemoglobin	>13.5 g/dL	0
	11–13.5 g/dL	1
	<11 g/dL	2
Sodium	≥135 mmol/L	0
	<135 mmol/L	2
Creatinine	<141 μmol/L	0
	>141 μmol/L	2
Glucose	≤10 mmol/L	0
	>10 mmol/L	1

A score of ≥6 is suspicious for NSTI, a score of ≥8 is highly predictive of NSTI.

NSTI, necrotizing soft-tissue infection; *LRINEC*, Laboratory Risk Indicator for necrotizing fasciitis.

Table 5. Evidentiary Table

Reference	Description	Data Class	Comments
Faucher et al[1]	Retrospective review of 57 patients	II	Burn center experience with NSTI, showed successful and cost-effective care
Barillo et al[2]	Retrospective review of 10 patients	II	Patients with NSTI transferred into a burn center needed frequent surgery and had high rate of complications
Endorf et al[3]	Retrospective review of 65 patients	II	High rate of polymicrobial infections, 46% of patients needed rehabilitation or further hospitalization after discharge
O'Loughlin et al[4]	Prospective collection of CDC surveillance data, 5,400 cases	II	Invasive group A *Streptococcus* cases only (including toxic shock syndrome), 13.7% mortality rate
Mehta et al[5]	Retrospective review of 62 patients	II	ICU patients with invasive group A *Streptococcus*, 40% mortality
Golger et al[6]	Retrospective review of 99 patients	II	Overall mortality 20%
Widjaja et al[7]	Retrospective review of 92 patients	II	Average in-hospital costs of $64,517 per NSTI patient
Endorf et al[8]	Retrospective review of 10,940 patients	II	Comparison of outcomes of NSTI patients at burn centers and nonburn centers
Elliott et al[9]	Retrospective review of 198 patients	II	Risk factors for mortality include delay in surgery. Hyperbaric oxygen hastens wound closure
Miller et al[10]	Retrospective review of 11 patients	II	Review of postprocedural NSTI
Wong et al[11]	Retrospective review of 89 patients	II	Advanced age, two or more comorbidities, and delay in surgery adversely affect outcomes
Wong and Wang[12]	Review of diagnostic techniques for NSTI	III	Radiologic findings in NSTI
Wall et al[13]	Retrospective review of 31 patients	II	Developed predictive model for NSTI using WBC $>15.4 \times 10^9$/L and serum Na <135 mmol/L
Anaya et al[14]	Retrospective review of 166 patients	II	Clostridial infection predictive of limb loss and mortality
Wong et al[15]	Retrospective review of 145 patients	II	Developed predictive laboratory model using WBC, hemoglobin, sodium, glucose, creatinine, and C-reactive protein
Yaghoubian et al[16]	Retrospective review of 124 patients	II	High lactate and low sodium predict mortality
Yilmazlar et al[17]	Retrospective review of 67 patients	II	APACHE II scores of 13 or higher risk factor for mortality
Brandt et al[18]	Retrospective review of 37 patients	II	Elderly and transplant patients at increased mortality risk. Early surgery is protective
Bilton et al[19]	Retrospective review of 68 patients	II	Higher mortality with delay in surgery
Endorf et al (unpublished data)	Retrospective review of 334 patients	II	Improved outcomes with early surgery in pediatric patients with NSTI
Gallup et al[20]	Retrospective review of 23 patients	II	Review of NSTI in obstetric and gynecologic patients, 13% mortality
Heinle et al[21]	Retrospective review of 29 patients	II	Improved wound closure in NSTI patients using mafenide solution for wound care
De Geus and Van der Klooster[22]	Case report	III	Use of vacuum-assisted closure in NSTI
Bronchard et al[23]	Case series of 6 patients	III	Vacuum-assisted closure is safe and decreases workload in patients with perineal NSTI
Akhtar et al[24]	Case report	III	Use of Integra in NSTI
Muangman et al[25]	Case series	III	2 patients with NSTI, successful graft taken with Integra and autograft

(*Continued*)

Table 5. (*Continued*)

Reference	Description	Data Class	Comments
Riseman et al[26]	Retrospective cohort study of 29 patients	II	Decrease in mortality and number of debridements in NSTI patients using hyperbaric oxygen
Korhonen[27]	Retrospective review of 33 patients	II	Increased subcutaneous tissue oxygenation with hyperbaric oxygen in perineal NSTI
Escobar et al[28]	Retrospective review of 42 patients	II	Low mortality and amputation rate using hyperbaric oxygen in NSTI
Shupak et al[29]	Retrospective cohort study of 37 patients	II	No difference in mortality or morbidity of NSTI patients treated with hyperbaric oxygen
Mascini et al[30]	In vitro comparison in 14 isolates of *Streptococcus pyogenes*	II	Clindamycin superior to penicillin in inhibiting exotoxin production in vitro
Zimbleman et al[31]	Retrospective review of 56 patients	II	Improved outcomes in invasive streptococcal infections with clindamycin plus beta-lactams vs beta-lactams alone
Wang et al[32]	Laboratory examination of MRSA isolates	II	Identification of new virulence factors in invasive MRSA infections
Dinubile and Lipsky[33]	Review of treatment guidelines in skin infections	III	Recommended antibiotic treatment durations in skin infections
Norrby-Teglund et al[34]	Case series of 7 patients	III	Successful use of intravenous immunoglobulin in NSTI patients
Cawley et al[35]	Case report	III	Successful use of immunoglobulin in a NSTI patient
Simmonds[36]	Case report	III	Successful use of plasmapheresis in a NSTI patient
Purnell et al[37]	Case report	III	Successful use of drotrecogin alfa in a NSTI patient
Graves et al[38]	Retrospective review of 26 patients	II	Patients with NSTI have increased energy requirements, averaging 124% of basal energy expenditure
Kotb et al[39]	Genetic analysis of patients with invasive streptococcal infection	II	Specific human leukocyte antigen class II haplotypes protect from severe systemic disease in invasive streptococcal infection
Walker et al[40]	Laboratory investigation of *streptococcus* isolates	II	DNase Sda1 influences bacterial switching to invasive group A streptococcal infection
Johansson et al[41]	Analysis of tissue biopsy specimens from NSTI patients	II	Bacteria-mediated inactivation of cathelicidin LL-37 is a bacterial resistance mechanism at the infected site in NSTI patients

NSTI, necrotizing soft-tissue infection; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *ICU*, intensive care unit; *WBC*, white blood cell; *APACHE*, Acute Physiology and Chronic Health Evaluation; *CDC*, Centers for Disease Control and Prevention.

process.[17] No laboratory-based scoring system should supplant careful physical examination or a high clinical suspicion.

The most important component in the treatment of NSTI is prompt and aggressive surgical debridement.[18] Early surgical intervention has repeatedly been proven to improve outcomes in both adults[19] and children (F.W.E., MD, unpublished data, 2008) with NSTI. All necrotic or infected skin and subcutaneous tissue should be radically debrided at the initial surgery. The extent of excision should be the tissue that gives way to moderate digital probing. Skin bridges and flaps should be avoided. Deep fascia and muscle should be inspected for potential involvement, which may herald invasion into the muscle (eg, streptococcal myositis or a clostridial infection). Fluid and tissue cultures should be sent for immediate Gram stain and culture. Early involvement of a plastic surgeon may be helpful in planning later coverage, especially if there is exposure of bone, tendon, or neurovascular structures.[20] Frequent repeat wound examination is mandatory, and any hints of ongoing infection, including an inadequate response to resuscitation, should initiate a second-look operation. On average, these patients require between four and five procedures on their initial hospital stay.[8]

Postoperative wound management consists of serial dressing changes initially, until the wound is free of recurrent or ongoing infection. Simple saline or Dakin's solution wet-to-dry or wet-to-wet dressing changes are appropriate. Furthermore, the use of 5% mafenide acetate solution has been shown to improve

the success rate of initial wound closure.[21] The vacuum-assisted closure device (Kinetic Concepts, Inc., San Antonio, TX) is increasingly being used in secondary wound management after debridement of NSTI.[22,23] After debridement is complete and the wound bed contains adequate granulation tissue, wounds not suitable for primary closure can be covered with split-thickness skin grafts. Integra has been used for reconstruction of large NSTI wounds—particularly wounds that cross large joints—but should be frequently inspected for signs of infection.[24,25]

The use of HBO has been investigated as additional therapy in the treatment of necrotizing fasciitis. Several studies have shown decreased morbidity and mortality when HBO is used postoperatively.[26,27] Some authors claim decreased rates of both mortality and amputations,[28] whereas others report no mortality benefit.[29] HBO therapy should not interfere with or delay aggressive, repeated surgical debridement.

Empiric antibiotic therapy is an important adjunct to operative debridement. Antibiotic regimens vary widely but typically consist of Gram-positive coverage with penicillin or extended-spectrum penicillin, Gram-negative coverage with aminoglycosides, cephalosporins, or carbipenems, and anaerobic coverage with clindamycin.[9] Clindamycin has also been shown in vitro to inhibit the production of streptococcal exotoxin[30] and has proven clinical benefit.[31] A commonly used combination is a continuous infusion of penicillin G in combination with clindamycin and an aminoglycoside if renal function permits. An increasing number of MRSA infections have been shown to have cytolytic properties causing NSTI,[32] and empiric MRSA coverage (eg, vancomycin) may be appropriate in areas with high rates of community and hospital-acquired MRSA. Review of culture data may permit tailoring of the antibiotic regimen. It is recommended to continue antibiotic therapy for 3 days after systemic signs and symptoms and most local signs of infection have resolved.[33]

Other pharmacologic adjuncts have been attempted, including intravenous immunoglobulin G, which has had success in several case reports.[34,35] Plasmapheresis has also been used in combination with surgery and antibiotics in severely septic patients, but the data are limited.[36] Recombinant activated protein C is commonly used in critically ill patients with severe sepsis, but use of this drug in patients with NSTI has only been noted in case reports.[37] Use of this drug may be limited due to potential bleeding complications in the large wounds and the need for serial surgical debridement. Patients with NSTI require aggressive nutritional supplementation to meet their increased metabolic needs. One study found that 94% of patients with NSTI needed either supplemental enteral or total parenteral nutrition, for an average of 24 days. Indirect calorimetry may be helpful to determine individual energy requirements in patients with NSTI, because of higher than predicted basal energy expenditure.[38]

SUMMARY

NSTI is relatively rare but potentially lethal. The principles of prompt, aggressive surgical debridement in combination with appropriate antibiotics continue to be the mainstays of therapy. Clinical scoring systems, especially those using white blood cell counts and serum sodium levels, may be helpful in clinically equivocal cases. HBO may have some benefit in the postoperative period. Supplemental nutrition is typically needed, and indirect calorimetry may better determine increased caloric needs. Secondary wound management may be aided by the use of vacuum-assisted devices.

KEY ISSUES FOR FURTHER INVESTIGATION

Much research has been devoted to finding causes for NSTI. Certain human leukocyte antigen haplotypes may predispose people to risk for necrotizing fasciitis, and others seem to be protective, suggesting some genetic factors in the development of NSTI.[39] Other studies show that bacteriophage-encoded DNases help bacteria escape from neutrophil traps and facilitate rapid spread in NSTI.[40] Bacterial exotoxins may mediate inactivation of human cathelicidins, which are important to host immune-defense mechanisms against bacterial infection.[41] Targets against these specific molecular mechanisms may be goals for future therapies.

EVIDENTIARY TABLE

Table 5 summarizes the current research pertinent to the management of patients with NSTI.

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