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NECROTIZING SOFT TISSUE INFECTIONS

SUMMARY

Necrotizing soft tissue infection (NSTI) is a broad term applied to infections of “flesh eating bacteria” that may cause cellulitis, fasciitis, or myositis. NSTI’s can rapidly progress to systemic toxicity, resulting in major morbidity and mortality without prompt recognition and treatment. This guideline reviews recommendations for diagnosis, antibiotic selection, and surgical debridement of NSTIs.

RECOMMENDATIONS

- **Level 1**
 - **Early operative intervention is paramount in necrotizing soft tissue infections (NSTI) and should involve wide debridement of all infected tissues.**
- **Level 2**
 - **The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score may be used to screen patients with suspected NSTI. A score > 6 should raise the suspicion of NSTI, whereas a score > 8 is highly suggestive of NSTI.**
 - **Recommended empiric antibiotics in NSTI include:**
 - **Ampicillin/sulbactam 3 gm IV Q6hr +/- vancomycin +/- clindamycin 900 mg IV Q8hr**
 - **Penicillin allergy: Ertapenem IV 1 gm Q24hr +/- vancomycin +/- clindamycin 900 mg IV Q8hr**
 - **If Clostridial myonecrosis is confirmed, tailor antibiotics to penicillin G IV 4 million IU Q4hr**
- **Level 3**
 - **Perform percutaneous needle aspiration at the site of suspected NSTI to evaluate for the presence of “dishwater-like” fluid and send the sample for Gram stain and sensitivity.**
 - **Wound closure should only be performed when there is no longer evidence of infection and the patient has been adequately resuscitated.**
 - **Intravenous immunoglobulin (1 gm/kg on day 1 then 0.5 gm/kg on day 2 and 3) may be considered in patients with Streptococcal toxic shock.**

INTRODUCTION

Necrotizing soft tissue infections (NSTI’s) are characterized by rapidly progressive necrosis of soft tissue planes due to bacterial infection. It was first described in 1871 during the American Civil War by Confederate Army surgeon Joseph Jones who treated some 2600 cases (1). The incidence appears to be increasing, with NSTI’s specifically due to Group A streptococcus reported to be 3.5 cases per 100,000 persons in the United States (2). Risk factors include diabetes mellitus, malnutrition, IV drug use, obesity, peripheral vascular disease immunosuppression, recent surgery, and traumatic wounds. The pathophysiology typically involves a point of entry such as a minor laceration or insect bite, but many

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

patients report no such event. The microbiology of NSTI's is divided into two major categories: Type I (polymicrobial, 80%) and Type II (monomicrobial, 20%). Frequently isolated causative organisms include Group A Streptococcus, Clostridia, Bacteroides, and Staphylococcus aureus (3).

The diagnosis of NSTI can be particularly challenging, as initial signs and symptoms can be subtle. Early findings include erythema, edema, pain, and fever. Increased scrutiny should be placed upon the presence of pain out of proportion to the physical examination, hemorrhagic skin bullae, grayish skin discoloration, and "dishwater-like" discharge. Crepitus can also occur with gas-forming organism but is not often present until late. As these initial symptoms can quickly progress to signs of systemic toxicity, altered mental status, tachycardia, and hypotension, vigilance is paramount (4). Laboratory tests including serum sodium < 135 mEq/L and white blood cell count > 14,000/mm³ have been shown to have good diagnostic accuracy (5). To quickly assess patients for the possibility of NSTI, Wong et al described the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score which is shown in the table below (6).

Table 1: Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) scoring system

Parameter	Value	Points
C-reactive protein (mg/L)	< 150	0
	> 150	4
WBC (mm ³)	< 15	0
	15-25	1
	> 25	2
Hemoglobin (g/dL)	> 13.5	0
	11-13.5	1
	<11	2
Sodium (mEq/L)	> 135	0
	< 135	2
Creatinine (mg/dL)	< 1.6	0
	> 1.6	2
Glucose (mg/dL)	< 180	0
	> 180	1

A LRINEC score of > 6 points should raise the suspicion of NSTI, whereas a score of > 8 points is strongly predictive (92%). While the diagnosis should possible based on physical findings and laboratory evaluation alone, it may remain difficult in patients with minimal symptoms or the morbidly obese patient with a deep seated infection. In these cases, computed tomography is sensitive for the presence of soft tissue stranding and edema of the muscle and fascial layers, and can demonstrate soft tissue gas. However, these findings are not mandatory for the diagnosis of NSTI and radiographic evaluation should never delay definitive surgical care. Percutaneous needle aspiration can rapidly be performed to asses for the "dishwater-like" fluid of NSTI, with the sample then being sent for Gram stain and culture to identify the causative organism (7). The presence of Gram positive rods indicates Clostridial infection.

LITERATURE REVIEW

Initial Management

Necrotizing soft tissues infections are a true surgical emergency and timely definitive care is essential. The main components of treatment are goal directed resuscitation, broad-spectrum antibiotic therapy, and surgical debridement. Most patients are septic with signs of shock and thus will require admission to an intensive care unit. Adequate fluid administration to resuscitation endpoints is essential. A Foley catheter should be placed to maintain urine output > 0.5 mg/kg/hr. Invasive hemodynamic monitoring may be indicated in some patients with a goal mean arterial pressure > 65 mmHg. Normalization of arterial lactate and base deficit should be sought. (1)

Antibiotic Selection

As previously noted, the majority of NSTI's are polymicrobial in nature. Thus, empiric antibiotic coverage for gram-positive, gram-negative, and anaerobic organisms is essential. Acceptable regimens advocated by the Infectious Disease Society of America are shown in the table below (8).

Table 2

First-line antimicrobial agent, by infection type	Adult dosage	Antimicrobial agent(s) for patients with severe penicillin hypersensitivity
Mixed infection		
Ampicillin-sulbactam	1.5–3.0 g every 6–8 h iv	Clindamycin or metronidazole ^a with an aminoglycoside or fluoroquinolone
or piperacillin-tazobactam	3.37 g every 6–8 h iv	
plus clindamycin	600–900 mg/kg every 8 h iv	
plus ciprofloxacin	400 mg every 12 h iv	
Imipenem/cilastatin	1 g every 6–8 h iv	...
Meropenem	1 g every 8 h iv	...
Ertapenem	1 g every day iv	...
Cefotaxime	2 g every 6 h iv	...
plus metronidazole	500 mg every 6 h iv	
or clindamycin	600–900 mg/kg every 8 h iv	
Streptococcus infection		
Penicillin	2–4 MU every 4–6 h iv (adults)	Vancomycin, linezolid, quinupristin/dalfopristin, or daptomycin
plus clindamycin	600–900 mg/kg every 8 h iv	
S. aureus infection		
Nafcillin	1–2 g every 4 h iv	Vancomycin, linezolid, quinupristin/dalfopristin, daptomycin
Oxacillin	1–2 g every 4 h iv	...
Cefazolin	1 g every 8 h iv	...
Vancomycin (for resistant strains)	30 mg/kg/day in 2 divided doses iv	...
Clindamycin	600–900 mg/kg every 8 h iv	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in methicillin-resistant <i>S. aureus</i>
Clostridium infection		
Clindamycin	600–900 mg/kg every 8 h iv	...
Penicillin	2–4 MU every 4–6 h iv	...

^a If *Staphylococcus* infection is present or suspected, add an appropriate agent. iv, intravenously.

Our institutional recommendation for a first-line agent is ampicillin/sulbactam (Unasyn). In patients with penicillin allergies, ertapenem (Invanz) is used as an alternative. While empiric monotherapy with either of these agents is acceptable, coverage for MRSA with an agent such as vancomycin is advisable as methicillin resistance is now found in over 60% of *Staphylococcus aureus* strains. In cases of confirmed Clostridium infection (gas gangrene), intravenous penicillin is the treatment of choice.

Clindamycin has been shown to have anti-toxin properties in necrotizing infections, although this has not been confirmed by Class 1 data. *In vitro* studies have shown that clindamycin inhibits production of staphylococcal toxin in toxic shock syndrome (9). Ohlsen et al were able to demonstrate inhibition of alpha toxin production by *Staphylococcus aureus* in the presence of clindamycin, whereas antibiotics such as beta-lactams and fluoroquinolones may actually induce expression (10). Thus, clindamycin has a theoretical therapeutic advantage in NSTI caused by certain strains of staphylococcus and streptococcus.

Antibiotic therapy should be tailored once culture and sensitivity results are available.

Surgical Treatment

Necrotizing soft tissue infections are true surgical emergencies and wide debridement must be undertaken. Multiple studies have shown that the elapsed time between onset of symptoms and initial operative debridement is the most important factor affecting morbidity and mortality (11). Infected appearing layers of skin, subcutaneous fat, and fascia should be removed until viable appearing tissue is encountered. Due to fluid within the tissue layers, finger dissection of the involved areas can often be performed quite easily. Muscle layers are usually spared from infection due to their generous blood supply. If the margin of viability is difficult to determine, frozen section can be helpful. Wounds should be thoroughly irrigated, and wet-to-dry dressings or vacuum-assisted closures can be placed to cover the wound. Fasciotomies or early amputation should be considered for NSTI of the extremities in the certain settings. NSTI of the perineum may require diverting colostomy to allow healing. All debrided areas should be re-examined routinely with repeat debridement performed as needed. Delaying repeat debridements increases mortality and risk of acute kidney injury, thus should be performed as early as feasible (12). Wound closure or grafting should only be performed when there is no longer evidence of necrotic tissue and the patient has been adequately resuscitated.

Adjunctive Therapies

Intravenous immunoglobulin (IVIG) has been advocated by some to neutralize Streptococcal and Clostridial exotoxins, however definitive data is lacking. In an observational study of patients with streptococcal shock syndrome, 30-day survival was 67% among those receiving IVIG and 33% for those who did not. However, patients in the IVIG group were more likely to have received clindamycin and undergone surgical debridement (13). Darenberg et al performed a double-blinded trial in which 21 patients with streptococcal shock syndrome were randomized to IVIG or placebo. While mortality was 3.6 times higher in the placebo group, this result failed to achieve statistical significance (14).

Hyperbaric oxygen is controversial in the management of NSTI, and there is little Class I data supporting its use. Hyperbaric oxygen is theorized to improve wound healing by increasing oxygen delivery and generation of reactive oxygen species. A nationwide database review of 405 patients found that those who underwent hyperbaric oxygen therapy for NSTI had a lower mortality (4.5%) versus those who did not (9.4%). However, this came at a price of increased overall length of stay and increased cost of hospitalization (15). The transport of a critically ill patient to the hyperbaric chamber and remaining there for several hours can be both challenging and dangerous, and thus may outweigh the potential benefits.

Outcomes

Necrotizing soft tissue infections carry a mortality risk of 16-45%. In a cohort study of 350 patients, Anaya et al identified six risk factors identified at initial evaluation of patients with NSTI that predicted mortality. These included: heart rate > 110 bpm, temperature > 36 C, creatinine > 1.5 mg/dL, age > 50 years, WBC > 40K, and hematocrit > 50 (16). Clearly, rapid diagnosis and treatment of NSTI is paramount and has the best outcomes. Amongst survivors, median survival is 10 years and many go on to die of infectious causes including pneumonia, urinary tract infections, cholecystitis, and sepsis (17).

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Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Gregory Semon, DO; Xi Liu, PharmD
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Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net