Necrotizing Fasciitis and Deep Soft Tissue Infections in the ICU

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Objectives

1. Describe the epidemiology and microbiology of necrotizing fasciitis and deep soft tissue infections.
2. Review common clues to the diagnosis of necrotizing soft tissue infections.
3. Review diagnostic tools used for necrotizing soft tissue infections.
4. Describe the management of deep soft tissue infections.
5. Review the role of IV immunoglobulin and hyperbaric oxygen therapy in the management of necrotizing soft tissue infections.

Key words: necrotizing fasciitis, necrotizing soft tissue infection

Abbreviations: CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus;* GAS = group A streptococcus; IVIG = IV immunoglobulin; NSTI = necrotizing soft tissue infection

Introduction

Necrotizing soft tissue infections (NSTIs) are infrequent but highly lethal infections associated with necrotizing changes of any of the layers within the soft tissue compartment. These infections may affect the dermis, subcutaneous tissue, superficial fascia, deep fascia, or muscle. The clinical spectrum ranges from invasive cellulitis to myonecrosis. Necrotizing fasciitis is characterized by widespread fascial necrosis with relative sparing of skin and underlying muscle. Many terms have been used interchangeably to describe this spectrum of disease. For example, necrotizing fasciitis limited to the perineal, genital, or perianal regions is referred to as Fournier's gangrene. Clostridial myonecrosis has been termed "gas gangrene" and primarily affects skeletal muscle. Though sometimes seen as discrete clinical syndromes, all NSTIs are associated with rapid progression of tissue necrosis due to angiothrombotic microbial invasion, and all are associated with a predilection for development of multiorgan dysfunction and death in the absence of early diagnosis and appropriate treatment. These similarities in the pathophysiology, clinical characteristics, and management strategy permit a common discussion of these clinical syndromes.

Epidemiology and Microbiology

About 500 to 1,500 cases of NSTI occur per year in the United States.[1] Although NSTIs occur in all age groups, they are most likely to occur in patients older than 50 years with comorbid medical conditions such as diabetes, hypertension, peripheral vascular disease, alcoholism or cardiopulmonary disease.[2-5] Other known predisposing factors include HIV infection, history of IV drug abuse, cancer, and corticosteroid use.[6] Surgical procedures, especially those involving the bowel, and blunt abdominal trauma may also increase the risk of NSTI.[7]

The majority of NSTIs are synergistic polymicrobial infections, often referred to as type I necrotizing fasciitis. A recent single-center review[5] of 89 patients treated for necrotizing fasciitis between 1997 and 2002 revealed multiple organisms in 54% of patients, a single organism in 28% of patients, and no organisms in 18% of patients. Streptococcal species were the most commonly associated isolates in this series (42% of positive culture results), consistent with other published data.[5,8] The majority of the positive culture results (66%) in this series were polymicrobial. Other organisms commonly recovered in NSTIs include *Staphylococcus* species, *Enterococcus* species, Enterobacteriaceae, *Bacteroides* species, anaerobic gram-positive cocci, various *Clostridium* species, and fungal species. Another study[4] of 182 confirmed cases of necrotizing soft tissue infections in a single center between 1985 and 1993 reported an average of 4.4 organisms in 154 (84.6%) of 182 original wound cultures. In recent years, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a prominent causative pathogen in community-acquired necrotizing fasciitis, occurring in 9 of 31 cases of necrotizing fasciitis over 15 months in one series.[9,10] All isolates were the USA 3000 CA-MRSA clone and carried the Panton-Valentine leukocidin virulence genes.[9] Other organisms associated with community acquired NSTIs include *Aeromonas* species and *Vibrio* species, including *Vibrio cholera, Vibrio vulnificus,* and *Vibrio parahaemolyticus,* and they are found classically in patients with cirrhosis with water or marine animal exposure.[11] *Candida, Aspergillus, Cryptococcus, Rhizopus,* and *Apophysomyces* have all been cultured from NSTI.[8]

Monomicrobial NSTIs, sometimes called type II necrotizing fasciitis, are most commonly associated with *Streptococcus pyogenes, S aureus, V vulnificus,* and anaerobic streptococci.[7] Group B streptococcus, classically associated with obstetric complications, is increasingly being reported as a causative organism in patients with diabetes who are not pregnant.[5] Among patients with liver disease, data suggest high rates of monomicrobial infections with gram-negative rods; 97% of 42 episodes in one series from Taiwan,[12] with majority of infections caused by *Vibrio* species (36%), *Klebsiella* species (21%), and *Aeromonas* species (14%). Monomicrobial *Klebsiella*-related necrotizing infections are associated with diabetes mellitus, and patients often have other septic foci of infection, such as liver abscesses and endogenous endolphthalmitis.[13,14] Multidrug-resistant *Acinetobacter* is also being increasingly reported as a causative organism in NSTIs.[15,16]

The wide spectrum of organisms associated with NSTI necessitate initial broad-spectrum antimicrobial coverage and wound cultures at initial surgical debridement to confirm involved pathogens in order to ensure appropriate antimicrobial coverage.

Clinical Diagnosis

Clinical diagnosis of NSTIs can be difficult because patients may have signs and symptoms of a simple soft tissue infection, or they may lack any symptoms whatsoever. Physical examination of patients with mental status changes or sepsis should include a complete skin exam. Although the groin, perineum, extremities, abdomen, and traumatic wounds are the most common sites of NSTIs,[4] there are increasing reports of NSTIs in atypical sites of the head and neck, such as the eyelids, face, scalp, and ear.[17] These atypical cases are most commonly linked to dental infections

and skin or mucosal injuries.[17]

Typical initial signs and symptoms include swelling, erythema, exquisite pain, and tachycardia that rapidly progresses to tense edema of the area surrounding compromised skin, pain out of proportion to lesions, skin discoloration, blisters/bullae and necrosis, crepitus, and subcutaneous gas.[18] As the disease progresses, patients become increasingly febrile and tachycardic, progressing to hypotension and shock.

Shock associated with NSTIs caused by group A streptococcus (GAS) is classically referred to as streptococcal toxic shock syndrome (STSS). Clinical criteria for a diagnosis of STSS requires the presence of at least one of the following: renal impairment, coagulopathy, liver dysfunction, acute respiratory distress syndrome, or a generalized erythematous macular rash.[14] STSS is believed to be caused by production of superantigens, notably pyrogenic exotoxins A, B, or C, and most commonly by M1 and M3 strains of GAS.[19] Toxic shock-like syndromes have also been associated with *Clostridium sordelli* infections secondary to obstetric complications and black tar heroin use among injection drug users.[11,20,21]

Findings of hypotension, skin crepitance or necrosis, bullae, or subcutaneous air are considered most specific of NSTIs but are only seen in less than 40% of patients.[4] Of 89 patients in a single-center study,[5] fever and hypotension were found in only 53% and 18% of patients, respectively, at presentation. Relative immunodeficiency associated with poorly controlled diabetes may blunt the immunologic response to these infections and account for the relatively low rates of a systemic inflammatory response at presentation. The most consistent finding in most cases is pain out of proportion to physical findings.[5] Bullae filled with serous fluid have also been suggested as a diagnostic clue that should raise suspicion for the disease.[5] Presence of risk factors or predisposing factors for NSTIs such as diabetes mellitus, immune suppression, or obesity should raise suspicion and prompt evaluation for a necrotizing component of soft tissue infections in these patients. Unfortunately, this is not enough to guarantee an early diagnosis because no clear etiology is found in ≥20% of patients eventually found to have NSTIs.[3] These cases without associated predisposing factors are more likely to be caused by GAS or CA-MRSA.[1,9]

Diagnostic Tools

Difficulties with clinical diagnosis have led to evaluation of a number of diagnostic tools to aid rapid and accurate diagnosis of NSTIs. These include the use of common laboratory findings, imaging studies, and tissue-based methods.

Laboratory Findings

Basic laboratory values may provide clues to the presence of a necrotizing soft tissue infection. In one retrospective analysis, Wall and colleagues[22] compared admission variables of patients with NSTI and non-necrotizing soft tissue infections, and found that a WBC count >15,400 cells/mm^3 or a sodium level <135 mmol/L was associated with NSTI. The combination of both was found to be a very sensitive tool with a negative predictive value of 99%. However, it is nonspecific with a positive predictive value of only 26%. This would suggest that the absence of leukocytosis or hyponatremia may reduce suspicion of NSTI, but their presence does not confirm diagnosis. The laboratory risk indictor for necrotizing fasciitis (LRINEC) score has been proposed for use as a model for predicting a necrotizing component to a soft tissue infection (Table 1). This model is based on a 13-point scale with weighted scores assigned to each of the following values: C-reactive protein, hemoglobin, WBC count, and serum sodium, creatinine, and glucose. After external validation, a score of >6 had a positive predictive value of 92% and a negative predictive value of 96% in intermediate- and high-risk patients.[23] This tool, however, has not done as well in other validation studies.[24]

Table 1—*The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score*

Parameter	Value	Score
Serum C-reactive protein (mg/L)	≥150	4 points
WBC count (cells/μL)	15,000-25,000	1 point
	>25,000	2 points
Hemoglobin (g/dL)	11-13.5	1 point
	<11	2 points
Serum sodium (mmol/L)	<135	2 points
Serum creatinine (mg/dL)	>1.6	2 points
Serum glucose (mg/dL)	>180	1 point

Adapted from Wong et al.[23]

Imaging Studies

Imaging should never delay surgical intervention when clinical suspicion is high for NSTI. In equivocal cases, imaging may be useful. Plain radiography may detect subcutaneous gas.[25] Though specific, subcutaneous gas on radiographs is not very sensitive; in one series, it was found in only 17% of patients, and it is often a late finding.[5,6] CT scanning is more sensitive and has the advantage of being able to identify other causes of deep infection such as abscesses.[1] Although MRI studies have reported high sensitivity rates of 93% to 100%, it also is nonspecific. More importantly, it is time consuming and may delay needed surgical intervention. Reported findings on MRI include subcutaneous thickening, with fluid collections and hyperintense signal of subcutaneous tissue and superficial fascia on T2- weighted images.[26] In patients in whom there is a low index of suspicion, ultrasound, CT scan, and MRI have the advantage of providing additional anatomic information and possibly identifying other sources of infection.

Tissue-Based Methods

Examination of frozen section biopsy specimens from affected sites has been evaluated and is associated with a decrease in mortality compared with historical controls.[27,28] The "finger test" is often seen in the literature in relation to necrotizing fasciitis. It involves the creation of a small surgical opening through which one can use a probe or finger to bluntly dissect to deep fascia. Ease of dissection of subcutaneous tissue to deep fascia is believed to be consistent with a diagnosis of necrotizing fasciitis.[3] The gold standard for detection of necrotizing soft tissue infections is tissue biopsy obtained at the time of wound exploration and surgical debridement. Overall, clinical suspicion remains central to making a diagnosis of NSTI regardless of any other ancillary tools of diagnosis.

Treatment

The management of NSTIs includes source control, antimicrobial therapy, close monitoring, and supportive care usually in an ICU setting. Early and complete debridement is required for source control and is the cornerstone of management of NSTI. Broad-spectrum antimicrobial therapy should also be started early in conjunction with close monitoring and appropriate supportive care.

Surgery

Early and adequate surgical debridement is the most important determinant of survival in NSTIs. Delay in debridement and inadequacy of the first debridement has been linked to an increased risk of death.[2,5,29,30] In one

series,[5] a 24-h or greater delay from admission to surgical debridement was associated with a mortality risk over nine times that of patients who received earlier surgical intervention. Immediate resection of all compromised tissue to healthy, viable bleeding tissue is essential for definitive management.[6] Repeat debridement in the days following initial debridement is generally necessary to control the necrotizing process. Many experts advocate for a second-look surgery within 24-36 h of the first surgery, and daily thereafter, until there is no longer a need for surgical debridement.[7] Patients require frequent wound checks through the course of care with surgical evaluation for further debridement if concerns arise for disease extension. Close management and follow-up with a surgical team is essential for management of all cases of NSTIs.

Antibiotic Therapy

Antimicrobial therapy is an important adjunct in the management of NSTIs. Initial antibiotic coverage should be broad and include coverage for gram-positive, gram-negative, and anaerobic organisms. Options for initial empiric coverage include β-lactam/β-lactamase inhibitor combinations (eg, piperacillin/tazobactam) or carbapenems (eg, imipenem, meropenem, or ertapenem) to cover gram-negative organisms and anaerobes. This should be combined with either vancomycin, linezolid, or daptomycin to cover for methicillin-resistant staphylococcal infection until it has been excluded. If GAS is suspected, clindamycin should be added to the regimen because it is not affected by inoculum size or the stage of bacterial growth; it suppresses toxin production[31]; it has inhibitory actions on protein synthesis, including streptococcal superantigens; and it has a long postantibiotic effect. This makes it an important component of initial NSTI regimens until streptococcal and clostridial infections have been excluded.[32] Inhibition of toxin production by clindamycin may also exert a beneficial effect for control of the inflammatory response in NSTI.[33] There are some data to suggest that linezolid may suppress production of GAS virulence proteins in a manner similar to clindamycin.[34] In patients who are allergic to penicillin, options for antibiotic coverage include vancomycin combined with a fluoroquinolone (eg, ciprofloxacin or levofloxacin) and clindamycin or metronidazole. Although blood culture results may be positive in about 20% of polymicrobial necrotizing infections, blood culture results may not completely reflect all organisms present in infected tissues.[5] Initial coverage should be tailored down based on microbiology data from initial debridement. High-dose penicillin plus clindamycin remain the drugs of choice for *S pyogenes* and clostridial necrotizing infections.[7,14] Antibiotics should be continued until no further surgical debridements are necessary. Continuing antibiotic therapy beyond that is arbitrary and may expose patients to an unnecessary prolonged course of antibiotics with the attendant risks of developing resistant infections.

Despite appropriate antibiotic therapy, thrombosis of blood vessels in many instances prevents effective antibiotic penetration, permitting accumulation of bacteria and bacterial toxins.[29] As such, in the absence of complete surgical debridement, sepsis will develop.

Supportive Care

These patients will invariably have ICU care needs both for monitoring and supportive care. Overwhelming sepsis with attendant respiratory, renal, or multiorgan failure is responsible for majority of the mortality in NSTI.[29] Shock syndromes should be managed appropriately with aggressive fluid resuscitation and vasopressors when indicated. Respiratory support, central cardiovascular monitoring, and hemodialysis may also be indicated. Adequate nutritional support may also improve outcomes, with a recommendation of twice the basic caloric requirements in the acute phase of management of NSTIs by some authors.[3,4,35]

Adjunctive Therapies

IV Immunoglobulin

Neutralization of streptococcal toxins by antibodies present in IV immunoglobulin (IVIG) may improve outcomes in patients with STSS. The role of IVIG in management of invasive group A streptococcal infection is supported both by case reports and case series, the largest of which showed an increase in 30-day survival from 34% to 67% in 21 patients with streptococcal toxic shock syndrome who received IVIG at a median dose of 2g/kg compared with historical control subjects.[36] Patients receiving IVIG were, however, more likely to have had surgical intervention and more likely to have received clindamycin. A subsequent double blind, placebo-controlled trial[37] of IVIG to placebo in 21 patients with STSS suggested a 3.6-fold higher mortality in the placebo group compared with the IVIG group. However, statistical significance was not achieved, and in the 13 patients with necrotizing soft tissue infections, there was no difference in time to stop further progression of necrotizing infection (69 h for the IVIG group vs 36 h for the placebo group).[37] Although primarily given as therapy for STSS, the use of IVIG in streptococcal NSTI remains controversial, with no consensus on optimal dosing or therapeutic window.[6]

Hyperbaric Oxygen Therapy

Like IVIG, the use of hyperbaric oxygen therapy in necrotizing soft tissue infections remains controversial. Some observational studies suggest a need for fewer debridements and lower mortality rates in patients treated with hyperbaric oxygen compared with untreated patients, with mortality rates of 7% vs 42% in one study[38] of 26 patients and rates of 23% vs 66% in another study[39] of 29 patients. In contrast, use of hyperbaric oxygen was associated with increased mortality, morbidity, and cost of therapy in a subsequent larger observational study of 42 patients with Fournier gangrene.[40] Use of hyperbaric oxygen is further limited by unavailability at most institutions and the difficulties of managing a critically ill patient in a pressurized chamber.

Conclusions

NSTIs, though relatively uncommon, are still associated with high mortality rates. A high index of suspicion is needed to make an early diagnosis given the paucity of signs on presentation in many cases. The most common diagnostic clues are pain out of proportion to physical findings, fever, and signs of systemic toxicity. While antibiotics, monitoring, and supportive care in a critical care setting are important components of care for patients with NSTIs, early and complete surgical debridement is necessary to reduce the significant morbidity and mortality associated with these infections.

Claim CME

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