Skin and soft tissue infections (SSTIs) span a spectrum of clinical entities from limited cellulitis to rapidly progressive necrotizing fasciitis, which may be associated with septic shock or toxic shock syndrome.\textsuperscript{1,2} These SSTIs may result in critical illness and require management in the ICU.\textsuperscript{3} The complex interplay of environment, host, and pathogen is important to consider when evaluating SSTIs and planning therapy. The key to a successful outcome in caring for patients who have severe SSTIs is:

- Early diagnosis and differentiation of necrotizing versus non-necrotizing SSTI
- Early initiation of appropriate empiric broad-spectrum antimicrobial therapy with consideration of risk factors for specific pathogens and mandatory coverage for methicillin-resistant \textit{Staphylococcus aureus} (MRSA).
- Source control of early SSTI (ie, early aggressive surgical intervention for drainage of abscesses and debridement of necrotizing soft tissue infections)
- Pathogen identification and appropriate de-escalation of antimicrobial therapy

In addition, appropriate critical care management, including fluid resuscitation, organ support, and nutritional support are necessary components of treatment of severe SSTIs.

EARLY DIAGNOSIS AND DIFFERENTIATION OF NECROTIZING VERSUS NON-NECROTIZING SKIN AND SOFT TISSUE INFECTIONS

\textbf{Classification of Skin and Soft Tissue Infections}

The US Food and Drug Administration (FDA) classifies SSTIs into two broad categories for the purpose of clinical trials evaluating new antimicrobials for the treatment of SSTIs: uncomplicated and complicated (Box 1). Uncomplicated SSTIs include superficial infections such as cellulitis, simple abscesses, impetigo, and furuncles. These infections can be treated by antibiotics or surgical incision for drainage of...
abscess alone. In contrast, complicated sSTIs include deep soft tissue infections that require significant surgical intervention, such as infected ulcers, infected burns, and major abscesses. Additionally, these patients also have significant underlying comorbidities (ie, disease states that complicate [and usually delay] response to treatment). Complicated SSTIs are a significant clinical problem, in part related to the increasing resistance of infecting bacteria to current antibiotic therapies.

Uncomplicated SSTIs are associated with low risk for life- or limb-threatening infection. Patients who have uncomplicated SSTIs can be treated with empiric antibiotic therapy according to likely pathogen and local resistance patterns.

Complicated SSTIs are associated with high risk for life- or limb-threatening infection. In patients who have complicated SSTIs, it is of paramount importance to initiate appropriate and adequate broad-spectrum initial empiric antimicrobial therapy with coverage for MRSA and to consider the need for surgical intervention for abscess drainage or debridement.

Patients who have complicated SSTIs require hospitalization for treatment. Specific circumstances that warrant hospitalization include the presence of tissue necrosis, sepsis, severe pain, altered mental status, immunocompromised state, and organ failure (respiratory, renal, hepatic). SSTIs can lead to serious potentially life-threatening local and systemic complications. The infections can progress rapidly, and early recognition and proper medical and surgical management are the cornerstones of therapy.

Another classification for SSTIs that is used commonly is the differentiation of necrotizing soft tissue infections (NSTIs) from non-necrotizing infections. This differentiation is critical, because necrotizing infections warrant prompt aggressive surgical debridement. Clinical clues to the diagnosis of NSTIs are listed in Box 2. The differentiation of necrotizing infections from non-necrotizing infections is critical to achieving adequate surgical therapy. A clear approach to these infections must allow rapid identification and treatment of NSTIs, because they are limb- and life-threatening.

When “hard clinical signs” (bullae, crepitus, gas on radiograph, hypotension with systolic blood pressure less than 90 mm Hg, or skin necrosis) of NSTI are present,
establishing the diagnosis of NSTI is not difficult. Hard signs of NSTIs, however, are often absent on presentation, thus potentially delaying diagnosis and surgical intervention. Studies have documented that less than 50% of patients who had a definitive diagnosis of NSTI presented with hard clinical signs of NSTI. Admission white blood cell count greater than 15,400 × 10⁹/L or serum sodium less than 135 mEq/L was documented to help differentiate NSTI from non-NSTI and aided in early diagnosis. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is also helpful as a laboratory aid in distinguishing necrotizing from non-necrotizing SSTIs.

If there is any question regarding the possible diagnosis of an NSTI, it is imperative to proceed with surgical intervention and to be certain that the surgical incision is continued down to the fascial and muscle level to make a definitive diagnosis.

EARLY INITIATION OF APPROPRIATE EMPIRIC BROAD-SPECTRUM ANTIMICROBIAL THERAPY WITH CONSIDERATION OF RISK FACTORS FOR SPECIFIC PATHOGENS AND MANDATORY COVERAGE FOR METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

Antimicrobial therapy is an essential element for managing severe SSTIs. As in all serious life-threatening infections, it is important to initiate early and appropriate empiric antimicrobial therapy. It has been established that prompt appropriate treatment of hospitalized infections reduces mortality. Similar findings were reported in studies of patients with ventilator-associated pneumonia and sepsis. A study of ICU patients found that the higher mortality rate associated with inappropriate initial therapy was still observed when antibiotics were switched from an inappropriate to an appropriate treatment.

Furthermore, appropriate and timely antibiotic therapy improves treatment outcomes for SSTIs caused by MRSA. In a study of 492 patients who had community-onset MRSA SSTIs, 95% of episodes treated with an active antibiotic within 48 hours were treated successfully, compared with an 87% rate of successful treatment.
in patients who did not receive an active antibiotic \((P = .001)\). In logistic regression analysis, failure to initiate active antimicrobial therapy within 48 hours of presentation was the only independent predictor of treatment failure (adjusted odds ratio [OR], 2.80; 95% CI, 1.26 to 6.22; \(P = .011\)). Similarly, in a study of patients admitted to the hospital with MRSA sterile-site infection, multivariate analysis found inappropriate antimicrobial treatment to be an independent risk factor for hospital mortality (adjusted OR, 1.92; 95% CI, 1.48 to 2.50; \(P = .013\)).\(^{13}\)

An empiric treatment algorithm for SSTI directed against community-associated (CA-MRSA) in the emergency \(^{14}\) department (ED) that promotes both the use of antibiotics likely active against CA-MRSA and early incision and drainage of abscesses was examined. Clinical failure occurred in only 3% of cases treated according to the algorithm, compared with 62% of those not treated according to the algorithm \((P < .001)\). Furthermore, among cases that underwent immediate incision and drainage, initial treatment with antibiotics active in vitro against the MRSA isolate was associated with a decreased clinical failure rate when compared with those treated with inactive antibiotics (0% versus 67%, \(P < .001\)).

Empiric antibiotic therapy should be initiated in all patients who have complicated SSTIs (cSSTIs). Intravenous broad-spectrum antimicrobial therapy should be initiated:

- When an infection is severe or progresses rapidly
- When there are signs of systemic illness
- When the patient has comorbidities or is immunosuppressed
- For very old or young patients
- When an abscess cannot be completely drained
- When the infection does not respond to incision and drainage\(^ {15}\)

**Timely** initiation of antimicrobial therapy is also important for treating severe SSTIs, particularly if associated with septic shock. In a study of 2731 adult patients who had septic shock, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted OR 1.119 [per hour delay], 95% CI 1.103 to 1.136, \(P < .0001\)).\(^ {16}\) Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, the in-hospital mortality rate was increased significantly relative to receiving therapy within the first hour (OR 1.67; 95% CI, 1.12 to 2.48). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Interestingly, only 50% of septic shock patients received effective antimicrobial therapy within 6 hours of documented hypotension.

**Epidemiology and Microbiology of Skin and Soft Tissue Infections**

An understanding of the changing epidemiology and microbiology of all SSTIs is required for diagnosing and selecting appropriate empiric antibiotic therapy. Staphylococci and streptococci long have been the leading microbiologic causes of cSSTIs.\(^ {17}\) In recent years, however, *S aureus* has emerged as the most common cause of SSTIs. In addition to Group A streptococci and *S aureus*, the indigenous aerobic and anaerobic cutaneous and mucous membranes’ local microflora usually are responsible for polymicrobial infections, such as NSTIs and diabetic foot infections. Severe SSTIs also
can be caused by *Clostridium spp*, microorganisms associated with water sources (*Vibrio spp*, *Aeromonas*), and polymicrobial/mixed infections.

CA-MRSA infections have risen rapidly in the last decade, and SSTIs are the predominant site of infection, accounting for 74% of all CA-MRSA infections in one study. A 15-year study of the changing epidemiology of MRSA infections from military medical facilities in San Diego from 1990 to 2004 documented that 65% of MRSA infections were community-acquired, with SSTIs as the major site of infection in 95% of cases.

MRSA was the most common identifiable cause of SSTI presenting to EDs in a recent prospective multicenter United States study. *S aureus* was isolated from 320 (76%) of 422 patients who had SSTIs. The prevalence of MRSA was 59% overall and ranged from 15% to 74% by ED. Pulsed-field type USA300 accounted for 97% of MRSA isolates; 72% of these were a single indistinguishable strain (USA300-0114). SCCmec type IV and the Panton-Valentine leukocidin (PVL) toxin gene each were detected in 98% of MRSA isolates. Among methicillin-susceptible *S aureus* (MSSA) isolates, 31% were USA300, and 42% contained PVL genes. The spectrum of skin infections caused by CA-MRSA is wide and can range from simple cutaneous abscesses to large abscesses, severe pyomyositis, and fulminant necrotizing soft tissue infections. Other studies have confirmed similar findings.

MRSA also has been identified as the most common cause of severe SSTIs requiring surgical drainage and debridement in a single-center 7-year study from Houston. From 2000 to 2006, 288 patients who had SSTIS that required operative debridement were identified. The most common microorganism retrieved from intra-operative cultures was *S aureus*, 70% of which were MRSA. *Streptococcus* species accounted only for 15% of microbes isolated. Monomicrobial etiology was identified in 67% of patients, and MRSA was also the predominant microbe isolated from such cultures (68%). The frequency of MRSA isolates increased significantly during the study, from 34% in 2000 to 77% in 2006 (*P*<.001) Fig. 1. Interestingly, the examination of vancomycin minimum inhibitory concentration (MIC) demonstrated a shift for MRSA isolates over this time period, with 38% of the isolates having an MIC greater than or equal to 1 μg/mL, with 31% of isolates with an MIC of 2 μg/mL. This is concerning given recent reports documenting high treatment failure rates for MRSA infections with increased MIC.

In a study of 12,506 hospitalized patients who had culture-proven skin, soft tissue, bone, or joint infection, *S aureus* caused infection in 54.6% of patients, and 28.0% of

![Fig. 1. Incidence of methicillin-resistant *Staphylococcus aureus* isolated from patients presenting with severe skin and soft tissue infections and requiring surgical intervention over 7 years (2000 through 2006). (From Awad SS, Elhabash SI, Lee L, et al. Increasing incidence of methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections: reconsideration of empiric antimicrobial therapy. Am J Surg 2007;194:606–10; with permission.)](image-url)
the *S aureus* isolates recovered were methicillin-resistant. Health care-associated infections and complicated SSTIs were associated with significantly higher mortality rates and longer and more costly length of hospital stay.\textsuperscript{27}

Based on this change in microbiologic etiology of SSTIs, all patients who present with severe cSSTIs should be treated with broad-spectrum antimicrobial therapy, including mandatory coverage for MRSA. Patients who present to the hospital with severe infection or infection progressing despite antibiotic therapy should be treated aggressively. In these cases, if *S aureus* is cultured, the clinician should assume the organism may be resistant and should treat with agents effective against MRSA, such as vancomycin, linezolid, or daptomycin.\textsuperscript{28} Although risk factors for MRSA SSTIs have been identified, in patients who have severe SSTIs, one should not rely solely on the use risk factors for MRSA in the decision making regarding whether empiric anti-MRSA antimicrobials should be used (Box 3).

Choice of empiric antimicrobial therapy for SSTIs is guided by several factors. For patients who have severe SSTIs that are surgical site infections (SSIs), it is important to choose an empiric antimicrobial agent that is different than the class of antibiotics that was used for SSI prophylaxis at the time of the initial surgery. In the case of SSI, the type and site of operation dictate which pathogens are suspected. Infections following operations in the gastrointestinal or genitourinary tract may be monomicrobial or mixed, and may be caused by gram-positive or gram-negative bacteria. In contrast, infections following clean operations in other parts of the body typically are caused by gram-positive pathogens. Immunocompromised or neutropenic patients are, of course, at increased risk of infection and are less able to control local infection and therefore should be treated with empiric, broad-spectrum antibiotics at the first clinical signs of infection, including fever.

Several antimicrobials are approved by the FDA for treating SSTIs. It is important to provide anti-MRSA coverage in the empiric regimen of all patients who have severe

<table>
<thead>
<tr>
<th>Box 3</th>
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<tbody>
<tr>
<td><strong>Risk factors for community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infections</strong></td>
</tr>
</tbody>
</table>

*Persons at risk for skin and soft tissue infections caused by community-associated MRSA*

- Household contacts of a patient who has proven community-associated MRSA infection\textsuperscript{29}
- Children\textsuperscript{30}
- Day care center contacts of hospitalized patients who have MRSA infections\textsuperscript{31,32}
- Men who have sex with men\textsuperscript{33}
- Soldiers\textsuperscript{34,35}
- Incarcerated persons\textsuperscript{35}
- Athletes, particularly those involved in contact sports\textsuperscript{36}
- Native Americans\textsuperscript{37}
- Pacific Islanders\textsuperscript{38}
- Persons with a previous community-associated MRSA infection\textsuperscript{39,40}
- Intravenous drug users\textsuperscript{41}

SSTIs. A list of anti-MRSA antimicrobials studied in recent cSSTI clinical trials includes:

- The most common comparator antimicrobial (vancomycin)
- Those currently approved by the FDA (linezolid, daptomycin, tigecycline)
- Those in development (dalbavancin, telavancin, ceftobiprole, iclepram, ceftaroline)

(Table 1).

A comprehensive review of these studies has recently been published.42 When selecting empiric antimicrobials to treat severe cSSTIs, selection of specific antimicrobials that inhibit toxin production may be helpful, particularly in those patients who have evidence of toxic shock syndrome. This is commonly present in patients who have streptococcal and staphylococcal infections. Protein cytotoxins play an important role in the pathogenesis of various staphylococcal infections, and toxin production should be considered when selecting an antimicrobial agent for gram-positive pathogens.43 The recent identification of a class of secreted staphylococcal peptides [phenol-soluble modulin (PSM) peptides] documents that they have a remarkable ability to recruit, activate, and lyse human neutrophils, thus eliminating the main cellular defense against MRSA infection.44 The β-lactams actually enhance toxin production. In contrast, both clindamycin and linezolid have the ability to inhibit toxin production by suppressing translation, but not transcription, of toxin genes for S aureus and by directly inhibiting synthesis of group A streptococcal toxins. Particularly when patients exhibit signs and symptoms of streptococcal toxic shock syndrome (shock, coagulopathy, organ failure and NSTI), antitoxin antimicrobials should be initiated promptly.45

SOURCE CONTROL (IE, EARLY AGGRESSIVE SURGICAL INTERVENTION FOR DRAINAGE OF ABSCESSES AND DEBRIDEMENT OF NECROTIZING SOFT TISSUE INFECTIONS)

Source control includes drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies, and finally, definite measures to correct anatomic derangement resulting in ongoing microbial contamination and restoring optimal function.46 Source control represents a key component of success in the therapy of sepsis, because it is the best method of prompt reduction of the bacterial inoculum at the site of infection. Source control has been identified best as an important therapeutic strategy in treating complicated abdominal infections,47 but is of paramount importance for treating cSSTIs also. Appropriate and timely source control is mandatory for treating severe SSTIs, particularly in the case of NSTIs. This is depicted as the main pillar of the treatment triangle of SSTIs in Fig. 2.

PATHOGEN IDENTIFICATION AND APPROPRIATE DE-ESCALATION OF ANTIMICROBIAL THERAPY

Given the increasing prevalence of multidrug-resistant pathogens as the etiology of severe SSTIs, pathogen identification is of paramount importance. All patients who have severe SSTIs should have blood cultures obtained on admission, before initiation of empiric antimicrobial therapy if possible. In addition, cultures should be obtained directly from the SSTI site, either abscess fluid when incision and drainage are performed or tissue sample in the case of NSTIs when surgical debridement is performed.

Initial management of cSSTIs should include collection of specimens for culture and antimicrobial susceptibility testing from all patients who have abscesses or purulent lesions. Culture and susceptibility findings are useful for individual patient
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Comparator</th>
<th>Experimental Design</th>
<th>Total Patients</th>
<th>MRSA Patients</th>
<th>Outcome in MRSA Patients Agent Versus Comparator</th>
<th>Outcome in all Patients Agent Versus Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid⁹¹,a</td>
<td>Vancomycin</td>
<td>Open-label</td>
<td>1180</td>
<td>285</td>
<td>Clinical cure: 94.0% versus 83.6% Microcure: 88.6% versus 66.9%</td>
<td>Clinically evaluable: 94.4% versus 90.4%</td>
</tr>
<tr>
<td>Daptomycin⁹²,a</td>
<td>Vancomycin</td>
<td>Double-blind</td>
<td>1092</td>
<td>64</td>
<td>75% versus 69.4%</td>
<td>Clinically evaluable: 83.4% versus 84.2%</td>
</tr>
<tr>
<td>Tigecycline⁹³,a</td>
<td>Vancomycin</td>
<td>Double-blind</td>
<td>1116</td>
<td>65</td>
<td>78.4% versus 76.5%</td>
<td>Clinically evaluable: 86.5 versus 88.6%</td>
</tr>
<tr>
<td>Dalbavancin⁹⁴,b</td>
<td>Linezolid</td>
<td>Double-blind</td>
<td>854</td>
<td>278</td>
<td>91% versus 89%</td>
<td>88.9% versus 91.2%</td>
</tr>
<tr>
<td>Televancin⁹⁵,b</td>
<td>Vancomycin</td>
<td>Double-blind</td>
<td>1867</td>
<td>579</td>
<td>Clinical cure: 90.6% versus 86.4% Microcure: 90% versus 85%</td>
<td>Clinically evaluable: 88% versus 87%</td>
</tr>
<tr>
<td>Oritavancin⁹⁶,b</td>
<td>Vancomycin/cephalexin</td>
<td>Double-blind</td>
<td>1769</td>
<td>33</td>
<td>74% versus 80%</td>
<td>Clinically evaluable: 79% versus 76% clinical cure 75% versus 73% microcure</td>
</tr>
<tr>
<td>Ceftobiprole⁹⁷,b</td>
<td>Vancomycin</td>
<td>Double-blind</td>
<td>784</td>
<td>121</td>
<td>91.8% versus 90%</td>
<td>Clinical cure ITT: 77.8% versus 77.5% Clinically evaluable: 93.3% versus 93.5%</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Comparator</td>
<td>Study Type</td>
<td>Patients</td>
<td>microbiological outcomes</td>
<td>Clinical cure ITT</td>
<td>Clinical evaluable</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Ceftobiprole + Vancomycin + ceftazidime</td>
<td>Double blind (included Diabetic Foot Infections)</td>
<td>828</td>
<td>123</td>
<td>89.7% versus 86.1%</td>
<td>Clinical cure ITT: 81.9% versus 80.8%</td>
<td>Clinically evaluable: 90.5% versus 90.2%</td>
</tr>
<tr>
<td>Iclaprim + Linezolid</td>
<td>Double-blind</td>
<td>497</td>
<td>—</td>
<td>70% of pathogens were <em>S. aureus</em>, 25% of which were MRSA</td>
<td>Clinical cure ITT: 85.5% versus 91.9%</td>
<td>Clinically evaluable: 93.8% versus 99.1%</td>
</tr>
<tr>
<td>Microcure: 94.7% versus 98.8%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Iclaprim + Linezolid</td>
<td>Double-blind</td>
<td>494</td>
<td>Microcure MRSA: 77.0% versus 80.0%</td>
<td>60% of pathogens were <em>S. aureus</em>, 50% of which were MRSA</td>
<td>Clinical cure ITT: 84.9% versus 87.2%</td>
<td>Clinically evaluable: 89.6% versus 96.4%</td>
</tr>
<tr>
<td>Microcure: 83.5% versus 84.7% MSSA 77% versus 80% MRSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ceftaroline + Vancomycin + aztreonam</td>
<td>Double-blind</td>
<td>702</td>
<td>Microcure MRSA: 94.9% versus 91.8%</td>
<td>30% with confirmed pathogen were MRSA</td>
<td>Clinical cure MITT: 86.6% versus 85.6%</td>
<td>Clinically evaluable: 91.1% versus 93.3%</td>
</tr>
<tr>
<td>Microcure: 91.8% versus 92.5%</td>
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<td></td>
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</table>

**Abbreviation:** MRSA, methicillin-resistant *Staphylococcus aureus*.

*US Food and Drug Administration-approved for treatment of CSSTIs caused by MRSA.*

*Investigational antimicrobial.*
management and in monitoring local patterns of antimicrobial resistance. It has been documented that physicians and other health care workers cannot predict accurately if an SSTI is caused by MRSA. A prospective observational study conducted in an urban tertiary academic center in ED patients presenting with purulent wounds and abscesses that received wound culture (n=176) documented that physician suspicion of MRSA had a sensitivity of 80% (95% CI 71% to 87%) and a specificity of 23.6% (95% CI 14% to 37%) for the presence of MRSA on wound culture with a positive likelihood ratio (LR) of 1.0 (95% CI 0.9 to 1.3) and a negative LR of 0.8 (95% CI 0.5 to 1.3). Prevalence was 64%. Emergency physicians’ suspicion of MRSA infection was a poor predictor of MRSA infection.

Clinicians have a responsibility for appropriate de-escalation of antimicrobial therapy in the treatment of severe SSTIs once culture results return. Pathogen-directed antimicrobial therapy then is initiated, with de-escalation from the initial
broad-spectrum empiric antimicrobial regimen, with an attempt to decrease to monotherapy if at all possible.\textsuperscript{48} De-escalation of antimicrobial therapy should occur as early as possible, but is only possible if appropriate microbiologic specimens are obtained at the time of SSTI source control. De-escalation is founded on identification of the pathogen and its antibiotic susceptibilities.

In patients who have presumed CA-MRSA SSTIs, it has been recommended that uncomplicated SSTI in healthy individuals may be treated empirically with clindamycin, TMP/SMX, or tetracyclines, although specific data supporting the efficacy of these treatments in large multicenter prospective randomized clinical trials are lacking.\textsuperscript{49}

**SPECIFIC SEVERE SKIN AND SOFT TISSUE INFECTIONS**

**Necrotizing Soft Tissue Infections**

Necrotizing Soft Tissue Infections (NSTIs) are aggressive soft tissue infections that cause widespread necrosis, and they can include necrotizing cellulitis, fasciitis, and myositis/myonecrosis.\textsuperscript{50} Establishing the diagnosis of NSTI can be the main challenge in treating patients who have NSTI, and knowledge of all available tools is key for early and accurate diagnosis.\textsuperscript{51} There have been several recent advances in the definition, pathogenesis, diagnostic criteria, and treatment of necrotizing soft tissue infections.\textsuperscript{52,53}

Patients who have NSTIs require prompt aggressive surgical debridement, appropriate intravenous antibiotics, and intensive support. Despite aggressive treatment, their mortality and morbidity rates remain high, with some series reporting mortality rates of 25\% to 35\%.\textsuperscript{54} A high index of suspicion should be used in conjunction with laboratory and imaging studies to establish the diagnosis as rapidly as possible. Successful treatment requires early, aggressive surgical debridement of all necrotic tissue, appropriate broad-spectrum systemic antibiotic therapy, and supportive care (fluid resuscitation, organ, and critical care support) to maintain oxygenation and tissue perfusion. Delayed definitive debridement remains the single most important risk factor for death.

A recent single-institution series of 166 patients documented that the overall mortality rate was 16.9\%, and limb loss occurred in 26\% of patients who had extremity involvement.\textsuperscript{55} Independent predictors of mortality included white blood cell count greater than 30,000 $\times 10^3/\mu$L, creatinine level greater than 2 mg/dL (176.8 $\mu$mol/L), and heart disease at hospital admission. Independent predictors of limb loss included heart disease and shock (systolic blood pressure less than 90 mm Hg) at hospital admission. Clostridial infection was an independent predictor for both limb loss (OR, 3.9 [95\% CI, 1.1 to 12.8]) and mortality (OR, 4.1 [95\% CI, 1.3 to 12.3]) and was highly associated with intravenous drug use and a high rate of leukocytosis on hospital admission.

**Aids to Diagnosis of Necrotizing Soft Tissue Infections**

Early operative debridement is a major determinant of outcome in NSTIs. Early recognition of NSTIs, however, is difficult clinically. A novel diagnostic scoring system for distinguishing NSTIs from other severe soft tissue infections based on laboratory tests routinely performed for evaluating severe SSTIs is called the LRINEC score (Table 2).\textsuperscript{56}

The LRINEC score initially was developed in a retrospective observational study including 145 patients who had necrotizing fasciitis and 309 patients who had severe cellulitis or abscesses admitted to two tertiary care hospitals. Hematologic and biochemical results done on admission were converted into categorical variables for analysis. Univariate and multivariate logistic regression was used to select significant
predictors. Total white cell count, hemoglobin, sodium, glucose, serum creatinine, and C-reactive protein were selected. The LRINEC score was constructed by converting into integer the regression coefficients of independently predictive factors in the multiple logistic regression model for diagnosing necrotizing fasciitis. The cutoff value for the LRINEC score was 6 points, with a positive predictive value of 92.0% and negative predictive value of 96.0%. Model performance was very good (Hosmer-Lemeshow statistic, $P = .910$); area under the receiver operating characteristic curve was 0.980 and 0.976 in the developmental and validation cohorts, respectively. The LRINEC score is a robust score capable of detecting even clinically early cases of necrotizing fasciitis. The variables used are measured routinely to assess severe soft tissue infections. Patients who have a LRINEC score of greater than or equal to 6 should be evaluated carefully for the presence of necrotizing fasciitis.

Since the initial development of the LRINEC score, several other cohort studies have validated its utility for diagnosing NSTIs. A recent multicenter study in 229 patients who had NSTIs from 2002 to 2005 reported an overall mortality rate of 15.8% and amputation rate of 26.3%. This study also documented that a LRINEC score greater than or equal to 6 was associated with a higher rate of mortality and amputation (receiver operating characteristic curve, area under the curve 0.75).

### Diagnostic Imaging in Necrotizing Soft Tissue Infections

A high clinical index of suspicion is required if the diagnosis is to be made sufficiently early for successful treatment. NSTIs necessitate prompt aggressive surgical

<table>
<thead>
<tr>
<th>Variable, Units</th>
<th>Score</th>
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<tbody>
<tr>
<td>C-reactive protein, mg/L</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>0</td>
</tr>
<tr>
<td>≥150</td>
<td>4</td>
</tr>
<tr>
<td>Total white cell count, per mm$^3$</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
</tr>
<tr>
<td>15–25</td>
<td>1</td>
</tr>
<tr>
<td>&gt;25</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td></td>
</tr>
<tr>
<td>≥135</td>
<td>0</td>
</tr>
<tr>
<td>&lt;135</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td></td>
</tr>
<tr>
<td>≤141</td>
<td>0</td>
</tr>
<tr>
<td>&gt;141</td>
<td>2</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1</td>
</tr>
</tbody>
</table>

The maximum score is 13; a score $\geq 26$ should raise the suspicion of necrotizing fasciitis, and a score of $\geq 8$ is strongly predictive of this disease.

<table>
<thead>
<tr>
<th>Variable, Units</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein, mg/L</td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>0</td>
</tr>
<tr>
<td>≥150</td>
<td>4</td>
</tr>
<tr>
<td>Total white cell count, per mm$^3$</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0</td>
</tr>
<tr>
<td>15–25</td>
<td>1</td>
</tr>
<tr>
<td>&gt;25</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td></td>
</tr>
<tr>
<td>≥135</td>
<td>0</td>
</tr>
<tr>
<td>&lt;135</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td></td>
</tr>
<tr>
<td>≤141</td>
<td>0</td>
</tr>
<tr>
<td>&gt;141</td>
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The maximum score is 13; a score $\geq 26$ should raise the suspicion of necrotizing fasciitis, and a score of $\geq 8$ is strongly predictive of this disease.
debridement for satisfactory treatment in addition to antimicrobial therapy. It is critical to remember that because of the rapidly progressive and potentially fatal outcome of this condition, if imaging cannot be performed expeditiously, delaying treatment is not justified.

Plain film findings may reveal extensive soft tissue gas. CT examination can reveal asymmetric thickening of deep fascia in association with gas, and associated abscesses also may be present. MRI additionally can assist in diagnosing NSTIs. MRI has been documented to effectively differentiate between necrotizing and non-necrotizing infection of the lower extremity, but should not delay prompt surgical intervention in NSTI management.

**Microbiology of Necrotizing Soft Tissue Infections**

Necrotizing fasciitis and myonecrosis typically are caused by infection with group A Streptococcus, Clostridium perfringens, or, most commonly, aerobic and anaerobic organisms as part of a polymicrobial infection that may include *S aureus*. In case series, CA-MRSA recently was described as a predominantly monomicrobial cause of necrotizing fasciitis. A retrospective review of patients presenting with necrotizing fasciitis between 2000 and 2006 indicated that MRSA was the most common pathogen, accounting for one third of the organisms isolated.

NSTIs are categorized into three specific types based on the microbiologic etiology of the infection.

**Type 1, or polymicrobial**

**Type 2, or group A streptococcal**

**Type 3, gas gangrene, or clostridial myonecrosis**

Increasingly, MRSA has been identified as the causative microbe in NSTIs, but a separate category for this NSTI does not exist. Given this finding, anti-MRSA empiric antimicrobial therapy should be initiated in all patients who have NSTIs, and pathogen-directed antimicrobial therapy should be considered once tissue culture results are available.

Uncommon microbiologic causes of NSTIs and primary sepsis include *Vibrio* and *Aeromonas* species, virulent gram-negative bacteria and members of the *Vibrionaceae* family that thrive in aquatic environments. These NSTIs are likely to occur in patients who have hepatic disease, diabetes, and immunocompromised conditions. These organisms are found in warm sea waters and are often present in raw oysters, shellfish, and other seafood. The diagnosis of *Vibrio* NSTIs should be suspected when a patient has the appropriate clinical findings and a history of contact with seawater or raw seafood. *Aeromonas hydrophila* is a gram-negative bacillus commonly found in soil, sewage, and fresh or brackish water in many parts of the United States. The contact history of patients who have a rapid onset of SSTIs can alert clinicians to a differential diagnosis of soft tissue infection with *Vibrio vulnificus* (contact with seawater or raw seafood) or *Aeromonas* species (contact with fresh or brackish water, soil, or wood). Early fasciotomy and culture-directed antimicrobial therapy should be performed aggressively in those patients who have hypotensive shock, leukopenia, severe hypoalbuminemia, and underlying chronic illness, especially a combination of hepatic dysfunction and diabetes mellitus. The rate of amputation and mortality is very high in these patients, and early definitive management is of paramount importance.
Several novel therapeutic strategies as adjuncts for treating NSTIs have been described, including vacuum-assisted wound closure (VAC) therapy, intravenous immunoglobulin, and hyperbaric oxygen therapy.

**Vacuum-assisted wound closure therapy**
Several reports have documented the utility of VAC therapy for managing patients who have acute NSTIs. VAC therapy has been associated with reduced time for wound care, improved patient comfort, greater mobility, reduced drainage, and decreased time to wound closure. Although no prospective randomized trials have been conducted comparing VAC therapy with traditional wet dressing techniques, it can be considered, particularly in patients who have large wounds, where conscious sedation or general anesthesia is required for wound dressing changes.

**Intravenous immunoglobulin**
The use of intravenous immunoglobulin for treating NSTIs remains controversial, but is based upon a potential benefit related to binding of gram-positive organism exotoxins. The clinical studies that have been completed are not randomized blinded trials, but some show evidence of improved outcomes with intravenous immunoglobulin treatment. This treatment should be restricted, however, to critically ill patients who have either staphylococcal or streptococcal NSTIs.

**Hyperbaric oxygen therapy**
The benefit of hyperbaric oxygen (HBO) as an adjunctive treatment is controversial, and no prospective randomized clinical trials have been performed. A recent retrospective review investigated the effect of HBO in treating NSTIs. Clinical data were reviewed for 78 patients who had NSTIs. Thirty patients at one center were treated with surgery, antibiotics, and supportive care; 48 patients at a different center received adjunctive HBO treatment. Demographic characteristics and risk factors were similar in the HBO and non-HBO groups. The mean patient age was 49.5 years; 37% of the patients were female, and 49% had diabetes mellitus. Patients underwent a mean of 3.0 excisional debridements. The median hospital length of stay was 16.5 days; the median duration of antibiotic use was 15.0 days. In 36% of patients, cultures were polymicrobial; group A Streptococcus was the organism most commonly isolated (28%). No statistically significant differences in outcomes between the two groups were identified. The mortality rate for the HBO group (8.3%) was lower, although not significantly different \( P = .48 \) than that observed for the non-HBO group (13.3%). The number of debridements was greater in the HBO group (3.0; \( P = .03 \)). The hospital length of stay and duration of antibiotic use were similar for the two groups. Multivariable analysis showed that hypotension on admission and immunosuppression were significant independent risk factors for death. These authors concluded that the use of HBO to treat NSTIs did not reduce mortality rate, number of debridements, hospital length of stay, or duration of antibiotic use. Immunosuppression and early hypotension were important risk factors associated with higher mortality rates in patients who had NSTIs. Several other published peer-reviewed retrospective studies have identified variable treatment effects with HBO therapy for NSTIs. These studies are limited, related to nonrandomized experimental design, retrospective reviews, and poor controls.

**Pyomyositis**
Myositis is a rare infection that may lead to serious and potentially life-threatening local and systemic complications. The infection can progress rapidly, and early...
recognition and proper medical and surgical management are therefore the cornerstones of therapy. With the increasing prevalence of community-associated MRSA as a pathogen in severe SSTIs, pyomyositis is more common than in past years. Myositis often occurs in muscle sites that have been compromised by injury, ischemia, malignancy or surgery. The predominant pathogens are *S. aureus*, group A streptococci (GAS), gram-negative aerobic and facultative bacilli, and the indigenous aerobic and anaerobic cutaneous and mucous membranes’ local microflora.

CT scan imaging is a rapid and sensitive diagnostic test, and it commonly demonstrates diffuse enlargement of the involved muscle. It additionally may demonstrate the presence of fluid or gas collections within the muscle, suggesting the presence of abscesses. MRI is more sensitive in showing early inflammatory changes before development of abscesses in myositis. Emergency surgical exploration is warranted to define the nature of the infective process, which is accomplished by direct examination of the involved muscles. Surgical intervention is required to perform appropriate abscess drainage and debridement and to also evaluate for necrotizing myositis. Fasciotomies and extremity amputation are sometimes necessary.

**Diabetic Foot Infections as Cause of Severe Skin and Soft Tissue Infections**

Diabetic foot infections (DFIs) also can be a cause of severe SSTIs. These patients:

- Can present with severe sepsis and septic shock
- Frequently require surgical abscess drainage and debridement
- May require vascular evaluation for improved arterial inflow
- Can require extremity amputation for source control sometimes

<table>
<thead>
<tr>
<th>Table 3 Risk stratification for patients with diabetic foot infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Manifestation of Infection</strong></td>
</tr>
<tr>
<td>Wound lacking purulence or any manifestations of inflammation</td>
</tr>
<tr>
<td>Presence of ≥ 2 manifestations of inflammation Any cellulitis/erythema extends ≤ 2 cm around the ulcer Infection limited to the skin or superficial subcutaneous tissues</td>
</tr>
<tr>
<td>Patient is systemically well and metabolically stable ≥ 1 of the following characteristics: Cellularis extending &gt; 2 cm Lymphangitic streaking Spread beneath the superficial fascia Deep-tissue abscess Gangrene Involvement of muscle, tendon, joint, or bone</td>
</tr>
<tr>
<td>Infection in a patient with systemic toxicity or metabolic instability</td>
</tr>
</tbody>
</table>


*Abbreviation:* PEDIS, perfusion, extent/size, depth/tissue loss, infection, and sensation.

Foot ischemia may increase the severity of any infection, and the presence of critical ischemia often makes the infection severe.

* International Consensus on the Diabetic Foot.
The Infectious Diseases Society of America Guidelines regarding Diagnosis and Treatment of Diabetic Foot Infections comprehensively review this topic (Table 3).\textsuperscript{89,90} Aerobic gram-positive cocci (especially \textit{S} aureus) are the predominant pathogens in DFIs. Patients who have chronic wounds or who recently have received antimicrobial therapy also may be infected with gram-negative rods, and those who have foot ischemia or gangrene may have obligate anaerobic pathogens. The fundamental management of patients who have severe cSSTIs related to DFIs is the same as described previously; however, in addition, special attention to a potential diagnosis of concurrent osteomyelitis, potential need for vascular reconstruction for ischemic arterial disease, and assessment of neuropathy and foot offloading must be considered in these patients.

**SUMMARY**

Severe cSSTIs are associated with significant morbidity and mortality, and it is important to differentiate necrotizing versus non-necrotizing SSTIs early in the course of treatment. Drug-resistant organisms are common causative pathogens in cSSTIs. MRSA is the most common cause of purulent cSSTIs. All patients who present with complicated SSTIs should be treated with broad-spectrum antimicrobial therapy, including mandatory coverage for MRSA. Source control, including abscess drainage and surgical debridement, are the mainstays of therapy in severe cSSTIs. It is of paramount importance to obtain specimens for culture and antimicrobial susceptibilities given the high prevalence of MRSA as a causative pathogen in cSSTIs. Empiric broad-spectrum antimicrobial therapy should be de-escalated to narrower-spectrum agents based on culture pathogen identification and the patient’s clinical response.

**REFERENCES**


