Treatment of Complicated Skin and Soft Tissue Infections

Addison K. May, Renae E. Stafford, Eileen M. Bulger, Daithi Heffernan, Oscar Guillamondegui, Grant Bochicchio, and Soumitra R. Eachempati

Abstract

Background: Skin and soft tissue infections (SSTIs) may produce substantial morbidity and mortality rates, particularly those classified as complicated or necrotizing.

Objective: To weigh the strength of recommendations using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology and to provide evidence-based recommendations for diagnosis and management for SSTIs.

Data Sources: Computerized identification of published research and review of relevant articles.

Study Selection: All published reports on the management of complicated and necrotizing SSTIs were evaluated by an expert panel of members of the Surgical Infection Society according to published guidelines for evidence-based medicine. The quality of the evidence was judged by the GRADE methodology and criteria. Practice surveys, pharmacokinetic studies, and reviews or duplicative publications presenting primary data already considered were excluded from analysis.

Data Extraction: Information on demographics, study dates, microbiology findings, antibiotic type, surgical interventions, infection-related outcomes, and the methodologic quality of the studies was extracted. Results were submitted to the Therapeutic Agents Committee of the Surgical Infection Society for review prior to creation of the final consensus document.

Data Synthesis: Current surgical and antibiotic management of complicated SSTIs is based on a small number of studies that often have insufficient power to draw well-supported conclusions, with the exception of antimicrobial therapy for non-necrotizing soft tissue infections, for which ample data are available.

Executive Summary and Recommendations

These abbreviated recommendations are not meant to replace the full document but to supplement it. Grading of recommendations is based on the system proposed by the American College of Chest Physicians (Table 1).

Definitions

For therapeutic studies, the U.S. Food and Drug Administration (FDA) uses the terms “un-complicated” and “complicated” skin and skin structure infections (SSSIs). Infections necessitating surgical intervention are by definition complicated. The FDA specifically excludes necrotizing infections from therapeutic studies, thus mandating extrapolation of data from the study of complicated SSTIs to formulate recommendations. Because necrotizing infections include soft tissues not generally considered skin structures, these authors prefer the term “complicated skin and soft tissue infections” (SSTIs).

Epidemiology

Skin and soft tissue infections are caused by a variety of pathogens, including aerobic gram-positive and gram-negative organisms, as well as certain unique pathogens acquired in specific settings. Overall, Staphylococcus aureus is the pathogen most frequently isolated from complicated SSTIs.

Necrotizing infections. Necrotizing soft tissue infections (NSTIs) have a pathogen distribution differing from that of non-necrotizing infections, with a much higher frequency of

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virulent organisms such as group A streptococci, community-
associated methicillin-resistant Staphylococcus aureus (CA-MRSA), and Clostridium spp. Such infections frequently are polymicrobial and may involve both aerobic and anaerobic and gram-
positive and gram-negative pathogens.

Nosocomial and chronic infections. Skin and soft tissue infections that occur in nosocomial or chronic disease settings are more likely to arise from antibiotic-resistant pathogens, including MRSA, methicillin-resistant S. epidermidis (MRSE), vancomycin-resistant Enterococcus (VRE), and resistant gram-negative pathogens.

Bite- and water-associated infections. Both bite- and water-associated infections frequently are polymicrobial and may involve pathogens seen only infrequently in other clinical settings. Some of these pathogens are associated with rapidly progressive infection and fatal sepsis and mandate a high index of suspicion. Such pathogens include Vibrio spp., water-associated infections caused by Aeromonas hydrophila, and bite-wound infections caused by Pasteurella spp. and Capnocytophaga canimorsus.

Community-acquired methicillin-resistant Staphylococcus aureus infections. In many regions and communities, a rapid rise in CA-MRSA has occurred, with this organism now being the single most frequent pathogen in SSTIs. This pathogen typically is associated with the production of virulence factors not common to methicillin-sensitive S. aureus (MSSA) isolates or to hospital-associated (HA)-MRSA isolates, including the Panton-Valentine leukocidin (PVL) toxin.

Table 1. Grading Recommendations

<table>
<thead>
<tr>
<th>Grade of recommendation/description</th>
<th>Benefit vs. risk and burdens</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
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<tr>
<td>1A/Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
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<td>1B/Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation; can apply to most patients in most circumstances without reservation</td>
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<tr>
<td>1C/Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but may change when higher-quality evidence becomes available</td>
</tr>
<tr>
<td>2A/Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances or patients’ or societal values</td>
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<tr>
<td>2B/Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances or patients’ or societal values</td>
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<tr>
<td>2C/Weak recommendation, low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>

Adapted from Guyatt et al., Chest 2006;129:174–181.
RCTs = randomized, controlled trials.

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Necrotizing skin and soft tissue infections. Necrotizing soft tissue infections (NSTIs) are discussed separately because of their greater severity, the variation of pathogens relative to non-necrotizing infections, the difficulty and importance of establishing an early diagnosis, and the impact of early, aggressive surgical debridement on the outcome. Necrotizing infections are serious, causing progressive tissue destruction with significant potential for soft tissue and limb loss and death. Limited studies have been performed to allow firm conclusions regarding therapy.

(a) Diagnosis

- Delays in diagnosis increase both the morbidity and the mortality rate (1C).
- The presence of gas in soft tissues is specific for necrotizing infections and more sensitive than physical examination (1C).
- Computed tomography and magnetic resonance imaging improve the detection of soft tissue gas (1B).
- Radiographic findings of tissue fluid and edema are neither sensitive nor specific for necrotizing infection (1C).
- Clinical features strongly suggestive of necrotizing infection are (1) pain disproportionate to the findings at physical examination; (2) tense edema; (3) bullae; (4) skin ecchymosis/necrosis; (5) cutaneous anesthesia; (6) systemic toxicity; and (7) progression despite antibiotic therapy (1C).
- Laboratory values predictive of the presence of necrotizing infection are: (1) White blood cell (WBC) count > 14×10^9/L; (2) serum sodium concentration < 135 mmol/L; or (3) blood urea nitrogen (BUN) concentration > 15 mg/dL (1C).

(b) Therapeutic approach

Although no randomized or important non-randomized studies of NSSTIs exist to direct therapy specifically, numerous retrospective studies of both sepsis and NSSTIs support the following recommendations:

- Early appropriate antibiotic coverage of inciting pathogens is indicated (1C);
- Timely surgical debridement improves outcome (1C).

(1) Surgical therapy

- Although no randomized or important non-randomized studies in NSTIs exist to direct therapy specifically, adequate surgical debridement of involved tissue is confirmed to improve the outcome (1C).
- Frequent re-evaluation or return to the operating room within 24 h should be undertaken to ensure adequacy of debridement and lack of progression (1C).

(2) Antibiotic therapy. No prospective studies have examined antibiotic therapy in NSTIs. The recommendations here are extrapolated from studies of complicated SSTIs (excluding necrotizing infections) and retrospective studies, case series, and expert opinion.

- Empiric antibiotic therapy should be directed toward the likely pathogens (1C);
- The likely pathogens differ depending on the clinical setting, inciting pathophysiology, and previous exposure to antibiotics (1C);
• Necrotizing infections are more frequently polymicrobial and may involve anaerobic and anaerobic gram-positive and gram-negative pathogens (1C);
• Assuming that relevant pathogens are covered appropriately, several single-agent regimens probably are effective, including imipenem/cilastatin, meropenem, ertapenem, piperacillin/tazobactam, ticarcillin/clavulanic acid, and tigecycline (2C);
• Increasing resistance of gram-negative bacilli to ampicillin/sulbactam raises concern about the use of this agent unless local sensitivities are known (1C);
• Numerous combinations of agents probably are equally effective in the treatment of NSTIs provided appropriate coverage of relevant pathogens is ensured (2C).

Rapidly progressive soft tissue infections.

(a) Rationale for use of protein synthesis-inhibiting agents in rapidly progressive infections

Both animal models and retrospective clinical data support the use of combination therapy with protein synthesis-inhibiting agents in rapidly progressive and large-inoculum settings.

• For rapidly progressive or severe infections caused by *Streptococcus pyogenes* or *Clostridium* spp. or in staphylococcal toxic shock syndrome (TSS), combination therapy including the protein synthesis-inhibiting agents clindamycin, erythromycin, or linezolid should be considered, provided the pathogen is sensitive to the agent (1C);
• For rapidly progressive infections caused by *Vibrio vulnificus* or *Aeromonas* spp., combination therapy with a member of the tetracycline class should be considered (1C).

(b) Staphylococcal toxic shock syndrome

Toxic shock syndrome, characterized by fever, hypotension, rash, organ failure, and skin desquamation, was first associated predominately with tampons but has shifted to other settings since. It is caused by methicillin-sensitive *S. aureus* as well as CA- and HA-MRSA. The pathogenesis is related to the production of superantigens, most commonly the toxic shock syndrome toxin-1 (TSST-1).

• Because of the rapidity of spread of this disease, early empiric therapy for *S. aureus* should be given (1C);
• The choice of agent should be based on the likelihood of methicillin-resistant strains (1C);
• Therapy with protein synthesis-inhibiting agents should be considered (1C).

(c) Community-acquired methicillin-resistant *S. aureus*

Community-acquired MRSA is more commonly associated with SSTI than is HA-MRSA, has increased in prevalence, and has become the most common pathogen causing soft tissue infections in some municipalities. No prospective studies have been performed specifically for CA-MRSA. Thus, treatment recommendations must be extrapolated from studies of MRSA in general.

• A CA-MRSA strain may be sensitive to a number of oral agents to which HA-MRSA are resistant, and empiric treatment of less severe infections may be based on local sensitivity patterns. No studies are available to establish firm guidelines (2C);
• Linezolid is superior to vancomycin in the treatment of complicated MRSA SSTIs (1A), but no studies have examined CA-MRSA specifically;
• Other approved agents equivalent for the treatment of *S. aureus* and MRSA infections are quinupristin/dalfopristin, daptomycin, and tigecycline (1A), but again, no studies examined the results against CA-MRSA specifically;
• For serious necrotizing infections associated with CA-MRSA, treatment with protein synthesis-inhibiting agents should be considered (1C).

(d) Group A streptococcal infections

Group A streptococi frequently are associated with severe NSTIs. Pathogenic strains of *S. pyogenes* produce a variety of exotoxins that contribute to their virulence in SSTIs.

• Early aggressive antibiotic therapy and surgical debridement and drainage should be performed in patients with necrotizing streptococcal infections (1C);
• For moderate-to-severe infections, parenteral penicillin (24 million U/day) is the agent of choice (1C);
• Treatment failures may occur with *β*-lactam agents alone in severe cases (1C);
• Protein synthesis-inhibitory agents alone or in combination with cell-wall-active agents should be given in severe cases; examples are clindamycin or a macrolide (1B/C);
• Increasing macrolide resistance among streptococci introduces concern about use of these agents (1C);
• In patients with signs of TSS attributable to streptococcal SSTIs, intravenous immunoglobulin (IVIg) may be considered (2C).

(e) Clostridial infections

Several clostridial species may cause severe NSTIs. Their production of a variety of exotoxins allows the obligate anaerobes to invade and spread rapidly through previously healthy skin, subcutaneous tissues, and muscle, producing a high mortality rate. These infections frequently have an abrupt onset, with intense pain, marked swelling, and severe systemic toxicity, with the pain preceding other signs and symptoms. Because of the rapid spread and anaerobic growth, clostridial soft tissue infections cause substantial gas accumulation in the involved tissues.

• Early aggressive antibiotic therapy and surgical debridement and drainage should be performed (1C);
• Frequent, repeated operative examination and debridement should be performed (1C);
• High-dose parenteral penicillin (24 million U/day) remains the agent of choice, although carbapenems show excellent activity in vitro (1C);
• Numerous animal studies as well as clinical data from other rapidly progressive infections suggest that treatment failures may occur with *β*-lactam agents alone in severe cases. A protein synthesis-inhibitory antibiotic (clindamycin 1200 mg q 6 h) should be administered (1C).

(f) Vibrio infections

*Vibrio* species, most frequently *V. vulnificus*, may cause rapidly progressive NSTIs. These infections most frequently
present after wound exposure to salt water or from acute wounds that occur from shellfish or handling seafood. These organisms are aerobic gram-negative bacilli and, thus, do not produce gas within tissue and can additionally be differentiated from clostridial species by gram stain.

- Early, aggressive antibiotic therapy and surgical debridement and drainage should be performed in patients with necrotizing *Vibrio* infections (1C);
- Frequent, repeated operative examination and debridement should be performed (1C);
- For severe infections with *V. vulnificus*, combination therapy with cell-wall-active agents and tetracycline or minocycline is recommended (1C);
- Susceptibility testing suggests that third-generation cephalosporins, imipenem meropenem, and ciprofloxacin/ofoxacin are all active. However, cefotaxime and tetracycline or minocycline outperformed the others in animal studies.

**Diabetic Foot Infections.** Diabetic foot infections (DFIs) are common and contribute to the need for amputation in this population. The pathogenesis of DFIs is multifactorial and complex. Considerations in the management have been reviewed extensively elsewhere, and in-depth discussion is beyond the scope of this guideline. However, because of their frequency, considerations are briefly presented.

(a) **Microbiology**

A wide variety of pathogens may be involved in DFIs, although separating colonizing bacteria from true pathogens may be difficult and requires adequate culture techniques. Gram-positive cocci are the most common pathogens, although aerobic gram-negative bacilli and anaerobes also may be involved. Chronic wounds may be infected with resistant pathogens, particularly MRSA.

(b) **Choice of antibiotic regimen**

- Numerous single or combination regimens probably are appropriate in the treatment of complicated DFIs, assuming the regimen provides an appropriate spectrum of activity for the pathogens involved. Because initial therapy is empiric until appropriate cultures are available, local sensitivity patterns, previous antibiotic exposure, previous pathogens, and likely pathogens all should be considered, and adequate tissue cultures should be obtained (1C);
- Agents (or combinations of agents) shown to be equivalent (assuming adequacy for the spectra of the pathogens involved) are cefazolin, ceftriaxone, cefoxitin, ampicillin/sulbactam, piperacillin/clindamycin, piperacillin/tazobactam, imipenem-cilastatin, ertapenem, daptomycin (+gram-negative coverage), and linezolid (+gram-negative coverage) (1A);
- For patients with MRSA infections, vancomycin, daptomycin, and linezolid may be considered. (1A).

**Adjunctive therapies**

**Extracorporeal plasma treatment.** The literature is insufficient to determine whether there is benefit in the use of extracorporeal plasma treatment for patients with severe sepsis caused by NSTIs.

**Hyperbaric oxygen.** The available literature is insufficient to recommend the use of hyperbaric oxygen treatment for patients with NSTIs.

**Intravenous immunoglobulin.** Intravenous immunoglobulin administration has been proposed as adjunctive therapy in the management of patients with TSS associated with either staphylococcal or streptococcal infection. Inadequate data exist to formulate strong recommendations. In patients with signs of TSS attributable to staphylococcal or streptococcal SSTIs, IVIg may be considered (2C).

**Soft tissue infections** are a common cause of hospitalization and disability and a frequent reason for antibiotic therapy. Less severe infections typically are managed without the need for surgical intervention or the involvement of surgeons. Guidelines have been published recently by the Infectious Diseases Society of America (IDSA) that address uncomplicated infections and complicated infections of lesser severity [1]. The following Surgical Infection Society (SIS) guidelines are directed toward infections that frequently mandate the involvement of surgeons for their management. Thus, these guidelines focus on complicated skin and soft tissue infections (SSTIs), particularly those with necrotizing components. Unfortunately, limited prospective data have been obtained for necrotizing infections, and U.S. Food and Drug Administration (FDA) guidelines for the study of soft tissue infection exclude these more severe infections from prospective studies [2]. The majority of randomized studies evaluating complicated SSTIs report clinical success rates ranging from 75% to 90%, with some having even higher success rates, depending on the study population and analysis group. Typically, no deaths are reported in these studies, and thus, the mortality rate is much less than 1%. For studies examining the outcome of necrotizing soft tissue infections (NSTIs), mortality rates range from 6% to greater than 70% (Table 2), raising the question of the validity of applying data from randomized studies of complicated SSTIs to severe necrotizing infections.

Provided below are evidence-based guidelines put forth by the SIS for the management of SSTIs. This document specifically includes management of deeper infections that are excluded from randomized studies of “skin and skin structure infections.” The paucity of randomized data or even large retrospective studies on the management of these more severe infections makes establishing firm recommendations difficult.

**Methods**

The SIS guidelines for the management of SSTI were developed by an expert panel within the Society and reviewed for content by the Therapeutic Agents Committee and the Executive Council. The expert panel conducted a thorough review of the published literature by searching the MEDLINE and Cochrane databases for articles published from 1966 to 2008 related to SSTIs, NSTIs, skin and skin structure infections (SSSIs), and infections caused by specific pathogens. Previous reviews also were used to identify relevant references. Randomized trials, retrospective cohort studies, and case series with analysis of outcomes and therapeutic approaches were used to establish recommendations. These reports were categorized by quality of study design and graded according to
methods described by Guyatt et al. [3] as provided in Table 1. As noted above, necrotizing infectious processes are specifically excluded from randomized trials designed to examine the efficacy of antibiotic therapy in complicated SSTIs. Thus, recommendations for these infections must be extrapolated from studies in other clinical settings. However, because of the paucity of prospective studies of necrotizing infections, data from these studies, as well as retrospective and animal data, were considered to establish guidelines.

Definitions

A variety of terms are applied to infections of the skin and underlying soft tissues. For randomized therapeutic trials, the FDA uses the term “skin and skin structure” infections (SSSI) [2]. However, as noted above, the FDA specifically excludes necrotizing deep space infections, which are those that will be addressed here. The authors prefer the term “skin and soft tissue infections” (SSTIs) to describe those that involve the skin, subcutaneous tissues, fascia, or muscle.

Additionally, SSTIs are classified by the FDA as “uncomplicated” or “complicated” (see below). Most SSTIs requiring the care of surgeons are complicated infections, with the exception of cases of minor cellulitis at incision sites. Complicated infections involve the invasion of deeper tissues and include complicated abscesses as well as a variety of necrotizing infections. A broad array of terms has been applied to various necrotizing processes. Some terms utilized frequently in the classification of SSTIs are provided in Table 3 [1,2,4]. Figure 1 demonstrates the normal structure of skin and the layers typically involved by various infection processes.

Epidemiology

Skin and soft tissue infections may occur with a variety of clinical presentations and in numerous clinical settings, with diverse etiologic processes, and with various severities. Numerous bacteria may be involved, with the likelihood of individual pathogens being altered by factors including the inciting disease process and the clinical presentation and setting. The majority of SSTIs are mild-to-moderate in severity and include simple cellulitis, folliculitis, furunculosis, and minor trauma-related wound infections [1,5]. In general,

### Table 2. Outcomes of Necrotizing Fasciitis over a 30-Year Period

<table>
<thead>
<tr>
<th>Senior author</th>
<th>Year</th>
<th>Number of cases</th>
<th>Mortality rate (%)</th>
<th>Senior author</th>
<th>Year</th>
<th>Number of cases</th>
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<td>128</td>
<td>19</td>
</tr>
<tr>
<td>Theis</td>
<td>2002</td>
<td>13</td>
<td>31</td>
<td>Gunter</td>
<td>2008</td>
<td>52</td>
<td>10</td>
</tr>
<tr>
<td>Singh</td>
<td>2002</td>
<td>75</td>
<td>27</td>
<td></td>
<td>Total (67 studies)</td>
<td>3,302</td>
<td>23.5</td>
</tr>
</tbody>
</table>

Not all studies are referenced in this document.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>General terms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and skin structure infection (SSSI)</td>
<td>Infection of skin and its supporting structures, but excluding deep tissues such as fascia and muscle and necrotizing infections (term utilized by FDA for therapeutic trials)</td>
<td></td>
</tr>
<tr>
<td>Skin and soft tissue infection (SSTI)</td>
<td>Infection involving the skin, subcutaneous connective tissue, fascia, or muscle (term utilized in this guideline)</td>
<td></td>
</tr>
<tr>
<td>Nosocomial infection</td>
<td>Infection that develops after a period of exposure to acute or chronic care facilities</td>
<td>Includes postoperative surgical site and deep space infections</td>
</tr>
<tr>
<td>Community-acquired infection</td>
<td>Infection that develops in community settings without exposure to health care facilities</td>
<td></td>
</tr>
<tr>
<td>Health-care associated infection</td>
<td>Infection in patient who has had recent exposure to the health-care environment but may not be within that environment at the time of onset of infection</td>
<td></td>
</tr>
<tr>
<td>FDA guidelines for antimicrobial trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated infection</td>
<td>Simple abscess, impetiginous lesions, furuncles, and cellulitis</td>
<td>Superficial infections or abscesses in site, such as the rectal area, where the risk of anaerobic or gram-negative pathogen involvement is higher</td>
</tr>
<tr>
<td>Complicated infection</td>
<td>Infection involving deeper soft tissues necessitating surgical intervention, such as infected ulcers, burns, major abscesses, or an underlying disease state that complicates the response to treatment (e.g., peripheral arterial disease, chronic kidney disease, diabetes mellitus)</td>
<td></td>
</tr>
<tr>
<td>CDC definitions for nosocomial infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical site infection (SSI)</td>
<td>Infection within 30 days of an operative procedure at the site of the procedure</td>
<td></td>
</tr>
<tr>
<td>Superficial incisional SSI</td>
<td>Infection involving only the skin and subcutaneous tissue of the incision; patient has at least one of the following: A. Purulent drainage from the incision B. Organisms isolated from an aseptically obtained culture of fluid or tissue from the incision C. At least one of the following: pain or tenderness, localized swelling, redness, or heat, and incision deliberately opened by surgeon, unless incision is culture-negative D. Diagnosis as superficial SSI by surgeon or attending physician</td>
<td></td>
</tr>
<tr>
<td>Deep incisional SSI</td>
<td>Infection within 30 days of the operative procedure if no implant is placed or within one year if an implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision, and the patient has at least one of the following: A. Purulent drainage from the incision but not from the organ/space component of the surgical site B. The incision spontaneously dehisces or is opened deliberately by a surgeon when the patient has at least one of the following signs or symptoms: fever (&gt;38°C) or localized pain or tenderness, unless the incision is culture-negative C. An abscess or other evidence of infection involving the deep incision is found on direct examination during reoperation or by histopathologic or radiologic examination D. Diagnosis as deep SSI by a surgeon or attending physician</td>
<td></td>
</tr>
<tr>
<td>Skin and soft tissue infection definitions from IDSA guidelines</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SSTIs managed by surgeons are classified as complicated and are of greater severity than the more common processes described above. These guidelines are directed toward these complicated infections. Antibiotic therapy for most complicated SSTIs is initiated empirically, hours-to-days before appropriate culture and sensitivity data are available. Thus, selection of an appropriate antibiotic is based on knowledge of the pathogens likely to be involved in a particular infection. Overall, *Staphylococcus aureus* is the pathogen most commonly isolated from SSTI, being found in one-quarter to one-quarter of cases.

### Table 3. Continued

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous abscess</td>
<td>Collection of pus within the dermis and deeper skin tissues</td>
<td></td>
</tr>
<tr>
<td>Furuncles and carbuncles</td>
<td>Infections of the hair follicle, usually caused by <em>S. aureus</em>, in which suppuration extends through the dermis into the subcutaneous tissue, where a small abscess forms</td>
<td></td>
</tr>
<tr>
<td>Cellulitis and erysipelas</td>
<td>Diffuse, spreading skin infections, excluding infections associated with underlying supplicative foci, such as cutaneous abscesses, necrotizing fasciitis, septic arthritis, or osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>Relatively rare subcutaneous infection that tracks along fascial planes and extends well beyond the superficial signs of infection, such as erythema or other skin changes</td>
<td>The fascia most commonly involved is the superficial, consisting of all the tissue between the skin and the muscle.</td>
</tr>
<tr>
<td>Anaerobic streptococcal myositis</td>
<td>Indolent infection of the muscle and fascial planes by anaerobic streptococci, usually associated with trauma or a surgical procedure</td>
<td></td>
</tr>
<tr>
<td>Pyomyositis</td>
<td>Presence of pus within individual muscle groups; usually caused by <em>S. aureus</em></td>
<td></td>
</tr>
<tr>
<td>Synergistic necrotizing cellulitis</td>
<td>Necrotizing soft tissue infection that involves muscle groups in addition to the superficial tissues and fascia</td>
<td></td>
</tr>
<tr>
<td>Fournier gangrene</td>
<td>Variant of necrotizing soft tissue infection involving the perineum, scrotum or penis, or vulva</td>
<td>Also referred to as clostridial gas gangrene.</td>
</tr>
<tr>
<td>Clostridial myonecrosis</td>
<td>Fulminant infections with muscle necrosis caused by <em>Clostridium</em> spp.; may be either traumatic or spontaneous</td>
<td></td>
</tr>
</tbody>
</table>

*CDC = U.S. Centers for Disease Control and Prevention; FDA = U.S. Food and Drug Administration; IDSA = Infectious Diseases Society of America.*

SSTIs managed by surgeons are classified as complicated and are of greater severity than the more common processes described above. These guidelines are directed toward these complicated infections. Antibiotic therapy for most complicated SSTIs is initiated empirically, hours-to-days before appropriate culture and sensitivity data are available. Thus, selection of an appropriate antibiotic is based on knowledge of the pathogens likely to be involved in a particular infection. Overall, *Staphylococcus aureus* is the pathogen most commonly isolated from SSTI, being found in one-quarter to one-quarter of cases.

![FIG. 1. Anatomy of skin and soft tissue structures and layers commonly involved with various infectious processes.](image-url)
half of all infections [5–7]. The most frequent pathogens identified in the SENTRY Antimicrobial Surveillance Program for SSTIs collected from participating medical centers in five provinces in Canada and 32 U.S. states between 1998 and 2004 are provided in Table 4 [7]. The total of 5,837 pathogens represent 50 consecutive cultures collected from hospitalized patients in participating centers and determined to be the major causes of pyogenic soft tissue infections. These cultures include both SSTI and surgical site infections (SSIs), as well as community-acquired (CA) and nosocomial infections. Thus, these results represent mainly complicated infections. These data may under-represent the frequency of β-hemolytic streptococci in SSTIs, because superficial cellulitis may not necessitate hospital admission, and adequate cultures are difficult to obtain even in severe cases of β-hemolytic streptococcal infections. A slightly different frequency distribution of pathogens in SSTIs is provided through analysis of culture data from patients in 584 hospitals in North America and Europe obtained through The Surveillance Network (TSN) during 2001 [5]. The most frequent pathogens reported in this study, in decreasing order of frequency, were S. aureus, Enterococcus spp., coagulase-negative staphylococci, Escherichia coli, and Pseudomonas aeruginosa. Again, streptococci were isolated only rarely, representing 1–2% of all isolates.

Surgical site infections are a specific type of SSTI seen as a complication of 2–5% of surgical procedures performed in the U.S. [8]. These infections have a slightly different pathogen distribution than other SSTIs because of the pathophysiology of the initiating process. As shown in Table 5, gram-positive pathogens account for the top four etiologic agents, with methicillin-resistant S. aureus (MRSA) among them [8].

Antibiotic resistance in isolates from SSTIs has increased significantly over time [9–13]. Figure 2 demonstrates the percentage of individual pathogens that were classified as resistant in the SENTRY program between 1998 and 2004 [7]. During this time period, there has been an increase in methicillin resistance among S. aureus (from 26.2% to 47.4%), vancomycin resistance among Enterococcus (from 8.6% to 14.8%), extended-spectrum β-lactamase production among Klebsiella spp. (from 4.9% to 16.3%) and E. coli (from 3.5% to 12.8%), and multidrug-resistant (non-susceptible to members of four drug classes) P. aeruginosa (from 1.3% to 3.9%). The increase in MRSA, in part, reflects the changing epidemiology of soft tissue infections as a consequence of the recent dramatic increase in the incidence of CA-MRSA SSTIs. In many locations in the U.S., CA-MRSA is now the pathogen most commonly isolated from SSTIs [9–11].

For each infection episode, the likelihood of encountering certain pathogens is altered by a number of factors, including infection severity, clinical setting, and etiologic process. Rapidly progressive, necrotizing infections more frequently involve pathogens that may be highly virulent, produce a variety of exotoxins, and have a rapid growth rate [14]. Necrotizing soft tissue infections arising from colonic pathology typically involve the same pathogens isolated in secondary peritonitis. Chronic wounds and nosocomial infections may involve highly resistant pathogens not commonly seen in acute CA infections. Skin and soft tissue infections arising from bites or that involve water exposure frequently involve pathogens that are uncommon in other settings. Pathogens specific to these settings are discussed below.

**Necrotizing skin and soft tissue infections**

Necrotizing infections usually are severe and complicated, involving a pathogen distribution somewhat different from what is isolated from less severe non-necrotizing infections. In an analysis of 198 consecutive patients with NSTIs, Elliot et al. documented a significant increase in the frequency of rapidly growing, virulent pathogens, particularly Streptococcus spp. and Clostridium spp. (Table 6) [6]. In contrast to the findings of the studies referenced above, streptococci were the organisms isolated most commonly, being found in greater than 50% of those patients from whom only one pathogen was isolated. Most patients with necrotizing infections have polymicrobial infections, with an average of 4.4 organisms isolated per infection. Such polymicrobial NSTIs arise from a number of initiating events, including peri-rectal infection and Fournier

<table>
<thead>
<tr>
<th>Table 4. Rank Order of Bacterial Pathogens Producing Skin and Soft Tissue Infections in North America, 1998–2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

As determined by the SENTRY Program [7].

<p>| Table 5. Organisms Isolated Most Commonly from Serious Surgical Site Infections in 26 Community Hospitals During 2005 |
|---|---|</p>
<table>
<thead>
<tr>
<th>Organism</th>
<th>No. (%) of SSIs (n = 1,010)</th>
<th>Prevalence rate, SSIs per 100 procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>331 (33)</td>
<td>0.37</td>
</tr>
<tr>
<td>Methicillin resistant</td>
<td>175 (17)</td>
<td>0.20</td>
</tr>
<tr>
<td>Methicillin sensitive</td>
<td>156 (15)</td>
<td>0.17</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>116 (11)</td>
<td>0.13</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>84 (8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>56 (6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>44 (4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>39 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>35 (3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fungi</td>
<td>29 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>26 (3)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note: Only deep incisional and organ space SSIs were included. SSI = surgical site infection.

gangrene, trauma, intravenous drug abuse, chronic diabetic ulcers, and SSIs [6]. An accurate clinical history and examination should be obtained to identify the likely source and probable polymicrobial nature of these infections. Although these polymicrobial infections can spread widely and become both limb- and life-threatening, they tend to be more indolent than infections caused by the limited number of highly virulent pathogens, which may cause rapidly spreading necrosis in an immunologically intact host. Such infection usually are caused by pathogens that produce exotoxins that contribute to their pathogenicity, including most commonly Streptococcus pyogenes (group A β-hemolytic Streptococcus) and Clostridium spp., but also Pasteurella spp., Vibrio spp., and Aeromonas hydrophila [14]. Again, the clinical history and examination should alert the surgeon to the possibility of such pathogens. Recently, there have been reports of NSTIs caused by CA-MRSA, either as a single pathogen or as a part of a polymicrobial population (see below) [15].

### Table 6. Organisms Recovered from 198 Consecutive Patients with Necrotizing Soft Tissue Infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. cultures</th>
<th>No. isolates (% of cultures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>182</td>
<td>83 (45.6)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>182</td>
<td>61 (33.5)</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>182</td>
<td>64 (35.2)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>182</td>
<td>57 (31.3)</td>
</tr>
<tr>
<td>Proteus spp.</td>
<td>182</td>
<td>38 (20.9)</td>
</tr>
<tr>
<td>Other gram-negative bacilli*</td>
<td>182</td>
<td>76 (41.8)</td>
</tr>
<tr>
<td>Anaerobic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptostreptococci</td>
<td>131</td>
<td>45 (34.4)</td>
</tr>
<tr>
<td>Bacteroides spp.</td>
<td>120</td>
<td>70 (54.7)</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>129</td>
<td>12 (9.3)</td>
</tr>
<tr>
<td>Other clostridia</td>
<td>128</td>
<td>17 (13.3)</td>
</tr>
<tr>
<td>Other anaerobic species</td>
<td>128</td>
<td>27 (21.1)</td>
</tr>
<tr>
<td>Fungal species</td>
<td>171</td>
<td>9 (5.3)</td>
</tr>
</tbody>
</table>


### Nosocomial and chronic skin and soft tissue infections

Particularly after previous antibiotic exposure, both nosocomial and chronic infections have a greater risk of containing resistant pathogens such as MRSA, methicillin-resistant S. epidermidis (MRSE), vancomycin-resistant Enterococcus (VRE), and resistant gram-negative bacilli [16,17]. These settings typically alter the host’s resistance to bacterial colonization and invasion, change the commensal bacterial flora, and cause exposure to more-resistant pathogens. Thus, an “ecologic vacuum” provides an opportunity for more-resistant pathogens to establish an ecologic niche. More importantly, whereas MRSA historically has been associated with previous antibiotic exposure and nosocomial settings, the increase in CA-MRSA SSTIs has altered this association permanently (see discussion below).

### Bite wound- and water-associated infections

Both bite wound- and water-associated-wound infections frequently are associated with pathogens that are unusual in other settings; commonly, such infections are polymicrobial [1,14,18–21]. Some of these pathogens can be associated with rapidly progressive infections (Pasteurella spp., Vibrio spp., and Aeromonas hydrophila) and may require special consideration. Bite wounds are common, with nearly one-half of all Americans having been bitten during their lifetimes. The most common sources are human beings, dogs, and cats, although bites by exotic pets and feral animals also are seen. Bite wounds, particularly those on the hands, must be evaluated.
carefully because of the mechanism of injury, as the bites may inoculate substantial numbers of bacteria into deep tissues, causing tissue disruption and trauma. In addition, deep hand infections may travel freely along fascial plains and tendon sheaths. Thus, although these wounds may appear innocuous, they should be considered high-risk. Most bite-wound infections are polymicrobial, with an average involvement of five bacterial isolates, commonly (~60%) a mixture of aerobic and anaerobic bacteria. The pathogens most often isolated from bite wound infections are listed in Table 7. Staphylococcal and streptococcal species are common aerobic isolates, and Bacteroides spp., peptostreptococci, Fusobacterium spp., and Prevotella heparinolytica are common anaerobic isolates. Two pathogens, Pasteurella spp. and Capnocytophaga canimorsus, are almost unique to bite wounds and can cause rapidly progressive infection or fatal sepsis. Pasteurella spp. are particularly common in both dog (50%) and cat (75%) bite wounds. These organisms are gram-negative coccobacilli that are commensals in the oral cavity of many animals. In human bite wounds, both Haemophilus spp. and Eikenella corrodens are common aerobic isolates.

Water-associated SSTIs are similar to bite wound infections in that they frequently are polymicrobial, frequently include staphylococci and streptococci as aerobic isolates, and are associated with pathogens uncommon in other settings. Pathogens almost unique to water-associated skin infections are Aeromonas spp., Vibrio spp., Edwardsiella tarda, Erythromelthrix rhusiopathiae, and Mycobacterium marinum [22].

**Community-acquired MRSA infections**

As noted above, *S. aureus* is the pathogen most commonly isolated from SSTIs. Rapidly changing epidemiology has made CA-MRSA one of the most common strains. Historically, SSTIs caused by MRSA usually were seen in nosocomial or chronic wound settings, particularly when selection pressure was present from previous antibiotic therapy. However, the epidemiology of MRSA is changing rapidly with the recent increase in CA-MRSA. Methicillin-resistant *S. aureus* is now the most common cause of all nosocomial infections, accounting for more than 55% of staphylococcal isolates in hospitalized patients, and also is the most common isolate from SSIs [8, 23]. Traditionally, MRSA has been thought of as a nosocomial or hospital-acquired (HA) organism associated with pneumonia, SSIs, and bacteremia and usually to be multidrug resistant [24,25]. Risk factors previously established for MRSA infection included recent exposure to a healthcare setting, including a long-term care facility; indwelling catheters; the presence of an open wound; and previous exposure to antibiotics.

Until recently, staphylococcal infections acquired outside the healthcare setting were most frequently methicillin-sensitive *S. aureus* (MSSA) and responsive to several antibiotics. However, as early as 1981, MRSA was reported in community outbreaks among patients with and without risk factors for the infection [26]. These organisms have come to be called CA-MRSA. Outbreaks have been reported in otherwise-healthy Alaskan natives, children, inmates in correctional facilities, institutionalized adults with developmental disabilities, nursing home residents, and athletes involved in team sports [27–36]. The majority of infections caused by CA-MRSA are of the skin and soft tissues. However, CA-MRSA may be associated with respiratory, blood stream, and urinary tract infections. The two pathogens, CA-MRSA and HA-MRSA, differ in their chromosomal make-up, pathogen, and resistance, as outlined in Table 8 [9]. In addition, CA-MRSA often has a different antibiotic susceptibility profile than HA-MRSA [9,11,15]. Typically, HA-MRSA has been resistant to at least three β-lactam antibiotics but usually is susceptible to vancomycin, sulfamethoxazole, and nitrofurantoin, whereas CA-MRSA is more likely to be susceptible to clindamycin and has differing susceptibility to tetracycline, fluoroquinolones, erythromycin, and vancomycin [37]. However, as CA-MRSA moves into the hospital setting and gains resistance determinants, the distinction between the two pathogens according to the current nomenclature is becoming considerably blurred.

A number of recent reports highlight a dramatic and continued increase in the identification of CA-MRSA in SSTIs in the community as well as the hospital setting [10,11,15,38–40]. These CA-MRSA infections represent a change in the epidemiology of staphylococcal infections, as they are being identified in patients both with and without typical risk factors for MRSA. Community-acquired MRSA has become the most common pathogen causing SSTIs in several communities, and has been identified as a cause of NSTI in otherwise-healthy patients.

---

**Table 8. Characteristics of Staphylococcal Cassette Chromosome mec (SCCmec) Types I–V**

<table>
<thead>
<tr>
<th>SCCmec type</th>
<th>SCCmec size, kb</th>
<th>Other antibiotic-resistant elements (genes) on SCCmec</th>
<th>Origin of isolates carrying specified SCCmec type</th>
<th>Presence of Panton-Valentine leukocidin in isolates carrying specified SCCmec type</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>34</td>
<td>–</td>
<td>Hospital</td>
<td>Infrequent</td>
</tr>
<tr>
<td>II</td>
<td>53</td>
<td>PUB110 (aadD), Tn554 (ermA)</td>
<td>Hospital</td>
<td>Infrequent</td>
</tr>
<tr>
<td>III</td>
<td>67</td>
<td>PUB110 (aadD), PT181 (tetK)</td>
<td>Hospital</td>
<td>Infrequent</td>
</tr>
<tr>
<td>IV</td>
<td>21–24</td>
<td>–</td>
<td>Community</td>
<td>Frequent</td>
</tr>
<tr>
<td>V</td>
<td>28</td>
<td>–</td>
<td>Community</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*In general, 15% of *Staphylococcus aureus* strains that carry SCCmec types I–III also carry the Panton-Valentine leukocidin (PVL) gene, with some exceptions; 40%–90% of *S. aureus* strains that carry SCCmec type IV carry the PVL gene.

Encodes resistance to tobramycin and kanamycin.

Encodes resistance to macrolide–lincosamide–streptogramin antibiotics.

Encodes resistance to tetracycline.

individuals, either alone or in combination with other pathogens [11,15,39]. The USA300 genotype of CA-MRSA has accounted for the largest portion of this increase in SSTIs and has transitioned into the hospital [11,40]. In a study of SSI pathogens encountered during 2005, Patel et al. found that MRSA accounted for roughly one-quarter, and greater than one-half of the MRSA isolates were of the USA300 genotype [40].

Treatment of Skin and Soft Tissue Infections

The majority of SSTIs treated by surgeons are classified as complicated and are more frequently severe than are those treated by non-surgeons or on an outpatient basis. Uncomplicated skin and subcutaneous abscesses respond well to incision and drainage (I&D) with appropriate wound care and do not require antibiotics [41]. Complicated SSTIs include severe skin and subcutaneous abscesses, non-necrotizing cellulitis, necrotizing cellulitis, fasciitis, myositis, and SSIs. Antibiotic therapy commonly is begun empirically; thus, an understanding of the likely pathogens in various clinical settings is required. Clinical presentation, history, and physical examination should direct the clinician to the likely pathogens and thus direct empiric therapy. If culture data become available, de-escalation of antibiotics may be undertaken. In the recommendations to follow, the discussion of antibiotic and therapeutic decision-making is divided into treatment of non-necrotizing cellulitis, including bite wounds; complicated abscesses; mixed necrotizing infections; rapidly progressive NSTIs caused by single pathogens, including toxic shock, CA-MRSA, group A Streptococcus (GAS), and Clostridium and Vibrio infections; and diabetic foot infections.

Non-necrotizing cellulitis

The term “non-necrotizing cellulitis” incorporates two entities, erysipelas and cellulitis, which are diffusely spreading skin infections not associated with supplicative foci. The term “cellulitis” frequently is interchangeable with “erysipelas,” and the latter term is preferred in Europe. However, a fine distinction exists between erysipelas and cellulitis. Erysipelas has two classic features: (1) A clear line of demarcation between involved and uninvolved tissue; and (2) lesions raised above the surrounding normal skin [42]. Cellulitis involves deeper layers of the dermis and subcutaneous tissue and has less distinctive features than erysipelas, although both conditions involve rapidly spreading areas of edema, erythema, and warmth and may be accompanied by lymphangitis [43]. These non-necrotizing infections most commonly are caused by β-hemolytic streptococci (usually group A) but may be caused by other streptococcal species [43–45]. In specific clinical situations, other bacterial species may cause a spreading, non-necrotizing cellulitis such as Haemophilus influenzae in children, and pneumococcal cellulitis in the limbs of patients with altered immunity. Rarely, S. aureus is involved, but such infections usually are more suppurative and less diffuse. Superficial, non-necrotizing infections caused by certain strains of GAS may be associated with streptococcal toxic shock syndrome (TSS), characterized by rapid progression of septic shock and organ failure [46–48].

These infections generally arise when organisms enter through breaches in the skin. Predisposing factors broadly include conditions involving alterations of skin integrity (i.e., dermatoses, fungal infections, ulcerations), alterations in lymphatic and venous drainage (i.e., saphenous vein harvest, lymph node dissections), alterations in the vascularity of the skin, and alteration of host defenses (e.g., diabetes mellitus) [49–53]. Antibiotic therapy most commonly is based on empirical diagnosis established by clinical findings, as cultures usually are negative. Blood cultures are positive in <5% of cases, and the likelihood of positive results from either needle aspiration or punch biopsy ranges from ≤5–40% [54–58].

Antibiotic therapy. Treatment options for erysipelas and cellulitis have not been established through randomized studies, but clinical practice has established standards of therapy. For severe erysipelas or cellulitis caused by streptococci, penicillin given parentally is the agent of choice [1]. Other regimens include anti-staphylococcal penicillins, cefazolin, and ceftriaxone [43,59,60]. However, treatment failures occur with β-lactam antibiotics despite in vitro microbial sensitivity to the agents [61–64]. The mechanism of failure is believed to be failure of bacterial killing by cell wall-inhibiting agents when high numbers of bacteria in the static phase decrease the expression of penicillin-binding proteins [64–66]. Protein synthesis-inhibitory agents such as macrolide and lincosamide antibiotics may be as effective, and indeed potentially superior in certain settings [63,64,67]. Clindamycin, either alone or in combination with a cell wall-inhibiting agent, was more effective than cell wall-inhibiting agents alone in a retrospective analysis of pediatric GAS infection [64,67]. Roxithromycin proved to be equivalent to penicillin for the treatment of erysipelas in a randomized, multicenter trial [68]. However, increasing macrolide resistance among streptococci creates concern about these agents, and local sensitivity patterns should be considered when using them alone for the treatment of complicated GAS infections [64,69,70]. Additionally, because clindamycin reduces exotoxin and superantigen production by pathogenic strains of GAS, the drug used is frequently as an adjunct in the treatment of streptococcal TSS [63,66,71]. However, the most effective antibiotic regimen in this setting has not been established in prospective studies. If MSSA is suspected, the treatment of choice is a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin [1,43]. However, as discussed previously, the recent dramatic increase in CA-MRSA makes the empiric treatment of staphylococcal infections with β-lactam antibiotics problematic, and other agents should be considered unless the risk of resistant Staphylococcus is low (see discussion below) [11,15].

Treatment of bite wounds. The majority of bite wounds are mammalian in origin, produced predominately by human beings, dogs, and cats [72,73]. Infection rates differ widely depending on the severity and location of the wound and the animal source. Non-human bites that are low risk and that do not involve the hand have infection rates <2%; human bites involving the hand with deep penetration have infection rates >50%. Unfortunately, few data exist to guide the management of bite wounds. Investigators have advocated irrigation, debridement, or decontamination of the wound; primary closure; prophylactic antibiotics; and therapeutic antibiotics. Most recommendations are based on consensus and not randomized trials.

The main principles of treatment for bite wounds are the recognition of the risk of complications, thorough wound
care, and appropriate antibiotic therapy. Wounds at high risk of infection include those causing deep puncture, crush injury, or devitalized tissue and those with heavy contamination [73]. Bites involving the hand appear to have a higher infection risk, and complications portend a greater risk of long-term dysfunction. Human bites generally have a higher infection risk than do either dog or cat bites [73]. Irrigation, debridement, or decontamination of wounds is considered standard of care, although no randomized or large cohort studies have examined such management techniques. Primary closure is believed to be advantageous for most bite wounds, assuming adequate debridement and irrigation [73]. However, limited data exist to support this practice, as only one small randomized study has been performed regarding primary closure. Tetanus immunization is considered standard of care, although no studies have been performed to confirm its value for bite wounds [73].

The use of prophylactic antibiotics in the setting of bite wounds is controversial, and their value likely differs depending on the risk of infection, bite source, wound location, and timing of antibiotics. A Cochrane review found no significant difference in the overall infection rate of mammalian bites with prophylactic antibiotics, with significant heterogeneity among trials [73]. When the results were analyzed by wound site, antibiotic prophylaxis decreased infection rates for human-bite hand wounds only, although the total numbers of patients in all groups were small, and positive results were observed in a single study of human-bite hand wounds with 48 patients in total [74]. A randomized trial in 127 low-risk human bite wounds less than 24 h old that did not involve the hand demonstrated no benefit from prophylactic antibiotics [72]. Penicillins (with and without β-lactamase inhibitors) and cephalosporins have been tested, without significant differences in infection rates, although the studies were powered inadequately to conclude that this practice is of no value.

For the treatment of established infections from bite wounds, no study has compared antibiotics and placebo. However, antibiotics are standard. Inadequate studies exist to guide any recommendation for antibiotic selection, although choosing an antibiotic that covers the mouth flora of the biting animal or human is standard.

Complicated abscesses

Complicated SSTIs may involve a variety of pathogens, frequently more than one [6,7,75–77]. The majority of infections occur in individuals who have some alteration in host defenses, such as diabetes mellitus, vascular insufficiency, or traumatic injury. Common sites of origin are perianal or perirectal infection in diabetic patients, perirectal abscesses, traumatic injury. Chronic cutaneous cysts, intravenous drug injection sites, SSIs, gastrointestinal pathology with perforation, genitourinary pathology, animal bites, and pressure ulcers [6,75,77]. The initiating pathogens often differ according to the originating site. Aerobic gram-positive pathogens are isolated in >50% of all complicated abscesses and necrotizing infections, and, depending on the origin, anaerobes, *Pseudomonas* spp., *Enterobacteriaceae*, and *Clostridium* spp. may be present. An accurate clinical history and physical examination should suggest the etiology and direct empiric therapy. Complicated skin and subcutaneous abscesses typically are well circumscribed, and respond to I&D with adjuvant antibiotic therapy. Inadequate resolution should prompt consideration of further drainage, resistant pathogens, or host immune failure. During I&D, appropriate precautions must be undertaken to ensure that all loculations have been identified and that there is no occult involvement of the fascia or deeper tissue spaces. Certain areas, such as the perineum and perirectal space, may have deep-space involvement that is difficult to identify; computed tomographic (CT) imaging should be considered preoperatively to rule out deep tissue involvement.

Empiric antibiotic therapy should be directed to the likely pathogens. For polymicrobial infections, several classes of agents or combinations of agents provide adequate coverage. Broad-spectrum agents with coverage of gram-positive, gram-negative, and anaerobic pathogens may be required, depending on the clinical setting. In nosocomial situations, coverage of resistant pathogens encountered locally should be considered. De-escalation should be considered on the basis of the culture results. Given the high frequency of MRSA, this pathogen should be covered empirically unless specific data indicate otherwise. No randomized studies are available on the treatment of SSTI caused by CA-MRSA. Sensitivity patterns usually are used to direct the choice. A number of oral agents have been used for outpatient treatment of less severe infections [11]. In the patient with a simple abscess suspected to be caused by MRSA, I&D of the abscess should be performed. The use of antibiotics as an adjunct to I&D may be considered, particularly for patients with substantial cellulitis, and should be directed against MRSA. Whereas historically, cultures of abscesses often were not obtained for simple SSTI, the increase in CA-MRSA prevalence suggests that cultures may be useful, particularly if there is no response to presumably adequate therapy. If CA-MRSA is suspected and the patient can be treated as an outpatient, oral antibiotics such as trimethoprim/sulfamethoxazole, clindamycin, tetracycline, erythromycin, and some quinolones may be used. Other oral agents such as linezolid, an oxazolidinone antibiotic that inhibits bacterial protein translation at the initial phase of protein synthesis, were efficacious for MRSA in randomized trials [78,79].

Complicated SSTI necessitating hospital admission usually requires intravenous broad-spectrum antibiotics. Again, no randomized studies exist specifically on the treatment of CA-MRSA, and therapeutic options are extrapolated from other studies of infections caused by MRSA. Whereas vancomycin has been the gold standard, one randomized study demonstrated the superiority of linezolid in the treatment of complicated SSTI (88.6% vs. 66.9% cured for linezolid vs. vancomycin, p <0.001) [78], and another retrospective subset analysis reached a similar conclusion [79]. Additionally, linezolid inhibits toxin production in vitro, providing a theoretical advantage [80]. Newer agents with activity against MRSA tested in randomized trials of complicated SSTIs include quinupristin/dalfopristin, daptomycin, and tigecycline [9,81]. Although each is approved for the treatment of complicated SSTI, randomized studies of the efficacy of these agents contained too few MRSA isolates to formulate recommendations. Quinupristin/dalfopristin is a combination of two streptogramins that inhibits protein synthesis but requires central intravenous (IV) administration and has major side effects. Daptomycin is a cyclic lipopeptide with bactericidal activity against gram-positive pathogens including...
MRSA, and tigecycline is a broad-spectrum glycyclcline antibiotic with activity against gram-positive organisms, including MRSA [82]. Agents being studied but not yet approved are dalbavancin, telavancin, and ceftobiprole. Another anti-MRSA cephalosporin, cefatoline, was effective in phase II trials and is undergoing further study.

**Mixed necrotizing skin and soft tissue infections**

Necrotizing SSTIs are discussed separately because of their greater severity, the differences in the pathogens relative to non-necrotizing infections, the difficulty and importance of establishing an early diagnosis, and the beneficial impact of early, aggressive surgical debridement on the outcome. Necrotizing infections are serious, causing progressive tissue destruction with a risk of tissue and limb loss and death. Despite advances in therapy over the past three decades, the mortality rate from NSTI remains approximately 25%.

Necrotizing infections may involve any combination of the dermis, subcutaneous tissue, fascia, or muscle. Notably, each of these layers has various degrees of intrinsic resistance to infection. The blood supply to the fascia typically is more tenuous than that to muscle or healthy skin, making the fascia more vulnerable to infection. Additionally, the propensity for fluid to collect between involved fascia and adjacent tissues further weakens fascial immune function by altering host clearance of pathogens by decreasing phagocytic function. Thus, necrotizing fasciitis is more common than necrotizing processes involving other soft tissue layers, as infection can spread widely across the fascial planes with minimal involvement of surrounding skin or muscle.

**Diagnosis.** Distinguishing an NSTI that necessitates surgical debridement from a non-necrotizing cellulitis that will respond to antibiotic therapy alone can be difficult. However, any delay is potentially catastrophic, as it clearly increases the mortality rate [6,83,84]. Certain features of the presentation may facilitate the detection of a necrotizing process. The presence of gas in tissue on a plain radiograph is more sensitive in recognizing a necrotizing process than is physical examination [85,86]. Computed tomography scanning and magnetic resonance imaging (MRI) also assist in detecting severe infections. These imaging techniques may reveal fluid along fascial planes, edema within tissues, and gas not seen by plain radiography [87,88]. Notably, neither fluid nor edema is specific for necrotizing infection, and the sensitivity and specificity of these modalities have not been established.

Clinical features that suggest NSTI are (1) pain disproportionate to the physical findings; (2) bullae; (3) skin ecchymosis that precedes skin necrosis; (4) gas in the tissues identified by examination or radiographic evaluation; (5) edema that extends beyond the area of erythema; (6) cutaneous anesthesia; (7) systemic toxicity; and (8) progression of infection despite antibiotic therapy [1,6,75,84].

The triad of crepitus, skin blistering, and radiographic evidence of soft tissue gas may be present in more than 80% of patients with NSTIs, but such findings suggest an advanced stage and may be absent [6]. In a study by Wall et al. [84], 21 patients with necrotizing fasciitis were matched with 21 patients with non-necrotizing infections. Both univariable and multivariable analyses were performed, and the predictors of necrotizing infection and death were analyzed. Physical examination and laboratory and radiographic parameters predictive of necrotizing fasciitis are shown in Table 9. An admission white blood cell (WBC) count >14×10^9/L, serum sodium <135 mmol/L, and blood urea nitrogen >15 mg/dL were shown by multivariable analysis to predict the presence of a necrotizing infection [84]. However, the small number of patients limits the power to evaluate a number of parameters of interest in this setting. The use of full-thickness biopsy and frozen section has been advocated, but neither has been evaluated adequately or adopted widely [89]. If the presence of a necrotizing infection cannot be excluded, surgical exploration is indicated.

**Therapeutic approach.** The mortality rate from necrotizing infections remains high: The rate in 67 studies including 3,302 patients treated between 1980 and 2008 (see Table 2) was 23.5% [6,75,83,84,85–150]. Although the mortality rate has trended down slightly in recent studies (27.8% for studies from 1980–1999 vs. 21.7% since 1999), it remains above 20%. Aggressive and timely resuscitation, prompt administration of appropriate antibiotic therapy, certain adjunctive therapies, and, especially, early surgical debridement all may be required for an optimal outcome. Among these maneuvers, surgical intervention is the mainstay. Unfortunately, no randomized studies of surgical therapy for SSTIs have been published. Retrospective studies have identified potentially alterable factors that predict death. Such factors include the extent of infection, time to first debridement, degree of organ dysfunction, extent of hemodynamic stability, and the adequacy of debridement.

In a study by Wall et al., multivariable analysis identified admission WBC of >30×10^9/L and patient transfer prior to

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**Table 9. Accuracy of Physical, Laboratory, and Radiographic Findings in Predicting Necrotizing Fasciitis**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tense edema</td>
<td>38</td>
<td>100</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>Bullae</td>
<td>24</td>
<td>100</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td>White blood cell count 0.14×10^9/L</td>
<td>81</td>
<td>76</td>
<td>77</td>
<td>80</td>
</tr>
<tr>
<td>Sodium &lt;135 mmol/L</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>Chloride &lt;95 mmol/L</td>
<td>30</td>
<td>100</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>Blood urea nitrogen &gt;0.15 mg/dL</td>
<td>70</td>
<td>88</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>Gas on roentgenogram</td>
<td>39</td>
<td>95</td>
<td>88</td>
<td>62</td>
</tr>
</tbody>
</table>

therapy as independent predictors of death. Transfer of patients resulted in a delay in therapy of 5.8 h [84]. In another retrospective analysis of 68 patients with NSTI, the mortality rate for patients who underwent early aggressive surgical debridement was 4.2%, whereas the rate for those patients with either a delay in therapy or inadequate initial therapy was 38% [83]. Unfortunately, the definitions of delayed or inadequate initial therapy were not described clearly. In a study of 45 NSTIs by Bosshardt et al., regression analysis revealed three independent predictors of death: The extent of initial debridement, the initial blood pressure, and the initial temperature [75]. The extent of debridement (reflecting the extent of tissue involvement) was the strongest predictor, with an involvement of >250 cm² being predictive of death. Utilizing these three factors, the authors predicted survival correctly for 100% of patients, but death correctly for only 50% of patients (87% correct overall). In the largest retrospective review identified, Elliott et al. examined 198 NSTIs and, using multivariable regression analysis, identified age, female sex, serum creatinine concentration, serum lactate concentration, time between admission and first debridement, size of the affected body surface area, and the number of organs failed on admission as predictors of death [6]. Survivors had an average of 1.2 days between admission and debridement vs. 3.1 days for non-survivors. These findings are similar to those of McHenry et al., in which survivors had an average time of 1.1 days between admission and initial debridement vs. 3.8 days for non-survivors [86].

A number of studies support early aggressive debridement as a predictor of a better outcome [86,109,127,136,139]. The Vanderbilt group recently reviewed 52 NSTIs managed by the Emergency General Surgery (EGS) service [116]. The EGS service is staffed by in-house faculty board certified in surgical critical care. This system of in-house faculty with expertise in the management of SSTIs enabled a reduction in time from diagnosis to operation to a median of 8.6 h. The time to operation is favorable relative to that in other reports; the overall mortality rate for the 52 patients was 9.6%. The median Acute Physiology and Chronic Health Evaluation (APACHE) II score for this population was 13 points, and a mean number of 3.3 debridements were performed per patient. This mortality rate compares favorably with those in previously published studies, and suggests that early recognition and surgical intervention could reduce the mortality rate to <10%. By this and previous studies, the weight of evidence indicates that early, adequate surgical debridement of NTSIs could improve outcomes and reduce the mortality rate substantially.

**Surgical therapy.** Surgical drainage and debridement of involved tissues is the mainstay of therapy in NSTI. However, no randomized studies or substantive case series are available to direct surgical therapy. Retrospective reviews identify adequate, early surgical debridement as a predictor of survival, but do not report quantifiable methods of defining adequate debridement [6,75,77,83,86]. Several issues should be considered: (1) The extent of resection; (2) full-thickness vs. fascial excision for necrotizing fasciitis; (3) serial wound examinations and debridements; and (4) colostomy vs. other methods of control of the fecal stream for perineal and scrotal infections. The determination of the extent of resection most commonly is based on clinical judgment and the gross appearance of the tissues involved. Depending on the clinical setting, the microbiology, inciting insult, fascial layers, skin, subcutaneous fat, and muscle must all be considered. The most common clinical entity usually is called “necrotizing fasciitis” and involves and spreads along fascial planes, typically with little involvement of surrounding tissues. The ability to separate the fascia easily from normally adherent surrounding tissue strongly suggests infection [77,86,139,151]. However, in elderly and critically ill patients with extensive edema, the ease of separation can be difficult to distinguish from that of non-infected fascia, and identification of NSTI requires considerable clinical judgment. For skin, fat, and muscle involvement, the absence of inflammation and purulence and the presence of normal bleeding at the line of incision commonly are used to judge the adequacy of debridement. Additionally, viable muscle will demonstrate contractility. For fasciitis without involvement of surrounding tissues, debridement and drainage of involved fascia through a series of parallel incisions without resection of overlying tissue may preserve overlying tissues [152]. However, if surrounding tissues are involved, full-thickness excision is required.

Necrotizing infections have the potential for rapid and continued progression despite surgical debridement. No randomized or large cohort studies exist to guide the timing and frequency of debridement, in part because of the wide variation in clinical presentation and course of NSTIs. Thus, the wound should be re-evaluated frequently. Many authors recommend return to the operating room within 24 h to ensure the adequacy of debridement and absence of progression [77,83,86]; the average number of operative procedures is 3–4 per patient [6,75,83,86,139]. Prevention of heavy, recurrent contamination of dressings may be problematic in patients with perineal, perianal, or scrotal involvement. When fecal soilage of dressings is significant, fecal diversion is recommended by many [153,155]. Recently, a rectal tube system specifically designed to control the fecal stream has been used successfully to avoid colostomy [156,158]. In summary, the surgical management of NSTIs continues to be driven by clinical experience and expertise. Early, adequate surgical debridement is linked to improved outcomes but remains poorly defined.

**Antibiotic therapy.** Antibiotic regimens for NSTIs have not been studied rigorously. Current recommendations are garnered from prospective studies of complicated SSTIs, prospective studies in clinical settings with similar pathogens (i.e., intra-abdominal infection trials), and interpretation of current sensitivity patterns of the pathogens typically involved. As most of these infections are mixed and may involve aerobic and anaerobic gram-negative and gram-positive pathogens, broad-spectrum antibiotic coverage is indicated in most cases. The rapidity of the process, clinical presentation, and clinical findings should alert the practitioner to the potential presence of specific virulent pathogens such as GAS, *Clostridium*, and *Vibrio* spp., as discussed below. If such pathogens are expected, antibiotic therapy should be altered appropriately.

For the majority of complicated and necrotizing soft tissue infections, a number of single-agent or combination regimens that provide anaerobic, gram-positive, and enteric gram-negative coverage may be effective. Several single-agent regimens have been compared in randomized trials in complicated SSTIs, including imipenem-cilastatin [159], meropenem [159], ertapenem [166,167], piperacillin-tazobactam [166,167], ticarcillin-clavulanic acid [160,161], levofloxacin
in the course of infection, or following a large inoculum. Few, if any, randomized studies of multi-drug regimens are also available to support recommendations of one regimen over another in severe infections. Numerous combination regimens are recommended by different sources, but have not been studied rigorously. These combinations typically include penicillins or cephalosporins with either an aminoglycoside or a fluoroquinolone, plus an anti-anaerobic agent such as clindamycin or metronidazole.

Recommended antibiotic therapy depends on the suspected pathogens and the rapidity of infection’s progression. For non-rapidly progressive SSTIs, a single agent is recommended, with an anti-MRSA drug added if one suspects this pathogen is present. If the infection is rapidly progressive or severe, combination therapy with protein synthesis-inhibiting agents such as clindamycin (or linezolid if resistant S. aureus is suspected) may be beneficial, particularly if toxin production is important pathogenically, or in the presence of large inocula (see discussion below).

### Rapidly progressive soft tissue infections

As noted above, some pathogens can cause clinical syndromes with rapidly progressive deterioration of clinical status, even in intact hosts. Such pathogens generally produce a variety of exotoxins that contribute to the pathogenesis. Many of the pathogens are characterized by rapid growth rates and tissue invasion. The rapidity of clinical deterioration and high mortality rate for this group of necrotizing infections warrants special consideration. The authors have grouped the relatively more common (although rare in general) pathogens below. The pathogens discussed are: (1) S. aureus because of this pathogen’s ability to produce TSS and the occurrence of NSTI associated with Panton-Valentine leukocidin (PVL)-positive CA-MRSA; (2) Strep. pyogenes; (3) Clostridium spp., and (4) Vibrio spp.

**Rationale for use of protein synthesis-inhibiting agents.** In certain SSTIs, specific consideration may be given to the potential benefit of agents that limit toxin production via protein synthesis inhibition and the ineffectiveness of cell wall-active agents when large inocula are present. These considerations are important in rapidly progressive NSTIs in which toxin production by the invading bacteria is an important component of the pathophysiology of the infection, and in those infections in which toxin production by the bacteria creates systemic illness. Examples of such infections include those caused by C. perfringens and C. septicum, necrotizing streptococcal infections, streptococcal infections producing TSS-like symptoms, severe Vibrio and Aeromonas infections, and necrotizing infections caused by Staphylococcus spp. producing the PVL toxin. Because of the relative infrequency and the severity of such infections, clinical studies generally are lacking, and randomized studies are nonexistent.

In 1952, Eagle demonstrated in a murine S. pyogenes myositis model that penicillin was ineffective if administered late in the course of infection, or following a large inoculum. These findings were replicated by Stevens et al. in 1988, who also demonstrated that both clindamycin and erythromycin were more effective than penicillin when antibiotics were administered after S. pyogenes had achieved significant numbers (either a large inoculum or delayed antibiotic administration). Subsequently, similar findings were demonstrated in a murine myositis model with C. perfringens. The Eagle effect is believed to reflect reduction of penicillin-binding proteins during the stationary growth phase, allowing persistence of the organism. This effect also was noted clinically for S. aureus infections relatively early in the antibiotic era. In a retrospective review of 56 infections caused by S. pyogenes in children, Zimbelman et al. found clinical outcomes to be significantly better when protein synthesis-inhibiting antibiotics (predominately clindamycin) were used, either alone or in combination with cell wall-inhibiting agents, than when cell wall-inhibiting agents were used alone. Treatment with clindamycin also appeared to improve the outcome of NSTIs caused by GAS in a population-based surveillance study that identified 77 infections, but the small numbers precluded statistical significance.

Protein synthesis-inhibiting agents inhibit toxin production and limit pathogenicity for a variety of bacteria. Clindamycin (even at sub-inhibitory concentrations) inhibits toxin and superantigen production by S. pyogenes, S. aureus, and C. perfringens. However, increasing resistance of both S. pyogenes and S. aureus to clindamycin raises concern about the continued efficacy of this agent in severe SSTIs, particularly if used alone. Linezolid is a newer protein synthesis-inhibiting agent with broad activity against gram-positive bacteria (including MRSA) that reduces production of toxins by S. aureus, including toxic shock syndrome toxin-1 (TSST-1). The inhibition of toxin production by antibiotics in the tetracycline class may explain their superiorit relative to cell wall-inhibiting agents alone in the treatment of severe SSTIs caused by the gram-negative pathogen V. vulnificus.

Thus, summation of the in vitro, in vivo, and limited clinical studies provides a rationale to include protein synthesis-inhibiting agents when treating severe infections in which toxin production may be a major part of bacterial pathogenesis. Because of the severity and high mortality rate of these infections, the authors recommend these agents in combination with cell wall-inhibiting drugs. The choice of protein synthesis-inhibiting agent should be based on the known or predicted sensitivity of the organism(s) to the agents considered. Recommended agents include clindamycin (if resistance is not a concern), linezolid for gram-positive infections, and members of the tetracycline class for the gram-negative pathogens V. vulnificus and Aeromonas spp.

**Staphylococcal toxic shock syndrome.** Although S. aureus typically does not exhibit the rapid replication demonstrated by many other pathogens discussed in this section, the potency of the exotoxin that produces staphylococcal TSS enables rapid presentation and progression.

**Epidemiology.** Staphylococcal TSS is characterized by fever, hypotension, rash, organ failure, and skin desquamation. The syndrome came to national attention in the U.S. in 1980 after several reports of this constellation of symptoms in menstruating women using tampons. After public health recommendations were made regarding tampon use,
the incidence dropped from 6–12/100,000 in 1980 to 1/100,000 in 1986 [182,183]. As early as 1982, clinicians noted an increase in the proportion of TSS cases not associated with menstruation [184]. Surveillance revealed that whereas menstrual TSS made up the majority of the 5,296 cases reported between 1979 and 1996, the proportion declined from 91% during 1979–1980 to 71% during 1981–1986 and to 59% between 1987–1996 [185]. Despite the increasing proportion of non-menstrual cases of TSS, most still were reported in women. Additionally, there was an increase in the proportion of non-menstrual cases associated with surgical procedures, from 14% during 1979–1986 to 27% during 1987–1996. Finally, whereas the case-fatality ratio decreased significantly over time for menstrual cases, this was not observed for the other types. The increasing prevalence of non-menstrual cases is particularly important for the clinician who cares for surgical patients, and the surgeon who often is consulted to evaluate critically ill patients with severe SSTIs.

Staphylococcal TSS occurs in those situations normally associated with the acquisition of staphylococcal infections such as trauma causing a breach of the skin barrier, surgical incisions, and the presence of foreign bodies. In an early report of 54 non-menstrual TSS cases, nearly one-half were associated with skin or subcutaneous lesions, and eight of the 54 cases occurred in conjunction with a variety of surgical procedures [184]. Of particular interest, the majority of the surgical cases of TSS had no evidence of SSI. Since then, cases have been reported in a variety of clinical scenarios such asopharyngeal surgery [186], vulvar necrotizing fasciitis [187], exit sites for continuous ambulatory peritoneal dialysis [188], joint injection [189], laparoscopic cholecystectomy [190], and infusion of contaminated platelets [191]. There also are reports of cases without identified risk factors [192]. More recently, TSS has been associated with CA- and HA-MRSA [193–195].

Pathogenesis. *Staphylococcus aureus* expresses a wide range of virulence factors that lead to various clinical syndromes, including cellulitis, furunculosis, impetigo, bacteremia, pneumonia, endocarditis, abscess formation, necrotizing fasciitis, and TSS [196]. Also, *S. aureus* has the capacity for hematogenous seeding of otherwise sterile body sites. Several virulence factors have been associated with the development of TSS.

One of the primary virulence factors associated with TSS is TSST-1, produced by some strains of *S. aureus* and classified as a superantigen. Superantigens bind to major histocompatibility antigen class-II molecules on the surface of antigen-presenting cells and also to T lymphocytes [197,198]. Such binding causes the release of cytokines such as interleukins and tumor necrosis factor-alpha, causing an overwhelming pro-inflammatory response. This superantigen has been highly associated with menstrual TSS [199,200] but also is found in non-menstrual cases [200,201]. Other superantigens, including enterotoxins A, B, G, and I, also have been associated with the development of TSS, and it is common for more than one of these superantigens to be present in the same patient [199,200,201]. The absence of antibodies to these super-antigens is believed to lead to the development of TSS. The low incidence of menstrual TSS is believed to be attributable to the fact that the majority of women of menstrual age have antibodies to TSST-1 and therefore are protected [199]. Lack of antibodies is associated with the development of recurrent non-menstrual TSS [202]. Human antibodies to several bacterial superantigens inhibit T-cell activation, thus providing a rationale for the use of intravenous immunoglobulin (IVIg) as an adjunct in these patients [203].

Given the increase in the prevalence of MRSA isolates worldwide, MRSA-associated TSS is of particular interest. Historically, MRSA has been thought of as a hospital-acquired organism. However, multiple reports now confirm its presence in patients without traditional risk factors such as previous hospitalization, immunosuppression, indwelling foreign bodies, or recent exposure to antibiotics; such CA-MRSA accounts for 8–20% of all MRSA isolates [10]. The prevalence of MRSA, whether community-acquired or nosocomial, differs by region and hospital. Community-acquired MRSA may account for a larger proportion of SSTIs than for other classes of infections [1,10].

Certain staphylococcal strains also produce a cytotoxin that is a potent dermonecrotic toxin, PVL [204,205]. Whereas MRSA has the ability to produce the same superantigens as MSSA, PVL-producing strains are more commonly CA-MRSA. The organism is associated with severe necrotizing infections and pneumonias, many of which are accompanied by shock [195,206–208], but whether PVL confers clinical toxicity is debated.

Diagnosis. The standard case definition for TSS includes the presence of fever, hypotension, erythematous macular rash, organ failure, and desquamation of the skin primarily on the soles of the feet and the palms of the hands [180]. This description has been modified by some authors, because skin desquamation occurs late in the course of disease, after recovery. Those cases where the patient died or was discharged to home prior to the development of desquamation, or had any four of the five signs of the disease, were classified as probable cases [197]. *Staphylococcus aureus* may be cultured from any number of sites, including the skin, blood, lung, urine, deep space abscesses, nares, vagina, and prosthetic appliances.

A rapidly progressive disease that requires a high index of suspicion, staphylococcal TSS mandates early diagnosis, aggressive resuscitation, timely and appropriate antibiotic therapy, and early surgical intervention where appropriate. Inappropriate or delayed antibiotic therapy is associated with a higher mortality rate [16,127]. Those cases associated with necrotizing infections have a lower mortality rate if there is early surgical debridement [86,127].

Treatment. Appropriate empiric antibiotic therapy will be dictated by the clinical scenario and the staphylococcal antibiograms at each institution. Therefore, along with determining the risk factors associated with the development of STSS, clinicians must also know the prevalence rate of methicillin-resistant organisms at their own institutions [209]. Antibiotics such as claxacillin, oxacillin, and nacillin in high doses have been recommended [209]. Clindamycin therapy is advocated in addition to a penicillin owing to the possible synergistic effect from neutralization of some enterotoxins. Vancomycin has been preferred for penicillin-allergic patients. If the local prevalence of MRSA isolates is >20% or risk factors suggest the possibility of MRSA, consideration should be given to empiric coverage with vancomycin [209]. Linezolid is at least equivalent to vancomycin for the treatment of
Community-acquired methicillin-resistant *S. aureus*. As noted previously, CA-MRSA has recently become the most frequent pathogen causing SSTIs in some geographic locations, and has been associated with NSTIs [11,15,39]; CA-MRSA is associated more commonly with SSTIs than is HA-MRSA [215–218]. This association may be related to the virulence factor PVL, which may be carried by either methicillin-sensitive or methicillin-resistant strains of *S. aureus*, but is more likely to be produced by certain strains of CA-MRSA, particularly the USA 300 clone [15,37,38,219]. Enterotoxins and superantigens such as TSST-1 also may be produced by CA-MRSA and contribute to its virulence. Whereas the majority of SSTIs caused by CA-MRSA are associated with skin lesions such as furuncles and abscesses, they may also be associated with more serious manifestations such as necrotizing fasciitis [15], invasive infections [37,220], toxic shock [195], and necrotizing pneumonia [206].

The mechanism of resistance in both HA- and CA-MRSA is a mobile chromosome cassette (SCCmec) carrying the mecA gene. This gene encodes penicillin-binding protein 2a (PBP2a). Penicillin-binding proteins are involved in the last step of cell wall synthesis and are necessary for survival. Beta-lactam agents bind to and inactivate these proteins; PBP2a has a low affinity for β-lactam agents, altering the binding site on the bacterium and creating resistance to methicillin and other β-lactams [9]. Five types of SCCmec have been identified (designated I–V). Strains of HA-MRSA carry one of three types (I, II, or III), whereas CA-MRSA isolated in clinical cases in the U.S. is most commonly associated with SCCmecIV [9,216] (Table 8).

**Diagnosis.** The final diagnosis of a CA-MRSA infection ultimately rests on the results of culture and susceptibility testing [221]. There are multiple case definitions of CA-MRSA [37,222,223]. These definitions rely on the time after admission the culture was obtained (if in a hospitalized patient), absence of known risk factors for the acquisition of MRSA, and antimicrobial susceptibility results. Although CA-MRSA is associated with certain clonal types, this information is not practical to obtain on a routine basis. Therefore, a high index of suspicion for MRSA, particularly CA-MRSA, must be maintained when managing outpatients with SSTIs. Knowledge of the clinician’s own community and hospital prevalence of CA-MRSA and local sensitivity patterns for these organisms is helpful. Additionally, any known previous positive MRSA culture results and the clinical presentation will help guide empiric therapy. Rapid tests utilizing polymerase chain reaction have been used as a screening method to detect carriers of MRSA, but availability of these tests remains limited [224,225].

**Treatment.** No randomized studies have been published on the treatment of SSTI caused specifically by CA-MRSA. Sensitivity patterns usually are used to direct available options. Oral agents have been given for less severe infections in outpatients [37,226]. In the patient with a simple abscess suspected to be caused by MRSA, incision and drainage (I&D) of the abscess may be curative [227]. Antibiotics may be considered as an adjunct to I&D, particularly for patients with marked cellulitis (>5 cm diameter), systemic symptoms, co-morbidities, failure of I&D, or multiple sites of infection; therapy should be directed against MRSA. Whereas historically, cultures of abscesses often were not obtained for simple SSTIs, the increase in CA-MRSA prevalence suggests that cultures may be useful, particularly if there is no response to presumably adequate therapy. If CA-MRSA is suspected and the patient can be treated as an outpatient, oral antibiotics such as trimethoprim/sulfamethoxazole (TMP-SMX), clindamycin, tetracyclines (minocycline or doxycycline), erthyromycin, or some quinolones may be given [227]. Inadequate data exist to recommend one agent strongly over another. Although TMP-SMX has been successful in the ambulatory setting [228], two randomized studies suggest that this combination may be inferior to other agents, particularly in more severe infections [229,230]. Clindamycin is another oral (or IV) option. However, resistance rates among MRSA strains differ, and resistance may be difficult to identify using standard automated susceptibility testing because of the presence of inducible resistance, especially to erythromycin [227,231,232]. In a single-center study of MRSA pathogens isolated in an academic center in the southeastern U.S., 50% of all MRSA isolates demonstrated inducible resistance, with one-third of CA-MRSA strains having inducible resistance to clindamycin and macrolides [232]. To ensure that inducible resistance is not present, the double disk diffusion test (D-test) is required. Fluoroquinolone sensitivities differ both among agents and among geographic regions. The newer fluoroquinolones have better susceptibility profiles than ciprofloxacin (resistance range is 20%–81%) [227]. Other oral agents such as linezolid have been efficacious against MRSA in randomized trials [78,79,209,210].

Complicated SSTI necessitating hospital admission usually requires IV broad-spectrum antibiotics. Again, no randomized studies exist specifically on the treatment of CA-MRSA, and therapeutic options are extrapolated from other studies of SSTIs caused by all MRSA. Whereas vancomycin has been the gold standard, clinical isolates of MRSA from both SSTIs and non-soft tissue infections have demonstrated an increase in minimum inhibitory concentrations for vancomycin. One randomized study demonstrated superiority of linezolid for the treatment of complicated SSTI (88.6% vs. 66.9% cured with linezolid vs. vancomycin; p < 0.001) [79], although this has not been confirmed in follow-up trials. A number of studies suggest benefits of linezolid over vancomycin, including shorter hospital length of stay and lower cost [210,233,234]. Additionally, linezolid inhibits toxin production in vitro, providing a theoretical advantage [80,174,175]. Newer agents with activity against MRSA that have been tested in randomized trials for complicated SSTIs are quinupristin/dalfopristin [234], daptomycin [235], and tigecycline [81]. Although each is approved for the treatment of complicated SSTI, the randomized studies evaluating the efficacy of these agents contained too few MRSA isolates to make recommendations. Quinupristin/dalfopristin is a combination of two streptogramins that inhibit protein synthesis, but requires
central IV administration and has major side effects. Daptomycin is a lipopeptide with bactericidal activity against gram-positive pathogens, including MRSA, whereas tigecycline is a broad-spectrum glycyclycin antibiotic with activity against gram-positive cocci, including MRSA [78,79,82,209,210,212]. Investigational agents include dalbavancin [236], telavancin [237], oritavancin [238], ceftobiprole [239,240], and cefitaroline.

**Decolonization.** Patients may develop recurrent CA-MRSA SSTIs, most likely related to persistent colonization, which suggests a benefit from decolonization strategies. However, data regarding CA-MRSA colonization and decolonization are limited. Colonization with *S. aureus* may be persistent (20%), intermittent (60%), or absent (20%); and colonization typically precedes infection for both MSSA and HA-MRSA [227]. However, although the documented rate of colonization with CA-MRSA remains low, the prevalence of this pathogen in SSTIs has increased rapidly. This may be related to several factors: (1) Greater virulence may produce a higher incidence of infection among those colonized; (2) colonization with CA-MRSA may be more common at sites other than the nares relative to MSSA or HA-MRSA; and (3) documentation of colonization may be more difficult and simply lag behind the epidemiology of infection. Colonization at two or more body sites has been linked to persistent colonization and a presumed greater risk of re-infection. Only limited data regarding the success of decolonization specifically for CA-MRSA are available, and recommendations must be based on studies of *S. aureus* in general. Currently, the U.S. Centers for Disease Control and Prevention (CDC) recommend considering decolonization if an individual is having repeated CA-MRSA SSTIs despite other efforts at preventing infection. Given that colonization of sites other than the anterior nares, including wounds, pharynx, gastrointestinal tract, and inguinal region, may be present, and that the patient's environment may be contaminated, regimens probably should include combined efforts directed at the anterior nares and skin and the environment. Mupirocin ointment 2% applied twice daily for 5 to 7 days, bathing with chlorhexidine gluconate (2% and 4%) or dilute bleach, and cleaning sheets, clothing, and towels may all be required.

**Group A streptococcal infections.** A variety of streptococcal species can cause SSTIs. Of these species, GAS (Strep. pyogenes) is associated most frequently with severe necrotizing infections. Although GAS can cause a variety of clinical infections and syndromes, SSTI is most common. The presentation may range from relatively minor cellulitis to severe, rapidly progressive NSTI with pronounced systemic symptoms and a high mortality rate [47,48]. Pathogenic strains produce a variety of virulence factors and exotoxins that contribute to pathogenicity and the clinical presentation, including antiphagocytic M proteins, hemolysins, streptolysins O and S, leukocidins, and streptococcal pyrogenic exotoxins (associated with TSS) [46, 47,152,241–244]. Pathogenic strains have produced intermittent outbreaks of severe SSTI in otherwise healthy individuals, with both severe tissue involvement and the rapid progression to shock and organ failure that is characteristic of TSS [47,48]. The episodic nature of outbreaks is poorly understood, with the apparent increase in severe infections in Europe, Canada, and the U.S. in the late 1980s and 1990s having subsided in the past few years.

The dramatic speed with which these infections can spread through previously normal soft tissue, causing systemic manifestations such as shock, organ failure, and death, demonstrates why aggressive therapy is mandated. As with all NSTIs, immediate thorough debridement of necrotic tissue and drainage of fluid-filled spaces are indicated, and multiple operative procedures frequently are required. As discussed, clinical failures may follow the use of cell wall-active agents alone, so the addition of a protein synthesis-inhibiting agent is recommended [63–66,166,168,172,244]. Despite the lack of supporting prospective studies, the authors recommend high-dose parenteral clindamycin (at least 2.4 g/d) (unless regional resistance to clindamycin is known to be common) in combination with high-dose penicillin. Adjunctive IVIg for patients with symptoms of streptococcal TSS remains controversial because of the lack of adequately powered randomized studies (see discussion section). In patients with severe streptococcal TSS, IVIg use is recommended by the majority of critical care and infectious disease specialists.

**Clostridial infections.** Among soft tissue infections, those caused by *Clostridium* spp. are among the most aggressive and can rapidly be fatal. *Clostridium perfringens* is the most common pathogen, accounting for 70–80% of all such infections, but several other species have been reported [245]. Classical, clostridial infections have been associated with traumatic wounds, but recent studies have demonstrated an increasing incidence of these infections associated with the injection of illicit drugs [92,246,247]. Subcutaneous or intramuscular injection appears to be the primary route of inoculation, and because of the social circumstances of these patients, there often is a long delay in seeking medical attention. A recent outbreak of clostridial infections was reported in the United Kingdom, with emergence of additional species including *C. novyi*, *C. sordellii*, *C. botulinum*, *C. tetani*, and *C. histolyticum* [246]. In a recent report from the U.S., 52% of clostridial soft tissue infections in patients admitted to one institution could be attributed to injection drug use [92]. The mortality rate for clostridial infections in this series was 38% overall, with 45% of the patients requiring an amputation. Clostridial species may be isolated from the human gastrointestinal tract and perineum, and are common in soil contaminated with animal excreta. Infections that occur without a history of trauma or injection should precipitate a workup for an initiating source. *Clostridium septicum* has been associated with leukemia or gastrointestinal neoplasms [248].

**Clostridium spp. are spore-formers.** Under ideal conditions, growth is rapid, with a germination time for *C. perfringens* of approximately 8 min [152]. Although they are obligate anaerobes, *Clostridium* spp. are among the only pathogens that are able to invade and destroy healthy muscle rapidly. The clinical manifestations are related to the elaboration of potent extracellular toxins. The major virulence factors of *C. perfringens* are ε toxin (phospholipase C) and α toxin (perfringolysin) [245]. In addition to direct tissue injury, these toxins impede the migration of polymorphonuclear leukocytes and destroy neutrophils at the site of infection, allowing the infection to worsen [249]. These toxins also lead to hemolysis, microvascular thrombosis, and myonecrosis. The resulting reduction in oxygen tension encourages rapid multiplication of the bacteria in muscle. Rapid growth under
anaerobic conditions produces large amounts of poorly dif-

dfuse gas, resulting in crepitus to palpation. Alpha toxin
directly inhibits myocardial contractility and indirectly in-
duces systemic cytokine expression, both of which may con-
tribute to the rapid circulatory collapse observed in these
patients [245].

Diagnosis. The clinical characteristics of clostridial in-
fection include abrupt onset, intense pain, marked swelling,
and severe systemic toxicity. Patients frequently experience
intense pain before any other signs of infection are present.
Crepitus is present in fewer than one-half of patients during
early stages. As the infection advances, overlaying skin be-
tomes tense, and hemorrhagic bullae appear. Often, a thin,
foul-smelling discharge is present. Any delay in diagnosis is
associated with a higher mortality rate; thus, a high index of
suspicion for these infections is crucial [112]. In one series,
clostridial infections were associated with a marked elevation
of the WBC count on hospital admission (mean $26.5 \times 10^7$/
microliter), which in turn was predictive of death [92].

Treatment. Treatment of SSTIs caused by Clostridium spp.
includes aggressive and repeated surgical debridement of
devitalized tissue as well as antibiotics. Repeated examination
and debridement may be required at intervals ranging from
several hours up to 24 h, depending on the severity of the
process and the clinical course. High-dose aqueous penicillin
G (24 million U/day) remains the drug of choice, but other
agents such as carbapenems also are effective. Recent evidence
suggests that high-dose clindamycin (1,200 mg q 6h)
may be particularly beneficial in treating these infections be-
cause it neutralizes toxin [172,250]. Hyperbaric oxygen fre-
quently is discussed but is seldom practical, and its utility
remains controversial. Therapy in the hyperbaric oxygen
chamber should never delay surgical debridement.

Vibrio infections. Vibrio spp. can cause fulminant, rapidly
progressive SSTIs with a high mortality rate [14,251–254].
A number of species are associated with SSTIs, including
V. vulnificus, V. parahaemolyticus, V. damselae, and V. alginoly-
ticus. The most virulent and most common species producing
SSTIs in the U.S. is V. vulnificus, a halophilic gram-negative
organism that inhabits bodies of warm water with interme-
diate salinities, such as coastal waters in the southern U.S.
[14,253]. During the summer months, virtually 100% of oysters
carry V. vulnificus, V. parahaemolyticus, or both [255]. An un-
derstanding of the clinical presentation of these infections is
important for early recognition and appropriate therapy.

Diagnosis. Human V. vulnificus infections typically
present as one of three syndromes: Primary bacteremia,
traumatic wound infections, or acute gastrointestinal disease
[251,253,254]. Wound infections nearly always result from
exposure to seawater or inoculation of acute wounds when
handling shellfish or seafood. Skin and soft tissue infection
also develops frequently during primary bacteremia, pre-
sumably via hematogenous seeding. Primary bacteremia
typically occurs within 24–48 h after the ingestion of con-
taminated oysters or fish. Frequent presenting symptoms and
signs are fever, hypotension, and cutaneous manifestations,
including hemorrhagic bullae, ecchymosis, and cellulitis of
the extremities [253]. The majority of these patients have co-
morbidities, most commonly chronic liver disease but also
chronic kidney disease, diabetes mellitus, long-term steroid
use, or human immunodeficiency virus infection. In one
series, however, only 35% of patients had co-morbidities
[253]. Wound infections may have a similar presentation but
are distinguished by clear inoculation through a cutaneous
wound. A high index of suspicion must be maintained if these
highly lethal infections are to be treated successfully. Table 10
provides several clinical criteria that should lead to the pre-
sumptive diagnosis of Vibrio sepsis [14]. The virulence of
V. vulnificus is believed to be related to its toxin and produc-
tion of enzymes, including hemolysin, proteases, lipase,
hyaluronidase, mucinase, DNase, and sulfatase [257,258].

Treatment. Therapy for V. vulnificus SSTI includes sup-
portive care; aggressive, early surgical debridement; and an-
tibiotics. Halow et al. reported their operative management of
seven patients with V. vulnificus NSTI [252]. The time from
exposure to presentation ranged from 1–10 days, and the
presence of fever and leukocytosis was variable. All patients
had erythema, induration, edema, and pain of the affected
extremity, but gas was absent on radiographs. All patients
underwent operative debridement within 46 h of admission,
and all survived. Whereas only four of the patients had skin
necrosis, all had necrotic material deep to the skin that re-
quired debridement, highlighting the importance of explora-
tion. Early operative intervention was associated with shorter
intensive care unit (ICU) and hospital lengths of stay. Most
series have demonstrated a high mortality rate if therapeutic
intervention does not take place until after the appearance of
severe systemic symptoms and septic shock. In this rapidly
progressive infection, selection of correct empiric therapy may
be predicated on a good clinical history documenting expo-
sure to V. vulnificus, absence of gas within tissues (implying
absence of rapid anaerobic growth and Clostridium), and a
gram-negative bacillus in stained material.

The most appropriate antibiotic therapy for V. vulnificus
SSTIs is unknown; neither randomized nor large retrospective
clinical studies exist. The rarity of this disease makes adequate
study in human beings unlikely. Current recommendations
are based on in vitro sensitivity data, animal models, and
small, anecdotal reports. In vitro sensitivity studies of human
isolates generally demonstrate susceptibility to tetracyclines,
carbapenems, third-generation cephalosporins, and fluoro-

Table 10. Criteria for Presumptive Clinical Diagnosis of Vibrio vulnificus Sepsis

<table>
<thead>
<tr>
<th>Hypotension, shock, or other signs suggestive of sepsis (e.g., for wound infections, evidence of rapidly progressive cellulitis or myositis)</th>
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<tr>
<td>History of chronic liver disease (e.g., alcoholism, cirrhosis, hemochromatosis) or immunosuppression. Although not proposed in original criteria, chronic kidney disease/hemodialysis should be considered a risk factor.</td>
</tr>
<tr>
<td>Recent consumption of uncooked shellfish (and likely foods that have been exposed to them), or exposure of wounds to estuarine water.</td>
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<tr>
<td>Characteristic bullous skin lesions.</td>
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</table>

Diabetic foot infections

Diabetic foot infections (DFIs) are common and the most serious lower-extremity complication, contributing to many amputations. The underlying pathophysiologic alterations and the special considerations created by these alterations separate these infections from those in other settings and are beyond the scope of this article. Considerations specifically related to DFIs have been reviewed extensively in a recent publication [265]. However, the frequency of these infections mandates inclusion of a brief discussion in this guideline.

Diabetic foot infections are most frequently a consequence of ulcerations, which typically follow trauma to a neuropathic foot, although infections also develop with some regularity both spontaneously and after acute tissue trauma. Therapeutic decisions are determined in large part by the seriousness of the infection. The severity of DFIs has been classified broadly as mild, moderate, or severe. However, a lack of consensus and consistency in defining both ulceration and infection severity complicates comparison of published studies. Although a system of classification of ulceration (Wagner system) has been employed for nearly 30 years, it does not apply to infection severity. At a recent international consensus conference on diagnosing and treating diabetic foot infections, a system of classification of ulceration (perfusion, extent/size, depth/tissue loss, infection, and sensation [PEDIS]) was developed that includes all the key elements, including the severity of infection, as shown in Table 11 [266,267]. Gram-positive bacteria are the sole causative pathogens for mild-to-moderate infections, which usually can be treated in an outpatient setting with culture-based narrow-spectrum antibacterial agents along with appropriate surgical debridement. In contrast, severe infections often are polymicrobial, necessitating hospitalization and broad-spectrum antibiotics along with appropriate surgical intervention. The initial empirical antibacterial regimen may be tailored on the basis of the results of culture and sensitivity tests from properly obtained specimens (i.e., not superficial swabs, which may capture colonizing rather than infecting flora). Several regimens have demonstrated effectiveness in randomized controlled trials, but no single regimen has shown superiority. The management of diabetic foot osteomyelitis is particularly controversial and requires reliable cultures to select an appropriate antibacterial regimen.

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**Table 11. International Consensus on the Diabetic Foot: Infection Classification Scheme**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1</td>
<td>No symptoms or signs of infection</td>
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<tr>
<td>2</td>
<td>Infection involving skin and subcutaneous tissue only, with no involvement of deeper tissues and no systemic signs and symptoms. No other causes of an inflammatory response (e.g., gout, trauma, acute Charcot neuro-ostearthropathy, fracture, thrombosis, venostasis). At least two of the following manifestations are present: • Localized swelling or induration • Erythema &gt;0.5-2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge</td>
</tr>
<tr>
<td>3</td>
<td>Infection involving structures deeper than skin and subcutaneous tissues (e.g., abscesses, osteomyelitis, septic arthritis, or necrotizing fasciitis) • Erythema (cellulitis) extending &gt;2 cm around an ulcer in addition to one of the following: Edema, tenderness, heat, purulent discharge • No signs of a systemic inflammatory response as characterizes grade 4 infection</td>
</tr>
<tr>
<td>4</td>
<td>Any foot infection with signs of a systemic inflammatory response syndrome, manifested by two or more of the following: • Temperature &lt;36°C or &gt;38°C • Heart rate &gt;90 beats/min • Ventilatory rate &gt;20/min • P&lt;sub&gt;CO&lt;/sub&gt;₂ &lt;32 mm Hg • White blood cell count &gt;12,000 or &lt;4,000/mm³ • ≥10% immature (band) forms</td>
</tr>
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</table>

The selection of the appropriate spectrum for empiric coverage of likely pathogens has been determined historically by whether the patient had previous antibiotic exposure. In antibiotic-naïve patients, MSSA and streptococci are the most common pathogens, along with sensitive gram-negative and anaerobic bacteria. As the chronicity, previous antibiotic exposure, or severity of illness increases, the likelihood of more resistant or unusual pathogens rises, and empiric coverage typically should be broadened. The recent dramatic rise in the prevalence of CA-MRSA makes antibiotic susceptibility less predictable even in antibiotic-naïve patients. For this reason, appropriate cultures should be collected to guide the treatment. Coverage of MRSA should be considered empirically, particularly in more severe infections.

Numerous single-agent or combination regimens probably are appropriate for the treatment of complicated DFIs, assuming the regimens provide appropriate coverage of the pathogens involved. However, few randomized trials exist to enable firm recommendations [59,60,160–162,289–298]. Nearly all of the studies are small, and some address DFIs only as a subgroup. Only four randomized, blinded, controlled trials examining IV therapy in hospitalized patients could be identified. No single outcome was reported in all trials, and data on classification were not consistent. None of the trials comparing IV antibiotics for complicated DFIs not related to MRSA has demonstrated superiority with respect to the comparator. Agents (or combinations) shown to be equivalent were cefazolin, ceftriaxone, ceftoxitin, ampicillin/sulbactam, piperacillin/clindamycin, piperacillin-tazobactam, imipenem-cilastatin, ertapenem, daptomycin (+gram-negative coverage), and linezolid (+gram-negative coverage). Local sensitivity patterns, previous antibiotic exposure, and previous and likely pathogens should all be considered when selecting empiric coverage.

The significant increase in MRSA in DFIs has led to the study of newer agents with activity against this pathogen. In a recent study, patients with a diabetic ulcer infection were stratified to ensure they were equally represented in the treatment groups, then randomized to either daptomycin (4 mg/kg IV every 24 h) or a standard comparator (vancomycin or a semi-synthetic penicillin) for 7–14 days. Most infections were monomicrobial, and S. aureus was the predominant pathogen. Success rates for patients treated with daptomycin or the comparators were not statistically different for clinical (66% vs. 70%, respectively; 95% confidence interval [CI] -14.4, 21.8) or microbiological (overall or by pathogen) outcomes [295]. Lipsky et al. compared the efficacy and safety of IV and oral formulations of linezolid with that of IV ampicillin/sulbactam and IV and oral amoxicillin/clavulanic acid given for 7–28 days in a randomized, open-label, multicenter study of all types of DFI (ratio of linezolid to comparator drug recipients, 2:1) [294]. Among 371 patients, the clinical cure rates associated with linezolid and the comparators were statistically equivalent overall (81% vs. 71%, respectively) but were significantly higher for linezolid-treated patients with infected foot ulcers (81% vs. 68%; p = 0.018) and those without osteomyelitis (87% vs. 72%; p = 0.003). Cure rates were comparable for inpatients and outpatients and for both oral and IV formulations. Drug-related adverse events were significantly more common in the linezolid group, but they generally were mild and reversible [294].

### Microbiology

Determination of the true microbiology of a DFI may be challenging, complicated by colonization of chronic wounds by organisms that may not be pathogens, and by frequent exposure to numerous antibiotics. Gram-positive aerobic organisms are the pathogens most commonly isolated, but as the severity or chronicity of the infection increases, other pathogens appear with increasing frequency. Studies of culture results from DFIs [268–278] have identified the most frequent isolates (Table 12). Aerobic gram-positive cocci are the predominant microorganisms that colonize and acutely infect breaks in the skin. *Staphylococcus aureus* and the β-hemolytic streptococci (groups A, C, and G and, especially, B) are isolated most commonly [277,279–281]. Infections commonly are polymicrobial, containing both aerobic and anaerobic bacteria [282–284]. Chronic wounds develop a more complex colonizing flora, including enterococci, various *Enterobacteriaceae*, obligate anaerobes, *P. aeruginosa*, and, sometimes, nonfermentative gram-negative bacilli [285,286]. Hospitalization, surgical procedures, and prolonged or broad-spectrum antibiotic therapy may predispose patients to colonization or infection with antibiotic-resistant organisms (e.g., MRSA or VRE) [287]. Although MRSA strains previously were isolated mainly from hospitalized patients, community-associated cases are becoming common [216] and are associated with worse outcomes [288]. Vancomycin (or glycopeptide)-intermediate-resistant *S. aureus* has been isolated in several countries.

<table>
<thead>
<tr>
<th>Table 12. Microbiology of Diabetic Foot Infections</th>
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<tr>
<td><strong>Aerobes</strong></td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
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<tr>
<td><em>S. epidermidis</em></td>
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<tr>
<td>Coagulase-negative staphylococci</td>
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<tr>
<td>Group β <em>Streptococcus</em></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
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<tr>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em> and other <em>Proteus</em> spp.</td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
</tr>
<tr>
<td><em>Bacteroides melaninogenicus</em></td>
</tr>
<tr>
<td><em>B. fragilis</em></td>
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<tr>
<td><em>Peptostreptococcus</em> spp.</td>
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<tr>
<td><em>Peptococcus</em> spp.</td>
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<tr>
<td><strong>Fungi</strong></td>
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<tr>
<td><em>Candida tropicalis</em></td>
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<tr>
<td><em>C. albicans</em></td>
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</table>

### Choice of antibiotic regimen

Selection of the antibiotic regimen incorporates several factors, including (1) the route of administration (oral vs. parenteral); (2) previous antibiotic exposure and the likely pathogens; and (3) indications to treat as an inpatient vs. outpatient, typically determined by the severity of the illness. Because therapy is empiric until appropriate culture results are available, the patient’s previous antibiotic exposure, the pathogens most commonly isolated from DFIs, and local rates of resistance should all be considered. In the setting of a severe infection, most practitioners commence with broad-spectrum therapy and then modify antibiotics on the basis of culture data.
For mild infections, oral regimens may be appropriate; numerous regimens have been recommended. Again, only a few trials exist, and none demonstrates superiority. Difficulty in determining the true presence of infection complicates the interpretation of these trials.

Topical agents. Topical agents have been utilized for superficial and mild infections of foot ulcers. They should not be considered alone for invasive infections. The theoretical advantages of topical therapy include obtaining high local drug concentrations, avoiding systemic adverse effects, and the possibility of using novel agents. Furthermore, this route draws the attention of both patients and health care providers to the foot. Topical antiseptics, such as hydrogen peroxide, povidone–iodine, or chlorhexidine, are not recommended, as they generally are too harsh on the host tissues and are toxic to healing tissue [299]. Topical antibiotics, such as neomycin, polymyxin B, gentamicin, and mupirocin, have been used for SSTIs in other sites, but there are limited good-quality data on their efficacy in DFIs. Agents such as silver sulfadiazine and silver-coated dressings significantly reduce bacterial counts in diabetic foot ulcers [300]. For mild-to-moderate infections of these ulcers, the new agent pexiganan (MSI-78) was shown in two large, blinded, randomized trials to have broad-spectrum antimicrobial activity and to be about as effective (about 90% clinical response rate) as oral ofloxacin, with little cross-resistance [272].

Osteomyelitis. Osteomyelitis is a serious complication of diabetic foot ulcers generally treated with long-term antibiotic administration and removal of the infected bone [301]. The disease can be difficult to recognize in the context of bone destruction from the ulceration, as the classic radiographic signs are visible only when a substantial amount of bone has been destroyed and may take several weeks to appear [302]. Osteomyelitis should be suspected when an ulcer does not heal after at least six weeks of appropriate care. However, confirming its presence or absence is important, as the disease impacts the duration and cost of treatment significantly. Magnetic resonance imaging and bone biopsy have been suggested as the preferred diagnostic studies in patients with diabetic foot ulcers [303,304].

Surgical intervention. As noted previously, the appropriate management of DFIs requires that the underlying pathophysiology be addressed systematically. Complete review of this topic is beyond the scope of this guideline. Management by practitioners with specific interest and expertise is recommended.

Surgical intervention plays an essential role in the management of DFIs. Appropriate interventions require an assessment of tissue perfusion, the degree and depth of infection, the presence of bone involvement, and the contribution of altered weight-bearing and sensation to the presence of ulcers. Surgical debridement helps counter wound infection through removal of necrotic tissue and pus, which harbor and nourish microorganisms by a variety of mechanisms [266,281]. Ischemic tissue prevents the efflux of antibiotics into bacteria-rich areas, allowing overgrowth of pathogens. Also, the presence of vascular disease impairs the delivery of antibiotics and oxygen to areas of infection. In general, surgical drainage of pus is necessary when the infected ulcer is associated with a deeper soft tissue infection. Vascular reconstructive surgery to relieve peripheral arterial disease may help resolve the infection by increasing blood flow to the foot, thereby improving the supply of nutrients and drugs to infected tissue.

Whereas DFIs pose a serious risk of leading to amputation, appropriately applied reconstructive therapies are efficacious. In well-selected cases, reconstructive modalities have decreased the need for amputation [305–309]. Baumeister et al. reported healing rates of 71%, 50%, and 33% for stage II, III, and IV diabetic foot ulcers, respectively [306]. Local flap procedures of non-infected well-perfused ulcers led to a 97% rate of healing [309]. Attinger et al. reported an 84% healing rate after reconstructive procedures in a group of patients of whom 52% presented with osteomyelitis and 42% required revascularization [305].

Adjunctive Therapies

Extracorporeal plasma treatment

Necrotizing SSTIs may be complicated by severe sepsis; thus, consideration of adjunctive therapies for sepsis is appropriate. Several investigators have reported the use of extracorporeal plasma treatment for patients with severe sepsis [310–317]. These techniques include hemofiltration, plasmapheresis, and plasma exchange. Hemofiltration is performed via a veno-venous circuit similar to the process used for continuous renal replacement therapy. Plasmapheresis is a two-step process in which blood is separated into its cellular and plasma components, and the plasma is allowed to flow along columns containing different absorbents. The processed plasma is then re-infused. Plasma exchange involves separation of plasma and cells, with return only of the cellular fraction to the patient, the plasma being replaced with either donor plasma or albumin. The goal is to remove circulating inflammatory mediators or toxins that may contribute to the shock state on the assumptions that these mediators are present in a relevant concentration in the circulation at the time of the procedure, that they are removed by the filtration, and that their removal will attenuate the inflammatory response. Clinical trials have been inconsistent in demonstrating that these assumptions are correct [311].

Plasma exchange reduces the plasma concentration of endotoxin, C-reactive protein, haptoglobin, C3 fragment, and α1-antitrypsin; however, other markers of inflammation were unaffected, including interleukin 6, thromboxane B2, and granulocyte-stimulating factors [318]. Plasma removed during plasmapheresis stimulates monocye production of pro-inflammatory cytokines in the same way as serum from patients with sepsis [319]. Another study demonstrated a reduction in serum tumor necrosis factor-α concentration but no effect on other circulating cytokines [312]. Despite these inconsistencies, plasmapheresis and plasma exchange continue to be used in patients with sepsis. Several authors of case reports and small case series have reported improvements in physiologic parameters after these procedures [320,321]. One randomized controlled trial reported by Busund et al. enrolled 106 patients with severe sepsis and demonstrated a reduced mortality rate of 33.3% in the plasmapheresis group vs. 53.8% in the control group (p = 0.05) [312]. The data on the use of plasmapheresis for patients with NSTIs are limited to a single case report [322].
In summary, the current literature is insufficient to determine whether there is any benefit to the use of extracorporeal plasma treatment for patients with severe sepsis attributable to NSTI. The data regarding the ability of these techniques to modulate the inflammatory response are conflicting, and for generalized sepsis, there are insufficient outcome data to draw definitive conclusions. It is not known whether these techniques reduce the toxin load produced by clostridial or streptococcal infections, or whether reduction in the serum concentrations of these toxins improves outcomes. Further study is warranted.

**Hyperbaric oxygen**

Hyperbaric oxygen (HBO) therapy has been proposed as an adjunct to surgical debridement and antibiotics as a treatment for NSTIs. This technique involves the administration of 100% oxygen at a pressure exceeding 1 atm absolute. Resting tissue requires blood flow providing 60 mL of oxygen/L to maintain cellular metabolism. Under normal conditions, tissue oxygen is delivered primarily by hemoglobin, with a plasma oxygen concentration of 3 mL/L. When 100% oxygen is administered at 3 atm absolute, the plasma oxygen concentration increases to 70 mL/L; thus, more oxygen can be delivered to the tissues independent of the amount of hemoglobin. The proposed benefits of this increase in oxygenation include better leukocyte activity against aerobic bacteria, direct killing of anaerobic bacteria, stimulation of collagen formation, greater efficacy of antibiotics, inhibition of clostridial toxin production, and induction of angiogenesis in hypoxic tissues [323].

Despite the many theoretical benefits of HBO therapy in these patients, data from clinical trials are almost non-existent, and there are no randomized controlled trials of HBO therapy for NSTIs. Case series of the treatment of Fournier gangrene have claimed that HBO reduces the mortality rate and progression of the infection, but these results are limited by the lack of a control group for comparison [324,325]. Three other retrospective series have compared the outcome of patients with NSTIs treated by HBO vs. conventional therapy [326,327]. Riseman et al. reported a significant decrease in the mortality rate (66% vs. 23%) and number of debridements required (3.3 vs. 1.2) in the HBO group [326]. However, the other two series found no improvement in survival or number of debridements [109,327].

In summary, the current literature is insufficient to recommend the use of HBO for management of NSTIs. Furthermore, concern has been raised that HBO therapy could delay adequate surgical debridement and thus worsen the outcome. As HBO chambers are not readily available in most institutions, and in view of the hazards of transporting a patient to a HBO facility, HBO therapy cannot be recommended.

**Intravenous immunoglobulin**

Intravenous immunoglobulin has been proposed as an adjunctive agent for the management of streptococcal and staphylococcal infections with TSS. These patients are infected with organisms that produce “superantigens” [328–331], which bind class II molecules on antigen-presenting cells, causing T cells to release cytokines; the result is leaky capillaries, shock, and organ failure [330,331]. Patients infected with these superantigen-producing organisms have reduced ability to neutralize superantigenic activity as well as lower amounts of opsonic anti-M antibodies [329,332,333]. Intravenous immunoglobulin contains a high concentration of opsonic anti-M1 antibodies, which may have efficacy in severe invasive GAS infections [332]. The immunoglobulin is highly efficient in neutralizing superantigens associated with streptococcal infection, although less so with staphylococcal superantigens [328].

Several case reports describe the use of IVIg in clinical scenarios such as necrotizing fasciitis, septic arthritis, pregnancy-associated TSS, bacteremia, or pharyngitis [329,334–341]. These case reports detail the recovery of the patients when IVIg was used as an adjunct to antibiotics and to surgical intervention where appropriate. Despite the in vitro evidence and case reports, there are neither randomized clinical nor substantive observational trials to support the use of IVIg in invasive staphylococcal and streptococcal infection. The only randomized study was stopped early because of low recruitment, and therefore was underpowered to show a difference in the primary endpoint of 28-day mortality rate [328], although there was a reduction in sepsis-associated organ failure scores in the IVIg group on days two and three of therapy. In a comparative observational study, 21 patients with streptococcal TSS who were treated with IVIg were compared with historical controls and did show a statistical difference, the 30-day survival rate being higher in the IVIg group [342]. However, the IVIg-treated patients received surgical intervention more often than controls, and had different antibiotic regimens, making it difficult to draw conclusions about the efficacy of IVIg.

Despite the paucity of controlled clinical trial data and the lack of benefit in a murine model [343], 76% of Canadian critical care medicine and infectious disease specialists surveyed favored the use of IVIg in streptococcal TSS, 50% use it in necrotizing fasciitis without TSS, and 26% use it in staphylococcal TSS [344]. Although there were no reported adverse events associated with IVIg use in one study [328], the product has been associated with diffuse venous thrombosis [343].

Expert opinions and several case reports support the use of IVIg in patients with invasive GAS and staphylococcal infections with TSS. However, little has been documented about adverse events associated with IVIg in these syndromes, and there is no class I evidence to support its use. Given the available data and the high morbidity and mortality rates associated with these infections, IVIg use is recommended with caution but only as an adjunct to appropriate and timely antibiotic therapy and surgical debridement in the face of invasive soft tissue infection.

**References**


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