Treatment of severe skin and soft tissue infections: a review

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Purpose of review
To review the salient features of the management of severe skin and soft tissue infections (SSTIs), including toxic shock syndrome, myonecrosis/gas gangrene, and necrotizing fasciitis.

Recent findings
For severe SSTIs, intensive care, source control, and broad-spectrum antimicrobials are required for the initial phase of illness. There is an increasing focus on the utility of rapid diagnostic tests to help in selection and de-escalation of antimicrobials for SSTIs. In addition, clinical prediction scores have shown promise in helping predict patients who do not require antimicrobials directed against methicillin-resistant *Staphylococcus aureus*. Immune status has been shown to be important in clinical outcomes of some, but not all types of SSTIs. The debate for benefits of intravenous immunoglobulin continues to be waged in the recent literature.

Summary
Severe SSTIs are common and their management complex due to regional variation in predominant pathogens and antimicrobial resistance patterns, as well variations in host immune responses. Unique aspects of care for severe SSTIs are discussed including the role of surgical consultation and source control. The unique features of SSTIs in immunocompromised hosts are also described.

Keywords
gas gangrene, necrotizing fasciitis, severe skin and soft tissue infections

INTRODUCTION

Skin and soft tissue infections (SSTIs) are a common reason for patients seeking inpatient and outpatient medical care with more than 14 million outpatient visits a year [1], and almost 900 000 inpatient admissions in the United States [2]. Pathogen isolation in SSTIs is limited by currently available diagnostics and is influenced by host and geographic factors, making empiric antimicrobial therapy selection complicated [3▪▪,4,5]. Despite difficulties in empiric therapy selection, it is well recognized that patients with severe SSTIs require source control via surgical debridement. In this review, we summarize the salient features of the treatment of severe SSTIs.

DEFINING SEVERITY IN SOFT TISSUE INFECTIONS

Severity of illness due to SSTI loosely correlates with depth of skin structure involvement, though there is no universally agreed upon severity scoring system. For the purposes of this review, we will consider patients with toxic shock syndrome (TSS), necrotizing fasciitis, or gas gangrene/myonecrosis as having a severe SSTI. In addition, patients having any SSTI meeting criteria for severe sepsis or septic shock or having a quick Sequential Organ Failure Assessment score at least 2 will be considered to have a severe SSTI. Table 1 lists some of the common pathogens in severe SSTI, their features, and recommended antimicrobials.

TYPES OF SEVERE SOFT TISSUE INFECTIONS

For all SSTIs, immune status, exposure history (animals, water, trauma), and travel history (particularly to regions with high rates of multidrug-resistant

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KEY POINTS

- Severe skin and SSTIs initially require intensive care, source control, and broad-spectrum antimicrobials.
- Intravenous immunoglobulin use in toxic shock syndrome remains controversial, but can be considered for severe cases.
- For necrotizing skin and SSTIs, surgical consultation is paramount.
- Imaging studies cannot rule out necrotizing infection and should not delay surgical interventions.
- Pathogen-directed therapy and antimicrobial de-escalation should be the goal of severe skin and SSTI treatment when clinical stability is achieved.

organisms) are important to inform empiric antimicrobial decisions [4,6]. Patients with severe forms of purulent SSTIs, cellulitis, or surgical site infection should receive broad-spectrum antibiotic therapy [including a Methicillin-resistant *Staphylococcus aureus* (MRSA) agent when high risk] and source control, when applicable.

Toxic shock syndrome

TSS is a fulminant infection typically due to *Staphylococcus aureus* or *Streptococcus pyogenes*, though similar syndromes can occur with groups B, C, and G streptococci, and *Clostridium* species. The annual incidence of staphylococcal TSS (SaTSS) is ~0.5/100 000 and ~0.4/100 000 for streptococcal TSS (SeTSS), though local rates may vary [7]. Mortality rates are less than 5% for menstrual SaTSS, 5–22% for nonmenstrual SaTSS, and 30–70% for SeTSS [7]. Clostridial toxic shock is rare and its incidence is uncertain [8,9].

When TSS is suspected, empiric therapy must cover for drug-resistant infections. Expert opinion based on retrospective studies and in-vitro data highlight vancomycin and clindamycin or linezolid alone as possible treatment regimens [10–13]. Nafcillin or oxacillin are good choices for methicillin-sensitive SaTSS, but must be used in combination with clindamycin as nafcillin alone can increase toxin production [12]. Clindamycin or linezolid are essential in treatment as they reduce superantigen production in both SaTSS and SeTSS [11–13]. When susceptibilities are available, antibiotics should be de-escalated while still including an agent that suppresses toxin production until clinical stability is achieved. For clostridial TSS, clindamycin and penicillin should be used, though there is limited data on this syndrome to guide treatment.

Intravenous immunoglobulin (IVIG) nonspecifically binds and inactivates superantigens, limiting cytokine storm in TSS, though the clinical benefits are controversial. Recruitment for randomized controlled trials (RCTs) of IVIG has been difficult due to the rarity of TSS [14]. One study found significantly improved mortality in patients that received IVIG or clindamycin for SeTSS [15]. IVIG is less studied in SaTSS, though in one study five confirmed cases received IVIG and none expired [16].

In a cohort of patients with mixed bacterial causes of necrotizing SSTI, IVIG showed no benefit in mortality or functional outcomes [17▪▪], though only roughly one-thirds had *S. pyogenes* or *S. aureus*.

Table 1. Features of and treatment for particular organisms in severe soft tissue infections

Organism	Features	Antibiotic therapy
MRSA	Can be associated with TSS and purulent infections. More common with IVDU, previous MRSA colonization, low socioeconomic status	Vancomycin. Use linezolid or add clindamycin if suspicion for TSS. In patients with renal dysfunction, ceftaroline and daptomycin may be preferable
Streptococcus pyogenes	Predominant agent of cellulitis, type II necrotizing fasciitis	Penicillin + clindamycin, though not for empiric therapy. IVIG may be considered in refractory shock
Clostridium spp.	Gas gangrene, myonecrosis. Risk factors include trauma, 'skin popping', neutropenia, childbirth, 'home' abortions	Penicillin + clindamycin, though not for empiric therapy
Gram-negatives	More common in lower extremity, abdominal/perineal SSTI. More common in immunocompromised, diabetics, care facility residents, patients with recent antibiotic exposure	Antipseudomonal carbapenem, cefepime, or piperacillin-tazobactam
Anaerobes	More common in head and neck, perineal/abdominal, and lower extremity SSTI, including diabetics	Carbapenem, piperacillin-tazobactam, or metronidazole

IVDU, intravenous drug use; IVIG, intravenous immunoglobulin; MRSA, Methicillin-resistant *Staphylococcus aureus*; SSTI, Skin and soft tissue infection; TSS, toxic shock syndrome.

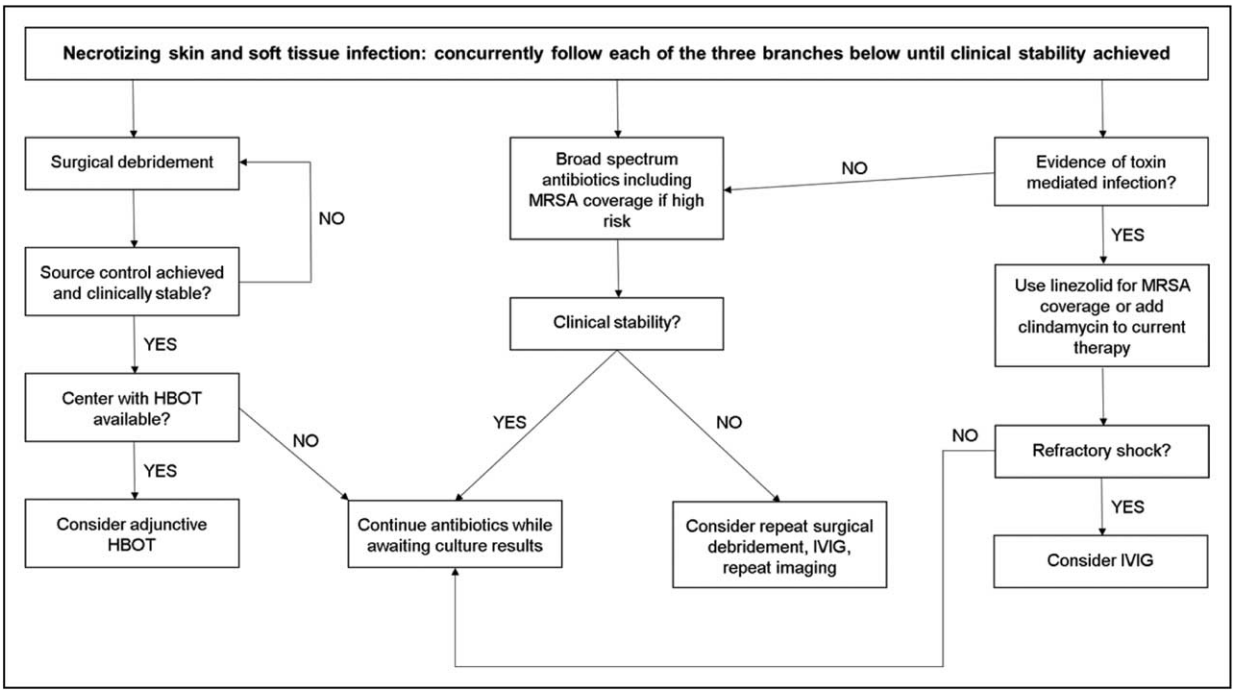

FIGURE 1. Proposed management algorithm for necrotizing soft tissue infections.

Adding further to the debate, in a recent propensity score-matched analysis of patients with necrotizing fasciitis and shock, IVIG use was rare, but not associated with improved outcomes, regardless of pathogen type [18▪▪]. Given the ongoing mixed evidence, IVIG can be considered in patients with TSS, but benefit is unclear and specific dosing regimens are not well studied (Fig. 1).

Necrotizing soft tissue infections: gas gangrene/myonecrosis and necrotizing fasciitis

Necrotizing SSTIs are difficult to treat and require aggressive surgical debridement, broad-spectrum antimicrobials, and intensive care. Table 2 and Fig. 1 demonstrate factors associated with increased likelihood of necrotizing infection and a proposed management tree [19]. Source control of infection is paramount and serial surgical debridements are generally required. The frequency and number of required debridements varies, but generally debridement should occur every 24–48 h until there is no evidence of necrosis. Daily wound dressing changes should be done to look for ongoing infection (e.g., bullae, devitalized tissue, spreading erythema) that would require repeat debridement. Increased requirements for intensive care support or laboratory parameters suggestive of worsening infection (e.g., progressive renal failure, increasing leukocytosis, increasing lactate) should prompt discussion of repeat debridement. Surgical control of infection is particularly important because diffusion of antimicrobials into affected tissues is limited due to significant tissue edema, necrosis, inflammation, and penetrating vessel thromboses [20].

Gas gangrene/myonecrosis

Gas gangrene or myonecrosis is caused by *Clostridium* species and should be managed surgically with adjunctive broad-spectrum antibiotics while awaiting culture results (Table 1). Though rare, *Clostridium sordellii* infections are notable as they can be

Table 2. Characteristics associated with increased likelihood of necrotizing infection

Clinical parameters	Laboratory parameters
Pain out proportion to examination	Serum sodium <135 mmol/l
Bullae	White blood cell count >15 400 cell/μl
Tenderness beyond area of erythema	Renal failure
Crepitus	Progressive lactic acidosis
Cutaneous anesthesia	
Cellulitis refractory to antibiotic therapy	
Rapid progression of cellulitis	
Dusky appearance of skin	
Systemic toxicity	

Adapted from [19].

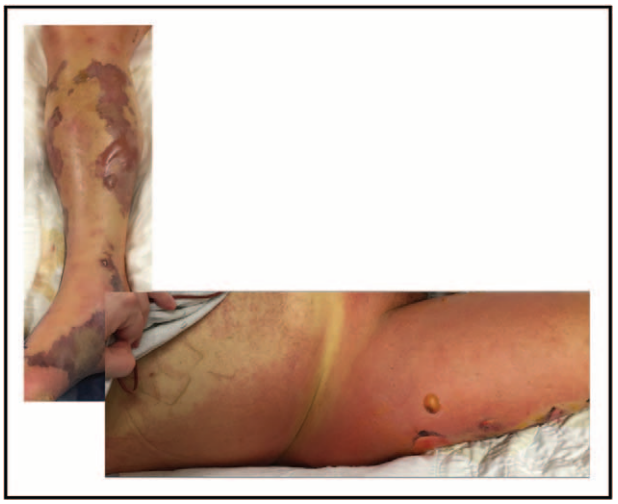

FIGURE 2. Necrotizing fasciitis of the lower extremity. Retiform purpura with bullae formation (a) or rapidly spreading erythema with bullae formation (b) should prompt urgent surgical consultation. Adapted from [19].

associated with a toxic-shock like syndrome, particularly in patients with recent parturition or abortion [8,9,21]. TSS from clostridial infection is pathophysiologically dissimilar to SeTSS or SaTSS, making IVIG of dubitable benefit [8,9,21].

Necrotizing fasciitis

Necrotizing fasciitis (Fig. 2) is a rare SSTI that involves the deep fascia [19]. Rates of necrotizing fasciitis vary widely based on region (0.18–15.5 per 100 000) and are increasing over time [22,23]. Despite patients with necrotizing fasciitis having a higher severity of illness than patients with cellulitis, a recent study found that patients with cellulitis and necrotizing fasciitis had similar in-hospital and 90-day mortality, presumably due to higher comorbidity burden in patients with cellulitis [24▪]. However, the study had a small number of patients and may not have been powered to detect a difference in mortality between the groups.

Type I necrotizing fasciitis is polymicrobial, including aerobic and anaerobic organisms. Type II necrotizing fasciitis is classically caused by *S. pyogenes*, though *S. aureus* also falls into this category. There are a variety of less frequently encountered agents causing necrotizing fasciitis, which makes it important for practitioners to realize the importance of surgical debridement with attendant bacterial cultures in combination with broad-spectrum antimicrobials as the first lines of therapy [25,26].

Though the classic teaching for necrotizing fasciitis is pain out proportion to physical examination findings, it is important to remember that superficial nerves can undergo necrosis, resulting in anesthesia of affected areas. A high degree of suspicion for necrotizing SSTI is required due to variability in physical examination findings and low sensitivity of imaging modalities. Imaging findings cannot rule out necrotizing fasciitis and may delay surgical intervention, which is associated with poor outcomes [27]. However, in clinically stable patients, MRI may be helpful in distinguishing necrotizing from nonnecrotizing infection [28].

Necrotizing fasciitis predominates on the lower extremity and predisposing conditions such as diabetes and peripheral vascular disease reflect this localization. Due to the relative rarity and heterogeneity of microbiologic causes, no clinical trials are available to guide duration of therapy. Based on expert opinion, recent guidelines suggest antimicrobial therapy directed against cultured organisms for at least 48–72 h after patients are clinically stable and require no further operative interventions [4].

Surgical considerations

For all patients with severe SSTIs, general resuscitative measures should be followed in accordance with institutional protocols. Source control is paramount, which may include surgical debridement, removal of invasive devices, or vaginal examination in the case of menstrual TSS. Prolonged time from presentation to first surgical intervention is associated with increased mortality [27,29]. In a mixed cohort of severe sepsis/septic shock patients that included patients with SSTIs, source control was associated with reduced mortality despite patients requiring source control having greater severity of illness [30▪▪].

In conjunction with serial debridements, vacuum-assisted closure of wounds may contribute to healing [31]. For cases of necrotizing infection involving the perineum or other sites with potential for stool contamination, temporary colostomy may be required to assist in wound healing. Rates of amputation in lower extremity necrotizing fasciitis vary from 15 to 72% based on comorbidities, with diabetes being a strong risk factor for amputation [32]. Although potentially life-saving, it is important to recognize that amputations, among other factors, may be associated with significant functional limitations after discharge [33].

Hyperbaric oxygen therapy

The use of hyperbaric oxygen therapy (HBOT) for necrotizing SSTI remains controversial due to mixed evidence of benefit, a lack of RCTs, and variable access to hyperbaric oxygen chambers [34–38]. In the absence of RCTs or well done propensity score

Table 3. Empiric antimicrobial dosing and duration guide for severe skin and soft tissue infections

Organism type	First-line antimicrobials	Second-line antimicrobials	Duration of therapy
Gram-positive	Vancomycin 15 mg/kg[a] and clindamycin 900 mg IV q8H	Linezolid 600 mg IV q12H	At least 48–72 h after clinical stability and no further surgical debridements. If bacteremic, refer to pathogen-specific guidelines, generally 14 days or more
Gram-negative and anaerobe	Cefepime 1 g IV q8H[b] (2 g IV q8H if BMI > 40)	Meropenem 1 g IV q8H[b]	

These recommendations are for patients in shock with risk factors for methicillin-resistant *Staphylococcus aureus* and multidrug-resistant Gram-negative bacterial infections. There is increasing evidence of nephrotoxicity from the combination of vancomycin and piperacillin-tazobactam, making carbapenems a more favorable second-line agent for Gram-negatives and anaerobes. IV, intravenous.
[a]Dosing interval dependent on creatinine clearance.
[b]Provided dose assumes a normal creatinine clearance.

analyses, we cannot recommend for or against the use of adjunctive HBOT for the management of necrotizing SSTI. For centers with HBOT readily available, its use can be considered, but should not be a substitute for or result in delays in surgical or antimicrobial therapy (Fig. 1).

Antimicrobial considerations

As a general rule, all severe SSTI should be treated empirically with broad-spectrum antibiotics directed against typical pathogens, specifically MRSA, resistant Gram-negatives, and anaerobes (Table 1 and Table 3). Notably, patients with complicated SSTI have more rapid achievement of clinical stability if empiric antimicrobials are appropriate for isolated pathogens [39▪▪]. All practitioners should consider local antibiograms when choosing empiric antimicrobials, as antibiograms can vary significantly. In regions such as Northern Europe with low rates of MRSA [40], it may be prudent to exclude MRSA coverage from empiric therapy in patients at low risk of MRSA infections. Preliminary work with MRSA risk prediction tools in SSTIs show promise, but more data are needed before implementing these tools and foregoing empiric MRSA coverage [41▪].

De-escalation of antibiotic therapy should be based on clinical improvement, cultured pathogens, and results of rapid diagnostic tests where available. Rapid diagnostic testing for SSTIs is a relatively new area, but there is some promising data to show that their use results in increased appropriateness of therapy as well as increased rates of de-escalation [42▪].

Considerations for selected antimicrobials

Dalbavancin and oritavancin are long-acting semisynthetic lipoglycopeptides that are approved for a wide range of Gram-positive organisms. However, further studies are needed before their use can be recommended for severe SSTI. Daptomycin use may be contraindicated in patients with necrotizing fasciitis and elevated creatine kinase levels. As MRSA is one of the most common causes of SSTIs and severe illness is associated with higher rates of bacteremia, caution is advised when using linezolid, as its use in MRSA bacteremia may be associated with worse outcomes in patients with acute physiology and chronic health evaluation II scores at least 14 [43]. Tedizolid has been shown to be noninferior to linezolid across a range of SSTI severity [44▪], but there is no reason to believe it would be more efficacious in MRSA bacteremia than linezolid, so concerns about its empiric use remain. Telavancin is associated with higher rates of toxicity than other available agents for SSTI, and we therefore do not recommend its use when other agents can be employed. Though approved for SSTIs, tigecycline has been linked with worse outcomes in patients with severe illness. Tigecycline may also be a risk factor for treatment failure in patients with drug-resistant infections. As such, we recommend avoiding tigecycline therapy when other options are available.

Future therapies

There are some exciting new drugs in the pipeline for SSTI treatment, including delafloxacin and omadacycline, but discussion of their use will be covered by other articles in this issue. Nontraditional therapies for SSTIs, such as an antistaphylococcal alpha toxin antibody, have recently shown some promise in animal models, but are not available for human use [45▪].

SPECIAL CONSIDERATIONS

Unusual causes of SSTI are outside the scope of this review, as most are rare and not typically associated with severe illness. For additional information, see recent reviews on this subject [19].

Immunocompromised hosts

Immunodeficiency changes the physical examination findings of SSTI, the putative pathogens, and the diagnostic and treatment plans. The differential diagnosis for dermatologic findings in the immunocompromised host includes noninfectious causes and a broader range of infections, including invasive fungal, mycobacterial, and parasitic infections [4,19]. With a broader differential diagnosis and greater potential for decompensation, early dermatologic consultation for immunocompromised patients may be beneficial [4,46▪]. Dermatology consultation can improve the diagnosis of dermatologic findings in critically ill patients and reduce antimicrobial use [46▪,47]. Many dermatologic conditions mimic infection, for which dermatologist expertise can be helpful in distinguishing [19,48].

All immunocompromised patients that are critically ill should undergo thorough cutaneous examination as immunosuppression tends to reduce physical exam findings of SSTIs. Immunosuppressed patients are more likely to have cutaneous dissemination of pathogens. A recent study showed that immunocompromised patients with *S. pyogenes* were more likely to have necrotizing fasciitis, septic shock, and die than immunocompetent patients [49▪]. Conversely, in a cohort of patients with *S. aureus* infections, some of which had SSTIs, immunocompromise was not a risk factor for mortality [50▪].

When possible, reduction of immunosuppression should be considered for severe infections. For patients with febrile neutropenia, Multinational Association of Supportive Care of Cancer score is important for predicting complication rates [51]. In neutropenic patients, factors to consider when contemplating surgery are probable duration of neutropenia and severity of infection. Patients with shorter durations of neutropenia have a higher likelihood of recovering from surgical interventions and are likely better candidates for surgery. Management of necrotizing SSTIs in neutropenic patients is poorly studied, and treatment strategies should be individualized.

CONCLUSION

SSTIs have a variety of presentations and can be severe enough to require intensive care. Practitioners should be familiar with the spectrum of clinical presentations for SSTI that require urgent surgical debridement to avoid delays in surgery as this can lead to worsened outcomes. Aggressive source control and broad spectrum antimicrobials are essential for all severe SSTI, with empiric therapy guided by knowledge of patient risk factors, the local antibiogram, and where available, rapid diagnostic testing.

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Conflicts of interest

The work was performed at Barnes-Jewish Hospital, St. Louis, Missouri.
There are no conflicts of interest.

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