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Original Article

Surgical Infection Society 2020 Updated Guidelines on the Management of Complicated Skin and Soft Tissue Infections

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Abstract

Background: The Surgical Infection Society (SIS) Guidelines for the treatment of complicated skin and soft tissue infections (SSTIs) were published in October 2009 in *Surgical Infections.* The purpose of this project was to provide a succinct update on the earlier guidelines based on an additional decade of data.
Methods: We reviewed the previous guidelines eliminating bite wounds and diabetic foot infections including their associated references. Relevant articles on the topic of complicated SSTIs from 2008–2020 were reviewed and graded individually. Comparisons were then made between the old and the new graded recommendations with review of the older references by two authors when there was disparity between the grades.
Results: The majority of new studies addressed antimicrobial options and duration of therapy particularly in complicated abscesses. There were fewer updated studies on diagnosis and specific operative interventions. Many of the topics addressed in the original guidelines had no new literature to evaluate.
Conclusions: Most recommendations remain unchanged from the original guidelines with the exception of increased support for adjuvant antimicrobial therapy after drainage of complex abscess and increased data for the use of alternative antimicrobial agents.

Keywords: antibiotics; necrotizing infection; skin; soft tissue

Soft tissue infections continue to be a common problem within the healthcare system resulting in prolonged hospitalization, disability, and mortality. The more severe infections require a combination of aggressive surgical and antimicrobial management. Since the original guidelines were published in 2009 [1], the Food and Drug Administration (FDA) revised its terminology for use in randomized controlled trials in 2013 [2]. The current term is acute bacterial skin and skin structure infections that includes cellulitis/erysipelas, wound infection, and major cutaneous abscess. Unfortunately, it continues to omit necrotizing infections thereby excluding these more severe infections from clinical trials. As noted in the original guidelines, mortality rates for FDA published trials demonstrate mortality rates of 1%, whereas those that include necrotizing infections are higher [3].

The focus of the Surgical Infection Society (SIS) is on those infections that require surgical as well as antimicrobial therapy. Hence, these guidelines are similar to those from 2009 by including the management of deeper infections that are excluded from randomized trials. The current authors also use the previous term skin and soft tissue infections (SSTIs) to describe those that involve the skin, subcutaneous tissues, fascia, and muscle as depicted in Figure 1 [1]. In this way, these guidelines reflect the current recommendations on topics included in the previous guidelines.

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Methods

The process used for these updated guidelines mirrored those utilized in 2009. Specifically, these guidelines were developed by an expert panel within the society mainly comprising members of the Therapeutics and Guidelines Committee. The panel conducted a PubMed search from 2008–2020 related to SSTIs, necrotizing soft tissue infections (NSTIs), skin and skin structure infections (SSSIs), and infections caused by specific pathogens. The original references from the 2009 guidelines were reviewed and incorporated with the newer randomized trials, retrospective cohort studies, and case series with analysis of therapy and outcomes used to establish guidelines. These reports were graded according to the methods described by Guyatt et al. [4] and are shown in Table 1. The expert panel determined that diabetic foot infections and hidradenitis suppurativa had well-established guidelines from other societies and were therefore excluded from this update. In addition, bite wounds were excluded because these guidelines focused on established infections. Similar to the challenges from the original guideline, some recommendations for necrotizing infections were extrapolated from studies in other clinical settings and utilized retrospective and animal data.

Definitions/Epidemiology/Pathophysiology of Complicated SSTIs

Definitions

There are multiple classification systems for the diagnosis and management of SSTIs. The Infectious Diseases Society of America (IDSA) classifies them into five categories including separate classification for bites and animal contact as well as one for infections in the immunocompromised host [5]. Eron et al. [6] classifies SSTIs in outpatients based on comorbidities as well as local and systemic signs of infection. However, the classification system developed by Sartelli et al. [7] through the World Society of Emergency Surgery (WSES) is the most consistent with the updated classification by the FDA with the addition of NSTIs. To maintain consistency with the 2009 guidelines the authors use similar terms as the WSES with two main differences. There is no specific focus on surgical site infections nor do the recommendations specify subtypes of necrotizing SSTIs given the paucity of data. Therefore, these guidelines focus on non-necrotizing SSTIs of the dermis, complicated infections to include abscesses, and necrotizing infections. In addition, rapidly progressive soft tissue infections that are pathogen-specific are addressed in a similar fashion to the 2009 guidelines.

Epidemiology

Skin and soft tissue infections are one of the most common bacterial infections that affect humans. The prevalence and incidence of these infections continues to increase in the United States and represents approximately 10% of hospital admissions [8,9]. These infections typically affect the lower extremities and have up to a 50% recurrence rate after the initial episode [10]. Skin and soft tissue infections may be from a single pathogen or polymicrobial. The most frequently isolated pathogen from complicated SSTI continues to be *Staphylococcus aureus*, although a combination of organisms may be involved including both aerobic gram-positive and gram-negative micro-organisms. Furthermore, differences exist between NSTIs and non-NSTIs related to the pathogens of concern. Necrotizing soft tissue infections are often polymicrobial, including more virulent strains such as group A Streptococcus, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), and *Clostridium* spp. It is the virulence of the pathogens that leads to a more than 30% mortality rate worldwide [11]. Moreover, there are specific exposure-related pathogens seen after certain injuries such as *Vibrio* spp. with warm water exposures because of its prevalence in this environment.

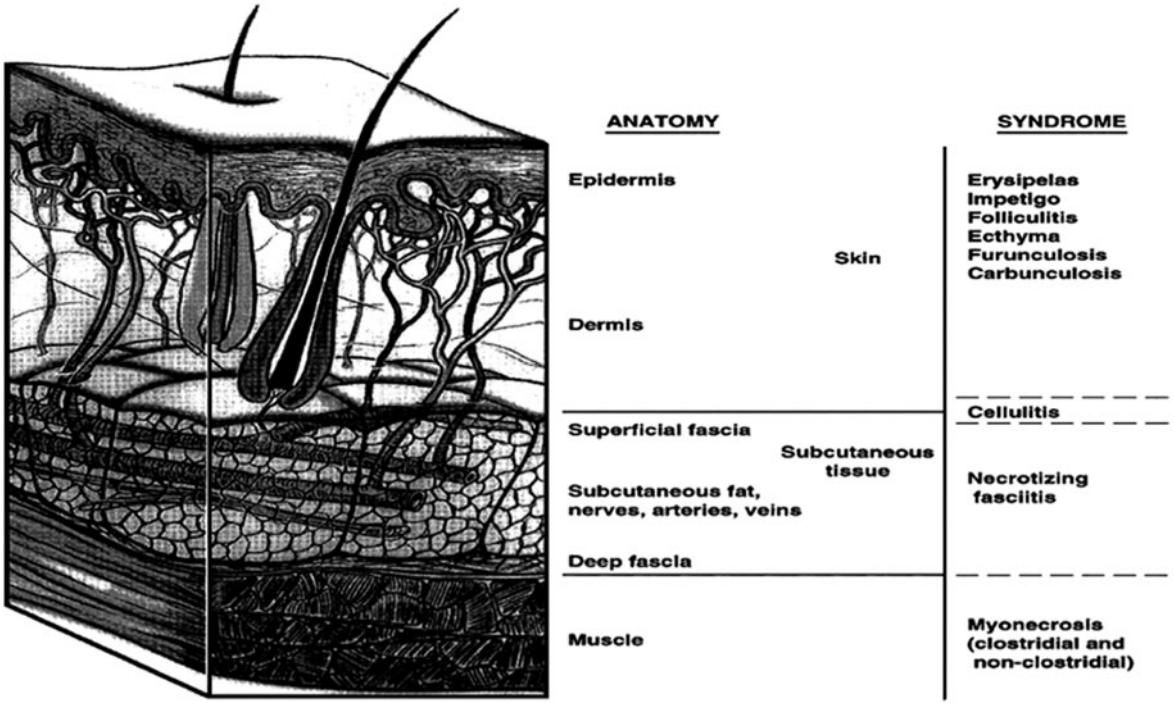

FIG. 1. Anatomy of skin and soft tissue structure and layers commonly involved with various infectious processes.

Table 1. Grading Recommendations

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

Adapted from Guyatt et al. [4].
RCTs = randomized controlled trials.

Pathophysiology

The cause of SSTIs usually stems from a compromise to the skin barrier. A second although much less common route for infection is hematogenous spread to tissue [12]. Skin and soft tissue infections include a spectrum of different presentations, causative agents, and depth of invasion from the skin down to the level of the fascia and muscle. In general, these infections begin with localized pain and swelling in the area of infection with associated erythema and induration. For those that go on to form an abscess, fluctuance may be present. Situations in which a necrotizing infection has developed, hyperesthesia or allodynia in the area without noticeable skin lesions can mask the extent of the infection leading to the classic ''pain out of proportion to the examination'' finding. In other cases of necrotizing infections there are skin bullae present as well as crepitus on physical examination. The key distinguishing characteristic between necrotizing and non-necrotizing infection is the presence of necrotic tissue; this necessitates prompt surgical intervention [1,7,13]. Many patients demonstrate signs of systemic illness and sepsis as the necrotizing infection continues regardless of the stage at which they present, resulting in significant morbidity and mortality.

The potential for the bacteria to cause local tissue damage and a systemic inflammatory response is mediated by the release of bacterial toxins. These toxins result in inflammatory changes of the skin and subcutaneous lymphatics. In the case of necrotizing infections, thrombosis of venules and arterioles can occur leading ultimately to ischemia and necrosis of affected tissue [14]. The systemic response to the toxins causes the cardiovascular compensatory tachycardia as a result of the toxin-induced hypotension, fever from the massive endogenous cytokine release, and subsequent inadequate end organ perfusion leading to multi-organ dysfunction late in the disease course [14]. It is this progression of local disease and systemic inflammation that mandates timely diagnosis and treatment with appropriate antibiotic agents and urgent surgical debridement.

What risk factors are associated with poor outcomes in patients with necrotizing fasciitis?

Independent risk factors for increased mortality in necrotizing fasciitis include septicemia and ICU admission. [1C]

Necrotizing fasciitis and/or multi drug resistant bacteria are associated with an increased mortality rate. [2B]

Previous studies evaluated risk factors associated with increased mortality seen at presentation, intra-operatively, as well as post-operative findings. Historically comorbidities such as diabetes mellitus, septicemia, and the need for

intensive care unit (ICU) admission were associated with an increase in mortality [15]. However, in a recent large retrospective cross-sectional analysis performed by Al-qurayshi Z et al. [3] diabetes mellitus was independently associated with a decreased mortality among patients diagnosed with necrotizing fasciitis as a primary or secondary diagnosis at admission. The findings of this study were consistent with the findings previously stated that septicemia on presentation increased the patient's risk of mortality [3,15]. Findings of necrotizing fasciitis intra-operatively is an independent risk factor for poor outcome. Malheiro et al. [16] showed that the presence of necrotizing fasciitis was the most common predictor of a poor outcome along with previous trauma and immunosuppression. Post-operative cultures of the wound are critical to allow for appropriate de-escalation of antibiotic agents, and the presence of multi-drug–resistant bacteria is also a major risk factor for a worse outcome [16].

Non-Necrotizing Cellulitis

Treatment: Antimicrobial considerations

What is the appropriate treatment of non-necrotizing, superficial infections?

Antimicrobial therapy directed against β-hemolytic streptococci is recommended for non-purulent infections. [1C]

For mild infections, oral formulations (i.e., penicillin VK, cephalexin, dicloxacillin) are recommended. [1A]

For moderate to severe infections requiring hospitalization, IV therapy with a narrow spectrum β-lactam (i.e., penicillin, cefazolin, ceftriaxone) is recommended. [1C]

For patients with severe allergic reaction (e.g., anaphylaxis) to β-lactams requiring IV therapy, clindamycin is recommended. [1C]

Protein synthesis-inhibitory agents alone or in combination with cell wall-active agents (e.g., clindamycin, linezolid) should be considered in severe cases. [1C]

Empiric MRSA coverage should be reserved for high-risk patients (e.g., prior colonization or infection, patients in septic shock.) or infection refractory to first-line therapy devoid of MRSA activity. [1C]

The use of cephalexin alone for cases of uncomplicated cellulitis is suggested based on current studies. [2B]

Cellulitis is an SSTI affecting the deeper layer of subcutaneous tissue. The presentation typically includes skin erythema, warmth, and tenderness. Without evidence of purulent drainage or abscess, the most common pathogens are β-hemolytic streptococci, commonly *Streptococcus pyogenes* [13]. Empiric therapy against streptococci is recommended with a narrow spectrum β-lactam to provide adequate coverage of the most prevalent organisms while limiting collateral damage (e.g., antimicrobial resistance, adverse drug effects, etc.). Reports of increasing rates of clindamycin resistance in β-hemolytic streptococci suggest cautious use of empiric clindamycin, especially in regions with high levels of resistance and in more severe presentations of the disease [17]. If concern or desire to cover methicillin-susceptible *Staphylococcus aureus* (MSSA), an anti-staphylococcal penicillin or cephalosporin is recommended (e.g., dicloxacillin, cephalexin).

Although CA-MRSA is becoming increasingly more prevalent in purulent skin infections, it is less common in uncomplicated cellulitis. Antibiotic agents against CA-MRSA are not recommended in uncomplicated cellulitis, however, they are prescribed frequently [18,19]. In a multicenter, double-blinded randomized superiority trial taking place in five separate emergency departments cephalexin was compared with trimethoprim-sulfamethoxazole (TMP-SMZ) in cases of uncomplicated cellulitis. The results of this study showed that TMP-SMZ did not result in higher rates of clinical resolution compared with cephalexin [20]. This strengthens the argument that uncomplicated cellulitis can be treated without the use of MRSA-active agents.

What is the optimal antimicrobial duration for the treatment of non-necrotizing cellulitis?

Insufficient evidence to support antimicrobial therapy with either oral or IV beyond 5 days. [1C]

Duration of antibiotic therapy. Current practice of antibiotic therapy duration for non-NSTIs varies anywhere from five to 14 days [13,21,22]. Patients with more severe cellulitis are typically hospitalized and receive parenteral antibiotic therapy and then converted to enteral antibiotic therapy with resolution of symptoms. The duration specific to parenteral antibiotic therapy has not been well studied. An observational study by Inaoki et al. [23] in 2017 evaluated clinical factors that impacted duration of therapy. Independent variables including increasing age, diabetes mellitus, elevated C-reactive protein (CRP), and concurrent bacteremia resulted in an extended duration of parenteral antibiotic therapy [23]. A more recent post hoc analysis evaluating procalcitonin as a marker to guide therapy found that it was not only a poor measure to diagnose cellulitis but also should not be used as a method to determine need for antibiotic agents [24]. Two large registrational trials, the Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy (ESTABLISH)-1 and ESTABLISH-2 demonstrated that six days of tedizolid was non-inferior to 10 days of linezolid, suggesting a shorter course is as effective [25,26]. A more recent meta-analysis by Brindle et al. [27] found no benefit for either intravenous (IV) or oral antibiotics beyond five days of treatment [27].

What is the role of suppressive antimicrobial therapy for patients at high risk for recurrence of non-necrotizing cellulitis?

Long term antimicrobial therapy may be beneficial in certain patients at higher risk for cellulitis recurrence after initial therapy. [2A]

Recurrence of non-NSTIs including both erysipelas and cellulitis has a recurrence rate of up to 50% [28]. Studies on prevention of recurrence have lacked high-level evidence. Since publication of the previous SIS guidelines, a number of studies have addressed this issue including a review of five randomized control trials assessing prevention of recurrence of lower extremity cellulitis with the use of antibiotic agents. Prophylactic therapy using either erythromycin or penicillin showed a 69% decrease in rate of recurrence compared with placebo or no treatment [10]. There was less benefit seen once antibiotic therapy was discontinued. Thomas et al. [29] in a randomized control trial using six months of low-dose penicillin after the first episode of cellulitis decreased recurrence although it failed to reach significance because of slow

patient recruitment. Despite this lack of significance, the number needed to treat in order to have an impact on outcome was only eight patients. Prophylactic antibiotic therapy may be effective for prevention of recurrence of lower extremity cellulitis and should be considered in patients at high risk defined by one or more episodes of recurrence.

Complicated infections

Are there new diagnostics strategies or modalities for complicated infections?

Diagnosis

Point of care ultrasound in the emergency department is a useful modality to accurately distinguish cellulitis from abscess. [2B]

Fever is an uncommon symptom in patients with SSTI and therefore, should not be used alone to diagnose SSTI. [2C]

Use of a rapid molecular assay testing following incision and drainage is recommended to facilitate targeting of antimicrobial therapy. [1A]

Distinguishing an abscess that will require an incision and drainage from cellulitis that will respond to antibiotic therapy alone can be challenging. However, the inability to distinguish these pathologies can lead to unnecessary invasive procedures [30]. The IDSA defines an abscess as painful, tender, and often with fluctuant red nodules surrounded by a pustule and surrounded by a rim of erythematous swelling [13]. The standard diagnostic approach is to use clinical examination such as fever and fluctuance to determine the presence or absence of an abscess, however, this has been shown to be neither sensitive nor specific [30,31]. Point-of-care ultrasound imaging can visualize the presence of an abscess cavity and prevent unnecessary procedures [30].

The use of MRSA rapid molecular assay testing is recommended after incision and drainage to allow for improved targeted antibiotic therapy [32]. Currently sampling of an abscess is either not performed or cultured by various methods. The lack of pathogen identification leads to inappropriate and unnecessary broad-spectrum antibiotic use. The use of a molecular assay to determine the presences or absence of MRSA has been proven to have a high specificity and sensitivity. Using this modality could lead to improved antibiotic stewardship in emergency department (ED) treatment of SSTI. At this time, there is a lack of ED access to these tests. The test will need to have results in less than 45 minutes to be ideal for a rapid test in the ED; previous research shows that it currently it takes 82 minutes [33,32]. Further studies are needed for a cost analysis benefit.

Treatment

What are the best available surgical interventions for the treatment of complicated infections?

Surgical

Incision and drainage without wound packing for uncomplicated abscesses in the immunocompetent patient should be considered. [2C]

Ultrasound guided aspiration as an alternative to incision and drainage for the management of uncomplicated SSTI is not recommended. [1B]

Closure utilizing either primary or secondary intention is recommended based on patient and provider preference. [1B]

Incision and drainage remains standard of care for SSTIs with associated abscess [30]. An alternative to incision and drainage, ultrasound-guided needle aspiration, has been tested in a prospective randomized control trial and has been found to be insufficient based on immediate treatment failure and the need to convert to a formal incision and drainage [30]. The method of incision and drainage does vary by provider based on preference including incision length, packing, and irrigation. Wound packing for uncomplicated abscesses has been shown to increase pain without a reduction in treatment failure, therefore, routine packing after incision and drainage should be avoided [34].

After drainage, many providers leave the cavity open to heal by secondary intention to prevent reformation of the cavity. A randomized control trial by Singer et al. [35] showed similar failure rates between primary and secondary closure after incision and drainage. Therefore, whether or not to close the cavity should be based on the clinical case and provider preference [35].

Antimicrobial considerations

What antimicrobials are recommended for the treatment of complicated SSTIs?

Empiric coverage of MRSA should be considered, especially in purulent infections. [1B]

Oral therapy for suspected or confirmed MRSA infection, recommendations include linezolid [1A], doxycycline or minocycline [1B], trimethoprim-sulfamethoxazole [1A].

Additional oral alternatives for MRSA coverage that may be considered include tedizolid [1A], delafloxacin [1A], and omadacycline [1A]

The following intravenous agents are recommended for suspected or confirmed MRSA infections: vancomycin [1A], linezolid [1A], daptomycin [1A], ceftaroline [1A], telavancin [1A].

Additional intravenous MRSA alternatives that may be considered include dalbavancin [1A], oritavancin [1A], omadacycline [1A], tedizolid [1A], delafloxacin [1A], and tigecycline [2B].

Narrow-spectrum antibiotics without gram-negative coverage for complicated SSTI can be considered in areas with low levels of antibiotic resistance and patient populations not needing immediate broad-spectrum due to severity of illness or risk for polymicrobial infections. [2C]

Infections caused by MRSA are an increasing concern, and most new antimicrobial agents studied for these types of infections target MRSA [36]. Vancomycin has been the standard of care for treating MRSA complicated SSTIs, however, with newer agents available several alternatives now exist [37]. Older tetracycline derivatives such as doxycycline or minocycline remain effective oral agents along with TMP-SMZ. Most of the data on efficacy of the new agents for treatment of complicated SSTIs has been derived from non-inferiority trials, not directly comparing the novel agents with one another. Here we review available anti-MRSA agents regarding their effectiveness in complicated SSTIs with particular focus on recent clinical trials.

Daptomycin, a cyclic lipopeptide, is bactericidal in a concentration-dependent manner with activity against gram-positive organisms including MRSA. Daptomycin is FDA-approved for the treatment of complicated SSTIs. Once daily administration makes this agent an attractive option for

patient requiring outpatient parenteral antimicrobial therapy. Bliziotis et al. [38] sought to review the efficacy and safety of daptomycin compared with other antimicrobial agents for the treatment of SSTIs. Four studies were included, including three randomized control trials, which compared vancomycin or semi-synthetic penicillin to daptomycin. They found no statistically significant difference in clinical success between comparator groups. No difference in other outcomes including treatment-related adverse events and withdrawal from treatment because of toxicity. Most studies using daptomycin used 4 mg/kg intravenous once daily for seven to 14 days [38]. In 2008, Katz et al. [39] studied a higher dose daptomycin 10 mg/kg intravenous of shorter duration of only four days versus standard of care of vancomycin or semi-synthetic penicillin. They found a similar safety profile but no statistically significant difference of clinical success rates among groups. Subgroup analysis suggested that high-dose short-duration daptomycin may be a better option for outpatients but possibly not for those with MRSA infections [39].

Linezolid has been shown to be an effective alternative to vancomycin in achieving clinical and microbiologic success in patients with complicated SSTIs caused by MRSA [40]. Linezolid has been associated with a reduced length of hospital stay, reduced cost of outpatient therapy, and reduced cost of hospital charges per patient compared with vancomycin [41]. Patients receiving linezolid for a complicated SSTI have been shown to have a lower probability of undergoing more than two surgical interventions compared with vancomycin. This can potentially further decrease healthcare costs and length of stay [42].

Tedizolid, a bacterial protein synthesis inhibitor, is a novel oxazolidinone with enhanced activity against a wide range of gram-positive organisms (four-fold to 16-fold greater gram-positive activity than linezolid). The agent is administered once daily with equivalent doses for intravenous and oral formulations [43]. Tedizolid demonstrated non-inferiority compared with linezolid for early clinical response with a six-day course of therapy. In the ESTABLISH-1 trial, tedizolid (200 mg orally for six days) proved non-inferior to linezolid (600 mg orally twice per day for 10 days) in the treatment of these infections including cellulitis and abscesses. Tedizolid had similar early clinical response 48 to 72 hours after initiation of treatment as well as similar response at one to two weeks after completion of treatment [25]. These results were corroborated by a similarly designed trial, the ESTABLISH-2 trial [26]. Tedizolid has a similar safety profile as well as less thrombocytopenia and gastrointestinal side effects compared with linezolid. In addition, drug–drug interactions resulting in serotonin syndrome are less of a concern with tedizolid [44]. These qualities make it a useful option for the treatment of complicated SSTIs.

Ceftaroline is an extended-spectrum cephalosporin antibiotic with broad-spectrum activity including MRSA and gram-negative bacteria similar to ceftriaxone [45]. Ceftaroline was found non-inferior to vancomycin plus aztreonam for the treatment of complicated SSSIs in two identical phase 3 randomized controlled trials, CANVAS-1 and CANVAS-2 [46]. In addition, adverse events and rates of discontinuation were similar to comparators in the trials. Taken together these studies suggest that ceftaroline is a potential safe option for the treatment of complicated SSTIs.

Fluoroquinolones are no longer recommended for uncomplicated infections because of increased safety risk, including severe and potentially irreversible side effects such as tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects [47]. Moxifloxacin is a broad-spectrum fluoroquinolone with activity against gram-positive and gram-negative aerobic pathogens, in addition to activity against anaerobic organisms [48,49]. Moxifloxacin also has good penetration into muscle, adipose tissue, and inflammatory blister fluid, making it a reasonable choice for treatment of a complicated SSTI [49]. A comparison of sequential intravenous to oral moxifloxacin 400 mg daily versus intravenous piperacillin-tazobactam 4.5 gm three times daily to oral amoxicillin-clavulanate 875/125 mg twice daily for complicated SSSIs found moxifloxacin to be non-inferior to the sequential intravenous piperacillin-tazobactam to oral amoxicillin-clavulanate regimen. The limited analysis of micro-organisms showed similar causative organisms among groups and although both regimens lack activity against MRSA, the bacteriologic success rate was similar. They were unable to determine the effect of surgery on clinical cure rates although rates were similar in patients with and without initial surgery [50]. Moxifloxacin does have limited activity against strains of MRSA, so if empiric treatment is chosen, it should not be used in areas of highly predominant MRSA infections [51].

Delafloxacin is a next-generation fluoroquinolone with activity against a wide array of gram-positive and gram-negative organisms, including MRSA and *Pseudomonas* spp. [52–54]. Its side effect profile does not include the previous class effect of phototoxicity or QTc prolongation. Given the broad-spectrum coverage, it represents another option for the treatment of complicated SSTIs and was recently approved by the FDA. Delafloxacin was found to be non-inferior to vancomycin plus aztreonam as intravenous only and intravenous with transition to oral therapy in two phase 3 randomized controlled trials [55]. In trials to date delafloxacin was well tolerated, however, similar to other quinolones, there were dysglycemic episodes in the phase 2 trials [19,20,56,57]. Post-marketing surveillance will be important to monitor for safety signals that have been reported with other fluoroquinolones.

Tigecycline is unique in its class as a glycylcycline antibiotic but shares tetracycline-like adverse effects as a derivative of minocycline, significant for gastrointestinal adverse effects. In a subset of a phase 3 randomized control trial of complicated SSSIs in Europe, the safety and efficacy of tigecycline 100 mg intravenous followed by 50 mg intravenous every 12 hours was compared with that of vancomycin 1 gm intravenous twice daily plus aztreonam 2 gm intravensou twice daily in the treatment of complicated SSSIs. Although this was not powered to prove non-inferiority in the European subset, the success rates between groups were similar and noted to align with the results of the larger phase 3 study. The rate of serious adverse events leading to study drug discontinuation were similar, however, the effects noted were different with nausea and skin disorders for tigecycline and vancomycin-aztreonam groups, respectively [58]. In 2012, Matthews et al. [59] found tigecycline (100 mg then 50 mg intravenous every 12 hours) was non-inferior to β-lactam/β-lactamase inhibitor (ampicillin-sulbactam 1.5–3 gm intravensou every six hours or amoxicillin-clavulanate 1.2 g intravenous every six to eight hours) with or without

vancomycin in the treatment of complicated SSSIs. Although this was an open-label randomized controlled trial, approximately 60% of the population was cellulitis with 20% previous antibiotic failure, which matched results of other previous trials that were double-blinded [59]. Meta-analyses of tigecycline for on and off label indications indicated a possible mortality signal with tigecycline [60]. This in conjunction with side-effect profile and broad-spectrum nature of the agent make it less ideal than some other agents.

Omadacycline is a tetracycline derivative, with activity against gram-positive and gram-negative organisms, including multi-drug–resistant pathogens. Omadacycline was found to be non-inferior in two large registrational trials, the Omadacycline in Acute Skin and Skin Structure Infections Study (OASIS)-1 and OASIS-2 compared with linezolid, either as oral therapy only or intravensous to oral sequential therapy [61]. Adverse events were similar between omadacycline and linezolid with the most common adverse effects reported for omadacycline being gastrointestinal symptoms. Given the activity of omadacycline against a number of multi-drug–resistant pathogens, we do not recommend it as a first-line agent.

Telavancin is a glycopeptide antibiotic with a lipophilic side chain moiety, resulting in an additional mechanism of disruption of membrane potential and changes to cell permeability, and a pharmacokinetic profile that provides standard daily dosing that differentiates it from vancomycin [62]. A post hoc review of the Antiretroviral Therapy as Long Acting Suppression (ATLAS)-1 and ATLAS-2, which was not powered to detect non-inferiority, compared telavancin with vancomycin and found consistent non-statistically significant differences in clinical cure rates among patients with different types of complicated SSTIs, those resulting from MRSA, and those with Panton-Valentine leukocidin (PVL)-positive strains of MRSA [63].

Two other lipoglycopeptide antibiotic agents have also been studied for complicated SSTIs. Dalbavancin is an intravenous medication that has activity against gram-positive pathogens, and with its long half-life, can be dosed once weekly either as a single dose or as two-dose strategy. It has been shown to be non-inferior to twice-daily intravenous vancomycin followed by oral linezolid, and well tolerated with less adverse effects than the vancomycin regimen [64]. Oritavancin is a novel semi-synthetic lipoglycopeptide with activity against gram-positive bacteria including MRSA, similar to dalbavancin. Oritavancin as a single dose has also been shown to be non-inferior to seven to 10 days of vancomycin, with a similar tolerability profile [65]. In a systematic review and network meta-analysis, oritavancin was found to be equivalent in terms of clinical efficacy compared with vancomycin, daptomycin, and linezolid at test of cure [66]. Further research, including comparative efficacy research, needs to be undertaken. These agents provide the opportunity to prevent admissions from the ED reducing or eliminating the need for hospitalization thus providing cost avoidance [67,68].

Several novel agents have been approved after the release of the previous SIS SSTI guidelines, including dalbavancin, delafloxacin, omadacycline, oritavancin, and tedizolid. Many of these agents demonstrated non-inferiority to comparators with limited adverse events in large, randomized controlled trials. These agents are all now FDA-approved for the treatment of acute bacterial skin/skin structure infections, including those caused by MRSA. The choice of a particular antimicrobial agent for complicated SSTI should be driven by multiple factors, including formulary availability, clinician experience, patient-related resources (cost, access to follow-up care), history of drug allergies or adverse events, drug interactions, and drug–disease interactions. Focused therapy for confirmed CA-MRSA infections is discussed in a separate section.

Are adjunctive antimicrobial agents necessary for simple abscesses?

Adjuvant antibiotic therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) or clindamycin for 7-10 days is recommended for simple abscesses after drainage. [1A]

Anti-MRSA therapy started initially is important to minimize recurrence with either TMP-SMZ or clindamycin with better tolerance of TMP-SMZ but lower recurrence with clindamycin. [1C]

What is the optimal antimicrobial duration for the treatment of complicated SSTIs?

In medically stable patients with cellulitis, patients who fail outpatient oral therapy can be safely treated with 3 days of outpatient IV therapy and conversion to oral therapy for an additional 7 days [2B]

Adjuvant antimicrobial therapy has gone through the most substantial change in recommendation since the original guideline. In 2009, May et al. [1] offered a 2B grade recommendation for simple abscess to be treated with incision and drainage alone. In 2015 a meta-analysis by Fahimi et al. [69] supported this recommendation although the recommendation was weak because it included randomized and observational trials. Since that time a prospective randomized controlled trial by Daum et al. [70] in 2017 demonstrated more than 80% cure when simple abscess of less than 5 cm was treated with incision and drainage along with 10 days adjuvant antimicrobial agents using either clindamycin or TMP-SMZ compared with less than 70% with incision and drainage alone ($p < 001$). A second trial by Talan et al. [71] in 2016 focused on wound infections in which more than 30% had associated drainage. In this prospective randomized trial they confirmed that both TMP-SMZ and clindamycin for seven to 10 days achieved excellent cures of more than 90%. This trial did not have a placebo arm but demonstrated a much higher cure than that seen in the study by Daum et al. [70] placebo arm of 68.9%. Both trials emphasized the need for anti-MRSA coverage initially because there was more than 40% of patients with cultures positive for MRSA. Additionally, Talan et al. [72] demonstrated the value of using a higher dose of 320 mg/1600 mg for the TMP-SMZ.

Cure of the initial condition is only one part of the challenge. Recurrence of abscess continues to be a major issue. Schmitz et al. [73] in 2010 performed a smaller randomized controlled trial comparing seven days of TMP-SMZ with placebo after incision and drainage of a simple abscess. Although initial cure at seven days was the same, recurrence was substantially different being 9% in the antibiotic group compared with 28% in the placebo group. Of note in both Daum et al. [70] and Talan et al. [71] clindamycin use resulted in lower recurrence rates compared with TMP-SMZ

but had higher adverse events, which needs to be taken into account when choice of adjuvant therapy is considered.

Recommendation of adjuvant and prolonged antimicrobial therapy needs to be balanced with the risk associated with the use of these medications as well as the cost associated with failure of treatment. A number of studies including a meta-analysis by Wang et al. [74] in 2018 found that particularly in the MRSA subset, associated antimicrobial use decreased recurrence and need for hospitalization. Others found that initial failure of oral therapy may also be salvaged emphasizing the value of outpatient therapy for the medically stable patient population [75]. Moreover, Lipsky et al. [76] in 2014 in a prospective observational trial found that lengths of stay increased when inappropriate therapy was used initially. As a consequence of these more recent high-quality trials, providers should use adjuvant antimicrobial therapy for seven to 10 days after adequate incision and drainage with either clindamycin or TMP-SMZ based on patient-specific factors such as allergies and tolerance.

Necrotizing skin and soft tissue infections

What studies aid in the diagnosis of NSTIs?

Diagnosis

Laboratory risk indicator for necrotizing fasciitis (LRINEC) score of high risk can be considered a marker for increased length of stay. [2C]

Plain radiographs are the first line study to look for gas in the soft tissue followed by computed tomography. Magnetic resonance imaging does not have a role. [1C]

Ficolin-2 level <1.9 mcg/ml can be used as an independent risk factor for increased short term (28 day) mortality. [1C]

Pentraxin-3 (PTX-3) level above 3.5 ng/mL show a correlation with increased morbidity and mortality in patients diagnosed with NSTI but it is not an independent risk factor. [1C]

Previous studies have shown delays in diagnosis increase the morbidity and mortality for complicated SSTI. Current research has focused on laboratory data that may be useful to identify risk factors that increase morbidity and mortality. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has been used for some time as a modality of risk assessment for the diagnosis of necrotizing fasciitis. A more recent trial confirmed that patients at high risk for having necrotizing fasciitis based on a LRINEC score of eight or more also had an increased length of stay [77]. Expert recommendations from the American College of Radiology identifies plain radiographs as first-line and computed tomography as second-line diagnostic modalities when investigating patients for gas within the soft tissue to confirm the diagnosis of necrotizing infection. They point out that there is no role for magnetic resonance imaging [78].

New data looking at biomarkers showed that Ficolin-2, a pattern recognition molecule, could be used to predict short-term mortality less than 28 days. Hansen et al. [79] concluded that a low Ficolin-2 level on admission (<1.9 mcg/mL) was independently associated with higher short-term mortality [79]. Another biomarker, Pentraxin-3 (PTX-3) is a marker of inflammation similar to C-reactive protein. Elevation in the levels of PTX-3 was shown to correlate with increased disease severity and mortality in a prospective study by Hansen et al. [80]. This current study, however, was not able to establish an independent association of morbidity and mortality but shows a potential role in the future pending further analysis.

Treatment

What are the optimal surgical interventions for NSTIs?

Surgical therapy

Adequate initial surgical debridement of involved tissue is recommended to improve outcomes in NSTIs. [1C]

Frequent re-evaluation or return to the operating room within 24 h is recommended to ensure the adequacy of initial debridement and absence of further tissue necrosis. [1C].

Early amputation should be considered for cases of necrotizing fasciitis with high independent risk factors for mortality including hemorrhagic bullae, peripheral vascular disease, bacteremia and a LRINEC >8. [2C]

Negative pressure therapy should be considered after adequate surgical debridement to facility wound healing. [2C]

Surgical debridement of ischemic and necrotic tissue remains the mainstay of therapy for NSTIs. Despite a paucity of high-level evidence, multiple retrospective reviews support early, adequate initial surgical debridement as a determinant of survival [1,11,81–83]. Since publication of the previous SIS guideline, no additional studies have addressed this topic. Considering that studies fail to define an ''adequate'' resection explicitly, surgical experience and judgment must guide this approach. Important factors include the ease with which fascia is separable from normally adherent overlying tissues, presence of bleeding to indicate healthy uninvolved tissue, and visible contractility of viable muscle after stimulation with electrocautery.

Frequent re-evaluation of the infected wound is recommended to help ensure the adequacy of initial debridement and absence of further tissue loss. Notwithstanding, there is no high-level evidence to help guide the timing or frequency of wound care for necrotizing infections. Retrospective reviews recommend returning to the operating room within 24 hours of the initial debridement for additional evaluation [81,83,84]. More recently, a prospective study by Okoye et al. [85] evaluated whether timing of repeat debridement affects morbidity or mortality in 64 patients with NSTIs. Patient demographics, comorbidities, infection site, laboratory values, cultures, and time to initial surgery were recorded. Multivariable analysis revealed that compared with early surgical reevaluation, delayed repeat debridement is associated with worse survival and increased incidence of acute kidney injury. Along with early debridement, a retrospective cohort study by Chang et al. [86] examined the effect of primary compared to delay amputation in patients with necrotizing fasciitis. Patients with independent risk factors for mortality including hemorrhagic bullae, peripheral vascular disease, bacteremia, and a LRINEC score higher than eight showed a mortality benefit from early amputation (<3 days) when this was compared to late amputation [86]. The optimal time interval for repeat debridement and number of procedures to accomplish definitive source control remain unknown.

Wound management after surgical debridement remains a challenge. Historically wet-to-dry dressings that allow for ongoing mechanical debridement have been used. This approach would be followed by skin grafting as needed once a

granulation base developed. Both Pan et al. [87] and Endorf et al. [88] demonstrated advantages with the use of negative pressure therapy including shorter lengths of stay and decreased time to heal. Higher level studies are needed to advance the recommendations further.

Antibiotic considerations

What is the optimal empiric antimicrobial therapy for NSTIs?

Broad spectrum empiric therapy covering gram-positive and gram-negative (aerobic and anaerobic) organisms, including MRSA, is recommended. [1C]

Numerous combinations of agents probably are equally effective in the treatment of NSTIs provided appropriate coverage of relevant pathogens is ensured. [2C]

Local resistance patterns should guide selection of empiric coverage. [1B]

For rapidly progressive or severe infections caused by toxin-producing organisms, combination therapy including the protein synthesis-inhibiting agents clindamycin or linezolid should be considered, provided the pathogen is sensitive to the agent. [1C]

Following identification of pathogen(s) via microbiological culture or rapid diagnostics, pathogen-directed therapy should be considered. [1C]

Large-scale trials to guide optimal therapy for NSTIs have not been conducted, therefore, empiric antimicrobial therapy should cover suspected pathogens based on clinical presentation, host, and exposure. Necrotizing soft tissue infections are commonly polymicrobial necessitating broad-spectrum antimicrobial agents covering gram-positive and gram-negative aerobic and anaerobic organisms, including MRSA and resistant gram-negative organisms based on local surveillance [1,89]. Local microbiologic susceptibility should guide empiric treatment options via institutional, regional, or national surveillance data. Several NSTI pathogens (e.g., group A Streptococcus, *Staphylococcus aureus*, and *Clostridium* spp.) produce toxins resulting in rapidly progressive or severe infections [1,89]. In these cases, including a protein-synthesis inhibiting agent either adjunctively (e.g., clindamycin) or as dual gram-positive coverage and protein-synthesis inhibition (e.g., linezolid) may be warranted. After identification of the causative pathogen directed therapy should be used based on the pathogen-specific recommendations section of these guidelines.

What is optimal antimicrobial duration for the treatment of NSTIs?

Shorter course antimicrobial therapy (<7 days) appears equivalent to longer therapy and should be considered. [2B]

Antimicrobial duration of therapy has remained somewhat elusive given the variability of the disease process and the difficulty with performing randomized controlled trials with equipoise. Since the publication of the previous guidelines, Lauerman et al. [90] performed a single-institution retrospective review on patients with necrotizing fasciitis, specifically Fournier gangrene. Their review of 168 patients demonstrated no difference in clinical outcome when patients were treated with seven days or less of antibiotic agents compared with those patients who were treated longer [90]. Given the associated risk with unnecessary antimicrobial agents these results demonstrate the need for further prospective evaluation into the duration of antimicrobial agents in necrotizing infections.

What pathogen-specific therapy is recommended?

Staphylococcal toxic shock syndrome

Early empiric therapy for S. aureus should be given because of the rapidity of spread of disease. [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. [2C]

The standard presentation of staphylococcal toxic shock syndrome (STSS) includes fever, hypotension, organ failure, erythematous macular rash, and the late finding of desquamation of the skin on the soles of the feet and palms of the hands [91]. Staphylococcal toxic shock syndrome first garnered attention nearly 40 years ago with reports of these symptoms in menstruating women using tampons [91–93]. Since then, the percentage of reported STSS cases not associated with menstruation has increased to approximately 40% [94,95]. The proportion of STSS cases associated with surgical procedures is also increasing [94]. Several virulence factors are associated with the development of STSS, including the superantigens TSST-1 and enterotoxins A, B, G, and I [96–98]. Lack of antibodies to superantigens is thought to predispose to STSS.

Successful treatment of STSS hinges on timely and appropriate antibiotic therapy along with early surgical intervention when indicated. Delays in therapy increase mortality substantially [99,100]. Knowledge of local staphylococcal antibiograms is paramount, with particular focus on the prevalence of methicillin-resistant organisms [1]. Consideration for empiric coverage with vancomycin is suggested if the prevalence of MRSA isolates exceeds 20% or other risk factors suggest MRSA infection [101]. Current recommendations for non-MRSA infections suggest utilization of cloxacillin, oxacillin, or nafcillin in high doses [101]. Because of the potential synergistic effect of enterotoxin neutralization, adjunctive therapy with clindamycin is suggested [1].

Group A streptococcal infections

Early aggressive antibiotic therapy and surgical debridement is recommended. [1C]

Parenteral penicillin is recommended as the agent of choice for moderate to severe infections. [1C]

Use of beta-lactam agents alone may result in treatment failures in severe cases. [1C]

Protein synthesis-inhibitory agents alone or in combination with cell wall-active agents are recommended in severe cases; examples are clindamycin or a macrolide. [1C]

Increasing macrolide resistance among streptococci introduces concern about the use of these agents. [1C]

Intravenous immunoglobulin (IVIG) is suggested for use in patients with signs of toxic shock syndrome (TSS) associated with streptococcal SSTIs. [1C]

The species most frequently associated with NSTIs is *Streptococcus pyogenes* [1]. These rapidly progressive NSTIs are associated with a high mortality rate [102–105]. Pathogenic strains produce multiple exotoxins and virulence factors and can cause life-threatening infections in otherwise healthy

individuals [102,103,106]. There is a lack of high-level evidence to guide treatment of these lethal necrotizing infections. Therapeutic recommendations are based, in part, on the perceived benefits of therapies outweighing potential risks or complications.

Similar to NSTIs caused by other organisms, early aggressive antibiotic therapy and surgical debridement are recommended. Parenteral penicillin is recommended as the agent of choice, although in severe cases β-lactam agents alone may result in treatment failures [107–109]. To avoid these instances, protein synthesis-inhibitory agents, including clindamycin or a macrolide, alone or in combination with cell wall-active agents, are recommended in severe cases [107–113]. Intravenous immunoglobulin (IVIG) is also suggested for use in patients with severe toxic shock syndrome (TSS) associated with streptococcal SSTIs [114,115]. In 2014, Linnér et al. [116] performed a comparative observational study on 67 patients with streptococcal TSS in Sweden to evaluate the effect of IVIG on 28-day survival. Twenty-three patients received IVIG therapy in addition to antibiotic agents with or without surgical debridement whereas 44 only received antibiotics with or without surgery. In terms of baseline demographics and interventions, the IVIG cohort was younger, more likely to have necrotizing fasciitis and undergo surgery, and less likely to have erysipelas. Nearly 99% of patients received a β-lactam antibiotic, and more patients in the IVIG group also received clindamycin (91% vs. 70%), although this difference did not achieve statistical significance. The authors reported that IVIG therapy improves survival in streptococcal TSS patients, but this effect did not reach statistical significance in patients with concomitant necrotizing fasciitis.

Clostridial infections

Early aggressive antibiotic therapy and surgical debridement is recommended. [1C]

Frequent, repeated operative examination and debridement is recommended. [1C]

High-dose parenteral PCN (24 million U/day) is recommended for therapy, although carbapenems show excellent activity *in vitro*. [1C]

Considering treatment failures may occur with beta-lactam use alone in severe cases, administration of a protein synthesis-inhibitory antibiotic is suggested. [2C]

Clostridial infections are regarded as highly aggressive and rapidly fatal [1]. The most common species is *Clostridium perfringens*, which accounts for 70%–80% of infections [117]. *Clostridium* spp. are routinely found in soil samples, and infections were historically associated with traumatic wounds. More recently, however, *Clostridium* spp. have been linked to infections in patients injecting illicit drugs [118–120]. Clostridial infections are unique in that they can destroy healthy muscle, possibly through the release of multiple extracellular toxins [117]. Chief among these is alpha toxin, which can damage tissue, impede local immune responses to infection, and elicit deleterious systemic inflammatory responses [117,121].

Treatment of clostridial NSTIs mirrors that of other virulent etiologies. The most important objective and recommendation is early aggressive antibiotic therapy and surgical debridement. Frequent, repeated operative examination and debridement is also recommended. It should be remembered that these recommendations are not supported by high-level evidence. Although high-dose parenteral penicillin (24 million units per day) has long been recommended for therapy, carbapenems show excellent activity in vitro and are suggested for clinical use [1]. Considering treatment failures may occur after β-lactam use alone in severe cases, administration of a protein synthesis-inhibitory antibiotic is suggested [1]. High-dose clindamycin is suggested because it can neutralize clostridial toxins [110,122].

Vibrio infections

Early aggressive antibiotic therapy and surgical debridement is recommended. [1C]

Frequent, repeated operative examination and debridement is recommended. [1C]

Combination therapy with cell wall-active agents and tetracycline or minocycline is suggested for severe infections. [2C]

Use of cefotaxime and tetracycline or minocycline is suggested based on preclinical studies. [2C]

Vibrio spp. cause rapidly lethal NSTIs [123–128]. The most common species is *Vibrio vulnificus*, which is found predominantly in warm coastal waters, including the southern United States [123,124,127]. Because of its natural habitat, *Vibrio* spp. cause NSTIs primarily through exposure of traumatic wounds to seawater or seafood harboring the organism. Another mechanism is hematogenous seeding during primary bacteremia, which can result from ingesting contaminated seafood. Presenting symptoms often include cutaneous manifestations, such as hemorrhagic bullae, ecchymosis, and cellulitis [127]. Many patients have serious comorbidities that likely predispose them to infection, including chronic liver or kidney disease, diabetes, human immunodeficiency virus, and long-term steroid use [124,127].

Treatment of *Vibrio* NSTIs requires a high index of suspicion for success. Early aggressive antibiotic therapy and surgical debridement are recommended, as well as frequent, repeated operative examination and debridement [126,129]. As with other organisms, these recommendations are not supported by high-level evidence. The most appropriate antibiotic class is currently unknown. Based on in vitro and preclinical models, infections should respond to third-generation cephalosporins, carbapenems, fluoroquinolones, and tetracyclines [130–136]. Tetracycline and cefotaxime perform best in animal models [137]. For severe infections, combination therapy with cell wall-active agents such as cefotaxime plus tetracycline or minocycline is suggested [138–141]. Studies also support the efficacy of very high-dose regimens [139,140].

Community associated-MRSA

Unlike HA-MRSA, CA-MRSA isolates are susceptible to many non-beta-lactam antibiotics. CA-MRSA is also the most common cause of SSTI in a geographically diverse network of emergency departments. [1B]

For serious necrotizing infections associated with CA-MRSA, treatment with protein synthesis-inhibiting agents should be considered. [1C]

The gram-positive bacterium *Staphylococcus aureus* is an important cause of SSTIs, as well as the most commonly isolated bacterial pathogen in human beings [142]. Data

suggest that more than 20% of the population is colonized with the bacteria [143]. Over the last 30 years, changes in epidemiology have resulted in CA-MRSA being one of the most common strains. Community-associated MRSA can be distinguished from healthcare-associated (HA) strains molecularly and tends to cause infections in healthy individuals outside of the hospital environment. The main strain identified with causing infection in the community is USA300 MRSA, although MSSA does share similar genetic characteristics [144,145]. When comparing CA-MRSA to HA-MRSA isolates, the CA-MRSA isolates are more susceptible to non-β-lactam antibiotic agents and genetically distinct in that they contain a novel cassette element, SCCmec IV and PVL. Panton-Valentine leukocidin is a pore-forming exotoxin, known to induce cell death by apoptosis or necrosis [146].

Healthcare-associated MRSA isolates contain SCCmec I, II, and III. Because of these recent findings, MRSA has become a complex bacterium with both HA-MRSA and CA-MRSA being present in the hospital and community setting [17,147]. Methicillin-resistant *Staphylococcus aureus* can cause a wide spectrum of illness, including SSTIs, bacteremia, endocarditis, pneumonia, bone and joint infections, central nervous system disease, toxic shock, and sepsis syndromes. Its prevalence is profound having been found to be the most common cause of SSTI in a geographically diverse network of EDs in the United States as early as 2006 [148].

As a result of the emergence of CA-MRSA, ED visits and hospital admissions for SSTIs have increased dramatically [19,149]. For minor skin infections, mupirocin 2% topical ointment is effective. Previously, the treatment for simple abscesses was incision and drainage alone. Antibiotic agents were recommended for abscesses associated with severe or extensive disease, rapid progression of cellulitis, signs/symptoms of systemic illness, immunosuppression, extremes of age, associated comorbidities, difficult areas to drain, associated septic phlebitis, or no response to incision and drainage alone [150]. A prospective cohort study and secondary analysis of a previous randomized control trial found that cellulitis and abscess size did not predict treatment failures within seven days or which patients would have cultures positive for CA-MRSA. Furthermore, patients testing positive for MRSA were more likely to fail treatment within seven days of incision and drainage [151]. Based on these results and those of other recent randomized control trials in which some show lower recurrence rates and others improved cure rates when treated with additional antibiotics the recommendations have changed to include adjuvant antibiotic agents [70,71,73].

Empiric oral therapies that can be used to treat outpatient CA-MRSA SSTIs include TMP-SMX, doxycycline or minocycline, and linezolid [152]. Clindamycin is another oral option, but local clindamycin resistance rates should be considered prior to using this agent empirically. Linezolid is an effective alternative but is not superior to alternatives [153]. A study comparing linezolid and vancomycin found that both are clinically effective for the treatment of MRSA of all SCCmec types, both HA-MRSA SCCmec types I, II, and III, and CA-MRSA SCCmec type IV [146]. Outpatients presenting with purulent cellulitis without a drainable fluid collection should empirically receive oral antibiotic agents active against CA-MRSA, until culture data results [148]. In patients presenting with non-purulent cellulitis, current data suggests that β-hemolytic streptococci are the primary pathogens. These situations prove difficult because cultures cannot be obtained, therefore it is recommended to cover for CA-MRSA in those patients who do not respond to β-lactam monotherapy or those with systemic toxicity. Patients who develop systemic toxicity or a rapidly worsening infection despite adequate oral antibiotic agents, warrant admission with surgical intervention [154].

Antibiotic agents with anti-MRSA activity approved for the treatment of complicated SSTIs include vancomycin, linezolid, daptomycin, ceftaroline, omadacycline, delafloxacin, tedizolid, oritavancin, dalbavancin, telavancin, quinupristin/dalfopristin, and tigecycline [155]. As stated earlier, the choice to use one of these agents preferentially should be driven by multiple factors that cannot be accounted for in these recommendations. For a hospitalized patient with non-purulent cellulitis, a β-lactam can be used with modification to cover MRSA if there is no clinical response [154]. Duration of therapy is not well defined in the literature; duration of therapy should be individualized on the premise of patient's clinical response.

Recurrent SSTI is defined as two or more discrete SSTI episodes at different sites over a six-month period. The etiology is unclear, but usually involves a combination of pathogen, host colonization, patient behavior, and environmental exposure [156]. Colonization can play a vital role in the pathogenesis of recurrent SSTI, so prevention strategies have focused on the process of decolonization. This process utilizes antimicrobials and/or antiseptic agents to help eliminate *Staphylococcus aureus*, therefore preventing autoinfection or transmission. In regards to CA-MRSA, a study found that even though mupirocin decreased the prevalence of nasal colonization, it did not reduce the chance of first-time SSTI compared with placebo [157]. Resistance to mupirocin has been documented among MRSA isolates in the community setting [158]. Mupirocin alone or combined with topical antiseptic agents is recommended if decolonization is being considered.

Adjunctive therapies

What adjunctive therapies are available for treatment of NSTIs?

Hyperbaric oxygen

The current literature is insufficient to recommend the routine use of hyperbaric oxygen for the treatment of NSTIs. [2C]

Administration of hyperbaric oxygen (HBO) is intended as an adjunct to adequate surgical debridement and appropriate antibiotic therapy for NSTIs. There is no high-level evidence that demonstrate efficacy of HBO for NSTIs. One retrospective review reported a decrease in mortality and number of debridements after HBO therapy, whereas others found no differences in survival or need for surgery [159–161]. Case series exploring HBO for the treatment of Fournier gangrene lack adequate control groups [162,163]. No additional studies address the topic since publication of the previous guideline. The current literature is insufficient to recommend for or against the routine use of HBO in the treatment of NSTIs.

Intravenous immunoglobulin

The current literature does not support routine use of IVIG for the treatment of NSTIs. [2B]

Administration of IVIG is intended as an adjunct to surgical debridement and appropriate antibiotic therapy for NSTIs. Until recently, the literature supporting IVIG consisted of case reports describing combination therapy with surgery with or without antibiotic administration [164,165]. As discussed previously in the 2014 study by Linnér et al. [116], IVIG therapy improves survival in streptococcal TSS patients, but this effect did not reach statistical significance in patients with concomitant necrotizing fasciitis [116].

In 2017, Kadri et al. [166] performed a retrospective review of 4,127 cases from 130 U.S. hospitals of adult patients with necrotizing fasciitis and vasopressor-dependent shock caused by group A Streptococcus or *Staphylococcus aureus* undergoing surgical debridement [166]. The authors identified 164 patients who received IVIG therapy. The primary outcome was in-hospital mortality and the secondary outcome was median length of stay. Patients in the IVIG group were younger with lower comorbidity indices but had higher illness severity. In their propensity analysis, the authors found that neither in-hospital mortality nor median length of stay differed between groups.

In 2017, Madsen et al. [167] performed a randomized, blinded, placebo-controlled trial (Immunoglobulin G for patients with necrotizing soft tissue infection [INSTINCT]) on 100 ICU patients with NSTI to evaluate the effect of once-daily IVIG on self-reported physical activity and function six months after treatment. Of the 87 patients included in the final analysis, 42 received IVIG and 45 received placebo. The groups had similar baseline characteristics, although the IVIG group had higher rates of acute kidney injury. The authors found no difference in median physical component summary (PCS) score between groups at the six-month follow-up period. The remaining literature consists of case reports detailing use of IVIG therapy in combination with surgery with or without antibiotic administration [164,165]. Taken together, the current literature does not support the use of IVIG for the treatment of NSTIs.

Ibuprofen

The current literature is insufficient to recommend the routine use of ibuprofen in the treatment of SSTI. [2B]

Administration of a non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen is intended to halt the inflammatory process of cellulitis when used in conjunction with appropriate antibiotic therapy. The proposed benefit is thought to result from halting the response to the bacterial endotoxin rather than the bacteria itself, which are rapidly eliminated following antibiotic administration usually within 48 hours [168,169]. A single unblinded study by Dall et al. [170] showed a decrease in time to resolution when NSAIDs were administered, whereas Davis et al. [171] in a double-blinded randomized control trial showed no statistical difference between ibuprofen use and placebo as it relates to accelerating resolution of inflammation. The current literature is insufficient to recommend for the routine use of ibuprofen as an adjunct treatment in SSTI.

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