

# Skin and Soft-Tissue Infections: A Critical Review and the Role of Telavancin in Their Treatment

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Skin and soft-tissue infections (SSTIs) are an important cause of morbidity and mortality among hospitalized patients and a major therapeutic challenge for clinicians. Although uncomplicated SSTIs are managed successfully on an outpatient basis, more serious infections extending to the subcutaneous tissue, fascia, or muscle require complex management. Early diagnosis, selection of appropriate antimicrobials, and timely surgical intervention are key to successful treatment. Surgical-site infections, an important category of SSTI, occur in approximately half a million patients in North America annually. SSTIs are also a potential source for life-threatening bacteremia and metastatic abscesses. Gram-positive organisms, such as *Staphylococcus aureus* and *Streptococcus pyogenes*, are the dominant organisms isolated early in the infectious process, whereas gram-negative organisms are found in chronic wounds. Methicillin-resistant *S. aureus* (MRSA) is a potential bloodstream invader that requires aggressive antimicrobial treatment and surgery. Recent concerns regarding vancomycin activity include heteroresistance in MRSA and increase in the minimum inhibitory concentrations (>1 or 2 µg/mL); however, alternative agents, such as telavancin, daptomycin, linezolid, ceftaroline, dalbavancin, oritavancin, and tedizolid, are now available for the treatment of severe MRSA infections. Here, we present a review of the epidemiology, etiology, and available treatment options for the management of SSTIs.

**Keywords.** telavancin; skin infections; soft-tissue infections; cellulitis; necrotizing infections.

Skin and soft-tissue infections (SSTIs) encompass a broad set of conditions encountered frequently in clinical practice [1]. SSTIs have been classified as complicated or uncomplicated [2], with a range of severity from simple subcutaneous abscesses to severe necrotizing infections. Uncomplicated infections are superficial, often self-limiting, and can usually be treated successfully by incision and drainage alone or in combination with oral antibiotics [1]. The complicated SSTIs (cSSTIs) extend to subcutaneous tissue, fascia, or muscle [3] and require complex treatment, combining careful selection of antimicrobials with expeditious surgical intervention. As a potential source for bacteremia and metastatic abscesses, SSTIs may be both limb and life threatening [4, 5].

In 2013, the US Food and Drug Administration (FDA) finalized its guidance for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) [6]. The definition of an ABSSSI now includes cellulitis/erysipelas, wound infection, and major cutaneous abscess with a minimum lesion surface area of approximately 75 cm<sup>2</sup>. In addition, an efficacy end point of 20% reduction in area of infection at day 3 of treatment has been established. In general, ABSSSI describes a broader cohort of infections, including some of lesser severity, than does complicated skin and skin structure infection (cSSSI), but there remains considerable overlap [1]. Omitted from this 2013 definition are diabetic foot infections, decubitus ulcers, infected burns, and myonecrosis. Because underlying disease and degree of severity at the outset are major contributors to therapeutic response to antimicrobials, the differences between ABSSSI and cSSSI, albeit subtle, are important. Seeking further clarity in definition, in January 2015, the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) Surveillance recommended a set of criteria that must be met for skin (skin and/or

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**Table 1. Centers for Disease Control and Prevention/National Healthcare Safety Network Surveillance Definitions for Specific Types of Infections<sup>a</sup>**

Skin infections (skin and/or subcutaneous) should meet  $\geq 1$  of the following criteria:

- Patient has purulent drainage, pustules, vesicles, or boils (excluding acne)  
OR
- Patient has  $\geq 2$  of the following localized signs or symptoms with no other recognized cause:
  - Pain or tenderness
  - Swelling
  - Erythema, or heat
- AND  $\geq 1$  of the following:
  - (1) Organisms cultured from aspirate or drainage from affected site (not a common commensal); if the only organism is a common commensal (ie, diphtheroids [*Corynebacterium* spp.], *Bacillus* [not *Bacillus anthracis*] spp., *Propionibacterium* spp., coagulase-negative staphylococci [including *Staphylococcus epidermidis*], viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp.), culture must be pure (single organism identified)
  - (2) Positive nonculture diagnostic laboratory test performed on infected tissue or blood (eg, antigen test, polymerase chain reaction)
  - (3) Multinucleated giant cells seen on microscopic examination of affected tissue
  - (4) Diagnostic single antibody titer (immunoglobulin M) or 4-fold increase in paired sera samples (immunoglobulin G) for organism.

Soft-tissue infections of muscle and/or fascia must meet  $\geq 1$  of the following criteria:

- Patient has organisms cultured from tissue or drainage from affected site, or
- Patient has purulent drainage at affected site, or
- Patient has an abscess or other evidence of infection at gross anatomic or histopathologic examination

<sup>a</sup> Definitions from Centers for Disease Control and Prevention [7].

subcutaneous) and soft-tissue infections (muscle and/or fascia, eg, necrotizing fasciitis, infectious gangrene, necrotizing cellulitis, infectious myositis, and lymphadenitis or lymphangitis) (Table 1) [7].

## EPIDEMIOLOGY

Given the variable presentation of SSTIs and the frequency of recurrent episodes, an accurate assessment of their incidence and prevalence has been difficult [8]. Nevertheless, in a 3-year retrospective study, the incidence of clinically diagnosed SSTIs was calculated as nearly 500 episodes per 10 000 person-years [9]. Among hospitalized patients, the estimated prevalence of SSTIs is 7%–10% [8, 10], with an increase of 29% reported for the total number of annual SSTI admissions to US acute-care hospitals from 2000 to 2004 [11] and an increase of 123% for *S. aureus*-SSTI-associated hospitalizations between 2001 and 2009 [12].

Surgical-site infection (SSI) is a specific type of skin-structure or deep-space infection that occurs at the incision or in the field of an invasive procedure within 30 days after operation (1 year for an implant) [3]. SSIs are the most common healthcare-associated infection (HAI), accounting for 31% of all HAIs among hospitalized patients, affecting >500 000 patients annually and leading to an estimated 8000 annual deaths [13–18]. The CDC HAI prevalence survey found an estimated 157 500 SSIs associated with inpatient procedures in 2011 [19, 20]. NHSN data for 2006 to 2008 (16 147 SSIs after 849 659 operative procedures) showed an overall SSI rate of 1.9% [17]. Thus, it has been estimated that patients with a diagnosis of SSI face prolonged hospital stays, treatment-associated risks, and potential

long-term sequelae, as well as a 2–11-fold increase in mortality [14, 21–24].

## ETIOLOGY

Cellulitis is a skin infection that develops as a result of bacterial invasion via breaches in the skin barrier [25]. Predisposing factors include disruption of the skin barrier as a result of trauma (eg, insect bites, abrasions, penetrating wounds, or injection drug use). In a multivariate analysis, disruption of the cutaneous barrier (eg, leg ulcer, wound, fissured toe-web intertrigo, pressure ulcer, or leg dermatosis) was identified as one of the most important factors, along with lymphedema, for the development of cellulitis (odds ratio, 23.8; 95% confidence interval [CI], 10.7–52.5) [26]. Other risk factors include chronic inflammation (eg, eczema or radiation therapy), preexisting skin infection (eg, impetigo or tinea pedis), varicella, and edema due to venous insufficiency [26, 27].

SSTIs, including abscesses and cellulitis, are the most common cause of hospital admission for subcutaneous and intravenous drug users (IDU) [28]. Subcutaneous or intramuscular injection is a major risk factor for abscesses among IDUs [29]. In 2001, the CDC reported that 54 of 169 IDUs (32%) in one San Francisco neighborhood had a drug-injection-related abscess or cellulitis [30]. Nevertheless, this risk may be lessened with the introduction of needle exchange programs that exist nationwide today. In 2009, 28% of IDUs in the United Kingdom reported an injection-site infection, ranging from uncomplicated cellulitis and localized abscesses to life-threatening necrotizing fasciitis and severe sepsis [31].

Diabetes mellitus, complicated by arterial occlusive disease and neuropathy, is a major risk factor for the development of SSTI [32]. In a North American study, individuals with diabetes were 1.5 times more likely to develop cellulitis compared with those without diabetes [32]. In another investigation, those with type 1 or type 2 diabetes were 1.6 and 1.3 times more likely to develop an SSTI, respectively, than those without diabetes [33]. More recently, Suaya et al [34] reported that between 2005 and 2010 abscess/cellulitis was the more common SSTI group in diabetic and nondiabetic individuals (66% and 59%, respectively), with significant differences in the frequencies of SSTI categories between diabetic and nondiabetic individuals ( $P < .01$ ).

Among SSTIs diagnosed in ambulatory settings, the SSTI-associated complication rate was >5 times higher in persons with diabetes than in those without diabetes (4.9% vs 0.8%;  $P < .01$ ), and SSTI-associated hospitalization rates were 4.9% and 1.1% in patients with or without diabetes, respectively. SSTIs diagnosed in the inpatient setting (including bacteremia, endocarditis, septicemia, and sepsis) were the most common associated complications, occurring in 25% of SSTIs in patients with diabetes and 16% of those without diabetes ( $P < .01$ ) [35].

## MICROBIOLOGY

The cSSSIs are caused predominantly by gram-positive pathogens, such as *S. aureus* and *Streptococcus pyogenes* [21]. However, a diverse etiology may be associated with some cSSSI, including gram-positive, gram-negative, and mixed infections. The causative pathogen for cSSSI is dependent on a number of factors, including infection severity and duration, microbial virulence, clinical setting, geographic location, initiating process, and host defenses. Early SSTIs are often caused by gram-positive organisms, whereas chronic infections, such as those of the diabetic foot, yield gram-negative and even anaerobic flora.

In many SSTI episodes, specimens for culture are not obtained, leading to some uncertainty about the most common causes of SSTIs, although *S. aureus* and  $\beta$ -hemolytic streptococci are the predominant pathogens found in culture-confirmed SSTIs [4, 10, 35, 36]. In North America, the most common pathogens found are *S. aureus*, and of these, almost 50% are methicillin-resistant *S. aureus* (MRSA) [37]. *Pseudomonas aeruginosa*, *Enterococcus* spp., and *Escherichia coli* have also been identified as important causes [8, 38–42]. After *S. aureus*, the most common pathogens found were  $\beta$ -hemolytic streptococci (9%), *E. coli* (4%), and *P. aeruginosa* (3%). Among  $\beta$ -hemolytic streptococci isolates, 44% were Lancefield group A, 45% group B, 3% group C, and 8% group G. Gram-negative bacteria of any kind were identified in 15% of SSTI episodes with a positive culture and are more often seen in chronic or postoperative wounds [37].

The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance program, a study of cSSSI isolates from 27 US medical centers collected in 2008, reported *S. aureus* (46.9%), *Enterococcus* spp. (14.2%), and *E. coli* (12.7%) as the most frequent bacteria isolated [43]. Similarly, in 2012, the AWARE program evaluated isolates from 163 US medical centers and reported *S. aureus* (55.5%), *E. coli* (5.9%), and *Klebsiella* spp. (5.5%) as the most frequently identified bacteria [44].

With regard to SSIs, surveillance data demonstrate a shift toward gram-positive pathogens, with common causative pathogens being *S. aureus* (33%), coagulase-negative staphylococci (11%), enterococci (8%), and *E. coli* (6%) [45]. Nevertheless, SSI cultures may be influenced by several external factors, including exogenous gram-positive flora, endogenous enteric pathogens (eg, *Enterococcus faecalis* or Enterobacteriaceae), or nosocomial pathogens within an institution, typically the intensive care setting [46]. MRSA has been historically limited to infections in patients with exposure to healthcare environments, but is now identified commonly in patients without this risk factor [47]. Such infections have been identified as community-acquired MRSA (CA-MRSA), now a major causative pathogen associated with cSSSI in the United States [40, 43, 45, 48–50].

*Enterococcus* spp. represent a substantial proportion of pathogens causing cSSSI, particularly after intra-abdominal surgery [40, 43]. Between 1998 and 2004, *Enterococcus* spp. increased from 8.3% to 9.8%, with an increase in vancomycin resistance from 8.6% to 14.8% of *Enterococcus* spp. isolates [40]. Risk factors for vancomycin-resistant *Enterococcus* infections include extended hospitalization, advanced age, severe underlying illness, interhospital transfer, and antibiotic exposure to vancomycin, third-generation cephalosporins, metronidazole, or other antianaerobic antibiotics [51].

Gram-negative pathogens, such as Enterobacteriaceae and *P. aeruginosa*, are isolated less frequently than gram-positive organisms from patients with cSSSI [40]. Resistant gram-negative pathogens, such as extended-spectrum  $\beta$ -lactamases (ESBLs), including *E. coli* and *Klebsiella* spp., are emerging, and the prevalence of bacteria expressing the ESBL phenotype is increasing. In 1998, 3.5% of *E. coli* and 4.9% of *Klebsiella* spp. were the ESBL phenotype, increasing to 12.8% of *E. coli* and 16.3% of *Klebsiella* spp. in 2004 [48].

The most lethal presentation of soft-tissue infection is necrotizing fasciitis, an infection of the deeper tissues that results in progressive destruction of the muscle fascia and overlying subcutaneous fat [52]. Most cases of necrotizing fasciitis are caused by gram-positive cocci and involve a single site of soft-tissue infection; multifocal necrotizing fasciitis has also been described [53]. In advanced infection, fever, tachycardia, and systemic toxicity are generally observed, with temperature elevation in the range of 38.9°–40.5°C (102°–105°F).

Type I necrotizing fasciitis is a mixed infection caused by aerobic and anaerobic bacteria. It occurs in the head and neck region or in the perineum (Fournier gangrene). Synergistic necrotizing cellulitis is a variant of necrotizing fasciitis type I that involves the skin, muscle, fat, and fascia. It usually occurs on the legs or perineum; diabetes is a known risk factor [52].

Type II necrotizing fasciitis is generally monomicrobial. It is typically caused by group A *Streptococcus* or other  $\beta$ -hemolytic streptococci, either alone or in combination with other pathogens, most commonly *S. aureus*; it has also been referred to as “streptococcal gangrene” [54]. Rapid progression is a hallmark of both types of necrotizing fasciitis. The mortality rates in different studies have included 21% in type I necrotizing fasciitis and 14%–34% in type II necrotizing fasciitis (in which streptococcal toxic shock syndrome is commonly associated with increased mortality) [55–57].

### ASSESSING THE SEVERITY OF SSTI

Efforts have been made to accurately classify the severity of SSTIs to predict morbidity, mortality, and response to antibiotic treatment. Predictors of severity include location and extent of infection, laboratory and microbiologic data, as well as concomitant disease. For example, in a retrospective study of 166 patients from Seattle who were diagnosed with necrotizing soft-tissue infections, the overall mortality rate was 17% [58]. Predictors of mortality after multivariate analysis included white blood cell count  $>30\,000/\mu\text{L}$ , serum creatinine level  $>2.0\text{ mg/dL}$  (177 mmol/L), clostridial infection, and the presence of heart disease on admission. In a second retrospective study from Taiwan, predictors of mortality included cirrhosis of the liver, soft-tissue air, *Aeromonas* infection, age  $>60$  years, band neutrophils  $>10\%$ , activated partial thromboplastin time  $>60$  seconds, bacteremia, and creatinine level  $>2\text{ mg/dL}$  [59]. The length of time from admission to surgery did not affect mortality, probably because surgical treatment in all patients was instituted within 24 hours of admission. In earlier studies, a delay in surgery of  $>24$  hours was a risk factor for mortality [60]. In general, infections involving the head, neck, thorax, and abdomen are associated with greater mortality due to difficulty in surgical debridement. Among patients with necrotizing fasciitis, the mortality rate is higher in patients with streptococcal toxic shock syndrome. This was illustrated in a series of 62 patients with group A streptococcal necrotizing fasciitis; the 52% who had streptococcal toxic shock syndrome experienced a significantly higher mortality rate (28% vs 8%) [61].

Wilson et al [62] developed a scoring system using data from a phase 3 study comparing antibiotics in hospitalized patients with cSSTIs. In study A ( $n = 682$ ), cure rates were lower in patients with  $\geq 1$  comorbid condition ( $P < .05$ ) and in the highest risk class ( $P = .05$ ). Elevated blood urea nitrogen, hyponatremia,

anemia, lesion size, and surgical wound infection were independent predictors of failure ( $P < .05$ ). In study B ( $n = 166$ ), findings were similar and significant for risk class ( $P < .05$ ). This validated risk assessment identified patients with higher severity scores who generally had poorer outcomes regardless of treatment group.

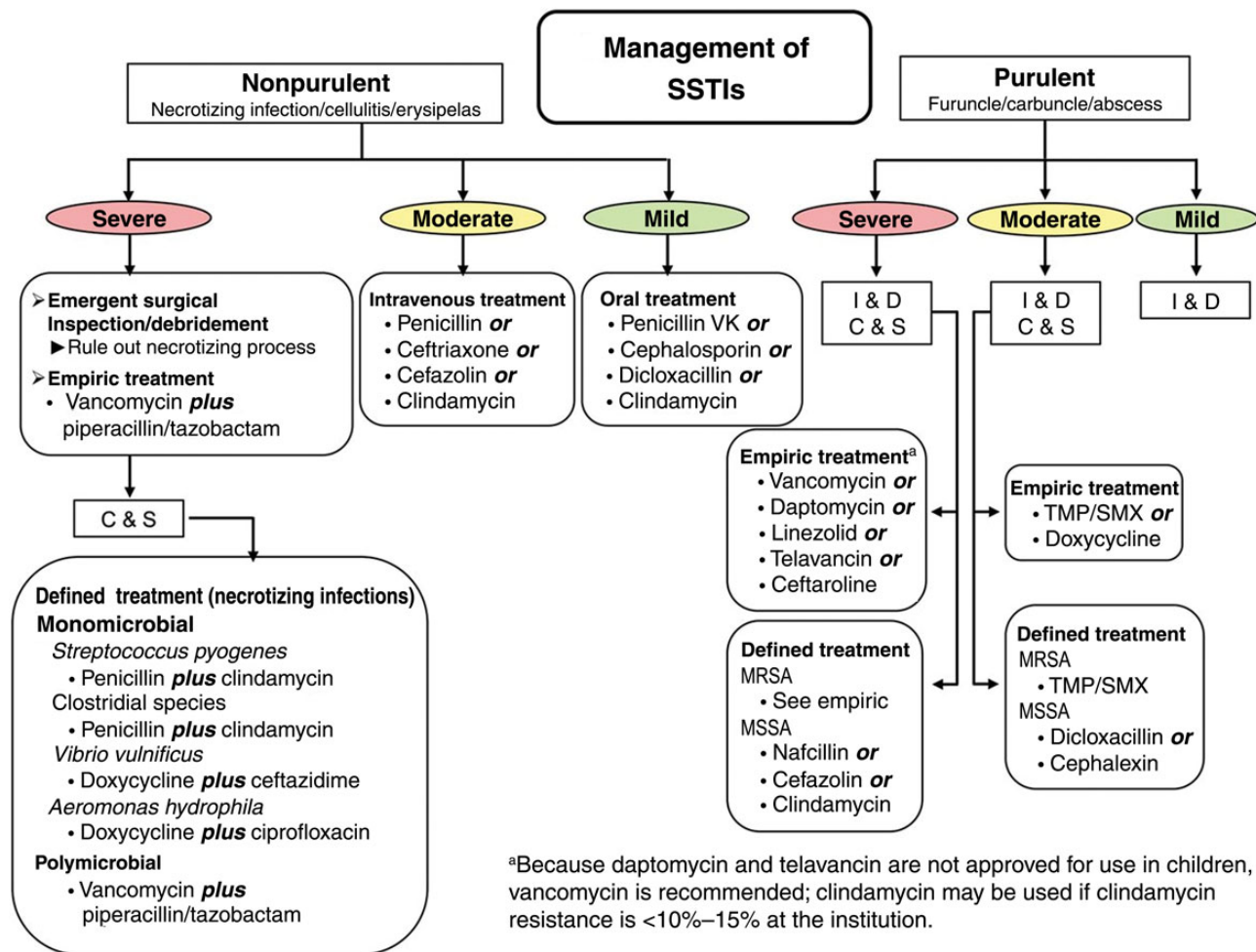
### TREATMENT

Effective management of cSSSI includes systemic antimicrobial therapy and surgical debridement or drainage [4, 5, 11, 46]. Important first steps in the treatment of cSSSI are prompt recognition, diagnosis, mapping of cellulitis margins, and obtaining specimens for culture and susceptibility, preferably not by superficial swab, which can be contaminated by commensal skin organisms [3]. Photographs of the lesion are invaluable to substantiate radical operation, or for that matter, no operation. Treatment begins with initiation of appropriate empiric antimicrobial therapy for likely pathogens, largely based on the area infected and Gram stain, as soon as infection is suspected. Depending on the particular infection, surgical drainage and debridement may be necessary. The surgeon should obtain wound or tissue samples for culture if possible, or an aliquot of pus aspirated directly from an abscess into a capped air-evacuated syringe, to minimize the possibility of contamination. Culture and susceptibility data should be reviewed as soon as available and deescalation of antibiotic therapy (ie, change to an agent of narrower spectrum) should be ordered when appropriate. Frequent evaluations after starting antibiotic therapy, or returning to the operating room within 24 hours (in cases of necrotizing infection) to ensure adequacy of debridement, may be necessary.

In 2009, the Surgical Infection Society developed useful guidelines for the treatment of severe SSTI [63]. In the intact host, uncomplicated skin infections respond well to incision and drainage and, depending on the degree of local inflammation, erythema, and tenderness, may or may not require oral antibiotics. Conversely, cSSSIs are more severe and always require empiric antibiotic therapy to cover likely pathogens. Clinical presentation, history, physical examination, and anatomic site can be used to determine the likely pathogen and to direct empiric antibiotic therapy.

The Infectious Diseases Society of America updated its guidelines for SSTI management in 2014 [5]. In general, clinical evaluation to establish the cause and severity of infection, and pathogen-specific and local antibiotic resistance patterns, must all be taken into account (Figure 1). It is recommended that patients with signs and symptoms of systemic toxicity undergo laboratory testing, including blood culture and susceptibility tests; complete blood cell count with differential; and serum creatinine, bicarbonate, creatinine phosphokinase, and C-reactive protein





**Figure 1.** For purulent skin and soft-tissue infections (SSTIs), incision and drainage is indicated for mild infection; moderate infection include systemic signs of infection; and severe infection includes failed incision and drainage plus oral antibiotics or systemic signs of infection, such as temperature >38°C, tachycardia (pulse rate >90/min), tachypnea (respirations >24/min), or abnormal white blood cell count (<12 000 or <400 cells/μL), or immunocompromise. For nonpurulent SSTIs, mild infection includes typical cellulitis/erysipelas with no focus of purulence; moderate infection, typical cellulitis/erysipelas with systemic signs of infection; and severe infection, failed oral antibiotic treatment, systemic signs of infection as defined above for purulent infection, immunocompromise, or clinical signs of deeper infection (eg, bullae, skin sloughing, hypotension, and evidence of organ dysfunction). Two newer agents, tedizolid and dalbavancin, are also effective agents in SSTIs, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Reproduced with permission of Oxford University Press and the Infectious Diseases Society of America from Stevens et al [5]. Abbreviations: C & S, culture and sensitivity; I & D, incision and drainage; MSSA, methicillin-susceptible *S. aureus*; TMP/SMX, trimethoprim-sulfamethoxazole.

concentrations. If the infection is severe, the patient should be hospitalized. Gram stain, rapid diagnostic tests (polymerase chain reaction), culture, and antimicrobial susceptibility should be used to guide therapy. Rapid diagnostic tests may be useful for early identification of *S. aureus*, particularly in abscesses and other infections where there is access to purulent fluids. In 2011, the Infectious Diseases Society of America developed guidelines specifically for MRSA infections [64]. For cSSSIs that require hospitalization, recommendations include surgical debridement and broad-spectrum empiric antimicrobial therapy that includes coverage for MRSA, pending culture data. Failure of initial antimicrobial therapy for hospitalized patients with

cSSSI increases the risk of morbidity and mortality, the hospital length of stay, and the overall cost of treatment [65].

Vancomycin remains the most frequently prescribed treatment for serious MRSA infections and is now the second most common antibiotic used in hospitals (Table 2) [66]. In 50 years of use, few clinical MRSA strains with complete vancomycin resistance have been identified, but there are several concerns about vancomycin, such as heteroresistance in MRSA (small numbers of organisms with high vancomycin minimum inhibitory concentrations [MICs]), and “MIC creep,” which describes an increase in recent years in numbers of clinical isolates of both MRSA and methicillin-susceptible *S. aureus* with

**Table 2. Clinical Results of Telavancin or Standard Therapy for the Treatment of Complicated Skin and Soft-Tissue Infections<sup>a</sup>**

Name of Study	Phase 2, FAST 1			Phase 2, FAST 2			Phase 3, ATLAS		Difference in Cure Rate, % (95% CI) <sup>d</sup>
	Telavancin (7.5 mg/kg)	Standard Therapy <sup>b</sup>	<i>P</i> Value <sup>c</sup>	Telavancin (10 mg/kg)	Standard Therapy	<i>P</i> Value	Telavancin (10 mg/kg)	Vancomycin (1 g/12 h)	
No. of patients	84	83	...	100	95	...	928	939	...
Patient age, mean (SD), y	44.6 (13.9)	44.3 (13.5)	...	44.7 (13.7)	42.3 (10.9)	.18	48.8 (16.6)	48.7 (16.6)	...
All treated, achieved cure	66/84 (79)	66/83 (80)	.53	82/100 (82)	81/95 (85)	.37	710/928 (76.5)	697/939 (74.2)	2.3 (−1.6 to 6.2)
Infected with <i>Staphylococcus aureus</i> , achieved cure	40/50 (80)	40/52 (77)	.80	48/50 (96)	37/41 (90)	.36	...	...	...
Infected with MRSA, achieved cure	18/22 (82)	18/26 (69)	1.00	25/26 (96)	17/19 (90)	.42	252/278 (90.6)	260/301 (86.4)	4.1 (−1.1 to 9.3)
Clinically evaluable, achieved cure	66/72 (92)	66/69 (96)	.53	74/77 (96)	72/77 (94)	.53	658/745 (88.3)	648/744 (87.1)	1.2 (−2.1 to 4.6)
Microbiologically evaluable, achieved cure	52/56 (93)	53/56 (95)	.79	62/64 (97)	53/77 (93)	.37	...	...	...
Microbiologic eradication of gram-positive pathogens at TOC	44/56 (80)	46/56 (82)	.53	46/50 (92) <sup>e</sup>	32/41 (78) <sup>e</sup>	.07	473/527 (89.8)	468/536 (87.3)	(−1.4 to 6.2)
Microbiologic eradication of MRSA at TOC	16/19 (84)	14/19 (74)	.83	24/26 (92)	13/19 (68)	.04	250/278 (89.9)	257/301 (85.4)	(−0.9 to 9.8)
Adverse events	47/84 (56)	50/83 (60)	...	56/100 (56)	54/95 (57)	1.0	735/928 (79)	676/939 (72)	...
Severe adverse events	3/84 (4)	6/83 (7)	...	6/100 (6)	4/95 (4)	...	69/928 (7)	42/939 (4)	...

Abbreviations: ATLAS, Assessment of Telavancin in Skin and Skin Structure Infections; CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; TOC, test of cure.

<sup>a</sup> Republished with permission of *Infection and Drug Resistance* from Jafari Saraf and Wilson [66]. Unless otherwise indicated, values represent No. with finding/total No. (%).

<sup>b</sup> Standard therapy: vancomycin (1 g/12 h), nafcillin or oxacillin (2 g/d), or cloxacillin (0.5–1 g/6 h).

<sup>c</sup> *P* values determined with the Bernard unconditional test of superiority. Indeterminate values were excluded from the calculations.

<sup>d</sup> Difference between proportions of patients who were cured with telavancin and with vancomycin.

<sup>e</sup> In this evaluation only *Staphylococcus aureus* pathogen was considered.

vancomycin MIC  $\geq 2$   $\mu\text{g/mL}$  (strains now considered only intermediately sensitive to vancomycin). Prolonged MRSA bacteremia has been observed in some patients despite adequate vancomycin levels; however, no study has shown a benefit of higher concentrations. The standard regimen of intravenous vancomycin is 1 g every 12 hours, and plasma/serum antibiotic levels need to be confirmed by assay. Dose adjustments must be made when using vancomycin in patients with impaired renal function. Alternatives to vancomycin include telavancin (10 mg/kg/d), linezolid (600 mg every 12 hours), daptomycin (6–8 mg/kg/d), clindamycin (600 mg every 8 hours), or trimethoprim-sulfamethoxazole (10/50 mg/kg/d) [67–70]. Dalbavancin, oritavancin, ceftaroline, tedizolid, tigecycline, and doxycycline are also alternatives to vancomycin.

Antibiotics for treatment of nosocomial MRSA strains are usually limited to vancomycin, telavancin, linezolid, daptomycin, ceftaroline, and tigecycline. Although USA300 strains continue to dominate community-acquired forms of *S. aureus* infection, they are found with increasing frequency in hospital settings and are increasingly resistant to antibiotics, including tetracycline and clindamycin [67].

For outpatient treatment of CA-MRSA infections, trimethoprim-sulfamethoxazole, minocycline, doxycycline, or clindamycin may be appropriate, depending on the severity of the illness and susceptibility of the organism [71–73]. However, the increasing prevalence of inducible macrolide-lincosamide-streptogramin B resistance/inducible clindamycin resistance among MRSA strains may limit the use of clindamycin in the

treatment of CA-MRSA infections [74]. Telavancin, dalbavancin, and oritavancin are lipoglycopeptides that kill *S. aureus* rapidly in a concentration-dependent manner in vitro [75]. Two cephalosporins, ceftobiprole (not FDA approved) and cef-taroline, have been shown to be clinically effective for treatment of SSTIs. Glycopeptide, glycolipopeptide derivatives of vancomycin, and anti-MRSA  $\beta$ -lactams can only be administered intravenously. However, orally bioavailable oxazolidinones such as linezolid or tedizolid (approved for skin infections in 2014) are active against MRSA [76–79]. Tigecycline may have limited efficacy in patients with secondary/concurrent bacteremia owing to low serum levels [80] and its mainly bacteriostatic activity [81].

## CLINICAL TRIALS OF TELAVANCIN

Telavancin is an injectable, semisynthetic lipoglycopeptide derivative of vancomycin that is bactericidal against staphylococci, streptococci, and vancomycin-susceptible enterococci. It has a dual mechanism of action that inhibits bacterial cell wall synthesis, by interfering with peptidoglycan synthesis, and disrupts membrane barrier function, by binding to the bacterial membrane. This dual mechanism potentiates telavancin activity against staphylococcal strains with increased resistance to vancomycin. Telavancin is also effective against strains resistant to linezolid and daptomycin.

The ATLAS (Assessment of Telavancin in Skin and Skin Structure Infections) program, consisting of 2 phase 3 clinical trials, demonstrated noninferiority of telavancin to vancomycin for the treatment of cSSSIs, including infections due to MRSA. These were the largest trials of cSSSI and enrolled more patients infected with MRSA than any such trials at the time. Telavancin (10 mg/kg intravenously every 24 hours, adjusted for renal function) was compared with vancomycin (1 g intravenously every 12 hours), which could be adjusted for renal function, body weight, and serum level monitoring as long as the study blind was not compromised. Among the nearly 1500 clinically evaluable patients, the clinical cure rate was 88.3% for patients treated with telavancin and 87.1% for those who received vancomycin. Of the 579 clinically evaluable patients infected with MRSA at baseline, 252 of 278 patients (90.6%) treated with telavancin and 260 of 301 patients (84.4%) treated with vancomycin were cured (95% CI for the difference,  $-1.1\%$  to  $9.3\%$ ). Among the 1603 patients evaluated for overall therapeutic response (cure plus microbiologic eradication), 88.6% and 86.2% of patients in the telavancin and vancomycin groups, respectively, were cured, with pathogens eradicated at test of cure (95% CI for the difference,  $-1.6\%$  to  $6.4\%$ ). Among clinically evaluable patients who had MRSA isolated at baseline, the overall therapeutic response was numerically higher with telavancin than with vancomycin (89.9% vs 84.7%; 95% CI for the

difference,  $-0.3\%$  to  $10.5\%$ ). The most common treatment-emergent adverse events with telavancin were taste disturbance (33%), nausea (27%), vomiting (14%), and foamy urine (13%, unrelated to proteinuria). Nausea and vomiting were mild to moderate in severity, leading to discontinuation in only approximately 1% of patients. Renal adverse events occurred in 3% of telavancin-treated patients and 1% of vancomycin-treated patients [82]. Telavancin was approved in the United States and Canada in 2009 and is indicated for the treatment of cSSSIs caused by susceptible isolates/strains of gram-positive bacteria, including *S. aureus*, both methicillin-susceptible *S. aureus* and MRSA [83, 84].

Wilson et al [85] compared telavancin with vancomycin for the treatment of cSSSIs associated with surgery and caused by gram-positive bacteria. This retrospective analysis assessed test of cure (7–14 days after completing therapy) in a subset of 194 patients from the ATLAS program, including 101 patients treated with telavancin and 93 treated with vancomycin. Baseline characteristics were similar for both treatment groups. Clinical cure and microbiologic eradication demonstrated consistent trends favoring telavancin over vancomycin; however, the differences were not statistically significant. The incidence of adverse events was mostly similar between groups. The authors concluded that the efficacy of telavancin was not inferior to that of vancomycin for the treatment of cSSSI associated with surgery. These data suggest that telavancin may be a useful alternative for treatment of cSSSI caused by *S. aureus*, particularly MRSA.

## DISCUSSION

In the past 2 years, more precise definitions of SSTIs have been developed by the FDA and the CDC NHSN Surveillance programs. Although designed for clinical trial entry criteria, these more accurate descriptions provide the practitioner guidelines on severity of infections likely to require hospitalization and parenteral antimicrobials. SSTIs are now a serious cause of morbid conditions and amputation in diabetics, immunocompromised persons, substance abusers, and the homeless. Although the rates of postoperative infections in healthy individuals are lower, the overall incidence is unchanged due to the age and higher risk status in patients undergoing operations. Indeed, the results of the Surgical Care Improvement Project are decidedly mixed [21].

Gram-positive organisms are still the dominant pathogens in SSTIs, and MRSA comprises almost 50% of *S. aureus* isolates. Accordingly, SSTIs of a severity requiring hospitalization and antimicrobials should be treated with an agent effective against MRSA until susceptibility data are available. Gram-negative and drug-resistant pathogens are usually present in long-standing infection, particularly in the chronic diabetic foot infection. In these infections time allows detection of pathogens;

therefore, antimicrobial selection can be determined based on susceptibility data.

Although vancomycin remains an effective agent for MRSA SSTI infection as demonstrated by the results of clinical trials, there is growing awareness of heterogeneity and MIC “creep,” and concerns about its effectiveness. Further, vancomycin is frequently used for surgical prophylaxis, which may accelerate these changes and further decrease its activity.

Newer anti-MRSA agents with excellent activity include telavancin (MIC<sub>90</sub>, 0.05–0.1 µg/mL) [86]. This agent may be useful in patients who have failed treatment with vancomycin or have recurrent *S. aureus* infections after recent vancomycin therapy. Consideration of alternatives to vancomycin should be contemplated when susceptibility data show vancomycin MIC<sub>90</sub> values above 1 µg/mL. Dose adjustment of telavancin is essential for patients in whom creatinine clearance is decreased and falls below 50 mL/minutes.

In summary, severe acute bacterial SSTIs require hospitalization, intravenous antibiotics effective against MRSA, and often surgical drainage and debridement. In addition to vancomycin, several new agents including telavancin, which is rapidly bactericidal, show high levels of activity against MRSA and should be considered in selected patients.

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