Is there still a role for vancomycin in skin and soft-tissue infections?

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Purpose of review
Skin and soft-tissue infections (SSIs) are among the commonest infections encountered in clinical practice. Spread of methicillin-resistant *Staphylococcus aureus* SSIs continues to increase in both health care and community settings and presents a challenge for the best treatment choice. Vancomycin has been the mainstay of SSIs treatment, but recently its use has been questioned because of concerns about its efficacy, tolerability, and unfavorable pharmacokinetic/pharmacodynamic profile. The purpose of this review is to establish the current role for vancomycin in light of the literature published from January 2007 to September 2017 on comparison with both old and new alternatives.

Recent findings
Meta-analyses show better clinical and microbiological outcomes for drugs approved for the treatment of SSI, including those sustained by methicillin-resistant *S. aureus*, in the last 10 years than for vancomycin. The newer glycopeptides and linezolid decrease the total treatment costs compared with vancomycin, by reducing the length of stay or avoiding the hospitalization.

Summary
Vancomycin is noninferior in efficacy and safety to all comparator drugs, including the newest on the market. However, the SSI treatment evidence base presents several shortcomings limiting the clinical applicability of the results. High-level clinical trials should be performed to obtain results that can be generalized and applied effectively in clinical practice.

Keywords
acute bacterial skin and skin-structure infections, methicillin-resistant *Staphylococcus aureus*, skin and soft-tissue infections, vancomycin

INTRODUCTION

Vancomycin is a glycopeptide produced by the fermentation of *Amycolatopsis orientalis*. Its bactericidal activity is cell-wall synthesis inhibition in Gram-positive cocci and bacilli [1]. Clinical use started in 1956 with the treatment of penicillin-resistant *Staphylococcus aureus*, and it is currently indicated for the treatment of severe infections, including skin and soft-tissue infections (SSIs) caused by susceptible strains of methicillin-resistant staphylococci, and for penicillin-allergic patients [2]. SSI burden varies with the setting of infection acquisition, patient comorbidities, diagnostics and antibiotics availability, and the etiological agent's susceptibility [3]. Methicillin-resistant *S. aureus* (MRSA), first recognized in the 1960 as a hospital-acquired pathogen, has become a major cause of SSIs worldwide [1,4]. These strains carry the larger staphylococcal cassette chromosome (SCC) mec types I, II, and III, conferring resistance toward several antibiotic classes in addition to penicillin and methicillin [5]. Community-acquired MRSA (CA-MRSA) strains emerged in the 1990s generally in young, healthy individuals without previous exposure to healthcare institutions [6,7]. Although CA-MRSA can cause also severe and invasive infections [8,9], SSI remain the predominant infection site [10]. Compared with hospital-acquired-MRSA, CA-MRSA isolates contain smaller SCCmec (type IV or V) mutations that limit resistance exclusively to methicillin and may produce an exotoxin. Panton–Valentine leukocidin is

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KEY POINTS

- SSI represent one of the commonest infections encountered in clinical practice and contribute to substantial morbidity and healthcare costs.
- Vancomycin use in clinical practice is limited because of its clinical efficacy, tolerability profile, and pharmacokinetic/pharmacodynamic properties.
- No clear evidence as measured by clinical SSIs outcomes exists for the superiority of other antibiotics to vancomycin.
- Cost-effectiveness analysis to define the role of vancomycin should be performed on the basis of local SSIs management programs and diagnostic and antibiotic stewardship.

in part responsible for their increased virulence [11▪]. In the United States, CA-MRSA is the major causative agent of CA-SSI, and by 2011, USA300 clone became the predominant strain type [12]. In Europe, the prevalence of CA-MRSA-SSI is quite heterogeneous; in seven emergency departments studied, prevalence ranged from no cases in northern European institutions to 16.1% in western and 29% in southern Europe [13▪].

Despite several shortcomings (poor efficacy and tolerability, complex pharmacokinetic features, increasing reports of reduced susceptibility, and clinical failure), vancomycin remains the mainstay of MRSA-SSI treatment. The most recent Infectious Diseases Society of America guidelines for severe purulent cellulitis with suspected or confirmed MRSA cause recommend vancomycin for first-line treatment with the highest strength recommendation [14,15] (Table 1). Since the guidelines publication, the SSIs therapy armamentarium has been augmented with three new parenteral antibiotics: the oxazolidinone tedizolid and the long-acting lipoglycopeptides oritavancin and dalbavancin. Table 2 summarizes the characteristics of all available antibiotics for SSIs.

The purpose of this review is to establish the current role of vancomycin in the light of the most recent evidence. We reviewed literature published from January 2007 to September 2017 on the efficacy, safety, pharmacology, and microbiology of vancomycin and explored the limitations of current evidence.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

Vancomycin is a time-dependent antibiotic, and its variable tissue distribution, inoculum size, and protein-binding affect its clinical activity [16]. Penetration is low and can be influenced by inflammation and comorbidities. For example, in diabetic

Table 1. Summary of treatment indications provided by Infectious Diseases Society of America guidelines

Summary of antibiotic treatment indication for SSIs (moderate/severe) at risk of MRSA cause. IDSA guidelines, 2014 (16)			
Clinical syndrome(s) Severity	**Drug of choice**	**Strength of recommendation**	**Quality of evidence**
Erysipelas, cellulitis Moderate	Vancomycin or another drug active against MRSA	Strong	Moderate
Erysipelas, cellulitis Severe and/or immunocompromised host	Vancomycin and Gram-negative coverage	Weak	Moderate
Surgical site infection Moderate/severe	Vancomycin or linezolid or daptomycin or telavancin or ceftaroline Addition of Gram-negative coverage in case of abdominal surgery	Strong	Low
Necrotizing fasciitis	Vancomycin or linezolid Gram-negatives/anaerobes coverage	Strong	Low
Cutaneous abscess, furuncles, carbuncles Severe and/or in immunocompromised host	Incision, drainage (best choice) Antibiotic with MRSA coverage (not specified which agent)	Strong	Low
Pyomyositis	Incision and drainage Vancomycin ± Gram-negatives coverage	Strong	Moderate
Clostridial gas gangrene or myonecrosis	Surgical debridement Vancomycin and Gram-negatives coverage	Strong	Moderate

Moderate infection: presence of systemic signs of infections. Severe infection defined by failure of oral antibiotic treatment and/or the following systemic signs of infections: fever ($T > 38\,^{\circ}C$), tachycardia (>90 bpm), tachypnea (>24 bpm) or abnormal white cell blood count (>12 000 or <400 cell/μl), or immunocompromised patients (patient with malignancy, ongoing chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, animal bites). IDSA, infectious diseases society of America; MRSA, methicillin-resistant *S. aureus*; SSI, skin and soft-tissue infection.

Table 2. Current parenteral available therapeutic options for skin and soft-tissue infections (all agents cover methicillin-resistant *S. aureus*)

Antibiotic agent (class)	Mechanism of action	Dosage/route of administration	Concentration at skin/soft tissue	Advantages	Disadvantages	Notable adverse effects
Vancomycin (glycopeptide)	Bactericidal Bacterial cell-wall inhibition	Only intravenous route 30 mg/kg/day in 2 divided doses	Poor	Long cumulative clinical experience	Slow bactericidal killing TDM requirement, poor outcome in *S. aureus* with MIC between 1 and 2 mg/l	Red-man syndrome, thrombophlebitis, reversible nephrotoxicity at high doses
Linezolid (oxazolidinone)	Bacteriostatic Protein synthesis inhibition	Oral and intravenous route 600 mg every 12 h	Excellent	100% bioavailable oral formulation	Off-label after 28 days of treatment, emergence of linezolid-resistant *S. aureus* observed	Myelotoxicity (duration dependent) reversible after treatment discontinuation; irreversible effects (>28 days of therapy): optic neuritis and peripheral neuropathy, lactic acidosis
Daptomycin (lipopeptide)	Rapidly bactericidal Depolarization of bacterial membrane	Only intravenous route 4 mg/kg every 24 h	Excellent	Rapid bactericidal, penetrates biofilm	Report of resistance during therapy	Myopathy (dose-related and/or duration-related), eosinophilic pneumonia (rare)
Teicoplanin (glycopeptide)	Bactericidal Bacterial wall synthesis inhibition	Intravenous and intramuscular route Loading dose: 6–10 mg/kg every 12 h for 3 doses; maintenance: 6–10 mg/kg once daily	Good	Long cumulative clinical experience	No approval in several countries, low bactericidal activity, TDM requirement, cross-allergic reaction with vancomycin	Dose-dependent nephrotoxicity (less frequent than vancomycin)
Tedizolid (oxazolidinone)	Bacteriostatic Protein synthesis inhibitor	Intravenous and oral route 200 mg every 24 h intravenous or oral	Excellent	No dose adjustment in renal failure, active against linezolid-resistant MRSA (no cross resistance with linezolid), in-vitro anti-MRSA potency 2–8 times more active than linezolid	Limited experience with prolonged dosing schedules (off-label after 6 days of treatment)	Gastrointestinal disorders
Telavancin (lipoglycopeptide)	Bactericidal Disruption of peptidoglycan synthesis and cell membrane function	Only intravenous route 10 mg/kg every 24 h	Good	Active against MRSA resistant to vancomycin, linezolid, and daptomycin	FDA black box warning: increased mortality in moderate or severe renal impairment	Nephrotoxicity

Table 2 (*Continued*)

Antibiotic agent (class)	Mechanism of action	Dosage/route of administration	Concentration at skin/soft tissue	Advantages	Disadvantages	Notable adverse effects
Oritavancin (lipoglycopeptide)	Bactericidal Cell-wall synthesis and function inhibition	Only intravenous route 1200-mg single dose	Good	New pharmacokinetic properties (long half-life) allows single dose, no renal adjustment, TDM not required	The long half-life might compromise the clinical management in case of allergic reactions Antimicrobial stewardship issue: no de-escalation or change is possible	Nausea, vomiting, diarrhea, headache
Dalbavancin (lipoglycopeptide)	Bactericidal Binds peptide, preventing cross-linking in cell wall	Only intravenous route 1000-mg single dose, 500 mg after 1 week	Excellent	New pharmacokinetic properties (long half-live) allows single dose, 4–8 times more active *in vitro* against VISA than vancomycin, TDM not required	The long half-life might compromise the clinical management in case of allergic reactions Antimicrobial stewardship issue: no de-escalation or change is possible	Nausea, diarrhea, vomiting, headache, increase of cholestasis parameter, skin rash
Ceftaroline (5th generation cephalosporin)	Bactericidal Cell wall synthesis inhibition	Only intravenous route 600 mg every 12 h	Excellent	Broad coverage (including Gram-negative bacteria)	Requirement for renal adjustment	Similar to cephalosporins (generally well tolerated)
Tigecycline (glycylcycline)	Bacteriostatic. Protein synthesis inhibition and change cell permeability	Only intravenous route Loading dose 100 mg, then 50 mg every 12 h	Good	Broad coverage (including multidrug-resistant Gram-negative)	Low bloodstream concentrations, requirement for hepatic adjustment, safety warning from EMA and FDA	Gastrointestinal disturbance (common)

EMA, European Medicine Agency; FDA, Food and Drug Administration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; TDM, therapeutic drug monitoring; VISA, vancomycin-intermediate *S. aureus*.

patients, penetration has been estimated at 10–30% [17,18] with a median skin tissue concentration of 0.1 mg/l (range: 0.01–0.45 mg/l) statistically significant lower than in patients without diabetes [19]. Vancomycin's bactericidal activity is reduced at a high inoculum of 109 log10 cfu/g over a 72-h period [17,19], becoming weak in case of infections characterized by high bacterial inoculum [20] or in the case of biofilm-associated ones [21]. In in-vitro models using standard (low inoculum of 105 bacteria) concentrations of *S. aureus* and coagulase-negative staphylococci, vancomycin's killing effect did not increase with increasing concentrations of 2–64 times the minimum inhibitory concentration (MIC), supporting a time-dependent killing effect [18]. A negative association between MIC more than 1 μg/ml value and the outcome of MRSA bacteremia has been reported, but this association is still under debate and has never been demonstrated for SSIs [22].

The ratio of the 24-h area under the concentration–time curve and MIC (AUC/MIC) is the best predictor of vancomycin activity against MRSA [19], and an AUC/MIC ratio at least 400 is the target [17]. In a meta-analysis, AUC/MIC ratio at least 400 was associated with a significant decrease in mortality by 53% and treatment failure by 61% [23▪▪]. Measurement of vancomycin serum trough concentrations (a surrogate marker for AUC) is the most accurate and practical method for optimizing monitoring vancomycin effectiveness, especially in cases of critical illness, impaired renal function, older age, concomitant nephrotoxic drugs, or obesity. Trough serum concentrations should be maintained above 10 mg/l to avoid selection of strains with vancomycin-intermediate *S. aureus* (VISA)-like characteristics [17].

To rapidly attain target concentrations and optimize AUC/MIC, a loading dose of 25–30 mg/kg body weight is recommended for seriously ill adult patients [17,24]. This recommendation is supported mainly by a small study of critically ill patients with serious *S. aureus* infections, in which a 25-mg/kg loading dose infused at 500 mg/h was well tolerated without producing toxic peak serum drug levels [25]. In the absence of randomized clinical trials (RCTs) supporting the loading dose approach, the last consensus review on therapeutic drug monitoring (TDM) of vancomycin in adults suggests consideration of a loading dose for serious MRSA infections (level of evidence: III) [17]. According to a meta-analysis published in 2015, an loading dose supports achievement of the target vancomycin concentration, but higher quality studies are needed to determine the advantage of loading dose for clinical and microbiological outcome and to assess its role in particular settings (pediatric patients, obesity, renal impairment) [24]. Monte Carlo simulation has determined that a twice-daily 15 mg/kg dose with target trough levels of 10–15 mg/l is required to provide 90% probability of attaining a target AUC/MIC of at least 400 in MRSA with vancomycin MIC of 1 mg/l [18,26].

Because of the relationship between drug exposure and clinical/microbiological response and although the time above MIC does not correlate with killing, vancomycin is conventionally administered by intermittent infusion [17,18]. Studies have shown that continuous vancomycin infusion may enable faster and more consistent attainment of therapeutic serum than intermittent infusion [27,28]. Two meta-analyses demonstrated a better safety profile with significantly lower nephrotoxicity incidence for continuous infusion than for intermittent infusion without significant changes in treatment failure and mortality [29▪]. However, these results are supported mainly by observational studies with high selection biases and therefore should not be considered conclusive.

CLINICAL EFFICACY AND SAFETY OUTCOMES

Numerous meta-analyses have assessed the efficacy and safety outcomes of vancomycin and comparators in SSI treatment RCTs (Table 3). Linezolid is the first oxazolidinone and is the antibiotic most compared with vancomycin. In a review of six meta-analyses published between 2008 and 2013, linezolid showed stronger clinical and microbiological efficacy against both SSIs and MRSA-SSIs in most included meta-analyses. Linezolid was significantly associated with more frequent onset of hematological and gastrointestinal adverse events than vancomycin. Vancomycin had a significantly higher renal toxicity rate [30]. Similar results were described in another meta-analysis of nine RCTs and 3144 participants. Significantly better clinical and microbiological efficacy was seen in patients treated with linezolid and in the MRSA infection subgroup. Thrombocytopenia and nausea were reported significantly less frequently for vancomycin than for linezolid. Renal adverse effects were not analyzed [31▪▪].

In two meta-analyses comparing clinical and microbiological efficacy of vancomycin and daptomycin (mainly administered at the labeled dose of 4 mg/kg), daptomycin safety and efficacy were noninferior to vancomycin for *S. aureus* SSI, and the treatment with daptomycin reduced the treatment duration [32,33]. A significantly lower incidence of adverse events (renal impairment, nausea,

Table 3. Summary of the most relevant systematic reviews and meta-analyses comparing the available therapeutic options for the treatment of skin and soft-tissue infections

Reference	Treatment Type of infection	Comparator(s)	Included studies (publication years)	Efficacy outcome	Safety outcome and other outcomes
Tsoulas *et al.* [30]	Vancomycin SSIs and cSSIs	Daptomycin Telavancin Tigecycline Linezolid	21 MAs (2008–2014)	Pairwise comparison Linezolid: six MAs included. In Gram-positive (5 MAs) and MRSA-SSIs (4 MAs) significantly higher clinical and microbiological efficacy Telavancin: one MA included. In MRSA-SSIs was associated with trend toward higher cure rates in clinical efficacy and was significantly more effective than vancomycin in microbiological efficacy (OR: 1.71, 95% CI: 1.08–2.70) Tigecycline: four MAs included. No statistically significant differences Daptomycin: two MAs included. No statistically significant differences Indirect comparison Dalbavancin, linezolid, and telavancin was superior to vancomycin in microbiologic outcome Vancomycin ranked third among six antibiotics in cSSIs treatment	Pairwise comparison: Linezolid: five MAs included. No differences in common AEs (3 MAs), more frequent onset of thrombocytopenia (statistically significant; 3 MAs) and gastrointestinal events (statistically significant, 2 MAs). Vancomycin group showed more frequently nephrotoxicity (3 MAs, statistically significant) Telavancin: one MA included. Significant increase of serum creatinine (OR: 2.22, 95% CI: 1.38–3.57) and AE-related withdrawals (OR: 1.48, 95% CI: 1.14–1.93) Tigecycline: 4 MAs included. Significant higher all-cause mortality in all infections; no significant differences in SSIs group Daptomycin: two MAs included. No statistically significant differences
Yue *et al.* [31▪▪]	Linezolid SSIs and cSSIs	Vancomycin	9 RCTs (2002–2010)	Linezolid was associated with a significantly better clinical (RR: 1.09, 95% CI: 1.03–1.16) and microbiological (RR: 1.08, 95% CI: 1.01–1.16) rate in SSIs group	Higher onset of thrombocytopenia (RR: 13.06, 95% CI: 1.72–99.22) and nausea (RR: 2.45, 95% CI: 1.53–3.94) in linezolid group. No difference in all-cause mortality
				Linezolid was associated with a significantly better clinical (RR: 1.09, 95% CI: 1.03–1.17) and microbiological (RR: 1.17, 95% CI: 1.04–1.32) rate in MRSA-SSIs group	Other outcomes: Length of stay in hospital was shorter in the linezolid group. The daily cost of outpatient therapy was less with oral linezolid than intravenous vancomycin, although the inpatients costs were higher per day. Thus, total hospital charges per patients were less with linezolid treatment than with vancomycin treatment
Wang *et al.* [32]	Daptomycin SSIs	Vancomycin	6 RCTs (2004–2013)	Noninferiority of daptomycin in clinical and microbiological efficacy	Daptomycin tended to have a similar treatment AE incidence as other antibiotics The trend showed that daptomycin might cause less discontinuation due to AEs and death compared with other first-line antibiotics Significant creatine phosphokinase elevation than those in control group, but it can be reversed when the therapy ended (OR: 1.95, 95% CI: 1.04–3.65, $P=0.04$)

Table 3 (*Continued*)

Reference	Treatment Type of infection	Comparator(s)	Included studies (publication years)	Efficacy outcome	Safety outcome and other outcomes
He *et al.* [33]	Daptomycin All infections	Vancomycin	13 RCTs (7 on SSIs) (2004–2013)	No difference to vancomycin in ITT population but lower efficacy among the clinically evaluable population (RR: 0.96, 95% CI: 0.93–1.00) Subgroup analyses according to the quality of the trial, the type of antibiotic, and the type of infection did not alter the results	No difference was identified for all-cause mortality, but daptomycin therapy reduced the duration of treatment Daptomycin caused a significantly lower incidence of renal impairment, nausea, and headache but caused a reversible increase in creatine phosphokinase
Bally *et al.* [36]	Vancomycin All cSSIs	Linezolid Daptomycin Tigecycline Telavancin Ceftaroline (indirect comparison through NMA)	17 RCTs (2000–2010)	Pairwise comparison Linezolid and ceftaroline were nonsignificantly more effective than vancomycin both MITT and MRSA m-MITT populations Indirect comparison Vancomycin ranked third (after linezolid and ceftaroline)	Pairwise comparison Significant creatine phosphokinase elevation than those in control group, but it can be reversed when the therapy ended (OR: 1.95, 95% CI: 1.04–3.65, $P=0.04$) Indirect comparison Vancomycin ranked third (after linezolid and ceftaroline)
El Hajj *et al.* [38]	Ceftaroline Only cSSI	Vancomycin and aztreonam	3 RCTs (2007–2010)	No significant difference in clinical cure between ceftaroline and vancomycin and aztreonam	No difference in mortality and overall AEs between the two groups
McCool *et al.* [42▪]	NA ABSSSIs or cSSIs due to documented or suspected MRSA	Tedizolid Ceftaroline Daptomycin Linezolid Teicoplanin Tigecycline Vancomycin (indirect comparison through NMA)	15 RCTs (2002–2014)	Tedizolid had higher odds of clinical response at the end of therapy (OR: 1.7, credible interval: 1.0–3.0) and post-therapy evaluation (OR: 1.6, credible interval: 1.1–2.5) than vancomycin	No difference among treatments for discontinuation due to AEs

ABSSSI, acute bacterial skin and skin structure infection; AE, adverse event; CI, confidence interval; cSSI, complex complicated skin and soft-tissue infection; ITT, intention to treat; MA, meta-analysis; MITT, modified intention to treat; mMITT, microbiological modified intention to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; NMA, network meta-analysis; OR, odds ratio; RCT, randomized clinical trial; RR, risk ratio; SAE, severe adverse event; SSI, skin and soft-tissue infection.

headache) was observed with daptomycin. Increased creatine phosphokinase, rapidly reversed after discontinuation, was reported for daptomycin [33].

Telavancin, a semisynthetic lipoglycopeptide vancomycin derivative, was approved in 2009 for the treatment of Gram-positive complicated SSIs (cSSIs) [34]. One meta-analysis showed a statistically significantly higher microbiological efficacy for telavancin in patients with MRSA-SSIs than for vancomycin [30]. A phase III trial, comparing telavancin and vancomycin for cSSIs, showed a rate of nephrotoxicity or acute renal failure at the end of therapy of 6% ($n = 822$) for telavancin and 2% ($n = 856$) for vancomycin. The same study also showed serum creatinine levels increased by at least 1.5 mg/dl and at least 50% above baseline in 6% of participants who received telavancin [35]. Pooled data confirmed the higher risk of renal failure development for telavancin than for vancomycin (two-fold risk of serum creatinine increase) [30,36]. The Food and Drug Administration (FDA) required a black box warning for patients with moderate-to-severe renal impairment (creatinine clearance $\leq$50 ml/min) because of the higher mortality rates from hospital-acquired and ventilator-associated bronchial pneumonia for telavancin than for vancomycin and decreased clinical response in cSSIs [37].

Ceftaroline is a broad-spectrum cephalosporin offering potent activity against both MRSA and common Gram-negative bacteria. The most recent meta-analysis of three RCTs showed that ceftaroline is noninferior to vancomycin and aztreonam for clinical outcomes. No differences were found for overall mortality, serious adverse events, discontinuation due to adverse events, or overall adverse events [38].

Tedizolid, a next-generation oxazolidinone, was approved for acute bacterial skin and skin-structure infections (ABSSSIs) treatment after two trials (ESTABLISH 1 and 2) demonstrating efficacy noninferior to linezolid [39,40]. Tedizolid was better tolerated than linezolid; pooled data demonstrated lower incidence of thrombocytopenia [41]. No direct comparison of tedizolid and vancomycin has been conducted. A network meta-analysis of 16 RCTs indirectly comparing the efficacy of tedizolid and vancomycin showed the superiority of tedizolid to vancomycin in clinical response for end of treatment and post-therapy evaluation outcomes [42▪].

Tigecycline has not shown statistically significantly stronger clinical efficacy than vancomycin for SSI treatment in meta-analyses. Concerns about its efficacy arose after the safety warnings issued by the European Medicines Agency and FDA in 2013 [43]. Pooled data from 13 phase III and IV RCTs in both FDA-approved and off-label indications showed an increase in overall mortality rates among patients with serious infections treated with tigecycline. However, this finding was not confirmed in the SSI subgroup [30].

The anti-MRSA lipoglycopeptides dalbavancin and oritavancin have recently been approved for ABSSSIs after noninferiority trials with vancomycin as the comparator. Long plasma half-life is their chief advantage and allows single-dose outpatient treatment regimens. The evidence of oritavancin's clinical efficacy in ABSSSI treatment is from two identically designed trials, SOLO I and II, demonstrating noninferiority to vancomycin [44]. The phase III trials DISCOVER 1 and 2 have demonstrated the noninferiority of dalbavancin to vancomycin followed by oral linezolid [45]. Although they show broad and potent activity against VISA and heterogenous VISA *in vitro* (dalbavancin four to eight times more active than vancomycin), extremely high protein binding may hinder their potency *in vivo*, and the extended half-life could be harmful for severe adverse events [46▪▪].

With the exception of the association of telavancin with more severe adverse events, the safety of vancomycin is comparable with that of old and new antibiotics approved for SSIs treatment. Some evidence suggests that linezolid offers an advantage over vancomycin because of its oral formulation and community management and that daptomycin may be associated with reduced treatment duration. However, current evidence has significant limitations. The quality of clinical trials is very poor, SSI definitions are inconsistent, and vancomycin or comparator dosages are not always appropriate. Although the SOLO studies were conducted in accordance with the current FDA ABSSSI definition, severe or invasive infections were scarcely represented: only 25% of participants had white blood cell counts more than 12 000 cells/μl, and only 3% were bacteremic [44]. In the DISCOVER trials, vancomycin duration and serum concentrations were not reported, and only 12% of the infections were caused by MRSA [45]. In some cases, use of antibiotics other than vancomycin was associated with higher *Clostridium difficile* infection risk and may promote antibiotic resistance.

The Cochrane review emphasized the strong limitation of available evidence for SSI treatment as much of the evidence, in particular on linezolid, is from poor designed open-label trials [31▪▪]. The superiority of tedizolid to vancomycin has been demonstrated through a mixed indirect comparison within a network meta-analysis that included poor-quality trials. The studies varied in design and quality. Some were double-blind, but others were not blinded. In general, only limited information was

reported on randomization and sequence allocation methods.

LENGTH OF STAY AND COST EVALUATION

Although the average daily cost of vancomycin is relatively low (approximatively $15–55) [47], an overall economic evaluation of vancomycin treatment should consider the costs associated with TDM, possible adverse reactions and their treatment, and hospitalization, including hospital room and board and diagnostic procedures. Because of the high burden of multidrug-resistant SSIs, length of stay (LOS) represents the key financial determinant. Therefore, decreasing the LOS by hastening hospital discharge significantly reduces overall costs [48,49]. Recent Cochrane Center meta-analysis results [31▪▪] demonstrate lower total per-patient hospital cost for linezolid than for vancomycin treatment. Although the inpatient costs with linezolid were higher than for vancomycin, linezolid treatment allowed shorter LOS and consequent earlier outpatient management than for vancomycin. Furthermore, the total hospital costs in this analysis could be even lower with the generic version of linezolid approved by the FDA last year. In a cost-efficacy analysis of vancomycin and daptomycin for cSSIs, no difference was observed in infection-related LOS, total LOS, and total inpatient cost (mean cost in vancomycin group $9083 versus daptomycin group $9641). A trend toward better clinical success rate for daptomycin was observed but was not statistically significant, but the open-label design may have affected the clinical response assessment. The total LOS contributed 85.9% to the total hospitalization costs, compared with 6.4% for the antibiotic cost [50]. Daptomycin use in outpatient parenteral antimicrobial therapy (OPAT) could represent a cost advantage as an alternative to an extensive and expensive LOS [51].

The mathematical model proposed by Stephens *et al*. provided the most comprehensive economic evaluation of MRSA-SSIs, by considering both direct outpatient costs (OPAT, physician office visit, central catheter placement, complication treatment) and inpatient costs (general ward, specialist, antibiotics). Despite the higher inpatient costs, linezolid reduced total treatment costs by 30–50% compared with vancomycin because of the switch to oral therapy once the patient was discharged [52]. The overall costs might be even further reduced by a cheaper generic equivalent that became available in several countries last year.

Agarwal *et al*. provided a comprehensive cost-comparison of vancomycin and newer glycopeptides for MRSA-SSI treatment, including both monetary and nonmonetary outcomes. All the drugs showed similar efficacy, but oritavancin and dalbavancin were cheaper than vancomycin by saving 7.5–11 and 6.5–10 treatment days, respectively. Moreover, with improved baseline assumptions (age-specific hospitalization costs, current drug costs) dalbavancin use could save third-party payers $1442–$4803 and oritavancin $3571–$6932 per cSSI patient treated [53▪▪].

LIMITATIONS OF CURRENT EVIDENCE

A major problem in evaluating the evidence for vancomycin's role in SSI treatment is the heterogeneity of SSI definition and classification. The 1998 FDA cSSI definition encompassed several clinical entities, including infections either involving deeper soft tissues or requiring significant surgical intervention (such as infected ulcers, burns, and major abscesses) and infections of any severity in the setting of specific medical comorbidities that may complicate the response to treatment [54]. The primary efficacy endpoint lacked objectivity, relying exclusively on clinicians' assessment at 7–14 days. In 2013, the FDA released new guidance for clinical trials, including revised terminology and endpoints. ABSSSIs now include cellulitis, erysipelas, major skin abscesses, and wound infections with a minimum surface area of 75 cm^2. The primary efficacy endpoints are at least 20% lesion size reduction and fever resolution within 48–72 h after treatment onset [55]. The earlier timing of the primary efficacy evaluation can confirm the rapid effectiveness of the antibiotic and minimize the confounding influence of the immune response [56▪]. The inclusion of only acute bacterial infections facilitates the microbiological outcome assessment.

The regulatory approval of new antibiotics for SSI treatment occurs through RCTs with prespecified outcome criteria, the current gold standard for efficacy, and safety profile assessment. Despite their well established internal validity, they have failed to address other relevant variables that may independently predict the SSI outcome such as the host-related (age, weight, baseline comorbidities), infection-related (type, site, severity), and pathogen-related factors [57]. The frequent primary outcome of clinical cure, that is, clinical resolution based mainly on physician evaluation, is not objective, clearly measurable, or reproducible. Moreover, strict study eligibility criteria exclude patients with medical conditions (e.g., neutropenia) that may affect the interpretation of primary outcome [55]. Therefore, the study populations do not reflect the real population, limiting the potential to detect differences in specific targeted subpopulations. Misreported data

are a further significant limitation; a meta-analysis of 17 RCTs evaluating antimicrobial treatment for SSIs revealed that only 37% of the trials reported data on comorbidities (no studies mentioned severe comorbidities), and infection type was provided only categorically without assessing the anatomic infection site. Furthermore, only six trials adhered to FDA guidance by including at least 70% of microbiologically evaluable patients [58].

CONCLUSION

The current literature indicates that the clinical efficacy of vancomycin is not inferior in direct pairwise comparison with old or new antibiotics approved for SSIs treatment. Vancomycin's unfavorable pharmacokinetic profile is its main weakness; the dose must be individualized and TDM must be carefully conducted to achieve the optimal trough concentration necessary for efficacy (especially for deep-seated infections), minimize renal toxicity, and reduce resistant strain selection. Other drugs in the SSIs armamentarium present advantages over vancomycin: linezolid offers oral formulation, daptomycin reduces intravenous therapy duration, and ceftaroline is a well tolerated alternative. Recently approved glycopeptides (oritavancin and dalbavancin) combine desirable pharmacokinetic properties with high potency against MRSA. Single-dose posology, requiring neither adjustments nor TDM, allows and simplifies SSIs management in an outpatient setting. However, these drugs were largely tested against infections that were relatively straightforward to manage, whereas no useful information is available in patients with severe or invasive infections. Furthermore, the empiric use of a drug with extended half-life may not be appropriate if therapy should be tailored on the basis of microbiological culture and susceptibility test results, and the inability to de-escalate may expose patients to prolonged selective pressure.

In conclusion, the SSIs treatment evidence base presents several shortcomings limiting the clinical applicability of the results. Assessment of the external validity of RCTs should be routinely performed to obtain results that can be generalized and applied effectively in clinical practice. Furthermore, consideration of the ecological impact of new drugs on the resistance development at the community and patient levels (e.g., change in the microbiome, selection of *C. difficile*) and how to include them in local antibiotic stewardship programs should be carefully evaluated.

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Conflicts of interest

There are no conflicts of interest.

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