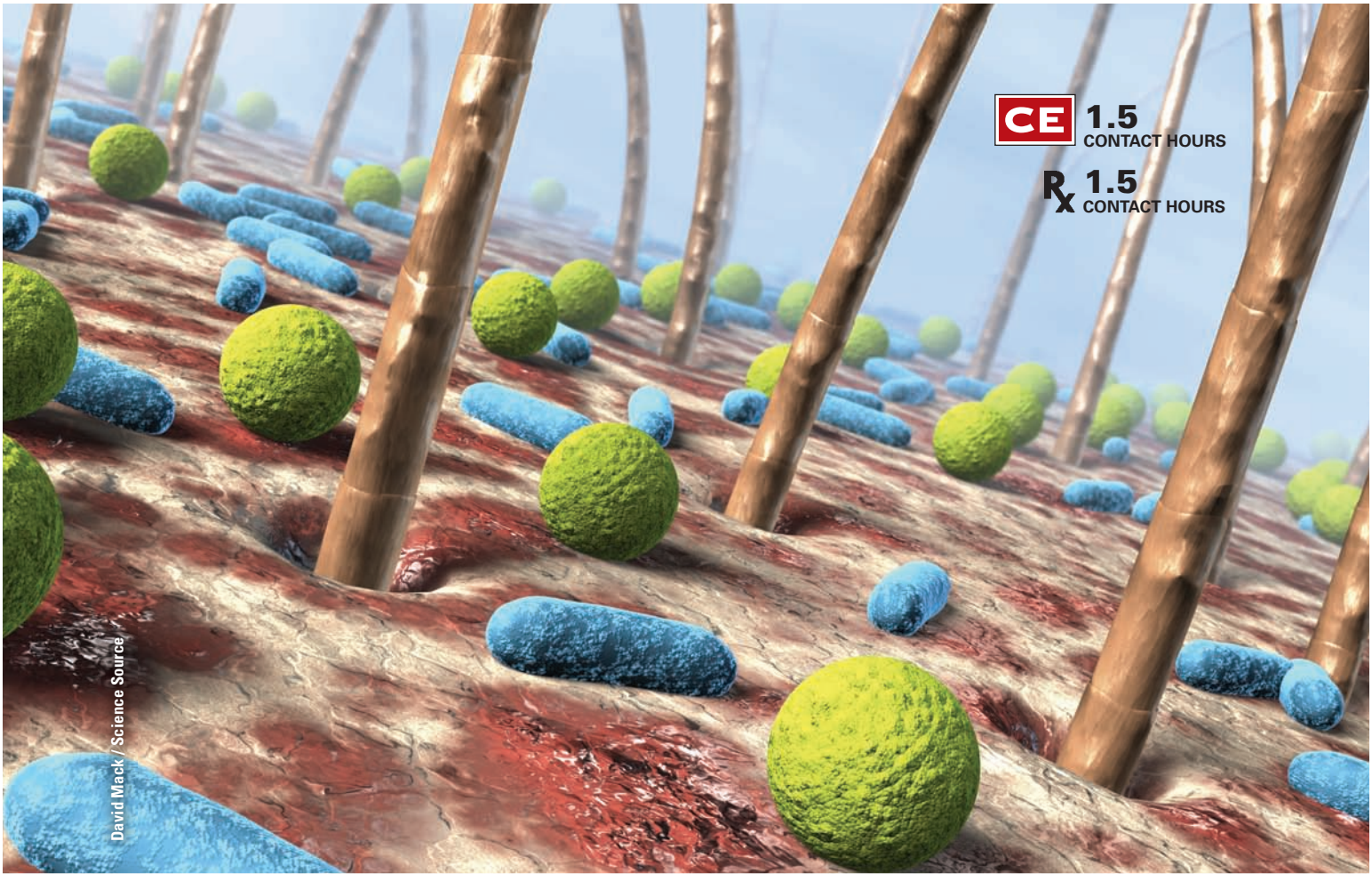

Newest lipoglycopeptides

for the management of acute bacterial skin and skin structure infections

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Abstract: Acute bacterial skin and skin structure infections (ABSSSIs) are some of the most commonly encountered infections worldwide. Hospitalizations as a result of ABSSSIs are associated with high mortality. This article discusses the role of oritavancin and dalbavancin, the two newest lipoglycopeptides, in the context of the other available I.V. infusion standard therapy options.

Skin and soft-tissue infections (SSTIs) represent a broad spectrum of infections ranging from superficial pyodermas to deep, necrotizing infections.[1,2] Most uncomplicated infections may be managed with topical therapies or simple surgical interventions; however, complicated SSTIs generally require systemic antibiotic therapy and are likely to require surgery.[1,2] The common terminology throughout the infectious disease literature has been SSTIs; however, in 2013, the FDA updated their industry guidance for treatment of acute bacterial skin and skin structure infections and changed the terminology from complicated SSTIs to acute bacterial skin and

Keywords: ABSSSIs, acute bacterial skin and skin structure infections, dalbavancin, daptomycin, lipoglycopeptides, oritavancin, telavancin, vancomycin

skin structure infections (ABSSSIs) to better describe the type of infection suitable for treatment with newer antibiotics.[3]

ABSSSIs are some of the most commonly encountered infections and represent a major reason for seeking medical care worldwide. The combined emergence of antimicrobial resistance over the last few decades and the lack of newly developed antimicrobial agents complicate matters further.

Only within the last few years has the antimicrobial armamentarium seen substantial growth. In particular, two recently approved lipoglycopeptides supplement the currently available options for ABSSSIs: dalbavancin and oritavancin.

Epidemiology

ABSSSIs are prominent in both the inpatient and ambulatory populations. Rates of infections have increased significantly over the past decades. When considering hospital admission rates for ABSSSIs from 2000 to 2004, Edelsberg and colleagues found a 29% increase in the number of admissions, whereas admissions for other infection types remained constant.[4] Of note, increases in ABSSSIs-related admissions were largest in adults under age 65 and in patients from urban areas.[4]

A more recent analysis of the Health-Core Integrated Research Database from 2005 to 2010 found over 2.2 million ABSSSIs episodes, with more than 90% diagnosed in the ambulatory setting.[5] Hospitalizations for ABSSSIs are now more common than for community-acquired pneumonia. These hospitalizations, particularly those associated with staphylococcal ABSSSIs, are associated with a longer length of stay, higher hospital costs, and increased mortality.[6]

Causative pathogens

Gram-positive organisms, specifically *Staphylococcus aureus* and *Streptococcus* species, are the most common causes of ABSSSIs. The distribution of these pathogens varies among infection types; however, among culture-positive ABSSSIs, *S. aureus* predominates.[7] Data from the SENTRY surveillance program found *S. aureus* to be the causative pathogen in 48.1% of all ABSSSIs, followed by *Pseudomonas aeruginosa* (9.4%) and *Enterococcus* species (8.8%).[8] Beta-hemolytic *Streptococcus* species accounted for only 4.2% of culture-positive infections. Despite the lack of culture positivity for *Streptococcus* species in numerous epidemiologic assessments, these pathogens still account for a significant proportion of nonpurulent cellulitis, particularly in ambulatory patients.[1,9,10]

Within the past decade, methicillin-resistant *S. aureus* (MRSA) infections have transitioned from a dominant healthcare-associated pathogen to a major cause of both community-acquired (CA) and healthcare-associated ABSSSIs.[1,7,11] In an analysis of ambulatory antibacterial therapy for uncomplicated skin infections in otherwise healthy adults, MRSA accounted for approximately 32% of all culture-confirmed infections and 77% of all *S. aureus* cultures.[7]

The emergence of CA-MRSA and other resistant phenotypes has altered the approach that clinicians must take when considering empiric antibiotic therapy. The CDC continues to list MRSA as a "serious" threat and strongly advocates for the development and approval of novel therapeutic agents.[12]

Overview of current therapy

Vancomycin. A slowly bactericidal glycopeptide, vancomycin has activity against many Gram-positive organisms, including pathogens frequently implicated in ABSSSIs. It is now a mainstay of therapy for the treatment of serious ABSSSIs.[13] Vancomycin disrupts the cell wall synthesis pathways by binding to the terminal D-alanyl–D-alanine amino acids on cell wall precursors, preventing transpeptidation reactions.[13] It is dosed based on actual body weight and administered by I.V. infusion every 8 to 12 hours for patients with normal kidney function.[14,15]

Current practice guidelines from the Infectious Diseases Society of America (IDSA) recommend I.V. infusion vancomycin as a first-line empiric treatment for management of severe purulent (abscess, furuncle, carbuncle) and nonpurulent (cellulitis, erysipelas, necrotizing infection) ABSSSIs.[1]

Although vancomycin has been the treatment of choice, its slow bactericidal activity, associated toxicities (including nephrotoxicity and ototoxicity), hematologic abnormalities (thrombocytopenia and neutropenia), infusion-related reactions, need for therapeutic monitoring, and frequent dosing schedule have led to concerns about its continued utility.[13]

Vancomycin should be monitored using serum concentrations.[1] In addition to necessary routine monitoring, the frequency of dosing required can make vancomycin a suboptimal choice for patients using outpatient I.V. infusion antibiotics for ABSSSIs.

Resistance to vancomycin is also an increasing concern due to an emergence of vancomycin-resistant *S. aureus*, vancomycin-intermediate *S. aureus* (VISA), and heteroresistant VISA (a possible precursor to VISA).[13] Additionally, *S. aureus* has most recently been displaying an "MIC creep" (a gradual increase in minimum inhibitory concentration [MIC] of a drug required to inhibit bacterial growth) toward vancomycin, with the majority of isolates demonstrating an MIC of 1 mcg/mL rather than 0.25 mcg/mL as in previous decades.[16]

As a result, an increased number of treatment failures and/or toxicities due to the use of elevated dosages needed to overcome the higher MICs are being observed.[16] Vancomycin utility in enterococci is also diminishing, as vancomycin-resistant enterococci (VRE) rates are approximately 83% in *Enterococcus faecium* and 10% in *Enterococcus faecalis* (up from 8%).[17]

Daptomycin. This cyclic lipopeptide antibiotic has rapid bactericidal activity against various Gram-positive organisms, such as *S. aureus* (including MRSA) and enterococci (including VRE). It was first approved by the FDA in 2003 for treatment of ABSSSIs.[18] Daptomycin binds in the septum of dividing bacteria, inducing rapid depolarization of cell membrane potentials and disrupting synthesis of DNA, RNA, and proteins, ultimately leading to cell death.[18] It is administered via I.V. infusion. Daptomycin is recommended as an option for empiric treatment of severe purulent ABSSSIs in adults in the current IDSA guidelines for treatment of severe complicated ABSSSIs.[1]

Although generally well tolerated for short courses, daptomycin use is not without risk. The use-limiting toxicity associated with daptomycin is rhabdomyolysis. Creatine phosphokinase should be monitored at baseline and weekly (at minimum) during treatment.[18] If rhabdomyolysis is suspected, serum creatinine and urine myoglobin should be monitored. Renal toxicity, acute kidney injury, and eosinophilic pneumonia have also been associated with daptomycin.[18]

Resistance to daptomycin has been observed in the last few years. While still infrequent, daptomycin nonsusceptible strains of staphylococci (MIC greater than 1 mcg/mL) and enterococci (MIC greater than 4 mcg/mL) have been documented.[18-20]

Telavancin. A lipoglycopeptide antibiotic originally derived from vancomycin, telavancin has concentration-dependent bactericidal activity against various Gram-positive organisms including *S. aureus* (both methicillin-sensitive *S. aureus* and MRSA), streptococci, and vancomycin-susceptible *E. faecalis*. Telavancin was first FDA approved for treatment of ABSSSIs in 2009.[21] Similar to the mechanism of action of vancomycin, telavancin inhibits bacterial cell wall synthesis and disrupts the bacterial membrane.[21,22] It is administered via I.V. infusion.[21]

Clinical success rates range between 80% and 96%.[23-26] Like daptomycin, telavancin is recommended in the current IDSA guidelines for ABSSSIs as an option for empiric treatment of severe purulent ABSSSIs in adults. Telavancin is only available as an I.V. infusion.[1,27]

Toxicities associated with telavancin include nephrotoxicity (with a black box warning for telavancin regarding increased mortality in patients with moderate-to-severe kidney impairment). Warnings include the risk of prolonged QT interval, hypersensitivity reactions, and prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT).[21] Despite a narrow spectrum susceptibility profile and comparable efficacy, the nephrotoxicity, black box warning, and increased cost compared with vancomycin have largely limited its clinical usage.

Overview of newer agents

Oritavancin. This semisynthetic lipoglycopeptide antibacterial is approved by the FDA for ABSSSIs caused by susceptible isolates of *S. aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus*, *Streptococcus intermedius*, *Streptococcus constellatus*, and *E. faecalis* in adult patients.[28] Oritavancin has activity against both vancomycin-susceptible and vancomycin-resistant enterococcus.[28]

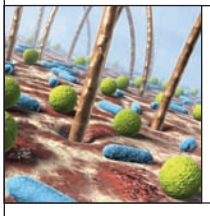
Oritavancin exerts antibacterial activity through multiple mechanisms, including inhibition of cell wall synthesis through inhibition of transpeptidation and disruption of bacterial cell membrane potential. It also has an increased affinity for binding sites, allowing it to increase membrane permeability in both stationary and growth phases of bacterial development.[29] The currently approved FDA susceptibility breakpoints are 0.12 mcg/mL or less for *S. aureus* and *E. faecalis* and 0.25 mcg/mL or less for *Streptococcus* species.[30]

Efficacy of oritavancin has been evaluated in two clinical trials: SOLO I and SOLO II.[31,32] In both, a single dose of oritavancin 1,200 mg was noninferior to a 7- to 10-day course of vancomycin for the treatment of acute bacterial skin infections. SOLO I had primary efficacy endpoint rates of 82.3% versus

78.9% for oritavancin and vancomycin, respectively, whereas SOLO II had rates of 80.1% versus 82.9%, respectively.[31,32] While there are some reports of in vitro success of oritavancin for prosthetic joint infection-related biofilms, this has not yet been studied in clinical trials.[33,34]

Oritavancin is highly protein bound and is not significantly metabolized by either the liver or kidneys.[29] It is administered by I.V. infusion over 3 hours and accumulates in the tissues, slowly releasing over a terminal half-life of 393 hours, so repeated dosing is not necessary when treating ABSSSIs.[30,35]

In contrast to vancomycin, blood concentration monitoring is not required with oritavancin.[30] Instead, patients receiving oritavancin should be monitored for signs of infusion-related reactions or signs of hypersensitivity during infusion. If these reactions occur, the infusion should be slowed or stopped.[36] Oritavancin artificially prolongs the PT and falsely elevates the aPTT, and use of I.V. unfractionated heparin sodium is contraindicated for 120 hours after oritavancin administration.[36]



Dose adjustments are needed for patients with kidney impairment based on creatinine clearance.

The most frequently reported adverse reactions were injection site reactions, nausea/vomiting, and pruritus.[28,30] There have been reports of transient increases in liver enzymes, which have been hypothesized to be a result of the high intracellular accumulation.[28,37] There are also reports of an increased frequency of osteomyelitis as compared with patients who received vancomycin, so patients should be monitored carefully for signs or symptoms of osteomyelitis.[36]

Dalbavancin. A semisynthetic lipoglycopeptide, dalbavancin has been approved by the FDA for ABSSSIs caused by susceptible, Gram-positive isolates of *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *S. anginosus*.[38] Dalbavancin inhibits transpeptidation within bacterial cell wall synthesis, binding with increased affinity to the binding site compared with the glycopeptides.[29]

In a large study comparing almost 82,000 isolates, dalbavancin demonstrated lower MIC_{90} values against *S. aureus* (1 mcg/mL versus 0.06 mcg/mL), coagulase-negative staphylococci (2 mcg/mL versus 0.06 to 0.12 mcg/mL), and beta-hemolytic streptococci (0.5 mcg/mL versus 0.03 mcg/mL or less) compared with vancomycin.[39] Dalbavancin has also shown activity against vancomycin-susceptible and resistant strains of enterococci.[39]

Additionally, when dalbavancin was tested against over 62,000 strains of either methicillin-resistant, daptomycin-resistant, linezolid-resistant, or tigecycline-resistant *S. aureus*, the drug retained an MIC_{90} of 0.06 to 0.12 mcg/mL.[40] Subsequently, the currently FDA-approved susceptibility breakpoint is set at 0.12 mcg/mL or less for *S. aureus*, *S. pyogenes*, *S. agalactiae*, and *S. anginosus*.[41]

Dalbavancin efficacy was originally assessed for efficacy and safety in two phase 3 clinical trials: DISCOVER 1 and DISCOVER 2.[42] In these evaluations, dalbavancin, given as a two-dose regimen spaced a week apart, was compared to vancomycin for the treatment of acute bacterial skin and skin structure infections for 10 to 14 days. A pooled analysis demonstrated early clinical success rates of 79.7% and 79.8% for dalbavancin and vancomycin, respectively. Later, a single-dose regimen of dalbavancin was compared to the two-dose regimen for ABSSSIs, and success rates were comparable (81.4% vs. 84.2%).[43]

Dalbavancin is widely distributed and extensively protein bound, with a terminal elimination half-life of 147 to 258 hours.[29] Dalbavancin is given as a 30-minute I.V. infusion either as a single-dose regimen or a two-dose regimen, with the second dose given 1 week after the first dose.[38] Dose adjustments are needed for patients with kidney impairment based on creatinine clearance.[38] Should an infusion-related reaction of flushing, urticaria, and/or rash occur, it is recommended to slow the infusion rate or stop the infusion.[38,44]

The most common adverse reactions of dalbavancin are nausea (5.5%), headache (4.7%), and diarrhea (4.4%).[38] Some more serious but rare potential adverse reactions include reversible alanine aminotransferase elevation greater than three times the upper limit of normal (0.8%) and hypersensitivity leading to anaphylaxis.[38] Therefore, dalbavancin is contraindicated in patients with known hypersensitivity to the drug; however, it is unclear if there is cross-reactivity with other glycopeptides.[44]

Unlike vancomycin, dalbavancin does not require any therapeutic monitoring to assess treatment efficacy; however, it is recommended to monitor for clinical

Agent comparison for the treatment of ABSSSIs[13,14,17,20,21,27-30,35,37-41]

Agent	Advantages	Disadvantages
Vancomycin	• Well-studied • Low drug cost • Standard of care for severe ABSSSI	• Monitoring required throughout treatment • Often dosed multiple times a day* • Red man syndrome • Nephrotoxicity
Daptomycin	• Well-studied • Dosed once daily*	• Moderate drug cost • Weekly monitoring of creatine phosphokinase required (monitor for rhabdomyolysis)
Telavancin	• Dosed once daily*	• High drug cost • Monitoring of kidney function required throughout treatment (nephrotoxicity) • Prolonged QT interval • Interaction with coagulation parameters
Oritavancin	• Single dose • May spare hospitalization • No monitoring required	• Not well-studied • Moderate drug cost • Interaction with coagulation parameters
Dalbavancin	• Option of one or two doses per treatment course • May spare hospitalization • No therapeutic monitoring	• Not well-studied • High drug cost • Dose adjustment based on creatinine clearance

*In the setting of adequate kidney function.

response to therapy between 48 and 72 hours after treatment initiation and to monitor for the development of *Clostridium difficile*-associated disease up to 2 months after administration.[44]

Pediatric considerations for management of ABSSSIs

Treatment of staphylococcal infections in the pediatric population is becoming challenging as *S. aureus* grows increasingly resistant to the agents currently available for pediatric use. Overcoming the lack of treatment alternatives in this patient population is more difficult, as many of the newer agents are not indicated for pediatric use.

Telavancin, oritavancin, and dalbavancin have demonstrated efficacy in the treatment of multidrug-resistant Gram-positive infections but have had limited exposure in the pediatric population. A recent pharmacokinetic study of dalbavancin in children ages 12 to 17 years evaluated the drug exposure in children as compared with adults by scaling to body weight using a population pharmacokinetic model.[45] Patients weighing 60 kg or more received a 1,000 mg dose, whereas those weighing less than 60 kg received a 15 mg/kg dose.

Following a single I.V. infusion dose of dalbavancin, similar pharmacokinetic profiles were revealed for the two weight groups, and both yielded similar drug exposures to the adult population. Although not statistically significant, the renal clearance of dalbavancin was approximately 42% higher in the higher weight group. As with the adult data, dalbavancin displayed unique pharmacokinetic properties that would allow for extended interval dosing.[45] In 2017, the pharmacokinetics of I.V. infusion dalbavancin was evaluated in a phase 1 study involving pediatric patients aged 3 months to 11 years.[46,47] These data together with the data from the previously published study described above was used in a population pharmacokinetic model to identify optimal dalbavancin dosing in children aged 3 months to less than 6 years and 6 years to less than 18 years.[46]

Analysis revealed that a 15 mg/kg on day 1 and 7.5 mg/kg on day 8 resulted in similar dalbavancin exposure compared with a two-dose regimen in adults. Similarly, children 6 years to less than 18 years achieved a comparable exposure to adults when dosed at 12 mg/kg on day 1 and 6 mg/kg on day 8. For a single dose regimen, children 6 to less than 18 years achieved matched adult exposure at a dose of 18 mg/kg, whereas children 3 months to less than 6 years required a dose of 22.5 mg/kg on day 1.[46]

Similar statistics are true for oritavancin.[47] There is currently no published data available for the use of oritavancin in the pediatric population.

Daptomycin was approved by the FDA in 2003. In 2017, daptomycin received approval for indications in pediatric patients 1 to 17 years.[18] Numerous clinical trials have evaluated the pharmacokinetic profile of daptomycin in children from neonates to age 17 years.[48-52]

A better class of antibiotics

Considering the increasing rates in both inpatient and outpatient medical visits for ABSSSIs, the the newer lipoglycopeptides represent a class of antibiotics with promise for treatment of these infections. (See *Agent comparison for the treatment of ABSSSIs.*) Dalbavancin and oritavancin display potent in vitro activity against Gram-positive organisms and equivalent clinical success rates against standard of care agents. Both are I.V. infusion options that may be useful for severe disease but have pharmacokinetic and pharmacodynamic principles that may make them useful to spare hospitalizations. Finally, the adverse reaction profiles of these agents make them an attractive option for the treatment of ABSSSIs. NP

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The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

This article is reprinted with minor updates from Bell AM, King ST, Barber KE, Adcock KG, Wagner JL, Stover KR. Managing acute bacterial skin infections: Focus on new lipoglycopeptides. *Nurs Pract*. ePub 2017. DOI:10.1097/01.NPR.0000515428.68779.87.

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