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PERSPECTIVE

New Perspectives on Antimicrobial Agents: Long-Acting Lipoglycopeptides

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ABSTRACT The long-acting lipoglycopeptides (LGPs) dalbavancin and oritavancin are semisynthetic antimicrobials with broad and potent activity against Gram-positive bacterial pathogens. While they are approved by the Food and Drug Administration for acute bacterial skin and soft tissue infections, their pharmacological properties suggest a potential role of these agents for the treatment of deep-seated and severe infections, such as bloodstream and bone and joint infections. The use of these antimicrobials is particularly appealing when prolonged therapy, early discharge, and avoidance of long-term intravascular catheter access are desirable or when multidrug-resistant bacteria are suspected. This review describes the current evidence for the use of oritavancin and dalbavancin in the treatment of invasive infections, as well as the hurdles that are preventing their optimal use. Moreover, this review discusses the current knowledge gaps that need to be filled to understand the potential role of LGPs in highly needed clinical scenarios and the ongoing clinical studies that aim to address these voids in the upcoming years.

KEYWORDS dalbavancin, lipoglycopeptide, oritavancin

Gram-positive bacterial pathogens significantly contribute to the morbidity and mortality associated with antimicrobial resistance (1). Dalbavancin and oritavancin are semisynthetic lipoglycopeptides (LGPs) with broad activity against Gram-positive bacteria. While these agents have a similar spectrum to glycopeptides (e.g., vancomycin), they exhibit higher potency for most target pathogens. More importantly, they have much longer half-lives, allowing for reduced dosing frequencies (i.e., weekly) or even single-dose therapy (2–5). Consequently, there is great enthusiasm to use these drugs to facilitate hospital discharge and decrease the need for long-term intravascular catheters, especially for infections requiring prolonged antimicrobial therapy, such as infective endocarditis (IE), osteomyelitis, and prosthetic joint infections (PJIs). However, the bulk of clinical evidence with long-acting LGPs, including all registrational trials, involves patients with acute bacterial skin and skin structure infections (ABSSSIs) and not the more clinically pressing situations (4, 6).

In this review, we discuss key knowledge gaps and challenges preventing the optimal use of dalbavancin and oritavancin, including (i) hurdles with routine susceptibility testing, (ii) mechanisms and development of resistance, (iii) evidence for combination therapy, (iv) optimal dosing strategies, and (v) real-world data to manage off-label, clinically challenging situations (e.g., bacteremia, IE, and PJIs). The chemistry, pharmacology, mechanism of action, adverse events and registrational trials of LGP have been thoroughly covered recently and are beyond the scope of this article (2–5, 7).

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SUSCEPTIBILITY TESTING

The *in vitro* MIC remains the primary metric to assess antimicrobial activity. The reference technique for MIC determination of most antimicrobials is the broth microdilution (BMD) method, which is based on the presence or absence of visible bacterial growth (8). Of note, the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints for oritavancin against staphylococci, streptococci, and enterococci are ≤0.12, ≤0.25, and ≤0.12 mg/L (9), respectively, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are ≤0.125 and ≤0.25 mg/L for *Staphylococcus aureus* and streptococci, respectively (10). Similarly, the CLSI susceptibility breakpoint for dalbavancin against staphylococci, streptococci, and enterococci is ≤0.25 (9), while the EUCAST equivalent is ≤0.125 mg/L for staphylococci and streptococci (10). Moreover, according to the literature, the oritavancin MIC_{50}/MIC_{90} for staphylococci, streptococci, vancomycin-susceptible enterococci (VSE), and vancomycin-resistant enterococci (VRE) are 0.03/0.06, 0.03/0.12, 0.008/0.008, and 0.015/0.06 mg/L, respectively (7), and the dalbavancin MIC_{50}/MIC_{90} for staphylococci, streptococci, enterococci are 0.03/0.03, 0.008/0.03, and 0.03/0.12 mg/L, respectively (11). While it is increasingly clear that *in vitro* susceptibility testing has many limitations and may not correlate with clinical outcomes, the situation with LGPs is particularly challenging. Herein, we discuss the main considerations and hurdles encountered when assessing the *in vitro* activity of these agents.

Broth microdilution. Early studies underestimated the potency of dalbavancin and oritavancin due to their proclivity to bind to plastic surfaces (12). Hence, performance of BMD with the addition of polysorbate-80 (P-80) was proposed as a potential solution (12, 13). P-80, a nonionic compound commonly used as a surfactant, was shown to reduce loss of these agents through adsorption (12, 14), resulting in a significant decrease in the MIC to oritavancin in methicillin-susceptible *S. aureus* (MSSA) ATCC 29213 and *Enterococcus faecalis* ATCC 29212 when tested in Mueller-Hinton broth (MHB) (14). Consequently, both CLSI and EUCAST recommend performing dalbavancin and oritavancin BMD testing for staphylococci and enterococci in MHB supplemented with 0.002% P-80, the lowest concentration shown to prevent surface adsorption (12, 13, 15). In contrast, streptococcal MIC values remained unchanged in the presence or absence of P-80 when tested in 2% lysed horse blood (14). Moreover, the addition of 2% lysed horse blood to MHB led to similar MIC values to those observed in the presence of P-80 (12). These results suggest lysed horse blood could exert a similar effect to P-80, preventing the binding of LGP to plastic surfaces. However, the use of lysed horse blood to evaluate the *in vitro* activity of dalbavancin or oritavancin is not currently recommended.

While neither CLSI nor EUCAST specifies the type of plate that should be used for BMD, the type of microtiter plate and even the manufacturer's brand itself appear to be important causes for variation of results (16, 17). In particular, the use of tissue-culture-treated plates for the determination of the oritavancin MIC led to >4-fold increases in MIC values, as well as poor reproducibility (17). In contrast, incubation time (up to 48 h), CO_2, and Ca^{2+} concentration did not influence BMD results for these agents (14). Lastly, while the impact of the inoculum effect has not been evaluated for dalbavancin, it has been studied with oritavancin, showing a 16-fold increase in MIC values when performed with a high inoculum (10^7 CFU/mL) compared to the standard 10^5-CFU/mL inoculum. However, time-kill assays suggested oritavancin retained its bactericidal activity at both the standard inoculum and high inoculum (18). The clinical relevance of this observation remains to be established.

Beyond BMD: susceptibility testing methods for the clinical microbiology lab. Although BMD is considered the reference technique for MIC determination, as a method it is impractical and not suitable to be implemented in most clinical laboratories. Dedicated, commercially available, lyophilized panels showed good performance and high reproducibility and are FDA approved (19). However, the widespread use of such panels is not a suitable option for many centers due to their high cost, which is particularly important in developing regions.

Among other methods, agar dilution (AD) was shown to underestimate the potency of LGPs against staphylococci and enterococci compared to BMD; no effect was exerted

by P-80 with this method (20, 21). In terms of agar diffusion methods, dalbavancin gradient diffusion strips have shown good performance for *Staphylococcus* spp., *Enterococcus* spp., and *Streptococcus* spp. compared to BMD (21). Of note, available strips do not include P-80 as it has been postulated that the dry-form chemistry used readily disperses dalbavancin without the need for a surfactant. Dalbavancin gradient strip tests have received FDA clearance for clinical use (19). In contrast, at the time of this report, the FDA has yet to clear any oritavancin gradient diffusion test. Unfortunately, strip tests are also costly, limiting their widespread use in resource-limited settings. Disk diffusion (DD) testing is an inexpensive, simple, and commonly used method for clinical laboratories. Unfortunately, neither CLSI nor EUCAST has published DD interpretive criteria for LGPs because available data suggest this method does not produce satisfactory results for these agents (21).

Finally, the ability of clinical laboratories to widely perform LGP susceptibility testing will largely depend on the agents' inclusion in commercially available automated systems (e.g., Vitek, Phoenix, and Microscan). Until this occurs and considering the problems with the other routinely used methodologies, susceptibility testing for these agents is likely to remain limited to larger academic medical centers and reference laboratory settings.

Vancomycin susceptibility as a surrogate agent. The dearth of widely available susceptibility testing methods for LGPs has promoted the search for alternate approaches. Initial observations suggesting that the MIC_{50} and MIC_{90} for oritavancin and dalbavancin increased along with vancomycin MICs prompted investigations to assess whether vancomycin could be used as a surrogate to predict susceptibility to LGPs (18, 22). Initial data suggested this could be a feasible approach, but they lacked sufficient representation of genera and of nonsusceptible isolates. More recently, larger studies have demonstrated the feasibility of vancomycin surrogacy (23–25). Vancomycin susceptibility highly correlated with dalbavancin MICs in a collection of >33,000 *S. aureus* isolates. The frequencies of dalbavancin nonsusceptibility in the subgroup of isolates with vancomycin MIC results of 2 μg/mL (susceptibility breakpoint) and 4 μg/mL (i.e., vancomycin-intermediate *S. aureus* [VISA]) were 2.9% and 100%, respectively (23). Similar findings have been published for oritavancin, with a 98.8% concordance over 17,000 vancomycin-susceptible *S. aureus* strains, all of which exhibited oritavancin MICs of $\leq$0.12 μg/mL (24). Importantly, the use of vancomycin as a surrogate agent in *S. aureus* does not account for the existence of heteroresistant VISA (hVISA) strains, a phenotype challenging to detect in clinical microbiology labs and which has been associated with higher clinical failure rates to vancomycin (26). Moreover, different studies have documented dalbavancin and oritavancin MICs that are several fold higher for hVISA strains, further highlighting a potentially relevant problem that needs further clarification (24–26).

In terms of other organisms, high concordance rates (>97%) have been observed with dalbavancin and oritavancin for beta-hemolytic streptococci and vancomycin-susceptible enterococci (27). However, some studies reported false-susceptible surrogate errors when analyzing coagulase-negative staphylococci (CoNS) and *Streptococcus agalactiae*. Importantly, a lack of reproducibility for both oritavancin and dalbavancin nonsusceptibility on retest was noted in these studies, highlighting the need for more robust data to clarify the possible role of vancomycin susceptibility as a surrogate to predict the *in vitro* activity of LGPs for bacterial species other than *S. aureus* (28, 29).

Even though CLSI no longer references vancomycin surrogacy to predict susceptibility to LGP, current EUCAST guidelines do include this information. While this technique is widely available in clinical laboratories, laboratorians and clinicians alike should be aware of its potential drawbacks, such as the issues observed with hVISA strains, the lack of representation of certain clinically relevant species and phenotypes (e.g., vancomycin-resistant enterococci [VRE]), and the problems described with CoNS, among others. In addition, clinical laboratories able to directly perform susceptibility testing for LGP (e.g., gradient diffusion, BMD) should always repeat a nonsusceptible result, and all reproducible nonsusceptible isolates should be sent to a reference laboratory for additional confirmatory testing and further molecular and phenotypic studies. Finally, the inclusion of dalbavancin and oritavancin as part of commercially available automated antimicrobial susceptibility platforms will likely result in wide availability of testing in health care institutions.

MECHANISMS AND DEVELOPMENT OF RESISTANCE

For every bacterial-antimicrobial combination, there exists a concentration range between the MIC and the mutant prevention concentration, where selection and proliferation of less susceptible subpopulations may occur (30). This range of concentrations is referred to as the "mutant selection window," and the time spent in this concentration range is largely determined by the physiologic half-life of the drug and dosing regimen (31, 32). As mentioned, dalbavancin and oritavancin have the longest half-lives of any commercially available antibacterial medications (8 to 16 days) (33, 34). Consequently, they continue to exert selective pressure on exposed bacteria for weeks or even months after the last dose, as opposed to hours or days, as typically observed with other antimicrobials. Arguably, selection of mutants exhibiting decreased susceptibility and/or tolerance is an area of particular theoretical concern for these compounds. While resistance is generally defined in light of established clinical breakpoints and correlates with increased MICs, the definition of tolerance is less straightforward (35, 36). Moreover, determination of antibiotic tolerance is cumbersome, often requiring evaluation of growth dynamics and antibiotic killing assays (35). Thus, data to inform the occurrence of this potentially relevant phenomenon are not well studied for LGPs. Herein, we summarize the current knowledge of the mechanisms of resistance to LGPs, as well as cross-resistance to other antimicrobials (e.g., vancomycin and daptomycin), and we discuss available data informing the theoretical concern of a higher risk for mutant selection due to prolonged selective exposures of LGPs.

Oritavancin. The molecular bases of oritavancin resistance have mostly been examined in VRE as related to the *van* gene cluster, a set of horizontally acquired genes that confer vancomycin resistance and have been extensively described in enterococci. Thus, these data may not be generalized to other organisms. There are multiple types of *van* gene clusters, among which the most frequently observed worldwide are *vanA* and *vanB*. Although oritavancin is largely active against *van*-harboring enterococci, the presence of multiple copies of the *van* gene cluster has been shown to result in low-level oritavancin resistance (3-fold increase in the MIC) (37). Similarly, VRE strains may also develop low-level oritavancin resistance via alterations in the VanS sensor, leading to increased expression of the *van* gene cluster (3-fold increase in the MIC) (37). Importantly, these mechanisms of resistance are shared with teicoplanin in enterococci; hence, these isolates display cross-resistance between the two compounds. In addition, the *vanZ* gene (a member of the *van* cluster) has also been shown to contribute to teicoplanin and oritavancin resistance via unknown mechanisms (37–39). VanZ is a large family of transmembrane proteins whose orthologs are found in genomes of other clinically relevant bacteria, such as *Bacillus* spp., *Streptococcus* spp., *Enterococcus* spp., and *Clostridium difficile* (40–42). Remarkably, the expression of *vanZ* paralogs resulted in increased MICs to oritavancin, dalbavancin, and teicoplanin in *S. aureus* and *Streptococcus pneumoniae* (39). Moreover, as part of the *van* gene cluster, *vanZ* can be transferred from enterococci to *S. aureus*, leading to high-level vancomycin-resistant *S. aureus* strains (43–45). Therefore, the horizontal transfer of *vanZ* alone or as part of the *van* gene cluster may threaten the utility of the LGPs in different Gram-positive cocci.

Although the emergence of oritavancin resistance in clinical settings remains extremely rare, nonsusceptible enterococcal isolates have been selected using *in vitro* and *in vivo* models. In an earlier *in vivo* rabbit model of IE, oritavancin selected only for nonsusceptible mutants in *vanA*-type vancomycin-resistant (VR) *Enterococcus faecalis*, but not in vancomycin-susceptible (VS) or *vanB* VR *E. faecalis*. The mutants had oritavancin MICs 4 to 10 times higher than that of the parental strain, and addition of gentamicin prevented the selection of resistant mutants (46). In serial passage assays using 0.5× the MIC of oritavancin, mutants exhibiting reduced oritavancin susceptibility (MIC range 2 to 32 times that of the parental strain) were selected after 20 days in both *E. faecalis* and *Enterococcus faecium*, regardless of vancomycin resistance. Importantly, oritavancin-resistant isolates also displayed elevated MICs to dalbavancin (4- to >128-fold MIC increase), telavancin (4- to 8-fold MIC increase), and daptomycin (4- to 32-fold MIC increase), but not to vancomycin, teicoplanin, linezolid, or rifampicin (47). These data suggested a potential common mechanism of resistance among lipoglycopeptides in enterococci. Information about oritavancin nonsusceptibility in

S. aureus and other Gram-positive pathogens apart from enterococci is limited. Of note, data from a phase 2, multicenter, randomized study of oritavancin in ABSSSIs did not find relevant changes in oritavancin MICs among *S. aureus* isolates colonizing the nostrils of participants over a 3-week period after oritavancin administration (48).

Data to inform the optimal dosing of oritavancin for the treatment of multidrug-resistant pathogens while preventing the emergence of resistant mutants are scant. In one study, a two-dose regimen of oritavancin at 1,200 mg each dose given 24 h apart was sufficient to eradicate a multidrug-resistant, daptomycin-nonsusceptible, *vanA*-type VR *E. faecium* isolate in a humanized pharmacokinetic/pharmacodynamic (PK/PD) model (49). However, the same study found that a single 1,200-mg oritavancin dose resulted in regrowth after 72 h, despite maintaining a concentration above the MIC throughout the study period. Interestingly, surviving isolates did not display a significant increase in oritavancin MICs. It remains to be elucidated whether survivors at concentrations above the MIC exhibit tolerance to oritavancin despite the lack of MIC increase. Finally, a significant increase of oritavancin MIC during therapy has not been reported.

Dalbavancin. Dalbavancin is a semisynthetic derivative of teicoplanin, and as such, the mechanisms of dalbavancin resistance are similar to those of teicoplanin and vancomycin. In contrast to oritavancin, dalbavancin lacks affinity for the substituted peptidoglycan precursors encoded by the *van* gene cluster; therefore, most VRE exhibit a dalbavancin-resistant phenotype. While dalbavancin nonsusceptibility is still uncommon outside enterococci, it can emerge by similar mechanisms to those observed in VISA strains (50–53). Indeed, dalbavancin-nonsusceptible *S. aureus* strains often acquire mutations in genes involved in multi-component regulatory systems previously linked to the VISA phenotype (e.g., *walKR* and *vraTSR*) (51). Also as observed in VISA strains, dalbavancin nonsusceptibility in *S. aureus* is often associated with changes in cell wall thickness and membrane metabolism. However, the precise molecular mechanisms and metabolic pathways leading to dalbavancin nonsusceptibility remain poorly understood and are likely to vary across bacterial species and genetic lineages (51–53).

A recent *in vitro* PK/PD study simulated free drug exposures associated with a standard 1,500-mg dose of dalbavancin to assess the resistance selection potential against a series of methicillin-resistant *S. aureus* (MRSA) isolates. After a single dose and in spite of initial bactericidal activity, dalbavancin exposure selected for dalbavancin-resistant MRSA between days 11 and 18 (MIC, $>$0.25 mg/L) across all genetic backgrounds assessed (51). Worrisomely, vancomycin- and daptomycin-resistant mutants also emerged from the same dalbavancin-exposed strains, even earlier than dalbavancin resistance was selected. Despite these findings, dalbavancin resistance has not been commonly observed in clinical settings (50). A potential explanation is the usage of these agents in patients with tenuous contact with the health care system (e.g., intravenous drug users [IVDUs]) or as part of completion of therapy in order to facilitate discharge, which might hamper resistance surveillance efforts.

COMBINATION THERAPY

The increasing complexity of antimicrobial regimens due to the high prevalence of multidrug-resistant organisms makes the possibility of combination therapy with LGPs a potentially interesting alternative, particularly in the context of challenging infections such as IE and osteomyelitis. However, clinical data to support the use of combination therapy with LGPs are lacking. In this section, we summarize all current available evidence related to the subject, most of which is based on *in vitro* studies.

Oritavancin. *In vitro* combinations with oritavancin have been evaluated against *S. aureus* and enterococci. In particular, the addition of linezolid, rifampin, or gentamicin with oritavancin has demonstrated added *in vitro* efficacy against hVISA, VISA, and VR *S. aureus* (VRSA) strains (16, 54–57). Oritavancin synergy with other agents has also been explored against resistant enterococci in time-kill assays and *in vitro* pharmacodynamic models. The addition of gentamicin to oritavancin has been consistently shown to be synergistic against vancomycin-susceptible and *vanA*-type VRE (58, 59). Combinations of oritavancin with other agents, such as β-lactams, rifampin, linezolid, daptomycin, or ciprofloxacin, have also been assessed (60, 61). Overall, the data suggest that synergy with these compounds is inconsistent and varies widely within strains and across species. Additionally, some have observed

antagonism between oritavancin and daptomycin, rifampin, or linezolid when tested against enterococci (59, 62, 63).

Oritavancin demonstrated decreased effectiveness in *in vitro* assays using high inocula of both VISA and enterococci (18, 64, 65). Increasing the concentrations of oritavancin in time-kill assays or adding another agent has been shown to restore its bactericidal activity (18, 62, 65), hinting toward the need to evaluate higher (or repeated) dosing strategies and the use of combination therapy for deep-seated, high-inoculum infections. While data supporting the use of oritavancin as part of a combination are largely limited to *in vitro* assays, a case of hardware-associated vertebral osteomyelitis caused by a vancomycin-resistant daptomycin-nonsusceptible *E. faecium* isolate was successfully treated with oritavancin plus continuous infusion of ampicillin (66).

Dalbavancin. Dalbavancin has been tested in combination with a wide range of β-lactams (ceftaroline, cefepime, cefazolin, oxacillin, ertapenem, meropenem, nafcillin, ceftriaxone, cephalexin, and cefoxitin), against different staphylococci (including MSSA, MRSA, hVISA, and VISA) and streptococci (53, 67–70). Results varied between strains, β-lactam molecules, and testing methodologies. Notably, none of the available data demonstrated *in vitro* antagonism with dalbavancin (53, 67–70). The combination of dalbavancin with other molecules, such as daptomycin, linezolid, fluoroquinolones, rifampin, vancomycin, and aminoglycosides, has also produced mixed results, but no evidence of *in vitro* antagonism (67, 71, 72). Combination assays with dalbavancin have not been examined to prevent the emergence of resistant strains. Similarly, we did not find any data evaluating the activity of dalbavancin against high-inoculum infections *in vitro*.

REAL-WORLD EXPERIENCE

Oritavancin. Oritavancin has been used off-label most commonly for the treatment of a number of different VRE infections. Here, we summarize the available observational studies and case reports detailing real-world use of oritavancin for deep-seated infections, including patients with bloodstream infections (BSIs) and bone and joint infections (BJIs) (Table 1). While there are some reports describing the use of oritavancin for other types of infections (e.g., pneumonia, abdominal infections, etc.), these data were not included in this review.

(i) Bacteremia/intravascular infections. The potential utility of oritavancin as a treatment for *S. aureus* bacteremia was evaluated early in its developmental history. A phase 2 study randomized patients with uncomplicated *S. aureus* bacteremia to receive either oritavancin or standard-of-care (SOC) therapy with a β-lactam or vancomycin (for MSSA or MRSA, respectively) (73). In contrast to the fixed-dose, prolonged-interval strategies currently approved, patients were randomized to oritavancin at 5 to 10 mg/kg of body weight on a daily basis. Out of the 86 patients in the oritavancin arm, 55 were evaluable for microbiological and clinical responses. Clinical and microbiological success was observed in 47 (85%) and 45 (78%) patients, respectively. While no information was provided regarding the patients' outcomes according to the dose received, exploratory pharmacokinetic/pharmacodynamic (PK/PD) analyses revealed a tenuous relationship between clinical success and percentage of time of free drug above the MIC (T_{MIC}). Importantly, the relevance of those observations in light of the modern dosing strategies remains unclear.

Apart from this clinical trial, experience with oritavancin as a therapeutic alternative for bacteremia is limited to case reports and small series. The top portion of Table 1 summarizes the cases in which oritavancin has been used for BSIs. Available data gather patients infected with a variety of Gram-positive pathogens, most of which involve staphylococci, enterococci, and streptococci. Of note, oritavancin has mostly been used as a consolidation regimen to complete therapy in subjects previously managed with other antimicrobials. Data regarding the use of oritavancin to manage IE are limited, with only 6 out of the 78 patients summarized in Table 1 being diagnosed with IE. The overall success rate of the remaining 72 subjects classified as having bacteremia was 82% (Table 1, top portion).

Based on the limited available evidence, secondary therapy with oritavancin (i.e., to complete therapy after an initial successful treatment) appears to be an interesting option for BSIs caused by oritavancin-susceptible pathogens. Data from case reports

TABLE 1 Summary of case series of patients with bloodstream infections or bone and joint infections treated with oritavancin[a]

Reference	*n*	Infection(s)	Bacterium or bacteria (*n*)	Most frequent dosage(s)	Duration/ no. of doses	Success, *n* (%)[b]	Adverse event(s) (*n*)
Bloodstream infections							
Bhavnani et al., 2006 (73)	55	Bacteremia	*S. aureus* (55)	5–10 mg/kg/day	10–14 days	45 (78)	N/R
Johnson et al., 2015 (109)	1	PVE	VR *E. faecium* (1)	1,200 mg every 48 h × 3 doses, then 1,200 mg weekly × 6 wk, then 1,200 mg biweekly × 10 wk	14 doses	1 (100)[c]	Anorexia, nausea, elevated LFTs (1)
Stewart et al., 2017 (82)	6	Bacteremia[d]	MSSA (4), CoNS (1), *Enterococcus* spp. (1)	1,200 mg	1 dose	4 (66.7)	None
Stewart et al., 2017 (82)	1	NVE	*S. agalactiae* (1)	1,200 mg	1 dose	0 (0)	None
Datta et al., 2018 (74)	3	Bacteremia	MRSA (1), *S. gallolyticus* (1), *Granulicatella adiacens* (1)	1,200 mg	1 dose	3 (100)	N/R
Brownell et al., 2020 (76)	4	Endocarditis	Not specified[e]	1,200 mg then 800–1,200 mg weekly	N/R[e]	4 (100)	None
Redell et al., 2019 (77)	7	Bacteremia	MRSA (2), MSSA (1), *S. epidermidis* (2), other (2)	1,200 mg once	1 dose	7 (100)	Not specified (29)[f]
Schulz et al., 2018 (80)	1	Bacteremia	VR *E. faecium* (1)	1,200 mg then 800 mg weekly	4 doses	0 (0)	None
Total	78					64 (82)	
Bone and joint infections							
Van Hise et al., 2020 (75)	134	Acute osteomyelitis	MSSA (35), MRSA (108), VISA (2), VRE (7)	1,200 mg once then 800 mg weekly	4–5 doses	118 (88.1)	Hypoglycemia (3), tachycardia (2)
Brownell et al., 2020 (76)	16	Osteomyelitis, diabetic foot, IAI	Not specified[g]	1,200 mg then 800–1,200 mg weekly	N/R[g]	16 (100)	Not specified (3)[f]
Redell et al., 2019 (77)	25	Acute osteomyelitis, septic arthritis, IAI	Not specified[g]	1,200 mg once or 1,200 mg every 6–14 days	1–10 doses	19 (76)	Not specified (29)[f]
Chastain and Davis, 2019 (78)	9	Chronic osteomyelitis	MRSA (5), other (4)[i]	1,200 mg LD then 1,200 mg every 13–52 days	2–6 doses	9 (100)	None
Dahesh et al., 2019 (66)	1	IAI	VR *E. faecium* (1)	1,200 mg weekly × 2 wk then 800 mg weekly	10 doses	1 (100)	N/R
Ruggero et al., 2018 (79)	1	Acute osteomyelitis	MRSA (1)	1,200 mg every 2–4 wk	5 doses	1 (100)	N/R
Schulz et al., 2018 (80)	4	Acute and chronic osteomyelitis, septic arthritis, diskitis	MSSA (1), other (3)[i]	1,200 mg then 800 mg weekly	2–8 doses	2 (50)[h]	Anemia and leukopenia (1)
Foster et al., 2017 (110)	1	IAI	Daptomycin-nonsusceptible VR *E. faecium* (1)	1,200 mg weekly	6 doses	1 (100)	None
Delaportas et al., 2017 (81)	1	Acute osteomyelitis	MSSA (1)	1,200 mg weekly	7 doses	1 (100)	None
Stewart et al., 2017 (82)	1	Bursitis	MRSA (1)	1,200 mg once	1 dose	1 (100)	Hearing loss (1)
Total	193					169 (87.6)	

[a]VRE, vancomycin-resistant *Enterococcus*; CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; N/R, not reported; VISA, vancomycin-intermediate *S. aureus*; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis; IAI, implant-associated infection; LD, loading dose.
[b]Definitions of clinical success were heterogeneous across the studies. For details, refer to the individual publication.
[c]Clinical improvement—partial resolution of clinical signs and symptoms.
[d]Includes bacteremia with wound infection, bacteremia with abscesses with and without osteomyelitis, and bacteremia with endocarditis.
[e]Not reported for infective endocarditis.
[f]Corresponds to the total cohort in studies that included cases with different sources of infection.
[g]Not specified for bone and joint infections.
[h]Cure, 2 (50%); improvement, 2 (50%).
[i]Includes sterile cultures or unavailable cultures.

and a small phase 2 study (73, 74) suggest oritavancin may be considered a primary regimen to manage uncomplicated bacteremia in selected patients with no alternative treatment options, but at this point, its use cannot be broadly recommended over other alternatives.

(ii) Bone and joint infections. Available data largely derive from case reports and retrospective series of patients with acute or chronic osteomyelitis, as well as joint infections caused by VRE, staphylococci, streptococci, and *Bacillus* spp. Similar to bacteremia, oritavancin was often used as a follow-up regimen to complete therapy in patients who previously received various antibiotics. A summary of the available clinical data for the use of oritavancin to manage BJIs is provided in the bottom portion of Table 1.

Overall, clinical cure (total resolution of signs and symptoms) or improvement (partial resolution of signs and symptoms) was achieved in the majority of patients, with most studies following patients for up to 6 months after the last oritavancin dose. Importantly, oritavancin dosing varied, with most patients receiving a 1,200-mg loading dose followed by 800 to 1,200 mg weekly (75, 76) (Table 1, bottom portion). Some reports have described successful results with a single dose of oritavancin (66, 77–82) (Table 1, bottom portion).

The limited available data on the efficacy of oritavancin to manage BJIs suggest it could be a safe and potentially efficacious alternative for patients where other options are not readily available. However, the data stem from small and highly heterogeneous retrospective reports that include different types of patients, infections, dosing regimens, and lengths of therapy. Therefore, further research is required to determine the role of oritavancin in the management of BJIs.

Dalbavancin. As with oritavancin, dalbavancin's potent *in vitro* activity, along with its prolonged half-life and good safety profile, makes it an appealing alternative to management invasive and chronic infections. In the remainder of this section, we will summarize the available data for the use of dalbavancin to manage BSIs and BJIs (Table 2).

(i) Bacteremia/intravascular infections. A randomized, controlled, open-label, multicenter trial assessed 75 adults with bacteremia of known or suspected catheter-related origin caused by CoNS or *S. aureus* (83). Patients were randomized to dalbavancin (1,000 mg on day 1 and 500 mg on day 8) or vancomycin (1,000 mg twice daily for 14 days). Catheter removal was mandatory for all patients with *S. aureus* infection and was discretionary for CoNS. Subjects allocated to the dalbavancin group attained a significantly higher overall success rate than those receiving vancomycin (87% versus 50%, respectively; $P < 0.05$) regardless of catheter removal (93.3% with catheter removed versus 55.6% with catheter retained at 75% versus 40% for dalbavancin and vancomycin, respectively) (81).

While data on the use of dalbavancin for the treatment of IE are more abundant than those for oritavancin, the data still derive largely from case reports and series. In the top portion of Table 2, we summarize the findings of reports including at least 5 IE cases with documented clinical outcomes. As shown, a total of 140 patients with IE have been treated with dalbavancin, with a wide variation in terms of type of IE (native/prosthetic valve, cardiac device related), causative pathogen, dosing regimen, and duration of therapy. Dalbavancin was mainly used as a second-line agent for consolidation therapy (i.e., after clearance of the causative pathogen from the bloodstream) and less frequently as rescue therapy (i.e., failure to clear the bloodstream with a prior antimicrobial regimen). Most of the published experience with dalbavancin involves infections due to staphylococci, enterococci, and streptococci (84–89). The most frequently reported dosing regimen is a 1,000- to 1,500-mg loading dose followed by 500 to 1,500 mg weekly, but dosing varies widely. Clinical and microbiological success ranged from 57% to 100%, with an overall success rate of 88%. Dalbavancin seems to be well tolerated in IE patients, with most adverse events considered to be nonsevere.

Recent reports have also highlighted the use of dalbavancin as suppressive therapy in a few specific clinical situations (90, 91). One case series reported on four patients with intravascular infections (1 with prosthetic valve IE, 2 with a left ventricular assist device, and 1 with a transcatheter aortic valve implant) due to MRSA and *Enterococcus* spp., who received dalbavancin with suppressive intention (500 mg weekly or 1,000 mg biweekly) because cardiac surgery was not feasible. One patient died after the second dose, and the other 3 patients received dalbavancin for 4, 8, and 12 months, respectively, without severe adverse events (90). One patient developed breakthrough bacteremia with a vancomycin-susceptible *E. faecalis*

TABLE 2 Summary of case series of patients with infective endocarditis or treated with dalbavancin[a]

Reference	*n*	NV/PV/CD or IAI/BJI	Bacterium or bacteria (*n*)[b,c]	Most frequent dosing	Duration/no. of doses	Success, *n* (%)[d]	Adverse events (*n*)
Infective endocarditis		NV/PV/CD					
Tobudic et al., 2018 (84)	27	15/7/5	*S. aureus* (9), CoNS (7), *E. faecalis* (4), other (9)	1,500 mg LD then 1,000 mg every 2 wk or 1,000 mg LD then 500 mg weekly	Median, 6 wk (range, 1–30)	25 (93)	Nausea (1), RCI (1)
Bouza et al., 2018 (85)	7	Not specified[e]	*S. aureus* (1), CoNS (2), *Enterococcus* spp. (2), other (2)[f]	1,000 mg LD then 500 mg weekly	Median, 3 doses (range, 1–24)	6 (86)	Rash (2), tachycardia (2), RCI (2), nausea (1), rectal bleeding (1)[g]
Hidalgo-Tenorio et al., 2019 (86)	34	11/15/8	*S. aureus* (10), CoNS (15), *E. faecalis* (3), other (7)	1,000 mg once or 1,500 mg LD then 500 mg at day 8	Median, 14 days (IQR, 14–21)	33 (97)	Fever (1), renal failure (1)
Bryson-Cahn et al., 2019 (87)	9	9/−/−	*S. aureus* (9)	1,000 mg once or 1,000–1,500 mg LD then 500 mg day 7	2 doses	9 (100)	Not reported
Wunsch et al., 2019 (88)	25	15/6/4	Not specified[e]	1,000 mg LD then 500 mg weekly or 1,500 mg once or 1,500 mg weekly × 2[g]	Median, 3 doses (range, 1–32)[g]	23 (92)	Dyspnea (1), hypertension during infusion (1), fatigue and vertigo (1)[g]
Dinh et al., 2019 (89)	19	9/10/−	Not specified[e]	1,500 mg once or 1,500 mg LD then 1,000–1,500 mg at day 7 or 14	1–2 doses	13 (68)	Hypersensitivity (2), headache (1), eosinophilia (1), phlebitis (1)[g]
Bork et al., 2019 (111)	7	Not specified[h]	Not specified[e]	Not specified[e]	Median, 4 doses	4 (57)	Acute kidney injury (2), rash and pruritus (1)[g]
Veve et al., 2020 (112)	12	Not specified[e]	Not specified[e]	1,500 mg once, 1,500 mg for 2 doses at day 1 and day 7, or 1,500 mg for 2 doses at day 1 and day 14	1–2 doses	NA (91)[i]	Catheter infection (1), hypersensitivity (1)[g]
Total	140	59[j]/38/18				113[j] (88)	
Bone and joint infections		IAI/BJI					
Rappo et al., 2019 (93)	67	−/67	*S. aureus* (42), CoNS (14), *Enterococcus* (8), other (33)[f]	1,500 mg weekly × 2	2 doses	65 (97)	Drug-related treatment adverse event (1)
Bouza et al., 2018 (85)	33	20/13	*S. aureus* (9), CoNS (16), *Enterococcus* spp. (3), other (6)[f]	1,000-mg LD then 500 mg weekly	Median, 3 doses (range, 1–24)[g]	28 (85)	Rash (2), tachycardia (2), RCI (2), nausea (1), rectal bleeding (1), candidiasis (1)[g]
Morata et al., 2019 (95)	64	45/19	*S. aureus* (14), CoNS (33), *Enterococcus* spp. (9), other (22)[f]	1,000-mg LD then 500 mg weekly	Median, 5 doses	45 (70)	GI problems (3), rash (1), phlebitis (1), asthenia (1), RCI (1)
Almangour et al., 2019 (96)	31	−/31	*S. aureus* (27), CoNS (1), other (6)[f]	1,000 mg LD then 500 mg weekly or 1,500 mg weekly × 2	Median, 3 doses	28 (90)	None
Tobudic et al., 2019 (97)	46	8/38	Not specified[k]	1,500 mg LD then 1,000 mg every 2 wk, 1,000 mg LD then 500 mg weekly, or 1,500 mg LD then 1,500 mg at day 8[g]	Range, 2–32 doses[l]	30 (65)	Nausea (1), exanthema (2), hyperglycemia (1)[g]
Dinh et al., 2019 (89)	48	−/48	Not specified[k]		Range, 1–10 doses	35 (73)	

(Continued on next page)

TABLE 2 (Continued)

Reference	*n*	NV/PV/CD or IAI/BJI	Bacterium or bacteria (*n*)[b,c]	Most frequent dosing	Duration/no. of doses	Success, *n* (%)[d]	Adverse events (*n*)
				1,500 mg every 7–14 days × 2 or 1,500 mg once			Hypersensitivity (2), headache (1), eosinophilia (1), phlebitis (1)[g]
Wunsch et al., 2019 (88)	62	32/30	Not specified[k]	1,000 mg LD then 500 mg weekly, 1,500 mg once, or 1,500 mg weekly × 2[g]	Median, 3 doses (range, 1–32)[g]	58 (94)	Dyspnea (1), hypertension (1), fatigue and vertigo (1)[g]
Matt et al., 2021 (98)	17	17/—	*S. aureus* (10), CoNS (10), *E. faecalis* (1), other (5)[f]	1,500 mg weekly × 2 or 1,500 mg once	Median, 2 doses (range, 1–10)[g]	8 (47)	None
Buzón-Martín et al., 2019 (99)	16	16/—	*S. aureus* (6), CoNS (7), *Enterococcus* spp. (6)	1,500 mg LD, then 500 mg on day 7, then 500 mg every 2 wk	Range, 6–12 wk	11 (69)	Leukopenia (1), rash (1)
Bork et al., 2019 (111)	15	Not specified	Not specified[e]	Not specified[e]	Median, 4 doses	7 (47)	Acute kidney injury (2), rash and pruritus (1)[g]
Veve et al., 2020 (112)	49	Not specified	Not specified[k]	1,500 mg once, 1,500 mg for 2 doses at day 1 and day 7, or 1,500 mg for 2 doses at day 1 and day 14	1–2 doses	NA (91)[i]	Catheter infection (1), hypersensitivity (1)[g]
Cojutti et al., 2021 (94)	15	11/4	*S. aureus* (5), CoNS (9), *E. faecalis* (1)	1,500 mg weekly × 2	2 doses	12 (80)	None
Total	463	149/250[j]				327[j] (79)	

[a]BJI, bone and joint infection without implant (e.g., vertebral osteomyelitis, septic arthritis); CD, cardiac device; CoNS, coagulase-negative staphylococci; GI, gastrointestinal; IAI, implant-associated infection (e.g., prosthetic joint infection); LD, loading dose; NV, native valve; PV, prosthetic valve; RCI, reversible creatinine increase.
[b]Includes methicillin-susceptible and -resistant *S. aureus*.
[c]Categories are not mutually exclusive; polymicrobial cultures are included.
[d]Definitions of clinical success were heterogeneous across the studies. For details, refer to individual publication.
[e]Not specified for infective endocarditis.
[f]"Other" also includes sterile cultures or unavailable cultures.
[g]Corresponds to total cohort for those studies that reviewed cases with different infection sources.
[h]One patient had a cardiac device infection; the other 6 patients had an unspecified endovascular infection that excluded bacteremia.
[i]Clinical success rate for entire cohort, not specified for infective endocarditis or bone and joint infections.
[j]Excludes studies where clinical outcomes were not specified for infective endocarditis or bone and joint infections.
[k]Not specified for IAI and BJI.
[l]Osteomyelitis median of 8 weeks (range, 4 to 32 weeks), vertebral osteomyelitis median of 9 weeks (range, 2 to 16 weeks), acute septic arthritis median of 3.5 weeks (range, 2 to 10 weeks), and prosthetic joint infection median of 12 weeks (range, 6 to 32 weeks).

isolate after 6 months of dalbavancin therapy (dalbavancin MIC not reported) and was treated with vancomycin, to be then switched back to dalbavancin (1,000-mg loading dose followed by 500 mg weekly) for 8 months until his death. Among the remaining 2 patients, one of them died due to a non-infection-related condition after 4 months of therapy, and the other is still under dalbavancin (week 52 of therapy) and in good clinical condition (90). Finally, one patient with an MSSA tricuspid valve IE complicated with septic pulmonary emboli and another diagnosed with a prosthetic valve IE due to *Staphylococcus epidermidis* managed without surgery were treated with 5 doses of dalbavancin (1,500 mg on days 1, 7, 42, 112, and 189). Both of them were reported to have a good clinical and microbiological outcome (91).

(ii) Bone and joint infections. Dalbavancin has demonstrated good penetration into synovium, synovial fluid, and bone (19.2, 11.6, and 3.8 μg/mL, respectively, 168 h after administration), with a bone-plasma ratio of 13%, similar to the free drug concentration observed in serum. This, coupled with its PK/PD profile, has raised great interest for clinicians managing BJIs (92). There are multiple reports of the off-label use of dalbavancin to treat patients with different types of BJIs. The bottom portion of Table 2 summarizes the largest case series available (i.e., $\geq$15 cases), along with the only randomized clinical trial published to date (93).

Rappo et al. performed a phase II, single-center, randomized, open-label, comparator-controlled, parallel-group study that included patients with non-implant-related acute or chronic osteomyelitis (93). All eligible patients underwent surgical debridement at baseline and had a Gram-positive pathogen recovered from a bone culture. Participants were randomized to dalbavancin (1,500 mg at days 1 and 8) or SOC (vancomycin intravenously [i.v.] for 30 days or vancomycin i.v. for 5 to 16 days followed by linezolid or levofloxacin i.v. to complete 30 days of therapy). Patients receiving dalbavancin exhibited a 97% (95% confidence interval [CI], 89.6 to 99.6%) clinical cure rate at day 42, compared to 88% (95% CI, 47.3 to 99.7%) in the SOC group. Clinical improvement and decrease in C-reactive protein were higher in the dalbavancin group than in the SOC group (94% versus 63%, respectively). Of note, the most frequently recovered bacterial organisms included MSSA, MRSA, CoNS (*S. epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, etc.), enterococci, and streptococci, without major differences between groups. Importantly, a recent pharmacokinetic study suggested that the dosing scheme utilized in this study (i.e., 1,500 mg at days 1 and 8) ensures efficacy against both MSSA and MRSA for up to 5 weeks (94), resulting in a probability of target attainment (area under the concentration-time curve [AUC]/$MIC_{24\ h}$ of $>$111) of $\geq$90% until day 36.

As mentioned, there are several retrospective cohorts reporting the use of dalbavancin to manage osteomyelitis, septic arthritis, PJIs, and other BJIs (85, 88, 89, 93–99). Taken together, the articles summarized in the bottom portion of Table 2 encompass a total of 463 patients with BJIs managed with dalbavancin either for consolidation therapy after a successful initial regimen or as salvage therapy. The most common pathogens included in these reports were *S. aureus*, followed by CoNS (Table 2, bottom portion). The clinical success rate ranged from 47% to 97% and varied widely across different types of infections, dalbavancin indications (salvage versus consolidation therapy), and surgical debridements. A major problem of the available clinical experience with dalbavancin is the variability in dosing regimens, even within the same case series. The more frequent dosing options were a 1,000- to 1,500-mg loading dose, followed by 500 to 1,500 mg weekly for 2 to 12 weeks. However, dosing regimens of 1,000 mg every 2 weeks have also been used.

CLOSING THE KNOWLEDGE GAP IN CLINICALLY RELEVANT QUESTIONS

As is frequently observed with new antimicrobials, both dalbavancin and oritavancin were initially approved for the management of infections against which clinicians do not face critical needs—in this particular case, complicated skin and skin structure infections. The main reason for the mismatch between "area of need" and "registrational trial" relates to the feasibility (in terms of both cost and ease of recruiting) of performing clinical trials attempting to address critically relevant gaps of knowledge (100, 101). As highlighted above, clinical experience with dalbavancin and oritavancin for severe infections is very limited and heterogenous with respect to indications, dosing regimens, and patient populations. Logistically, lack of accessible

susceptibility testing continues to be a major hindrance for the use of LGPs, especially in the management and monitoring of infections with multidrug-resistant organisms or poor therapeutic response.

An increasing number of initiatives and research groups across the world are attempting to close these knowledge gaps by approaching relevant clinical questions from refreshing perspectives. A good example of these efforts is the Antimicrobial Resistance Leadership Group (ARLG) (102), an NIH-funded group that has made advances such as the desirability of outcome ranking (DOOR), an innovative way of evaluating clinically meaningful outcomes beyond the classical endpoints (103–105). Similarly, recent studies have addressed highly relevant questions such as the need for long-term intravenous antimicrobial therapy in IE and BJIs, shifting the "Overton window" to normalize oral step-down in a significant group of patients (106, 107). Importantly, these clinical trials have been conducted following a pragmatic approach, highlighting the pertinence of such design to help close critical knowledge gaps in clinically relevant areas.

In the case of LGPs, their unique pharmacological properties and potent *in vitro* activity against pressing multidrug-resistant Gram positives make them particularly interesting tools to address several important clinical situations. In our opinion, the most highly pressing scenarios in which dalbavancin and oritavancin could play an important role include (i) complicated and uncomplicated BSIs, (ii) IE and cardiac device-related infections, (iii) acute and chronic osteomyelitis (with and without foreign material), (iv) vertebral osteomyelitis and spondylodiscitis, (v) acute and chronic PJIs, and (vi) other specific situations requiring prolonged antimicrobial therapy. The need for data in these clinical situations only increases when caused by multidrug-resistant organisms such as VRE or MRSA.

In addition, important questions regarding the use of LGPs remain unanswered, including the best therapeutic strategy in terms of dosing, combination therapy, interval of administration, and length of therapy. Indeed, their pharmacokinetic properties, while favorable to clinicians and patients, make it difficult to compare the efficacy of these agents with SOC. For example, a single dose of either LGP may inadvertently lead to overtreatment of nonsevere infections (e.g., ABSSSIs) as the concentrations will remain in the bloodstream longer than the typical 5 to 7 days of therapy for most indications. Similarly, dosing of LGPs challenges the conventional PK/PD principles that have been used to optimize efficacy, which relied on variables such as $AUC_{24\ h}$. With long half-lives, $AUC_{24\ h}$ is expected to decline each day with these agents, instead of remaining constant with repeated dosing like SOC antimicrobials. Likewise, the T_{MIC}, which is reported as a percentage of dosage interval in which the serum level exceeds the MIC, may be undefined when dosing frequencies are unknown. Overall, use of LGPs will challenge clinicians to reevaluate the means that have been used to optimize efficacy of antimicrobials. Similarly, given the benefit of combining lipopeptides or glycopeptides with other antimicrobials such as β-lactams to achieve synergistic effects or prevent the emergence of resistance, it is tempting to speculate that the same principles can be applied to LGPs. However, as discussed, clinical data regarding this issue are lacking, and the studies addressing it are scarce, heterogeneous, and restricted to very few organisms (66). Moreover, the unmatched pharmacokinetic profiles of LGPs bring forth new questions, such as the duration for the secondary antibiotic molecules. In addition, more importantly, although antibiotic combinations are sometimes useful to increase potency or prevent the development of resistance, this approach is not always beneficial and sometimes can have detrimental effects (35). Therefore, this is yet another knowledge gap for LGPs that requires attention from the scientific community.

As we continue to gather experience with these drugs, another crucial area of uncertainty is the possibility of collateral damage caused by long periods of bacterial exposure to both inhibitory and subinhibitory concentrations of these antimicrobials. Indeed, the unique pharmacokinetic profile of LGPs may result in unforeseen risks, such as profound dysbiosis and the development of antibiotic tolerance or resistance. Importantly, we found one ongoing study evaluating the resistance selection potential of LGPs, the results of which will be highly interesting for the scientific community (https://reporter.nih.gov/).

From the clinical perspective, Table 3 provides a summary of the currently ongoing clinical studies (https://clinicaltrials.gov/) attempting to understand the role of oritavancin and dalbavancin in the management of some of the infections highlighted above according

TABLE 3 Summary of currently active registered clinical trials studying oritavancin or dalbavancin[a]

Drug and trial identifier	*n*	Infection(s)	Design	Dosing	Comparator	Primary outcome	Status	Comments
Oritavancin								
NCT03761953	15	*S. aureus* bacteremia with or without IE	Single-center, open-label, pilot study	1,200 mg once[b]	None	Relapse at 6 wk	Recruiting	Focused on opioid users, requires prove of negative blood cultures
Dalbavancin								
NCT03982030	24	Bacteremia, right-sided IE, BJIs	Phase 4, single-center, open-label, pilot study	1,500 mg on day 0 and days 8–10	None	Clinical success and relapse at 6 wk	Not yet recruiting	Excludes left-sided IE, requires prove of negative blood cultures.
NTC03426761	50	BJI, including PJI and septic arthritis	Phase 4, randomized, open-label, pilot study	1,500 mg on day 0 and every 14 days (2–4 times)	SOC	Clinical cure at 6 wk	Recruiting	Confirmed Gram positive on culture
NTC04775953	200	Complicated *S. aureus* bacteremia or right-sided native valve IE	Phase 2b, multicenter, randomized, open-label, assessor-blind, superiority study	1,500 mg on days 1 and 8	SOC	Clinical success (DOOR)	Recruiting	Patients must have cleared their baseline bacteremia
NTC05046860	43	Acute or chronic PJI of knee or hip (1st episode) due to *Staphylococcus* spp.	Single group, open label	1,500 mg on days 0, 15, and 36	None	Clinical success at 48 wk	Not yet recruiting	Patients will also receive rifampin 600 mg daily, all patients undergo surgical debridement with implant retention (acute infections) or 1-stage revision (chronic infections)
NTC05117398	406	Noncomplicated CR-BSI due to *S. aureus*	Phase 3, pragmatic, open-label, noninferiority, randomized multicenter trial	1,500 mg once	SOC	Clinical cure and relapse at day 30	Not yet recruiting	Catheter removal required before entering study

[a]BJI, bone and joint infection; BSI, bloodstream infection; CR, catheter-related; DOOR, desirability of outcome ranking; IE, infective endocarditis; PJI, prosthetic joint infection; SOC, standard of care. Information was obtained from www.clinicaltrials.gov. Only clinical studies with primary endpoints focusing on clinical outcomes were included.
[b]The aim is to complete the last 2 weeks of therapy out of a total of 4 weeks for bacteremia and 6 weeks for infective endocarditis.

TABLE 4 Summary of knowns and gaps of knowledge

Category	Description
Knowns	Mechanism of action
	Mechanisms of resistance
	Pharmacokinetics
	Spectrum of activity
	Safety and tolerability of short-term duration
	Efficacy for FDA-labeled indications
	Dosing regimen for FDA-approved indications
	Target populations for FDA-approved indications
	Susceptibility testing methodology
	Combination therapy (*in vitro* data)
	Breakpoints available for limited organisms
Unknowns/limited knowledge	Efficacy and safety for off-label indications
	Optimal dosing for off-label indications
	Role and timing in therapy (initial, salvage, consolidation)
	Impact on microbiome
	Type and accessibility of susceptibility testing techniques
	Definition and assessment of tolerance
	Combination therapy (*in vivo* or clinical data)
	Efficacy against multidrug-resistant pathogens
	PK/PD targets
	Selection of resistance and mutant selection window
	Clinical impact of tolerance, resistance, and cross-resistance
	Cost-effectiveness
	Safety and tolerability for long-term duration
	Appropriate follow-up
	Accessibility of susceptibility testing

to the Clinical Trials Database (108). Notably, only one of the six active trials involves the use of oritavancin, four of them focus on BSIs (including IE), and the remaining two focus on BJIs and PJIs. Of note, only three of these studies correspond to randomized clinical trials, all of which will compare dalbavancin to the SOC for the management of uncomplicated, catheter-related *S. aureus* bacteremia (NTC05117398), complicated *S. aureus* bacteremia, including right-sided IE (NTC04775953), and BJIs (NTC03426761) (Table 3). Therefore, ongoing studies will provide relevant information to continue to understand the potential role of LGPs in highly needed clinical situations. As shown in Table 3, the utility of LGPs for treatment of severe infections caused by non-*S. aureus* organisms, particularly VRE, remains to be addressed and will continue to be an important unfilled gap of knowledge. Until other clinical trials can be started to address this void, our clinical experience is limited to case reports and small case series from those clinicians who are compelled to use these antimicrobials. To that end, we encourage clinicians to share their valuable experiences to help bridge the gap of our current knowledge and to take the lead on conducting clinical trials to answer these relevant questions.

Finally, Table 4 summarizes a list of topics for which there are considerable amounts of literature and the main gaps of knowledge regarding the clinical use of LGPs.

FINAL THOUGHTS

The tale of the LGP illustrates the increasing complexity of antimicrobial use and the ever-growing need for high-quality data to inform clinical decisions aimed to optimize and preserve critical antimicrobials. Their remarkable pharmacologic and pharmacokinetic characteristics make LGPs attractive as alternatives that may facilitate quicker hospital discharge, limit long-term intravenous accesses, and decrease the need for strict and frequent outpatient follow-up. Nevertheless, many gaps of knowledge remain to be addressed with high-quality clinical data before clinicians and institutions should broaden their use. While our current knowledge regarding the utility of LGPs for the management of non-FDA-approved

indications is limited to sporadic cases and case series, several ongoing studies promise to provide important answers. Other clinical questions, however, will continue to wait their turn.

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