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EDITORIAL

Multidose Regimens of Long-Acting Antibiotics: New Horizons for Difficult-to-Treat Infections

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Introduction

Historical Note

Over the last decade, clinicians have increasingly employed two long-acting antibiotics, oritavancin (ORI) and dalbavancin (DBV), for treating infections caused by Gram-positive pathogens. Both lipoglycopeptides—derived from vancomycin and teicoplanin, respectively—exhibit pharmacological profiles extending beyond their narrow spectrum of activity against Gram-positive bacteria. They are well tolerated and share similar pharmacokinetic/pharmacodynamic (PK/PD) properties, including a long elimination half-life ($t_{1/2}$), bactericidal activity via disruption of cell wall synthesis, intracellular penetration, a large apparent volume of distribution (Vd), slow predominantly renal elimination, optimal tissue penetration and no clinically significant drug-drug interactions (Baiardi et al, 2023; Leuthner et al, 2015; Pontali et al, 2025).

Originally approved for identical indications, ORI and DBV are administered as single doses to maintain efficacy for approximately two weeks in treating acute bacterial skin and skin structure infections (ABSSSIs) caused by Gram-positive organisms in adult and pediatric patients aged ≥3 months (Baiardi et al, 2023; Leuthner et al, 2015). However, post-marketing research and clinical experience, facilitated by their unique PK/PD profiles (Table 1), have supported their expanded use for other Gram-positive infections. These distinct PK/PD characteristics initially underpinned their approved use and subsequently provided the rationale for extending their application to other clinical indications (Pontali et al, 2025).

Consequently, new opportunities for ORI and DBV use have gradually emerged. These include: (1) treating non-ABSSSI infections; (2) completing antibiotic courses initiated with other agents; (3) initiating and finishing long-term treatments; and (4) suppressive treatment regimens.

New Therapeutical Evidences

The increasing clinical experience with multidose lipoglycopeptide regimens in off-label settings stems from their unique PK/PD characteristics, which allow subsequent administrations to be spaced weeks apart. For instance, administering a second full DBV dose (1500 mg) one week after the initial dose significantly

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Table 1. Key characteristics of long-acting antibiotics.

Characteristic		Oritavancin	Dalbavancin
Pharmacokinetics	Absorption	No oral formulation, intravenous infusion mandatory	No oral formulation, intravenous infusion mandatory
	Distribution	Apparent volume of distribution exceeds total body water (approximately 1 L/Kg). 85–90% protein-bound	Apparent volume of distribution is similar to the volume of extracellular fluids (0.2–0.7 L/Kg). 93% protein-bound
	Metabolism	No major metabolites. Weak inhibitor or inducer of cytochrome P450 isoenzymes	Main metabolites: hydroxy-dalbavancin and mannose aglycone-dalbavancin (<25% of the administered dose)
	Elimination	Slow mainly renal elimination as an unchanged moiety (<1% faecal over 2 weeks after dosing) ($t_{1/2}$ 393 h)	Mainly renal (approximately 10% as hydroxy-dalbavancin) and faecal (20% of administered dose) ($t_{1/2}$ 372 h)
Accumulation in macrophages		Yes	No
Pharmacodynamics		Inhibition of bacterial wall synthesis, permeabilisation of bacterial membrane	Inhibition of bacterial wall synthesis, permeabilisation of bacterial membrane
Susceptible microorganisms		Gram+, including MRSA, VRE (both Van A and B)	Gram+, including MRSA, VRE (Van B only)
Biofilm activity		Yes	Yes
Multidose off-label dosing		1200 mg + 800 mg weekly or 1200 mg + 1200 mg weekly	3000 mg over 4 weeks with flexibility (preferred 1500 mg day 0 + 1500 mg day 7), then TDM-guided with additional 1500 mg doses every few weeks
Therapeutic drug monitoring targets		Not yet defined	C_{trough} >8.04 mg/L for a MIC up to 0.125 mg/L (Cojutti et al, 2021); C_{trough} >14.29 mg/L for MIC up to 0.25 mg/L (Baiardi et al, 2025)

Note: The 'Gram+' indicates Gram-positive. Abbreviations: MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin resistant *Enterococcus*; TDM, therapeutic drug monitoring.

extends therapeutic coverage for up to 5–6 weeks. If necessary, additional full DBV doses can be administered at varying intervals, typically every 3 to 6 weeks, based on the patient's total body weight or guided by therapeutic drug monitoring (TDM) (Baiardi et al, 2025; Cattaneo et al, 2025; Senneville et al, 2023). In contrast, multidose ORI regimens have been less extensively studied. Although several reviews on repeated weekly (or longer interval) administrations of different ORI doses exist, no consensus has been reached on optimal doses and frequency (Baiardi et al, 2023; Lupia et al, 2023).

Non-ABSSSI clinical conditions amenable to treatment with repeated ORI or DBV administration include catheter-related infections, osteomyelitis, prosthetic joint infections, endocarditis (native or prosthetic valves), vascular implant infections, and infections in diabetic patients (Baiardi et al, 2023; Hidalgo-Tenorio et al, 2025; Lupia et al, 2023; Luque Paz et al, 2021; Thomas et al, 2020).

Lipoglycopeptides' ability to disrupt biofilm makes them a valuable option for infections where source control is unattainable or complicated by high surgical risk (Di Bella et al, 2025). This property is particularly relevant for infections involving catheters or prosthetic material, such as implantable cardioverter defibrillators, short- or long-term vascular catheters, vascular prostheses, prosthetic valve infections, and prosthetic joint infections (Baiardi et al, 2023; Cattaneo et al, 2024; Hidalgo-Tenorio et al, 2025; Lafon-Desmurs et al, 2024; Lupia et al, 2023; Pontali et al, 2025; Thomas et al, 2020). Early studies on resistance development, using both direct selection and serial passage, failed to produce stable mutants with decreased susceptibility to lipoglycopeptides (Goldstein et al, 2007). However, recent reports have begun to highlight concerns regarding this issue (Al Janabi et al, 2023; Werth et al, 2025).

Repeated administration addresses key challenges in managing patients requiring prolonged antibiotic treatment for Gram-positive bacterial infections. For instance, long-acting lipoglycopeptides reduce hospitalisation time by enabling treatment completion with one or two doses prior to discharge or facilitating early outpatient care (Sobrino et al, 2025). Indeed, outpatient parenteral antibiotic therapy (OPAT) with DBV or ORI is effective for a wide range of infections. Despite higher per-dose costs, DBV or ORI OPAT reduces treatment duration and yields cost savings across healthcare systems (Bai et al, 2023; Zinzi et al, 2022).

Furthermore, lipoglycopeptides reduce intravenous administration frequency, simplifying nursing management. Consequently, they may help avoid complications associated with central line placement, particularly in patients with limited venous access (e.g., persons who inject drugs, chemotherapy survivors) (Pontali et al, 2025; Sobrino et al, 2025). These features collectively improve patients' quality of life, mobility and help prevent also non-infectious or catheter-related complications (Luque Paz et al, 2021). Long-acting antibiotics also benefit "difficult-to-treat" patients facing socioeconomic barriers, such as residing distant from healthcare centers, lacking financial support/insurance, limited caregiver support, or inability to access home care services (Sobrino et al, 2025).

Suppressive or long-term lipoglycopeptide treatment can be challenging due to the limited predictability of redosing intervals. Individualising intervals using a

TDM-guided approach may optimise efficacy and safety by adjusting timing based on body weight and/or serum concentrations (Baiardi et al, 2025). TDM-guided dosing optimises lipoglycopeptide PK/PD relationships, preventing under- or over-dosing that could lead to treatment failure, increased costs, and toxicity (Baiardi et al, 2025; Cattaneo et al, 2024; Lafon-Desmurs et al, 2024; Pontali et al, 2025; Senneville et al, 2023).

Lipoglycopeptide pharmacokinetics can be affected in specific populations, such as obese individuals and vulnerable injecting drug users (IDUs), where factors like opioid use, malnutrition, hypoproteinemia, cachexia, and altered tissue distribution may contribute to unpredictable blood levels and efficacy duration (Baiardi et al, 2025). While DBV blood level assays are widely available (Cafaro et al, 2025; Chiriac et al, 2022), optimal target concentrations remain debated (Baiardi et al, 2025; Pontali et al, 2025). Consequently, empirical individualisation of redosing intervals based on total body weight may be necessary when TDM is unfeasible (Baiardi et al, 2025). In contrast, the absence of a published, validated quantitation method for ORI limits TDM-guided dose optimisation in special populations (Baiardi et al, 2023).

The excellent safety profile of both lipoglycopeptides, demonstrated in real-world studies including off-label use, further supports their expanded application (Baiardi et al, 2023; Hidalgo-Tenorio et al, 2025; Lupia et al, 2023).

Despite these advantages, significant knowledge gaps persist, particularly for long-term treatment. These include limited information on: the optimal number of administrations for a planned course, precise redosing timing and frequency, exact per-administration dosage (e.g., ORI: 800 mg *vs*. 1200 mg), criteria for antibiotic combination therapy, and clearly defined target concentration ranges for TDM-guided dosing to inform re-dosing decisions.

Conclusion

Lipoglycopeptides, as the only currently available long-acting antibiotics, possess unique properties and advantages supporting their expanded use beyond original indications. Further research is essential to address the identified knowledge gaps and optimise long-term use, thereby resolving outstanding clinical questions.

Availability of Data and Materials

Not applicable.

Author Contributions

EP, GB, FDP and FM contributed to conceptualization, writing and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Key Points

- Long-acting antibiotics possess unique pharmacokinetic/pharmacodynamic (PK/PD) characteristics that enable their expanded use in multidose regimens.
- Several experiences exist with lipoglycopeptide-based multidose regimens for treating difficult-to-treat infections caused by Gram-positive bacteria, including catheter-related infections, osteomyelitis, prosthetic joint infections, endocarditis, and vascular implant infections.
- Long-acting antibiotics enable innovative treatment strategies that permit early hospital discharge or may even avoid hospitalisation.
- Lipoglycopeptide-based multidose regimens administered for long-term antibiotic treatment may benefit from a TDM-guided dosing strategy to individualise infusion intervals.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

Al Janabi J, Tevell S, Sieber RN, Stegger M, Söderquist B. Emerging resistance in Staphylococcus epidermidis during dalbavancin exposure: a case report and in vitro analysis of isolates from prosthetic joint infections. The Journal of Antimicrobial Chemotherapy. 2023; 78: 669–677. https://doi.org/10.1093/jac/dkac434

Bai F, Mazzitelli M, Silvola S, Raumer F, Restelli U, Croce D, et al. Cost analysis of dalbavancin versus standard of care for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in two Italian hospitals. JAC-Antimicrobial Resistance. 2023; 5: dlad044. https://doi.org/10.1093/jacamr/dlad044

Baiardi G, Cameran Caviglia M, Boni S, Di Paolo A, Marini V, Cangemi G, et al. Multidose Dalbavancin Population Pharmacokinetic Analysis for Prolonged Target Attainment in Patients Requiring Long-Term Treatment. Antibiotics. 2025; 14: 190. https://doi.org/10.3390/antibiotics14020190

Baiardi G, Cameran Caviglia M, Piras F, Sacco F, Prinapori R, Cristina ML, et al. The Clinical Efficacy of Multidose Oritavancin: A Systematic Review. Antibiotics. 2023; 12: 1498. https://doi.org/10.3390/antibiotics12101498

Cafaro A, Mariani M, Pigliasco F, Baiardi G, Barco S, Biondi M, et al. Liquid Chromatography-Tandem Mass Spectrometry Method for Therapeutic Drug Monitoring of Dalbavancin in Plasma

of Pediatric and Young Adult Patients. Therapeutic Drug Monitoring. 2025; 47: 363–369. https://doi.org/10.1097/FTD.0000000000001260

Cattaneo D, Fusi M, Galli L, Genovese C, Giorgi R, Matone M, et al. Proactive therapeutic monitoring of dalbavancin concentrations in the long-term management of chronic osteoarticular/periprosthetic joint infections. Antimicrobial Agents and Chemotherapy. 2024; 68: e0002324. https://doi.org/10.1128/aac.00023-24

Cattaneo D, Fusi M, Mariani C, Passerini M, Scandiffio L, Birindelli S, et al. Effect of body mass index on the timing of therapeutic drug monitoring-guided dalbavancin dosing in patients with osteoarticular infections. The Journal of Antimicrobial Chemotherapy. 2025; 80: 1726–1732. https://doi.org/10.1093/jac/dkaf132

Chiriac U, Rau H, Frey OR, Röhr AC, Klein S, Meyer AL, et al. Validation and Application of an HPLC-UV Method for Routine Therapeutic Drug Monitoring of Dalbavancin. Antibiotics. 2022; 11: 541. https://doi.org/10.3390/antibiotics11050541

Cojutti PG, Rinaldi M, Gatti M, Tedeschi S, Viale P, Pea F. Usefulness of therapeutic drug monitoring in estimating the duration of dalbavancin optimal target attainment in staphylococcal osteoarticular infections: a proof-of-concept. International Journal of Antimicrobial Agents. 2021; 58: 106445. https://doi.org/10.1016/j.ijantimicag.2021.106445

Di Bella S, Mearelli F, Gatti M. The importance of antibiofilm antibiotics in hardware-associated infections. Clinical Infectious Diseases. 2025; ciaf064. https://doi.org/10.1093/cid/ciaf064

Goldstein BP, Draghi DC, Sheehan DJ, Hogan P, Sahm DF. Bactericidal activity and resistance development profiling of dalbavancin. Antimicrobial Agents and Chemotherapy. 2007; 51: 1150–1154. https://doi.org/10.1128/AAC.00620-06

Hidalgo-Tenorio C, Sadyrbaeva-Dolgova S, Aparicio-Minguijón E, Alarcón A, Plata A, Martínez Marcos FJ, et al. Real-world evidence of dalbavancin effectiveness as consolidation therapy in infective endocarditis due to Enterococcus spp. Journal of Microbiology, Immunology, and Infection. 2025; 58: 429–436. https://doi.org/10.1016/j.jmii.2025.03.001

Lafon-Desmurs B, Gachet B, Hennart B, Valentin B, Roosen G, Degrendel M, et al. Dalbavancin as suppressive therapy for implant-related infections: a case series with therapeutic drug monitoring and review of the literature. European Journal of Clinical Microbiology & Infectious Diseases. 2024; 43: 1475–1480. https://doi.org/10.1007/s10096-024-04849-0

Leuthner KD, Yuen A, Mao Y, Rahbar A. Dalbavancin (BI-387) for the treatment of complicated skin and skin structure infection. Expert Review of Anti-Infective Therapy. 2015; 13: 149–159. https://doi.org/10.1586/14787210.2015.995633

Lupia T, De Benedetto I, Bosio R, Shbaklo N, De Rosa FG, Corcione S. Role of Oritavancin in the Treatment of Infective Endocarditis, Catheter- or Device-Related Infections, Bloodstream Infections, and Bone and Prosthetic Joint Infections in Humans: Narrative Review and Possible Developments. Life. 2023; 13: 959. https://doi.org/10.3390/life13040959

Luque Paz D, Lakbar I, Tattevin P. A review of current treatment strategies for infective endocarditis. Expert Review of Anti-Infective Therapy. 2021; 19: 297–307. https://doi.org/10.1080/14787210.2020.1822165

Pontali E, Baiardi G, Del Puente F, Mattioli F. Long-Acting Antibiotics: New Opportunities Beyond Acute Bacterial Skin and Skin Structure Infections (ABSSSIs)! Antibiotics. 2025; 14: 164. https://doi.org/10.3390/antibiotics14020164

Senneville E, Cuervo G, Gregoire M, Hidalgo-Tenorio C, Jehl F, Miro JM, et al. Expert Opinion on Dose Regimen and Therapeutic Drug Monitoring for Long-Term Use of Dalbavancin: Expert Review Panel. International Journal of Antimicrobial Agents. 2023; 62: 106960. https://doi.org/10.1016/j.ijantimicag.2023.106960

Sobrino B, Luque S, Velasco-Arnaiz E, Lovatti González R, Del Pozo JL. Gram-positive infections in special populations. Expert view on the role of dalbavancin. Expert Review of Anti-Infective Therapy. 2025; 23: 265–275. https://doi.org/10.1080/14787210.2025.2477196

Thomas G, Henao-Martínez AF, Franco-Paredes C, Chastain DB. Treatment of osteoarticular, cardiovascular, intravascular-catheter-related and other complicated infections with dalbavancin and oritavancin: A systematic review. International Journal of Antimicrobial Agents. 2020; 56: 106069. https://doi.org/10.1016/j.ijantimicag.2020.106069

Werth BJ, Zhang R, Barreras Beltran IA, Penewit K, Waalkes A, Holmes EA, et al. Simulated exposures of oritavancin in in vitro pharmacodynamic models select for methicillin-resistant Staphylo-

coccus aureus with reduced susceptibility to oritavancin but minimal cross-resistance or seesaw effect with other antimicrobials. The Journal of Antimicrobial Chemotherapy. 2025; 80: 1108–1115. https://doi.org/10.1093/jac/dkaf042

Zinzi D, Vlachaki I, Falla E, Mantopoulos T, Nathwani D. Cost-minimisation analysis of oritavancin for the treatment of acute bacterial skin and skin structure infections from a United Kingdom perspective. The European Journal of Health Economics. 2022; 23: 1371–1381. https://doi.org/10.1007/s10198-022-01432-2