JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlag150

JAC-Antimicrobial Resistance

Oritavancin as consolidation or suppressive therapy in infective endocarditis and device-related infections: real-world experience with therapeutic drug monitoring

Simone Giuliano[1], Luca Martini [1]*, Maria Merelli [1], Giulia Turicchi[2], Jacopo Angelini[3], Sara Ferin[4], Antonio D'avolio[5], Paolo Gaibani [6,7], Marco Bongiovanni [2,8] and Carlo Tascini [1,4]

[1]Infectious Diseases Division, Department of Medicine (DMED), University of Udine and Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy; [2]Division of Infectious Diseases, Ente Ospedaliero Cantonale, Lugano Hospital, Lugano, Switzerland; [3]Clinical Pharmacology and Toxicology Institute, University Hospital Friuli Centrale ASUFC, Udine 33100, Italy; [4]Department of Medicine (DMED), University of Udine and Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy; [5]Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Turin—ASL 'Città di Torino', Turin, Italy; [6]Department of Diagnostic and Public Health, University of Verona, Verona, Italy; [7]Microbiology and Virology Unit, Department of Pathology, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [8]Division of Infectious Diseases, Ente Ospedaliero Cantonale, Lugano Hospital, Switzerland; Department of Biomedical Sciences, University of Southern Switzerland, Lugano, Switzerland

*Corresponding author. E-mail: luca.martini@asufc.sanita.fvg.it

Received 20 March 2026; accepted 25 June 2026

Background: Oritavancin is a long-acting semisynthetic lipoglycopeptide with potent activity against a broad range of Gram-positive pathogens. Its multimodal mechanism of action and prolonged terminal half-life allow for extended dosing intervals, making it an off-label option for invasive infections requiring long-term antimicrobial exposure. However, evidence supporting its use in infective endocarditis and cardiac device–related infections remain limited.

Methods: We performed a retrospective multicentre observational study including adult patients treated with multidose oritavancin for infective endocarditis and cardiac device-related infections between 2020 and 2025. Oritavancin was administered as consolidation or as long-term suppressive therapy. Demographic, clinical, microbiological, pharmacological, and outcome data were collected. Therapeutic drug monitoring was performed, and pre-dose plasma concentrations were analysed. Clinical outcomes included clinical cure, microbiological failure, adverse events, and 30- and 90-day all-cause mortality.

Results: Nine patients were included. Oritavancin was mainly administered at 1200 mg per dose, with a median dosing interval of 10 days. Clinical success was achieved in 6/9 patients (66.7%). One patient discontinued therapy due to infusion-related adverse events, and two experienced microbiological failure, both in left ventricular assist device-related infections. No 30- or 90-day mortality was observed. TDM, when performed, demonstrated persistent pre-dose plasma concentrations over several weeks, with marked interindividual variability across patients and intra-individual temporal changes over time, including drug accumulation in some cases.

Conclusion: Multidose oritavancin appears to be a promising consolidation or suppressive strategy in selected patients with complex Gram-positive endovascular infections. Prospective studies are needed to define optimal dosing regimens and the role of TDM in this setting.

Introduction

Oritavancin is a semisynthetic lipoglycopeptide, structurally related to vancomycin, approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI).[1] Because of its rapid bactericidal activity, long persistence in the body, and substantial *in vitro* activity against several resistant Gram-positive pathogens, including MRSA, vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* (VISA and VRSA), as well as vancomycin-resistant enterococci (VanA and VanB), its use has

progressively extended beyond labelled indications. In particular, oritavancin has attracted interest as a potential option for the treatment of invasive infections, such as infective endocarditis (IE).[1,2]

Oritavancin has a multimodal action: it binds to the D-Ala-D-Ala termini of peptidoglycan precursors (similar to vancomycin), inhibits transglycosylation, and disrupts bacterial membrane integrity, resulting in enhanced bactericidal activity compared with vancomycin.[1–3] Moreover, oritavancin retains the ability to bind effectively to the altered peptidoglycan termini found in vancomycin-resistant organisms.[1] This explains its strong *in vitro* potency against multidrug-resistant Gram-positive pathogens.

Pharmacokinetically, oritavancin is characterized by a very long terminal half-life (up to 200–300 h), wide tissue distribution, and slow clearance.[1] These properties allow for single-dose administration in ABSSSI and have encouraged exploration of alternative dosing regimens, such as two-dose or multiple-dose strategies (e.g. 1200 mg followed by 800 mg after 7 days or 1200 mg followed by 1200 mg or 80 0 mg every 7–28 days), to extend antibacterial exposure in invasive infections.[4,5] Such features make oritavancin a potential option for consolidation therapy, particularly in patients for whom prolonged intravenous therapy is impractical.

Although promising, evidence supporting the use of oritavancin in IE remains limited. Reports are restricted to isolated case studies and small series, including infections involving native and prosthetic valves and cardiac implantable devices, with variable outcomes.[4,6–8] To date, no randomized controlled trials have evaluated oritavancin use in IE. Consequently, major international guidelines do not include recommendations for oritavancin in IE; for example, the 2023 ESC Guidelines for the management of IE do not mention oritavancin.[9]

In summary, oritavancin combines potent pharmacodynamics with uniquely favourable pharmacokinetics, making it a rational candidate for the treatment of Gram-positive invasive infections such as IE. However, the lack of robust clinical evidence mandates caution, and prospective studies or registry data are required to better define its efficacy, safety, and optimal dosing in this setting.

Our article presents a case series of patients from Udine and Ente Ospedaliero Cantonale, Lugano Hospital, treated with oritavancin as consolidation or suppressive therapy for IE, cardiac implantable electronic device (CIED) infections, and left ventricular assist device (LVAD)-related infections. This article aims to highlight oritavancin as a potential alternative strategy for these complex endovascular infections.

Materials and methods

This retrospective case series was approved by the Institutional Review Board of the University of Udine (approval no. 299/2025) and adhered to the tenets of the Declaration of Helsinki. We enrolled adult patients (age ≥18 years) who received oritavancin as part of antibiotic therapy for IE and/or related cardiac device infections, who were hospitalized at the University Hospital of Udine and at Ente Ospedaliero Cantonale, Lugano Hospital between 2020 and 2025. Written informed consent was obtained from all participants. The following variables were collected: demographics (age, sex), underlying medical conditions (comorbidities such as cancer, diabetes, cardiovascular disease), infection characteristics (CIED- and/or LVAD-related infections, native valve IE, prosthetic valve IE), microbiology data (pathogens isolated, resistance profiles), antibiotic therapy (prior and concurrent antibiotics, duration of oritavancin treatment, dosing schedule), therapeutic drug monitoring (TDM; oritavancin plasma concentrations), and clinical outcomes (clinical cure, treatment failure, mortality). Data were anonymized and stored in a standardized Microsoft Excel spreadsheet with restricted access, ensuring compliance with data protection regulations. Oritavancin was administered as consolidation therapy or suppressive therapy, defined as follows: consolidation therapy was the use of oritavancin after an initial course of standard-of-care intravenous antibiotics to complete the intended treatment duration; suppressive therapy was prolonged antimicrobial therapy intended to control infection when definitive source control (e.g. device removal or surgery) was not feasible or was deferred. The primary clinical outcomes assessed included clinical cure (resolution of infection based on clinical and laboratory parameters at the end of therapy), clinical failure (persistent or relapsing infection, clinical deterioration requiring modification of antimicrobial therapy, or any drug-related adverse event occurring during oritavancin therapy), microbiological failure (lack of microbiological eradication or persistent bacteremia/culture positivity, when available), and 30-day and 90-day all-cause mortality. Descriptive statistics were used to summarize patient characteristics and clinical outcomes. Continuous variables were expressed as median with IQR, while categorical variables were reported as absolute numbers and percentages. No inferential statistical tests were applied due to the limited sample size.

Results

Nine patients were enrolled in this retrospective observational case series: eight men (88.89%) and one woman (11.11%). The median age was 65 (IQR 32) years. The median body weight was 70 (IQR 4) kg, and the median height was 178 (IQR 7) cm, with a median BMI of 22.3 (IQR 6.4). Among the nine patients included in the case series, chronic kidney disease (CKD) was present in three patients (33.3%), chronic obstructive pulmonary disease in 2 (22.2%), ischaemic/valvular or dilated cardiopathy in 3 (33.3%), and diabetes mellitus in 2 (22.2%). Other relevant conditions included chronic hepatitis C infection and factor V Leiden mutation.

Regarding cardiac devices and valve status, two patients were carriers of an implantable cardioverter-defibrillator (ICD), and two patients had an LVAD. Two patients had a native valve, while three had a prosthetic valve. Valve involvement included the aortic valve in two patients and the pulmonary or tricuspid valve in three patients. Clinical details are summarized in Table 1.

All nine patients received antibiotic regimens with variable treatment durations according to the type of infection, before oritavancin initiation (Table 2). In one case, oritavancin was administered to a postpartum, breastfeeding patient; no adverse effects were observed in the infant during follow-up.

During oritavancin therapy, three patients received concomitant antibiotic therapy (two received rifampicin, and one received amoxicillin).

Oritavancin was administered at a dose of 1200 mg in eight patients; in one patient, it was administered as a 1200-mg first dose followed by 800-mg subsequent doses. The median interval between consecutive doses was 10 (IQR 11.5–7) days, with a median of 5.5 (IQR 7–3) doses per patient. (Table 3)

Six out of nine patients achieved clinical success; one experienced treatment failure due to adverse events, and two had microbiological failure due to lack of eradication. Two of nine patients underwent surgical intervention (one heart transplant and one LVAD pedestal/driveline replacement); both procedures were

Table 1. Demographic data, comorbidities and type of infection

Patient	Age at TDM (years)	Sex	Weight (Kg)	Height (cm)	BMI	Major Comorbidities	Type of Infections
1	62	M	70	157	28.4	COPD; Chronic gastritis; AAA underwent Bentall surgery; High-grade AV block requiring permanent PM implantation	CIED-related endocarditis
2	65	M	105	196	27.3	CKD; LVAD carrier	LVAD-related infection; ICD infection
3	79	M	96	178	30.3	CKD; AF; dilated cardiomiopathy	LVAD-related infection
4	36	M	69	182	20.83	Aortic root and ascending aorta replacement with vascular graft and aortic valve repair for bicuspid aortic valve	PVE and aortic vascular graft infection
5	74	M	73	182	22	Peripheral arterial disease of the lower limbs; Ischaemic and valvular heart disease treated with CABG and valvular replacement	PVE with splenic/kidney/ CNS embolisms
6	36	F	71	173	23,7	Type 1 Diabetes, factor V Leiden mutation, PFO	Tricuspid/pulmonary NVE, pulmonary, hepatic, and renal emboli.
7	42	M	54	184	15.95	Tetralogy of Fallot	Pulmonary PVE; pulmonary vascular stent infection
8	66	M	64	175	20.9	HCV, COPD	Tricuspid NVE
9	82	M	70	177	22.3	Type 2 Diabetes, ischaemic heart disease, CKD	CIED-related infection
Median (IQR)	65 (74–42)	\\	70 (73–69)	178 (182–175)	22.3 (27.3–20.9)		

This table summarizes the demographic and clinical characteristics of the patients, including age in years, sex, weight in kilograms, and height in centimetres. BMI was calculated for each patient, and the main comorbidities and type of infection treated with oritavancin are also reported. Where appropriate, data are presented as median and interquartile range (IQR). Abbreviations: AAA, ascendant aortic aneurysm; AF, atrial fibrillation; AV, atrioventricular; BMI, body mass index; CABG, coronary artery bypass grafting; CIED, cardiac implantable electronic devic e; CKD, chronic kidney disease; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; F, female; HCV, hepatitis C virus; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; LVAD, left ventricular assist device; M, male; MI, myocardial infarction; NVE, native valve endocarditis; PFO, patent foramen ovale; PM, permanent pacemaker; PVE, prosthetic valve endocarditis; TDM, therapeutic drug monitoring.

performed in patients with LVAD-related infections. One patient is still under follow-up with no clinical or microbiological relapse. No 30- or 90-day mortality was observed. (Table 4)

Microbiological isolates included MSSA (4 cases), MRSA (1 case), methicillin-susceptible or methicillin-resistant *Staphylococcus epidermidis* (2 cases), *Enterococcus faecalis* (1 case), *Streptococcus mitis* (1 case), and *Staphylococcus haemolyticus* (1 case). Oritavancin MICs were determined only for *E. faecalis* and for one *S. epidermidis* isolate, whereas vancomycin MICs were determined for all isolates. All isolates were susceptible to vancomycin. (Table 5)

All doses of oritavancin were guided by TDM. In this manuscript, we report only the pre-dose concentration (ng/mL) of oritavancin. (Table 6; Figure 1)

All reported values refer to pre-dose plasma concentrations, measured immediately before the administration of each oritavancin dose. Therapeutic drug monitoring was performed at variable time points, ranging from 168 to 2136 h after treatment initiation.

Pre-dose plasma concentrations showed marked interindividual variability, with values ranging from 1400 to 10470 ng/mL. In patients 3, 6, 8, and 9, measurable plasma concentrations were consistently detected prior to each subsequent dose, even several weeks after the start of therapy. Patient 6 exhibited particularly high pre-dose concentrations early during treatment, reaching 7130 ng/mL at 336 h, with a peak value of 10470 ng/mL at 504 h and persistently elevated levels at 672 h (9000 ng/mL), suggesting substantial systemic accumulation. Patient 3 showed relatively stable pre-dose concentrations over time, ranging from 4230 to 7590 ng/mL up to 1272 h. In patient 8, pre-dose concentrations gradually increased before reaching a *plateau* of approximately 4400 ng/mL, which was maintained until 1344 h. Patient 9 presented lower but consistently measurable pre-dose concentrations, between 2000 and 2500 ng/mL, for more than 1300 h. In patient 5, the pre-dose concentration measured at 168 h was below the limit of quantification.

Table 2. Antibiotic therapy (duration and type of antibiotic used) before oritavancin therapy

Patient	AB therapy before ORV (days)	Type of AB used
1	27	GEN; DAP
2	50	PTZ; DAP; BPR; FOS; FLU
3	123	PTZ; DAP; DALB; CIP; AMC; CFZ
4	36	PTZ; DAP; FOS; OXA
5	34	PTZ; DAP; FOS
6	34	AMC; PTZ; OXA; DAP
7	51	DAP; AMP; PTZ; CRO; AMX
8	28	AMX; CRO
9	1045	VAN; DAP; DOX
Median (IQR)	36 (51–34)	

This table reports the total duration of antibiotic therapy administered before the initiation of oritavancin treatment, together with the antibiotics used. Abbreviations: AB, antibiotics; AMC, amoxicillin/clavulanic acid; AMX, amoxicillin; BPR, ceftobiprol; CFZ, cefazolin; CIP, ciprofloxacin; CRO, ceftriaxone; DALB, dalbavancin; DAP, daptomycin; DOX, doxycycline; FLU, flucloxacillin; FOS, fosfomycin; GEN, gentamicin; OXA, oxacillin; PTZ, piperacillin/tazobactam; VAN, vancomycin.

Table 3. Oritavancin doses administration

Patient	Dosage (mg)	Number of Doses	Median interval between doses (days) (IQR)
1	1200	3	18 (27–13.5)
2	1200	3	7 (7–7)
3	1200	6	7 (11.25–7)
4	1200	8	14 (14–11.5)
5	1200	2	7
6	1200	5	7 (7–7)
7	1200	3	14 (14–14)
8	1200	6	10 (10–10)
9	1200 first dose, then 800	9	10.5 (14–7.75)
Median (IQR)		5.5 (7–3)	10 (11.5–7)

This table reports the total number of oritavancin administrations and the dosage used for each patient. The interval between consecutive administrations is also reported as the median with the corresponding interquartile range (IQR).

Discussion

In this retrospective observational case series, multidose oritavancin, especially as consolidation or long-term suppressive therapy, was associated with encouraging effectiveness and safety in a highly complex population with Gram-positive IE, CIED infections, and LVAD-associated infections. Overall clinical and microbiological success was achieved in two-thirds of patients, with no 30- or 90-day mortality observed across all nine cases.

In our cohort, multidose oritavancin was associated with a favourable clinical and microbiological outcome, with clinical and microbiological success achieved in six out of nine patients (66.7%). Treatment failures were limited to three cases. Specifically, one failure was attributable to treatment discontinuation due to an adverse reaction, rather than lack of antimicrobial activity, while the other two failures occurred in the setting of LVAD-related infections, a clinical context known to be particularly challenging due to biofilm formation, high bacterial burden, and the frequent impossibility of complete device removal. Both patients underwent surgical treatment: one underwent heart transplantation, and the other underwent pedestal/driveline replacement. In the second case, a relapse of infection was observed one year after the surgical procedure.

Notably, no clinical or microbiological failures were observed among patients with native or prosthetic valve involvement or other cardiac devices. These findings might suggest that the overall effectiveness of oritavancin in our series was primarily limited by factors intrinsic to LVAD- associated infections, rather than by insufficient antimicrobial efficacy.

One patient in the cohort was still receiving oritavancin at the time of analysis; thus, treatment outcome was not yet evaluable. No relapse and no 30- or 90-day mortality were observed as of the last follow-ups.

The pharmacological rationale for using oritavancin in deep-seated and endovascular infections lies in its unique mechanism of action and favourable pharmacokinetic profile. Unlike vancomycin, oritavancin exhibits concentration-dependent bactericidal activity through multiple mechanisms, including inhibition of transglycosylation and transpeptidation, as well as disruption of bacterial cell membrane integrity, which enhances activity against stationary-phase and biofilm-embedded bacteria.[2,3] These properties are particularly relevant in infections involving prosthetic material, such as cardiac devices and LVADs, where biofilm formation plays a major pathogenic role.

The prolonged terminal half-life of oritavancin allows for extended dosing intervals and outpatient management, a key advantage in patients requiring long-term therapy who are poor candidates for prolonged hospitalization or continuous intravenous access. In some selected patients where definitive source control is not feasible or must be deferred, the long-acting profile of oritavancin may also support the use of a multidose regimen as a form of 'medical source control', as recently proposed in complicated Gram-positive infections.[10] This key concept is in line with how oritavancin has been used in our cohort. Pharmacokinetic modelling studies have demonstrated that multidose regimens, including a 1200 mg loading dose followed by 800 mg maintenance doses, maintain plasma concentrations above susceptibility breakpoints for several weeks, achieving high AUC/MIC ratios associated with clinical efficacy.[5] The dosing strategies adopted in our cohort, guided by TDM, are consistent with these pharmacokinetics/pharmacodynamics (PK/PD) observations and may have contributed to the favourable outcomes observed.

Our results align with those reported in a systematic review, which analysed more than 300 cases treated with multidose oritavancin and reported clinical cure or improvement in over 90% of patients, with a favourable safety profile.[4] Although osteomyelitis and skin and soft tissue infections represented the majority of cases in that review, IE and cardiovascular device infections were also included, supporting the expanding real-world use of oritavancin beyond its approved indication.

Table 4. Clinical and microbiological outcomes; Adverse events, Surgery procedures

Patient	Surgery	30-day Outcome	90-day Outcome	Outcome	Reported AEs
1	NO	Survived	Survived	Clinical cure	Rash and itching
2	YES, heart transplant	Survived	Survived	Microbiological failure	NO
3	YES, pedestal and drive line substitution	Survived	Survived	Microbiological failure	NO
4	NO	Survived	Survived	Clinical failure-AE	Red man syndrome–like reaction; angioedema
5	NO	Survived	Survived	Clinical cure	NO
6	NO	Survived	Survived	Clinical cure	NO
7	NO	Survived	ND	Ongoing therapy	NO
8	NO	Survived	Survived	Clinical cure	NO
9	NO	Survived	Survived	Clinical cure	NO

This table reports the cases in which patients underwent cardiac surgery and the corresponding outcomes. Drug-related adverse events are also reported. Abbreviations: AEs, Adverse events; ME, Microbiological eradication; ND, Not determinable.

Table 5. Microbiological isolates

Patient	Etiological Agent	Microbiological samples	Oritavancin MIC (mg/L)	Vancomycin MIC (mg/L)
1	*Staphylococcus epidermidis*	Blood	//	1
2	MRSA/MSSA	Blood/Wound swab	//	≤0.5
3	MSSA	L-VAD driveline culture	//	≤0.5
4	MSSA	Blood	//	≤0.5
5	*Staphylococcus haemolyticus*	Blood	//	≤0.5
6	MSSA	Blood	//	≤0.5
7	*Streptococcus mitis*	Blood	//	≤0.5
8	*Enterococcus faecalis*	Blood	0008	1
9	*Staphylococcus epidermidis*	Blood	0,03	2

This table reports the microbiological isolates, the clinical specimens from which the pathogens were recovered, and the MICs of vancomycin and oritavancin, expressed in mg/L, where available. Abbreviations: MRSA, *Staphylococcus aureus* meticillin-resistant; MSSA, *Staphylococcus aures* meticillin susceptible.

With specific regard to IE, accumulating evidence from case reports and small series suggests that oritavancin may represent a viable consolidation or salvage option in carefully selected patients. Frondizi et al. reported a case series of enterococcal IE treated with oritavancin as consolidation therapy, achieving cure in most patients.[8] Similarly, Bongiovanni and colleagues described successful long-term therapy with oritavancin in a patient with recurrent *E. faecalis* IE who was not a surgical candidate.[7] Earlier experience, including the prolonged use in vancomycin-resistant *Enterococcus faecium* prosthetic valve IE, further supports the feasibility of extended oritavancin regimens in endovascular infections.[6]

Although our cohort included only one case of *E. faecalis*, the choice of oritavancin over dalbavancin was based on available comparative data, which suggest that, while both agents are active against vancomycin-susceptible enterococci, oritavancin has a more favourable *in vitro* profile against *Enterococcus* spp., particularly because it retains activity against VanA/VanB phenotypes, whereas dalbavancin lacks activity against VanA VRE.[11–13] In direct *in vitro* comparisons, both lipoglycopeptides showed low MICs against vancomycin-susceptible *E. faecalis*, but only oritavancin showed consistent bactericidal activity in that setting, whereas dalbavancin did not show the same.[11] In an enterococcal dataset, including both *E. faecalis* and *E. faecium*, only oritavancin maintained rapid bactericidal activity at high inoculum density, a feature that may be relevant in deep-seated, high-burden infections such as endocarditis.[11] For all those things, in our single enterococcal case, oritavancin was considered the more appropriate long-acting option.

Notably, our cohort included patients with substantial comorbidities, such as chronic kidney disease, cardiopulmonary disease, diabetes mellitus, and implanted cardiac devices, reflecting a real-world population. The absence of short-term mortality and the limited number of treatment failures are particularly relevant when contrasted with the high morbidity and mortality traditionally associated with IE and device-related infections, as outlined in contemporary European recommendations.[9] Although oritavancin is not currently recommended in international guidelines for IE, our findings add to the growing body of observational evidence supporting its off-label use in selected cases managed by experienced multidisciplinary teams.

Safety outcomes in our series were consistent with previously published data, with suspected oritavancin-related adverse events occurring in two out of nine patients (22.2%), both

Table 6. Pre-dosing oritavancin concentrations (ng/mL)

Time (h)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
0									
168		5610	4230		ND	1670		1600	1400
192									
216									
336						7130		2400	2000
360			6420						
504						10470		3400	1500
528									
672						9000	4090	3600	2300
840								4400	2500
864									
936			4520						
1008								4400	2400
1104			7170						
1176								4400	2400
1200									
1272			7590						
1344								4400	2500
1824				2690					
2136				7437					

This table reports the pre-dose concentrations measured with TDM and the corresponding sampling times relative to time zero.
Abbreviation: ND, not determinable.

presenting with infusion-related reactions. One patient developed rash and itching after the third dose, requiring permanent discontinuation of therapy, with complete resolution of symptoms. Another patient experienced red man syndrome–like manifestations and skin swelling after the first dose, with recurrence during a subsequent attempted dose, which was not completed; symptoms resolved after drug suspension. Based on this experience, our current institutional practice is to administer oritavancin over a 3-h infusion period. In the event of infusion-related reactions, the infusion is first stopped, clinical symptoms are managed according to severity, and, once symptoms have resolved, re-challenge may be considered using a slower infusion rate under close monitoring. This pragmatic approach may help improve tolerability in selected patients and is consistent with the management of histamine-mediated infusion reactions observed with glycopeptide and lipoglycopeptide antibiotics. These findings are consistent with the known safety profile of oritavancin, in which infusion-related and dermatologic reactions are among the most frequently reported adverse events. Because oritavancin is structurally related to vancomycin, it can induce histamine release-mediated reactions, particularly in the setting of repeated administration or high cumulative exposure.[1,3] The red man syndrome–like reaction (flushing of the face and upper body, hives, itching, and/or rash) observed in our cohort is in line with previously described infusion-related events, which appear to occur less frequently and with lower severity than those associated with vancomycin.[14,15] In a published systematic review, adverse events were reported in a minority of patients receiving multidose oritavancin, with infusion-related reactions being the most frequent and treatment discontinuation remaining uncommon.[4] Similarly, case series and reports focusing on IE and other endovascular infections describe good tolerability of prolonged oritavancin regimens, with only sporadic adverse events necessitating therapy interruption.[7,8]

Importantly, all adverse events observed in our cohort were reversible, with complete resolution after therapy discontinuation or suspension, and no long-term sequelae were reported. No clinically relevant renal, hepatic, or haematological toxicities were observed, even among patients with chronic kidney disease or significant cardiovascular comorbidities. This observation is consistent with prior evidence supporting the favourable systemic safety profile of oritavancin and the lack of requirement for dose adjustment in renal impairment.[4]

When compared with published real-world data, the incidence and nature of adverse events in this series are comparable.

Oritavancin was also administered in one postpartum breastfeeding patient without observable adverse effects in the infant during follow-up, providing limited but relevant real-world data in a clinical setting where evidence remains scarce. In this case, oritavancin concentration was found in the mother's milk.

Interpreting these data as pre-dose concentrations markedly enhances the clinical significance of the results. The measured levels represent systemic trough concentrations and indicate that, even at the point when drug exposure is expected to be minimal, oritavancin remains detectable at concentrations above the MICs of the principal Gram-positive pathogens identified in our case series, including *S. aureus* and *Enterococcus* spp.[15–17] Oritavancin is characterized by a long terminal half-life (approximately 245 h), a large volume of distribution, and extensive tissue binding, pharmacokinetic properties that favour systemic accumulation during repeated administrations.[16,17] The particularly high pre-dose concentrations observed in some patients,

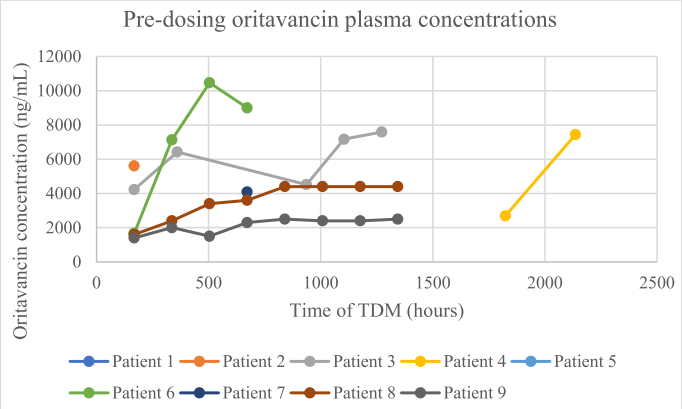

Figure 1. Pre-dosing oritavancin concentrations (ng/mL). Abbreviation: TDM, Therapeutic Drug Monitoring.

such as patient 6, suggest a progressive accumulation effect that may be advantageous in the treatment of deep-seated endovascular infections, where continuous and prolonged antibiotic exposure is required. The wide interindividual variability in pre-dose concentrations, together with the intra-individual variability observed over time during serial TDM, suggests that oritavancin exposure may differ substantially between patients and within the same patient across treatment. This is consistent with findings reported in previous clinical studies and case series and is likely influenced by factors such as body weight, renal function, inflammatory status, and dosing interval.[5,6,18] This variability highlights the potential role of therapeutic drug monitoring of oritavancin in off-label settings, particularly in infective endocarditis, although standardized pharmacokinetic targets have not yet been established. Based on the experience gained from this case series, oritavancin is currently considered in our institution for selected Gram-positive infections requiring prolonged antimicrobial exposure, particularly when conventional long-term intravenous therapy is not feasible or is associated with relevant clinical or logistic limitations. These include prosthetic joint infections, vascular graft-associated infections, IE as consolidation therapy after an initial standard treatment phase, acute bacterial skin structure and soft tissue infections, and cases requiring long-term suppressive therapy when definitive surgical source control cannot be achieved or must be deferred. Usually in our clinical practice, oritavancin is generally administered at fixed 7-day intervals when TDM is not available. On the other hand, in selected patients and whenever feasible, serial TDM is used to support individualized dosing and administration intervals, with the aim of maintaining prolonged antimicrobial exposure while limiting unnecessary drug accumulation and potential toxicity.

This study has limitations inherent to its retrospective design, small sample size, and heterogeneity of infections, dosing schedules, and concomitant or previous antibiotic therapies. Nevertheless, the systematic use of TDM represents a strength of this series, as it provides descriptive PK datas that may support individualized long-acting lipoglycopeptide therapy. However, because oritavancin MIC values were available for only a minority of isolates, formal PK/PD correlation was limited.

In conclusion, our findings support multidose oritavancin as a promising therapeutic option for selected patients with complex Gram-positive infections, including IE and cardiac device–related infections, particularly when standard therapeutic strategies are not feasible. Larger prospective studies are warranted to better define optimal dosing regimens, treatment duration, and patient selection criteria, as well as to clarify the role of TDM in guiding long-acting antimicrobial therapy.

Acknowledgements

The authors declare that no specific acknowledgments are required for this work.

Funding

This study was supported by internal funding as a part of clinical routine practice.

Transparency declarations

S.G. has received grants in the last 2 years from Pfizer, Novartis, Merck, Gilead, Zambon, Infectopharm, Shionogi, Menarini, Angelini, Advanz, Hikma, Avir Pharma, Mundipharma, Viatris. L.M. declared no conflicts of interest. M.M. declared no conflicts of interest. G.T. declared no conflicts of interest. J.A. has received grants in the last two years from Hikma. S.F. declared no conflicts of interest. A.D. is a founding member and consultant of CoQua Lab, he is consultant/advisor for Shimadzu, HDC, Gilead, Waters, CoQua Lab, Janssen, Infectopharm, Menarini, DiaSorin, EOS, AdvicePharma, Roche. P.G. declared no conflicts of interest. M.B. has received grants in the last 2 years for his Institution from Menarini, Pfizer, Gilead Sciences, ViiV Healthcare, MSD. C.T. has received research grants in the last 2 years from Menarini, Hikma, Pfizer, MSD, Thermofischer, Diasorin, Shionogi, Advanz, Angelini.

Authors' contributions

S.G. Conceptualization, Investigation, Methodology, Supervision, Writing - original draft. L.M. Investigation, Data curation, Writing - original draft. M.M. Investigation, Data curation, Visualization. G.T. Investigation, Data curation, Visualization. J.A. Investigation, Data curation, Visualization. S.F. Investigation, Data curation, Visualization. A.D. Investigation, Data curation, Visualization. P.G. Investigation, Data curation, Visualization. M.B. Data Curation, Writing - review and editing. C.T. Conceptualization, Methodology, Project administration, Supervision, Writing - review and editing.

Ethics statement

This retrospective case series was approved by the Internal Review Board of University of Udine (approval no: 299/2025) and adhered to the tenets of the Declaration of Helsinki. Patient's written consent were obtained.

Data availability

The data underlying this article are available in the article and in its online supplementary material. Additional data may be requested from the corresponding author and will be shared upon reasonable request, in compliance with privacy and data protection regulations

Bibliography

1 Brade KD, Rybak JM, Rybak MJ. Oritavancin: a new lipoglycopeptide antibiotic in the treatment of gram-positive infections. *Infect Dis Ther* 2016; **5**: 1–15. https://doi.org/10.1007/s40121-016-0103-4

2 Allen NE, Nicas TI. Mechanism of action of oritavancin and related glycopeptide antibiotics. *FEMS Microbiol Rev* 2003; **26**: 511–532. https://doi.org/10.1111/j.1574-6976.2003.tb00628.x

3 Zhanel GG, Schweizer F, Karlowsky JA. Oritavancin: mechanism of action. *Clin Infect Dis* 2012; **54**(SUPPL. 3): S214–S219. https://doi.org/10.1093/cid/cir920

4 Baiardi G, Cameran Caviglia M, Piras F *et al*. The clinical efficacy of multidose oritavancin: a systematic review. *Antibiotics* 2023; **12**: 1498. https://doi.org/10.3390/antibiotics12101498

5 Rose WE, Hutson PR. A two-dose oritavancin regimen using pharmacokinetic estimation analysis. *Drugs Real World Outcomes* 2020; **7**: 36–40. https://doi.org/10.1007/s40801-020-00188-6

6 Johnson JA, Feeney ER, Kubiak DW *et al*. Prolonged use of oritavancin for vancomycin-resistant Enterococcus faecium prosthetic valve endocarditis. *Open Forum Infect Dis* 2015; **2**: ofv156. https://doi.org/10.1093/ofid/ofv156.

7 Turicchi G, Bongiovanni M. Oritavancin in a patient with recurrent endocarditis by Enterococcus faecalis: a new therapeutic option? *J Antimicrob Chemother* 2025; **80**: 2873–2874. https://doi.org/10.1093/jac/dkaf215

8 Frondizi F, Leanza GM, Chiuchiarelli M *et al*. The use of oritavancin as consolidation therapy for infective endocarditis caused by *Enterococcus* spp. *Open Forum Infect Dis* 2025; **12**: ofaf416. https://doi.org/10.1093/ofid/ofaf416

9 Delgado V, Ajmone Marsan N, de Waha S *et al*. 2023 ESC guidelines for the management of endocarditis. *Eur Heart J* 2023; **44**: 3948–4042. https://doi.org/10.1093/eurheartj/ehad193

10 De Rosa FG, Lupia T, Fornari V *et al*. Medical source control with oritavancin in complicated gram-positive bacterial infections: a case series. *Int J Infect Dis* 2025; **161**: 108111. https://doi.org/10.1016/j.ijid.2025.108111

11 Sweeney D, Stoneburner A, Shinabarger DL *et al*. Comparative in vitro activity of oritavancin and other agents against vancomycin-susceptible and -resistant enterococci. *J Antimicrob Chemother* 2017; **72**: 622–624. https://doi.org/10.1093/jac/dkw451

12 Zhanel GG, Calic D, Schweizer F *et al*. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs* 2010; **70**: 859–886. https://doi.org/10.2165/11534440-000000000-00000

13 Hussein M, Barclay J, Baker M *et al*. A comparative review of the pharmacology of dalbavancin and oritavancin for gram-positive infections: birds of a feather or apples and oranges? *Infect Dis Ther* 2025; **14**: 2221–2246. https://doi.org/10.1007/s40121-025-01215-1

14 Hoover RK, Krsak M, Molina KC *et al*. Kimyrsa, an oritavancin-containing product: clinical study and review of properties. *Open Forum Infect Dis* 2022; **9**: ofac090. https://doi.org/10.1093/ofid/ofac090

15 Tenkasi (previously Orbactiv) | European Medicines Agency (EMA). https://www.ema.europa.eu/en/medicines/human/EPAR/tenkasi. Accessed December 23, 2025

16 Bhavnani SM, Passarell JA, Owen JS *et al*. Pharmacokinetic-pharmacodynamic relationships describing the efficacy of oritavancin in patients with *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2006; **50**: 994–1000. https://doi.org/10.1128/AAC.50.3.994-1000.2006

17 Rubino CM, Bhavnani SM, Moeck G *et al*. Population pharmacokinetic analysis for a single 1,200-milligram dose of oritavancin using data from two pivotal phase 3 clinical trials. *Antimicrob Agents Chemother* 2015; **59**: 3365–72. https://doi.org/10.1128/AAC.00176-15

18 Lupia T, De Benedetto I, Bosio R *et al*. 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 (Basel)* 2023; **13**: 959. https://doi.org/10.3390/life13040959