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The role of long-acting antibiotics in the clinical practice: a narrative review

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SUMMARY

Introduction. The increasing emergence of bacterial strains with new resistance determinants has become a threat to current antibiotic therapies in recent years. This has prompted research for innovative options with improved efficacy and safety profiles: long-acting glycopeptides, such as dalbavancin and oritavancin, are currently approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Their efficacy, microbiological profile, and ease of administration may provide an answer to this challenge, as well as reducing length of stay and hospital costs. This narrative review aims to explore the current evidence on the real-word use of dalbavancin and oritavancin, in labelled and off-label indications in clinical practice.
Methods. A PubMed library database search with no time limits was performed using the following terms: long-acting antibiotics, dalbavancin, oritavancin.
Discussion. Registration studies confirmed non-inferiority of long-acting glycopeptides to standard of care in ABSSSI (dalbavancin DISCOVER 1 and 2: 79.7% clinical success in the dalbavancin group and 79.8% in the vancomycin-linezolid group; oritavancin SOLO I: 82,3% clinical success in the oritavancin group versus 78,9% for the vancomycin group; SOLO II: 80,1% clinical success versus 82,9%). Large cohorts have confirmed similar success rates in ABSSSI treatment in real-world practice. Evidence for off-label indications is still rather scarce but promising, especially in bone and joint infections therapy for both dalbavancin and oritavancin, and infective endocarditis for dalbavancin. Moreover, these drugs may have their place in non-adherent patients, in setting of addition or difficult access to healthcare. Another potential use of these drugs is in patients with oral intake impairment or reduced gastro-intestinal absorption. However, the low penetration in cerebrospinal fluid of dalbavancin and the unfavourable outcomes in the only case report of oritavancin treatment in human meningitis despite encouraging animal models would seem to make these molecules unsuitable for central nervous system infection therapy. Most of the available evidence is based on small retrospective cohorts, so robust prospective studies investigating off-label indications are needed.

Keywords: Long-acting antibiotics, dalbavancin, oritavancin; ABSSSI; infective endocarditis; osteomyelitis; PJI; BSI.

INTRODUCTION

Long-acting antibiotics, such as dalbavancin and oritavancin, have emerged as important tools in the fight against bacterial infections. Initially approved for treating acute bacterial skin and skin structure infections (ABSSSI), they have gained attention for potential off-label use due to their extended half-lives, their excellent tissue penetration, which allows prolonged high therapeutic concentrations at the site of infection in many difficult to treat sites as bone, their *in vitro* demonstrated efficacy against biofilm, their potent activity against a broad spectrum of Gram-positive bacteria, along with a favourable safety pro-

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file. Furthermore, their features can help to reduce the length of stay and health care costs, while enhancing patient compliance and reducing the burden of daily medication administration: this makes them valuable options for outpatient antibiotic therapy or difficult to access populations. Although the off-label use should always be approached with caution, these unique strengths make them promising candidates for many off-label applications, particularly in the treatment of Gram-positive infections requiring prolonged therapy.

Dalbavancin

Dalbavancin is a long-acting, semi-synthetic lipoglycopeptide antibiotic derived from teicoplanin. It is only available as an intravenous formulation [1]. The main difference from older glycopeptides is the addition of lipophilic side chains, which allows binding to the D-alanyl-D-alanine portion of the peptidoglycan subunit, preventing transglycosylation and cross-linking of peptide bridges within bacterial peptidoglycan cell walls [2], with greater affinity than the older glycopeptides [3, 4]. This activity is limited to Gram-positive microorganisms, as the porin channels of the outer cell membrane in Gram-negative bacteria prevent lipoglycopeptides from reaching their target [4].

The key feature of dalbavancin is its reversible binding to plasma proteins (around 93%), with a half-life of 14.4 days. This prolongs the time at a drug concentration above the MIC90 (MIC at which 90% of isolates are inhibited) of methicillin-resistant *Staphylococcus aureus* (MRSA) and *β-haemolytic streptococci*, providing unique long-term activity.

Moreover, dalbavancin has good penetration into skin structures, synovial fluid and bone tissue, where it distributes at almost the same concentration 24 hours after the initial dose [5]. It is widely distributed in tissues except for the central nervous system. It has a volume of distribution of about 12 L, almost three times that of the central compartment, and a total volume of distribution of 15.7 L. After administration, its metabolism is not clearly defined, with about 33% being excreted unchanged in the urine, and it does not require dose adjustment unless in severe renal impairment [5].

The antimicrobial efficacy of this antibiotic in vivo is best related to free drug- area under the concentration-time curve to MIC ratio ($fAUC_{24H}$/MIC) [6]. This antimicrobial agent is defined as active against a broad spectrum of Gram-positive bacteria such as *Streptococcus spp.* (including multidrug-resistant pneumococci), *Enterococcus faecalis*, *Enterococcus faecium*, methicillin-susceptible *S. aureus* (MSSA), MRSA, *Clostridium spp*.

However, the emergence of some vancomycin-resistant *E. faecium* (VRE) strains developing resistance to dalbavancin has been observed. This resistance may be due to changes in the drug's target site on the peptidoglycan, increased expression of cell wall precursors, or the presence of efflux pumps (all mechanisms are similar to those encoded by the VanA cluster in vancomycin resistance) [7, 8]. Moreover, vancomycin-intermediate *S. aureus* (VISA) strains resistant to dalbavancin have also been reported in vitro and in some case reports, due to resistance selection during prolonged treatment regimens [9].

To be noted, dalbavancin is not compatible with any type of saline containing sodium chloride as such a composite solution may precipitate. It may be reconstituted for infusion with 5% glucose solution, in up to 500 ml in volume according to the dosage, so caution is needed in its use for therapy in diabetic patients.

Dalbavancin has been approved by the FDA (American Food and Drug administration) and EMA (European Medical Agency) for the treatment of acute skin structure infections caused by Gram-positive pathogens since 2014. The FDA/EMA-approved dose is 1000 mg followed by 500 mg after 7 days, administered intravenously over 30 minutes, in all patients with eGFR > 30 mL/min or on haemodialysis. New studies found out that a single 1500 mg dose once was not inferior to 2-dose regimen, with a similar safety profile and higher patient satisfaction [10].

The use of dalbavancin for the treatment of ABSSSIs has been validated by the DISCOVER studies, two multicentre, randomised, double-blind, phase 3 trials: DISCOVER 1 and DISCOVER 2 [1]. The trials enrolled adult patients with ABSSSI and compared dalbavancin on days 1 and 8 to intravenous vancomycin for at least 3 days, with the option to switch to oral linezolid for 10 to 14 days. The primary endpoint was early clinical response, defined as improvement in ABSSSIs 48-72 hours after the start of treatment. Results from the DISCOVER studies demonstrated that dalbavancin

was non-inferior to vancomycin plus linezolid in achieving early clinical response, with 79.7% in the dalbavancin group and 79.8% in the vancomycin-linezolid group. In terms of safety, dalbavancin had a generally safe profile with the most common adverse events being nausea, diarrhoea, and headache. Infusion-related reactions were rare and usually mild [1].

Oritavancin

Oritavancin, formerly known as LY333328, is a semi-synthetic lipoglycopeptide, very similar to vancomycin: the main differences are the hydrophobic 4'-chlorobiphenylmethyl substituent on the disaccharide sugar, together with an additional vancosamine epimer on the amino acid residue in ring 6, and the substitution of vancosamine by a 4-epi-vancosamine [12].

Oritavancin acts by multiple mechanisms, targeting both peptidoglycan chain elongation (transglycosylation) and cross-linking (transpeptidation), while, unlike vancomycin, it also anchors to the cell membrane through the lipophilic 4'-chlorobiphenylmethyl moiety, which interacts with bacterial lipid II, altering the bacterial membrane potential and modifying membrane permeability. This results in a rapid, dose-dependent bactericidal activity [14, 15]. Notably, this triple mode of action makes oritavancin bactericidal against biofilm inocula and non-dividing cells [16, 17].

Worth noting, the accumulation of this drug into the macrophages is quite exceptional, with intracellular concentrations up to 200-fold the extracellular after 24 hours of incubation in vitro, without affecting the cellular bactericidal activity, which may be useful when treating intracellular state of some microorganisms, such as *S. aureus* [18].

It exhibits linear pharmacokinetics, with no major metabolites described, and a multiexponential decline. It has a long half-life, up to 16 days, with a high protein binding of almost 85%. The volume of distribution is as high as 87 litres, with substantial tissue distribution, accumulation, and retention due to slow elimination. It is excreted slowly as unchanged drug in faeces and urine (<5% in urine 7 days after administration). No dose adjustment is required in patients with moderate renal or hepatic impairment or obesity. In addition, unlike vancomycin, it does not require central venous lines [19]. Its long terminal half-life and no need for central line may ease its use in outpatient antibiotic therapy (OPAT), as once weekly administration is possible.

Oritavancin is known to alter coagulation tests through interaction with phospholipid reagents, giving false elevation in prothrombin time and activated partial thromboplastin time. Acting as a weak inhibitor or inducer of the known P450 cytochrome, it may cause drug-to-drug interactions: for this reason, the coadministration with unfractionated heparin is contraindicated up to 120 hours after oritavancin infusion, and warfarin use is discouraged [19].

As mentioned above, the antimicrobial activity of oritavancin includes most Gram-positive aerobic bacteria such as enterococci (including VRE), staphylococci (both MSSA and MRSA), streptococci (*Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group -including S. *anginosus, S. intermedius, S. constellatus-)* and many anaerobic bacteria such as *Clostridium difficile, Clostridium perfringens, Peptostreptococcus spp.* and *Propionibacterium acnes* [20-22]. Activity against *Micrococcus spp, Corynebacterium spp.* and *Listeria monocytogenes* have also been described in vitro [20]. Overall, the spectrum is quite similar to vancomycin, but already active at a lower minimum inhibitory concentration (MIC) [25].

The antimicrobial activity of this antibiotic is best related to the maximum serum concentration to MIC ratio (maximum plasma concentration [C_{max}]/MIC), and as a result of its prolonged plasma half-life, the time during which the concentration in plasma exceeds the MIC (T>MIC) and the area under the concentration-time curve to MIC ratio (AUC/MIC) are also related to its efficacy [19].

Oritavancin is approved as a single dose injection of 1200 mg over 3 hours, based on the findings of the phase II clinical dose-finding study, SIMPLIFI [26]. Similar to dalbavancin, oritavancin must also be reconstituted in 5% glucose solutions and needs a high volume (1000 ml), which may become impractical when administered to congestive heart disease or diabetic patients.

FDA and EMA approvals were based on 2 phase III randomized, double-blinded, multicenter, non-inferiority clinical trials SOLO I and SOLO II, with an almost identical design [27, 28]. The 2 trials compared oritavancin 1200 mg once versus standard doses of vancomycin in 1959 patients with ABSSSI, suspected or proven to be due to a gram-positive pathogen (including cellulitis or

major skin abscesses), requiring intravenous antibiotic therapy for at least 7 days. The efficacy endpoints for non-inferiority were a primary composite endpoint at 48-72 hours defined as no spreading or reduction in lesion size, no fever and no need for an additional antibiotic, clinical cure 7-14 days after the end of treatment and a reduction ≥20% in the lesion area in the first 3 days. In both SOLO trials, primary composite endpoints reached non-inferiority as oritavancin reached 82,3% in SOLO I versus 78,9% for vancomycin, and 80,1% in SOLO II versus 82,9% in the comparator drug, with similar outcomes across causing microorganisms. The main adverse events registered were nausea and a higher rate of altered liver function. Noteworthy, SOLO I and II trials reported 6 cases

Table 1 - Main characteristics of the studies included in the review concerning dalbavancin (arranged by publication year).

	Authors (Year) [Bibliography Reference]	*Design of the Study (Country)*	*Pathogens*	*Cohort size*	*Dosing*	*Outcome*
ABSSSI						
	Pascale et al. (2022) [35]	Multicentric, retrospective study (Italy)	44.92% *Staphylococcus spp.* (86% MRSA)	48 sternotomic wound infection: 15 DAL group vs 33 SoC group	IVD 1000 mg then 500 mg	95.8% wound healing at day 90/180 follow-up DAL vs 82.9% SoC
	Bai et al. (2020) [33]	Multicentric, retrospective study (Italy)	ABSSSI group : - 39% MRSA - 17% MSSA - 17% CoNS	206 patients (69% ABSSSIs in the DAL group vs 46.3% other infections)	Multiple schemes: 60% 1500 mg once	85% clinical cure at 30-180 days follow-up in the ABSSSI group. 75% in the other site's infection group (not ABSSSI infection)
	Dunne et al. (2016) [10]	Multicentric, double-blind, randomized clinical trial (North America)	MRSA	698 patients (100% ABSSSI)	IVD 1500 mg once vs 1000 mg once, then 500 mg at day 8	*Single dose group:* 89% clinically evaluable success at day 14 and 92% at day 28 *2-dose group:* 89% at day 14 and 93% at day 28
	Boucher et al. (2014) [1]	Multicentric, double-blind, randomized clinical trial (USA, Europe, South Africa, Asia)	*S. aureus*, MSSA, *S. pyogenes*	1312 patients (100% ABSSSI)	IVD 1000 mg once, then 500 mg at day 8	Non-inferiority *DISCOVER 1:* 83% early clinical success at 48-72 hours in dalbavancin group vs 82% in vancomycin/ linezolid *DISCOVER 2:* 77% vs 78%
Infective endocarditis and cardiac device infection						
	Fazili et al. (2023) [4]	16 retrospective publications: 4 case reports, 12 case series (worldwide)	61% bacterial species reported: - 45% *S. aureus* (46% MSSA, 54% MRSA) - 2.6% CoNS - 19% *Streptococcus spp.* - 14% *Enterococcus spp.*	170 patients: - 49% native valve - 27% prosthetic valve - 12% cardiovascular devices	Multiple schemes: Loading dose of 1500 mg/1000 mg, then 500 mg weekly doses; Variable duration (median 3 weeks); medium number of doses range [0-4]	90% clinical and / or microbiological cure in the cohort
	Wunsch et al. (2019) [40]	Multicentric, retrospective study (Austria)	16% MSSA 8% MRSA	101 patients (25% endocarditis)	Multiple schemes: 1500 mg once 1500 mg at day 1 and 8 1000 mg once, then 500 mg weekly doses	89% clinical and microbiological success

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	Authors (Year) [Bibliography Reference]	*Design of the Study (Country)*	*Pathogens*	*Cohort size*	*Dosing*	*Outcome*
Bone and joint infection (including prosthetic joint infection)						
	Gatti et al. (2023) [51]	Monocentric, retrospective case series (Italy)	Staphylococci spp.: 60% MRSE 15% MSSA 15% MRSA 10% Others	17 patients: 9 PJI 3 infected pseudoarthrosis 2 fracture related chronic osteomyelitis 2 spondylodiscitis 1 post surgical spinal infection	Multiple schemes: 71% IVD 1500 mg on day 1 then 1500 mg on day 8	100% clinical success at 6 month follow-up (13/17 assessable)
	Doub et al. (2023) [50]	Monocentric, retrospective study (USA)	13% MSSA 13% MRSA 20% CoNS	15 patients: 8 spinal hardware 7 PJI	IVD 1500 mg on day 1 then 1500 mg on day 8	85.7% no recurrence at 1 year follow-up
	Ramadan et al. (2022) [48]	Multicentric, retrospective study (Italy)	NA	13 spondylodiscitis	Multiple schemes: 6 as first line regimen	85% clinical success
	Rappo et al. (2019) [46]	Monocentric, open-blind, randomized, comparator-controlled trial (Ukraine)	Different pathogens: MSSA 50% MRSA 5% No other pathogens over 10% recurrence in the DAL group	80 patients: randomization: 7:1 (70 DAL :10 SoC)	IVD 1500 mg at day 1 and 8 vs SoC for 4-6 weeks	Clinical cure at day 42: 97% DAL vs 88% SoC
	Wunsch et al. (2019) [40]	Multicentric, retrospective study (Austria)	16% MSSA 8% MRSA	101 patients: 30 PJI 28 osteomyelitis	Multiple schemes: 1500 mg once 1500 mg at day 1 and 8 1000 mg once, then 500 mg weekly doses	89% clinical success
	Morata et al. (2019) [47]	Multicentric, retrospective study (Spain)	*S. epidermidis* *S. aureus*	64 patients: 45 PJI 19 osteomyelitis	Multiple schemes: 1000 mg day 1 1500 mg day 1 Addition of 500 mg weekly doses (median of 5 weeks)	65% to 76% clinical success in PJI (depending on prosthesis retention); 73% in osteomyelitis
Other site infection						
BSI	Veve et al. (2020) [58]	Retrospective cohort study (USA)	NA	215 patients: 70 DAL group vs 145 SoC group	NA	17% 90-day infection related readmission in DAL group vs 28% SoC
BSI	Raad et al. (2005) [57]	Phase II, open label, controlled randomized clinical trial (USA)	*S. aureus* CoNS	75 patients: 35 DAL group vs 34 SoC group	IVD 1000 mg once, then 500 mg at day 8	87% efficacy in DAL vs 50% SoC*
Pneumonia	Bork et al. (2019) [59]	Multicentric retrospective	MRSA	28 patients (1 pneumonia)	Unknown	Early clinical success (lost-to-follow-up at 30 days)
Pneumonia	Barber et al. (2017) [60]	Case report (USA)	MRSA	1 patient	IVD 1500 mg 1 dose regimen	Early clinical success (exitus for other causes)

Abbreviations: ABSSSI: acute bacterial skin and skin structure infection; DAL: dalbavancin; SoC: standard of care; USA: United States of America; NA not available; IVD intravenous drip; CoNS: coagulase-negative staphylococci; MSSA: methicillin-sensible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; MRSE: methicillin-resistant *S. epidermidis*; PJI: prosthetic joint infection; BSI: blood-stream infection. * Statistically significant; † Not statistically significant.

of osteomyelitis in oritavancin treated patients (0,6% of all the pool of patients): SOLO I with 1 case in both arms and SOLO II with 5 cases in the oritavancin arm versus none in vancomycin [29]. As the study protocol actively excluded osteomyelitis, burns and wound infections, and diabetic foot infections, those diagnosis may have eluded the standard screening for inclusion. However, the median time to bone infection diagnosis was almost 5 days, so they were considered as pre-existing in half of these cases.
This narrative review aims to explore the current evidence on the real-world use of long-acting antibiotics, focusing on the potential advantages and disadvantages of dalbavancin and oritavancin in off-label indications.

METHODS

A literature search was conducted on PubMed library database to identify key articles that investigated the real-world use of long-acting antibiotics in clinical practice, with the main research question being describing labelled indications and off-label uses of these drugs reported to date. The search was performed using the following keywords: long-acting antibiotics, dalbavancin, oritavancin. The search had no time limits and was limited to results in Italian/English language.
Studies retrieved from this search underwent a screening process based on methods, setting, type of publication and practical relevance by the authors. Duplicated papers, studies not clearly describing clinical practice or with no reference to real-life application were excluded.
After the screening process, authors (G. M. and M. C.) independently reviewed and summarised data from all relevant articles to compile this paper.
A search about ongoing trials has been conducted on the Clinicaltrials.gov library database to identify ongoing trials exploring new indications for these molecules, who then underwent further se-

Table 2 - Main characteristics of the studies included in the review concerning oritavancin (arranged by publication year).

	Authors (Year) [Bibliography Reference]	*Design of the Study (Country)*	*Pathogens*	*Sample size*	*Dosing*	*Outcome*
ABSSSI						
	Sacdal et al. (2022) [75]	Monocentric, retrospective study (USA)	NA	51 oritavancin group vs 31 oral antibiotics group	IVD 1200 mg single dose	16% ED revisit (vs 36%)* 12% hospitalisation rate (vs 26%)†
	Dretske et al. (2021) [76]	Monocentric, retrospective study (USA)	MSSA, MRSA, *Streptococcus spp.*	11 patients	IVD 1200 mg single dose	63% clinical success
	Helton et al. (2020) [36]	Monocentric, retrospective study (USA)	MSSA, MRSA, *Streptococcus spp.*	61 oritavancin group vs 61 vancomycin group	IVD 1200 mg single dose	10% 30-day readmission (vs 10%)† 25% 30-day ED return (vs 29%) †
	Estrada et al. (2020) [38]	Multicentric, retrospective study (USA)	NA	115 outpatient cohort, 151 hospital discharge cohort	IVD 1200 mg single dose	*Outpatient cohort:* 6% 30-days admission, 10% antibiotics within 30 days post index treatment *Hospital discharge:* 7% 30-days readmission
	Redell et al. (2019) [39]	Multicentric, retrospective study (USA)	Not specified for all patients (MRSA, MSSA, *Streptococcus pyogenes*, CoNS, *Enterococcus faecalis*, *Corynebacterium spp.*)	401 ABSSSI (440 cases)	IVD 1200 mg single dose/ multiple doses (95% single dose)	88% clinical success overall

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	Authors (Year) [Bibliography Reference]	*Design of the Study (Country)*	*Pathogens*	*Sample size*	*Dosing*	*Outcome*
	Co et al. (2018) [41]	Multicentric, retrospective study (USA)	NA	37 ABSSSI (67 patients)	IVD 1200 mg single dose	0% 14-days readmission
	Anastasio et al. (2017) [37]	Monocentric, retrospective study (USA)	In the oritavancin group: 79% MSSA, 42% MRSA, 14% *E. faecalis*	59 oritavancin group vs 59 SoC group	IVD 1200 mg single dose	90% clinical success at 5-30 days completion (vs 77%)[†]
	Corey et al. (2014) [27]	Multicentric, double-blind, randomized clinical trial (Argentina, Canada, India, Israel, Mexico, Romania, Russia, Spain, Ukraine, USA)	MSSA, MRSA, streptococci (*S. anginosus, S. pyogenes, S. dysgalactiae, S. agalactiae*), *E. faecalis*	1019 patients: 509 oritavancin group vs 510 vancomycin	IVD 1200 mg single dose	80% efficacy at early clinical evaluation (vs 83%) 83% efficacy at 7-14 days post therapy (vs 80%)
Infective endocarditis						
	Ahiskali et al. (2020) [44]	Monocentric, retrospective study (USA)	1 MSSA, 1 MRSA	2 patients	IVD 1200 mg for 1 to 2 doses	50% cure, 50% failure (spondylodiscitis)
	Brownell et al. (2020) [77]	Multicentric, retrospective study (USA)	NA	4 patients	NA	Cure
	Morisette et al. (2019) [78]	Multicentric, retrospective study (USA)	*E. faecalis*	1 native valve endocarditis	IVD 1200 mg single dose	Lost to follow-up
	Terrero Salcedo et al. (2018) [43]	Monocentric case series (USA)	2 MSSA, 2 MRSA, 1 *S. pyogenes*/ group F *Streptococcus*	5 native valve endocarditis	IVD 1200 mg once weekly for 1 to 4 doses	60% cure 40% lost to follow-up
	Stewart et al. (2018) [54]	Multicentric, retrospective study (USA)	*S. agalactiae*	1 native valve endocarditis	IVD 1200 mg single dose	Failure (valve replacement surgery)
	Johnson et al. (2015) [42]	Case report (USA)	VRE	1 prosthetic valve endocarditis	IVD 1200 mg every 48 hours for 3 doses, then once weekly for 7 weeks At relapse, 1200 mg twice weekly for 10 weeks after surgery	Cure after valve replacement surgery
Endovascular graft						
	Schulz et al. (2017) [61]	Case series (USA)	*Staphylococcus lugdunensis*	1 patient	IVD 1200 mg once, then 800 mg weekly for 11 doses, then 1200 mg for 1 dose following 11-day interval, then 800 mg for 5 doses weekly	Improvement
Sternal wound/mediastinitis						
	Schulz et al. (2017) [61]	Case series (USA)	*Cutibacterium acnes*	1 patient	IVD 1200 mg once, then 800 mg weekly for 1 dose	Clinical success

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	Authors (Year) [Bibliography Reference]	*Design of the Study (Country)*	*Pathogens*	*Sample size*	*Dosing*	*Outcome*
Bone and joint infection (including prosthetic)						
	Van Hise et al. (2020) [53]	Multicentric, retrospective study (USA)	Monomicrobial: 71,9% MRSA, 19% MSSA, 5% VR *enterococci*, 2% VISA	134 acute osteomyelitis, of which 24 prosthetic osteomyelitis	IVD 1200 mg once, then 800 mg weekly for 4 to 5 doses	80% clinical success post treatment at 6 months follow-up
	Nguyen et al. (2020) [79]	Case report (USA)	VS-*E. faecalis*	1 PJI	IVD 1200 mg once weekly for 6 doses (following previous antibiotic therapy)	Cure at 10 months follow-up
	Rendell et al. (2019) [39]	Multicentric, retrospective study (USA)	Not specified for all patients (MRSA, MSSA, *S. pyogenes, Bacillus spp.)*	18 osteomyelitis, 4 septic arthritis/ synovitis, 3 PJI, 3 bursitis, 1 prosthetic lumbar infection	IVD 1200 mg every 6 to 14 days, for 1 to 10 doses (78% following previous antibiotic therapy)	*Osteomyelitis:* 88% clinical success *Joint infection (both native/ prosthetic):* 71% clinical success (follow-up unknown)
	Chastain et al. (2019) [80]	Monocentric case series (USA)	55% MRSA, remaining not available/sterile	9 chronic osteomyelitis	IVD 1200 mg (no consistent time between doses, for 2 to 6 doses)	100% Clinical cure at 6 months follow-up
	Dahesh et al. (2019) [56]	Case report (USA)	VRE	1 implant-associated vertebral osteomyelitis	IVD 1200 mg weekly for 2 doses, then 800 mg weekly for 8 doses plus ampicillin	Cure at the end of treatment
	Co et al. (2018) [41]	Monocentric, retrospective study (USA)	NA	8 osteomyelitis, 5 septic arthritis, 3 diabetic foot infection	NA	No readmission within 12 days
	Foster et al. (2018) [55]	Case report (USA)	VRE	1 PJI	IVD 1200 mg once weekly for 6 weeks	Cure
	Ruggero et al. (2018) [81]	Case report (USA)	MRSA	1 vertebral osteomyelitis	IVD 1200 mg every 2 weeks for 4 doses, then 1200 mg 1 onth later + TMP/SMX	Cure at 1 year follow-up
	Schulz et al. (2017) [61]	Case series (USA)	MSSA	4 osteomyelitis	*Multiple schemes:* 1200 mg once, then 800 mg weekly for 7 doses 1200 mg for 2 weekly doses 1200 mg once, then 800 mg weekly for 4 doses 1200 mg once, then 800 mg weekly for 2 doses	Clinical success at 2 weeks follow-up
	Stewart et al. (2017) [54]	Case series (USA)	MSSA	1 osteomyelitis	IVD 1200 mg single dose	Failure

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	Authors (Year) [Bibliography Reference]	*Design of the Study (Country)*	*Pathogens*	*Sample size*	*Dosing*	*Outcome*
	Delaportas et al. (2017) [82]	Case report (USA)	MSSA	1 osteomyelitis	IVD 1200 mg every week for 6 doses	Cure at 40 weeks follow-up to
Other sites infection						
Intraabdominal infection	Schulz et al. (2017) [61]	Case series (USA)	*Enterococcus* spp.	1 recurrent bacteremia in cholecystitis 1 hepatic abcess	IVD 1200 mg 2 doses	Failure
Pneumonia	Schulz et al. (2017) [61]	Case series (USA)	Small colony variant MRSA	2 patients	IVD 1200 mg 2 doses	Clinical success
Meningitis	Wenzler et al. (2021) [64]	Case report (USA)	VRE	1 patient	IVD 1200 mg for 6 doses, multiple intervals	Death by other cause

Abbreviations: ABSSSI: acute bacterial skin and skin structure infection; USA: United States of America; ED: emergency department; NA not available; IVD intravenous drip; ORI: oritavancin; CoNS: coagulase-negative staphylococci; MSSA: methicillin-sensible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; VISA: vancomycin-intermediate *S. aureus*; VRE: vancomycin-resistant *Enterococcus faecium*; VS: vancomycin-sensible; PJI: prosthetic joint infection. * Statistically significant; † Not statistically significant.

lection by the authors based on setting, novelty and clinical applications.
The results were then reported in a narrative review format.

IN-LABEL INDICATION

Acute bacterial skin and skin structure infection (ABSSSI)

Dalbavancin

Dunne et al. reported in 2016 one of the largest dalbavancin cohorts including 698 patients with various kinds of ABSSSI and treated with a single dose regimen or weekly regimen of dalbavancin, at days 1 and 7, (randomized 1:1), resulting in similar efficacy and safety outcomes (81.4% vs 84.2%). Moreover, tolerance for both treatment options was high, offering proof of a valid alternative to the in-label formulation. Indeed, the use of a single administration of a 1500 mg dosage of dalbavancin was found to be not inferior to a dosage of 1000 mg on day 1 and 500 mg on day 7, with a clinical resolution outcome at 48-72 hours of 81.4% versus 84.2%. Similar outcomes at 14 and 28 days have also been reported [10]. A multi-centric study in Italy in 11 centres between 2016-2019 enrolled 206 patients treated with at least one dose of dalbavancin, 60.2% ABSSSI, with a clinical cure rate of 85.5% in this subgroup group, in line with the data from randomized trials [33]. Worth noting, dalbavancin use in this real-life setting was positioned as second-line treatment or consolidation therapy, as few OPAT services exist in many Italian hospitals [33].
Concerning unusual skin and soft tissue infections, Pascale et al. reported a retrospective multicentric cohort in Italy in 2022, enrolling 48 patients with sternotomic wound infection without mediastinitis or osteomyelitis. 31% treated with dalbavancin and 69% with standard of care (SoC), in addition to surgical debridement and negative pressure wounds. The healing of wound rate was 95% in the dalbavancin arm vs 82%, and the cost savings in dalbavancin group were significant [35].

Oritavancin

In clinical practice, the labelled indication for oritavancin has been explored and reported in only a few retrospective cohorts, mainly in the USA, and in the setting of emergency departments (ED) or infusion centers, with the principal objective of reducing hospital admissions and related costs. Most reports describe a very high success rate, up to 90%, with a rather short follow-up period, not exceeding 30 days in most studies. Success was often defined by the rate of admissions within the same healthcare system and ED returns, as might be ex-

pected in this context, where continuous clinical assessment could not be ensured [27, 28, 36]. Anastasio et al. retrospectively reported 59 patients with ABSSSI treated with single-dose oritavancin versus 59 SoC, with a clinical success rate of 90% at 5-30 days after completion of therapy in the oritavancin group (compared with 77% in the SoC group) [37]. More recently, Estrada et al. described two large cohorts, the first of 115 outpatient cases and the second of 151 patients treated with oritavancin at hospital discharge, with similar results: for the outpatient cohort, 30-days readmission rate was rather low (6%) and only 10% needed rescue antibiotics within 30 days after the end of treatment with oritavancin; for the hospital discharge cohort, only 7% were readmitted within 30 days [38].
The largest set of evidence in ABSSSI comes from the retrospective cohort by Redell et al. which described real-world experience of oritavancin for different indications from 2014 to 2017. Overall, 380 patients with ABSSSI were treated with a single dose, while 21 patients with two doses, no more than 14 days apart. Most patients received oritavancin as sequential treatment, after at least one more antibiotic has been administered. Overall clinical success was as high as 88% in single-dose group and 94% in the multiple doses group, for all indications confounded and no sub analysis focused on ABSSSI only. Microbiological eradication was achieved in 76% of cases in the single dose group, as shown in a small subset of patients [39].

OFF-LABEL INDICATIONS

In the antibiotic research and development field, authorization for use in ABSSSI often represents a market entry indication, due to its easiness to monitor, and the rapid assessment of success. However, pharmacokinetic features of these drugs make them attractive for those infections requiring long therapy duration and action against biofilm/planktonic form.
Here we described the key evidence in off-label indications in clinical practice.

Infective endocarditis and cardiac implantable electronic device (CIED) infections

Dalbavancin
Not much evidence exists for dalbavancin use in endocarditis and CIED infection treatment. A multicentric retrospective study by Wunsch et al., in 2019, included 101 patients, treated with different dosing regimens, 25% of which affected by infective endocarditis (IE), with an overall success rate of 89% [40]. A narrative review by Fazili et al. in 2023 described almost 170 patients from 16 different case reports/series [4]. Overall, in this report, 49% were native valve IE, 47% prosthetic valve IE and 12% cardiac device-related infection. These patients were transitioned to dalbavancin mainly due to a history of drug abuse, and all of them except one received dalbavancin as a subsequent treatment, after a mean of 3 weeks of standard treatment. The most common dosing regimen of dalbavancin reported is a loading dose of either 1500 mg or 1000 mg, followed by one or more weekly doses of 500 mg, median being 3 weeks (range 0-4 weeks). On average, three doses of dalbavancin were given. The clinical success rate was about 90%, based on either clinical or microbiological cure.

Oritavancin
For this indication, mostly case reports/series exist with mixed results, mostly focusing on infective endocarditis and almost no evidence exists about oritavancin use in CIED infections with only a known case report [41].
The first evidence came from an American case report of a compassionate use of oritavancin for a VRE prosthetic aortic and native mitral valve IE in a patient with chronic kidney disease, spinal fusion at L5-S1, a long history of recurrent VRE bacteraemias and an acquired resistance to daptomycin. Oritavancin was chosen after an initial treatment with intravenous daptomycin and tigecycline for 2 episodes of VRE bacteraemia without endocarditis, followed by a daptomycin-resistant relapse treated with oral linezolid plus intravenous tigecycline, which were poorly tolerated. Oritavancin (dosing regimen: loading dose of 1200 mg every other day for 3 doses, then once weekly for 6 weeks) was pursued with significant clinical improvement for 7 weeks, followed by a new course (dosing regimen: 1200 mg twice weekly) as blood cultures at end of treatment continued to grow VRE and the patient developed mitral and aortic valvulopathy. Cardiac surgery was then needed, and both the native and prosthetic valve grew VRE on culture (prosthetic) and staining (native). Oritavancin was then continued for 10 weeks

postoperatively with clinical success and persistently negative blood culture at 17 months follow-up [42].
The largest case series reported 5 patients with native valve endocarditis (3 tricuspid valves, 2 mitral valves), which were treated with oritavancin at the end of their treatment (up to 4 doses, 1200 mg weekly). Worth noting, all patients were people who inject drug (PWID) and one had end stage renal failure. Clinical success was achieved in all patients that were present at follow-up (up to 30 days), but 2 patients were lost to follow-up [43]. Ahiskali et al. also focused on real-world use of oritavancin in complicated gram-positive infections in PWID and described 2 native tricuspid valve endocarditis due to *S. aureus* (50% MRSA) with a 50% clinical success [44].
Oritavancin may indeed represent the game-changing drug for infections treatment in this population, often at risk of relapse and ongoing bacteraemia due to persisting unsafe injections. To address this unmet need, a pilot single-center open-label clinical trial (NCT03761953) focusing on patients with opioid use disorder and/or intravenous drug use and systemic *S. aureus* infection had been proposed but it has recently withdrawn due to COVID-19 pandemic. The study aimed to evaluate a small series of patients for the final consolidation phase of treatment (last 2 weeks) of systemic infection with *S. aureus*, including native IE with no embolization to lung or central nervous system and no need for anticoagulation, evaluating safety, relapse, and therapeutic drug monitoring [45].

Bone and joint infection (including prosthetic joint infection)

Dalbavancin

Due to its good penetration in bone and synovial fluid [7], its antibiofilm activity and the possibility of OPAT, the use of off-label dalbavancin in the treatment of osteoarticular infections (including vertebral osteomyelitis) due to gram-positive pathogens is becoming a widely pursued alternative over time.
An open-blind randomized, comparator-controlled trial in Ukraine in 2018 has addressed this question: 80 patients with different osteomyelitis (spondylodiscitis excluded, main pathogen: *S. aureus*, main district: tibia) were included [46]. The patients were randomized 7:1 to dalbavancin two-dose regimen (1500 mg on day 1 then 1500 mg on day 8) vs SoC (mostly vancomycin followed by oral linezolid/fluoroquinolone). Clinical resolution was reached in 97% dalbavancin arm at day 42 vs 88% SoC.
In a retrospective multicentre cohort on the safety and efficacy of dalbavancin treatment of gram-positive infection, 32 cases of peri-prosthetic joint infection (PJI) and 30 of osteomyelitis were included [40]. The main treatment schemes used in the whole cohort were: 1500 mg single dose (24%), 1500 mg on day 1 then 1500 mg on day 8 (18%) and 1500 mg at day followed by 500 mg weekly. The overall success rate, defined as the absence of clinical or microbiological signs of infection at 90-days, for all kind of infections was of 89%.
In a multicentric study from Spain, 64 patients with a wide range of osteoarticular infections (septic arthritis, spondylodiscitis, osteomyelitis, or orthopaedic implant-related infection including PJI) treated with dalbavancin between 2016 and 2017 were included. Success was 65%-76% in PJI group, depending on whether the prosthetic implant was removed or not, and of 73% in native bone and joint infections [47]. A multicentric retrospective study on spondylodiscitis reported 13 patients from 4 Italian centers treated with dalbavancin from 2018 to 2021, in which dalbavancin was used as a first line regimen (46%) or as simplification: clinical success was observed in 11/13 patients during hospitalization, also confirmed at 5 months follow-up [48]. A monocentric retrospective study described 15 patients with MRSA spondylodiscitis, treated with dalbavancin after 2 weeks of vancomycin: the success rate was 93% [49].
A retrospective study included 8 cases of spinal hardware infection and 7 PJI between 2017 and 2021 receiving at discharge a two 1500 mg dose regimen at day 1 and day 8. Main pathogens observed were MSSA, MRSA (3 cases each) and *C. striatum* (2 cases in spinal hardware infections). 86% had no recurrence in 1 year of follow-up. A combination therapy with rifabutin or rifampicin was also administered in 53% of the patients (mainly staphylococcal infections). No adverse effects were observed [50].
A recent Italian case series explored PK/PD efficacy thresholds over time and their impact on clinical outcomes in staphylococcal osteoarticular infections: conservative PK/PD efficacy thresholds of dalbavancin concentrations lower ≥4.02 and upper ≥8.04 mg/L were applied in this report, as a proxy of the optimal target attainment of $fAUC_{24H}$/

MIC >111,1. Overall, 17 patients receiving at least 2 doses were included (dosing regimen: 1500 mg on day 1 and 8 for 71% of patients) and underwent at least 1 therapeutic drug monitoring assessment. Clinical success at 6-months follow-up, assessed in 76,5% of the cohort, was 100% and the percentage of the overall treatment period for which dalbavancin was above both the efficacy thresholds was 100% in most of the patients [51].

Oritavancin

Oritavancin's pharmacokinetic/pharmacodynamic have shown high efficacy for bone and joint infection treatment, including periprosthetic infections, as it has a wide distribution volume, good bone penetration and in vitro studies showed a keen ability to kill stationary-phase *S. aureus*, even in intracellular status, and biofilm eradication [16, 52].

Evidence from clinical practice on oritavancin efficacy in treating bone and joint infections is still scarce but encouraging. A multicentric, retrospective study conducted between 2016 and 2018 in 20 infusion centers in the USA comprising 134 acute osteomyelitis observed 88% clinical success at the end of the last dose and 80% clinical success post-treatment at 3- and 6-months follow-up after four to five doses of oritavancin, with an extremely low rate of patients lost to follow-up. Patients reported in this study received oritavancin 1200 mg as a loading dose then 800 mg once weekly as per study protocol. Worth mentioning, most of the patients had undergone debridement (90%), which may not totally represent real-life application in every setting, and MRSA was the main pathogen, retrieved in 72% of samples. Only 13% of patients had already received antibiotic therapy, thus suggesting a role for oritavancin as a standalone treatment for MRSA bone infection. However, the vertebral source was underrepresented, so these results may not be applicable to spondylodiscitis [53].

Another large set of evidence comes from the CHROME registry which included 18 osteomyelitis, 4 septic arthritis, 1 vertebral hardware-related infection, and 1 bursitis. 78% of patients with osteomyelitis received oritavancin as rescue therapy, since half of those was coming from previous clinical failures, and 8 patients received multiple doses [39]. Clinical success was extremely high in both single-dose and multiple-dose groups, up to 90%. Treatment failure with oritavancin was anecdotally reported in few case reports: Stewart et al. described a failure in a young intravenous drug abuser admitted for MSSA bacteraemia, iliopsoas abscess, and sacroiliac joint infection [54].

Key evidence is lacking on oritavancin use in periprosthetic joint infection, with the largest cohort reporting 3 periprosthetic joint infections unspecified with no microbiological data, with only one patient treated with more than one dose and no subanalysis for this group [39].

One case report described a daptomycin-non susceptible VRE and *Pseudomonas aeruginosa* hip periprosthetic infection with a history of multiple surgical revisions, finally treated by oritavancin (dosing regimen: 1200 mg once weekly for the last 2 weeks) and ciprofloxacin for 6 weeks with absence of growth on bone cultures performed at day 13 of oritavancin therapy. The patient completed the 2-stage hip revision and was infection free at 5 months follow-up after last revision [55].

Another case report described a microbiological successful case of VRE hardware-associated vertebral osteomyelitis treated with oritavancin plus ampicillin (oritavancin dosing regimen: 1200 mg once weekly for 2 weeks, then 800 mg weekly), in a patient previously treated for MRSA epidural abscess which relapsed despite proper antibiotic treatment and finally needed spinal decompression [56].

Other indications (blood-stream infection, endovascular graft infection, pneumonia, meningitis, etc.)

Dalbavancin

To date, there is no evidence of the use in real life of dalbavancin for meningitis, mainly due to the undocumented penetration in CSF, described as low to none in pharmacokinetic models [5].

Only one randomized trial in 2005 focused on dalbavancin in bloodstream infection (BSI): 75 patients with catheter-related BSI (*S. aureus*, CoNS, *E. faecalis*) have been treated with either vancomycin or dalbavancin (loading dose of 1000 mg then 500 mg on day 7), resulting in an overall success rate, defined as clinical and microbiological resolution, of 87% vs 50% [57]. More recently, Veve et al. compared retrospectively dalbavancin to SoC in many settings including BSIs, describing a lower percentage of readmissions and adverse effects in the dalbavancin group [58].

Not much evidence regarding dalbavancin as

pneumonia treatment in real life has been reported: a retrospective cohort by Bork et al. described one case of MRSA pneumonia with early clinical success but lost to follow-up at 30 days [59]. Another case report in 2017 described an AIDS patient with active intravenous drug abuse and MRSA pneumonia, where dalbavancin was administered as subsequent therapy to vancomycin (single dose of 1500 mg upon discharge). As the patient left against medical advice, he was readmitted 11 days later due to unfavourable evolution, even if there was no clear evidence of MRSA [60].

Oritavancin

Off-label use of oritavancin in other kind of infections has been anecdotical with mixed results.

The retrospective cohort from Schulz et al., comprising 17 patients with complicated infections, described a successful case of *Staphylococcus lugdunensis* endovascular graft infection treated with a compassionate use of oritavancin as suppressive therapy, because the patient was not suitable for surgery. In the same cohort, a patient with bacteriaemic cholecystitis caused by VRE with no source control was treated with oritavancin along with tigecycline. However, as tigecycline was switched to piperacillin/tazobactam due to altered liver function tests, septic shock arose leading to the patient's death. Two cases of pneumonia caused by small colony variant MRSA successfully treated by oritavancin have also been reported in the same paper: the first one was a patient with cystic fibrosis and bilateral lung transplant, for whom oritavancin was chosen in the context of moxifloxacin-resistant MRSA, history of vancomycin-related nephrotoxicity, ceftaroline failure in previous episodes and recent linezolid exposure; in the second case, oritavancin was chosen after the vancomycin MIC determination [61]. The authors also described a case of *Cutibacterium acnes* sternal wound infection, occurred after coronary artery bypass graft surgery, initially treated by vancomycin then switched to oritavancin for outpatient treatment with clinical success [61].

Oritavancin use in meningitis may be justified because animal models of pneumococcal meningitis demonstrated high bactericidal activity in the cerebrospinal fluid (CSF) and a beneficial effect on inflammatory markers in CSF, with no influence by dexamethasone use [62, 63]. Only a case report in humans described oritavancin therapy for multidrug-resistant *E. faecium* meningitis in a fragile immunocompromised patient with unsuccessful results: projected maximal CSF concentration was demonstrated at 0,014 mg/l at plasma T_{max} and considering CSF concentration/MIC ratio, oritavancin did not inhibit growth in vitro [64].

ONGOING TRIALS

Several trials regarding dalbavancin place in therapy are ongoing, some in BSIs [65], in osteoarticular infections [66-68], peritonitis [69] and on paediatric patients [70].

No registered trials for expansion of label indication have been found for oritavancin on clinicaltrials.gov, aside from an open-label study on children [71]. Other studies are ongoing to accurately describe oritavancin effect on cytochrome CYP450, on warfarin and coagulation tests [72-74].

CONCLUSIONS

Dalbavancin and oritavancin are long-acting antibiotics with peculiar pharmacodynamic and pharmacokinetic properties that make them viable treatment options against gram-positive infections. Moreover, these drugs may have their place in non-adherent patients, in setting of PWID or difficult access to healthcare. Another potential use of these drugs is in patients with oral intake impairment or reduced gastro-intestinal absorption. Their long terminal half-life, wide distribution volume, good tissue and intracellular penetration and anti-biofilm activity place them among the therapeutic tools for chronic infections, especially bone and joint infections, device-associated infection and endocarditis. Some observational evidence has emerged in bone and joint infections therapy for both dalbavancin and oritavancin, with a trial exploring efficacy of dalbavancin specifically, and infective endocarditis for dalbavancin. Current published studies show discouraging results for the use of these long-acting antimicrobials in central nervous system infections, such as meningitis, and data on intra-abdominal infections are still scarce. The existence of stronger clinical evidence would tend to favour dalbavancin over oritavancin in the treatment of chronic infections. Furthermore, the need for larger dilution volumes of glucose solution for oritavancin infusion would make it unwieldy

in patients with decompensated diabetes or congestive heart failure. On the other hand, oritavancin's proven activity against VRE makes it an attractive option for the treatment of chronic infections with this pathogen. Despite the scientific literature is flourishing on off-label use of long-acting antibiotics, solid data on dosing, number and interval of administrations are still lacking. Therefore, the results of the ongoing trials are awaited, to assess the efficacy and safety of the different dosing regimens of therapy of dalbavancin and oritavancin in difficult-to-treat infections.

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