The role of the new lipo-glycopeptides: oritavancin & dalbavancin

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Trend of blood isolates, Toscana 2018-2022

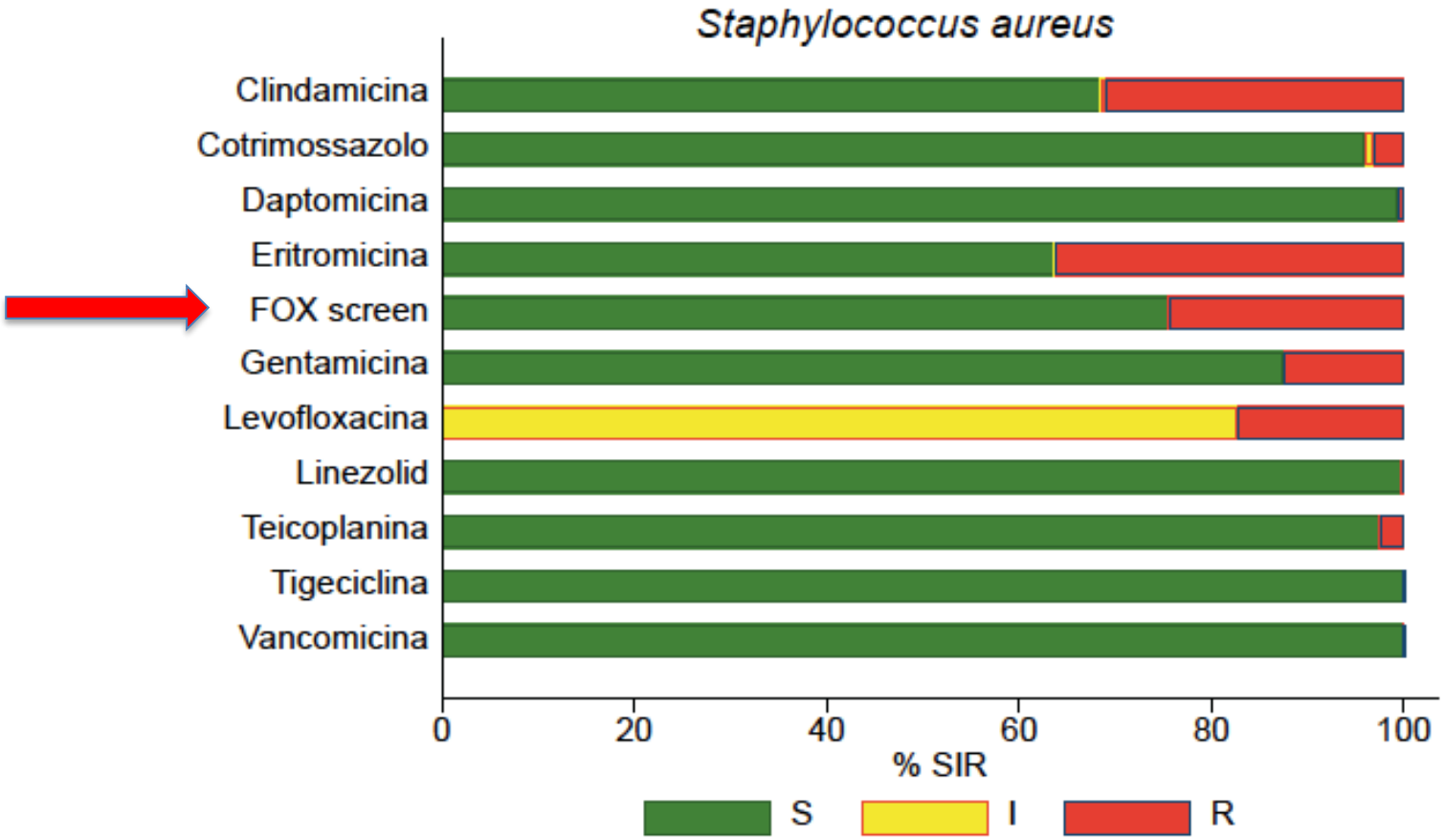
Tabella 1.3
Emocolture, numerosità delle specie sorvegliate - Toscana 2018-2022 - Fonte: ARS - Smart

		2022		2021		2020		2019		2018	
		N	%	N	%	N	%	N	%	N	%
n.3269 34,5% Gram positivi	*Staphylococcus aureus*	1.667	17,6	1.608	18%	1.295	17%	1.312	18%	1.315	17%
	Enterococcus faecalis	979	10,3	1.086	12%	805	11%	696	9%	740	10%
	Enterococcus faecium	623	6,6	623	7%	457	6%	389	5%	370	5%
	Streptococcus pneumoniae	104	1,1	74	1%	82	1%	192	3%	177	2%
Gram negativi	*Escherichia coli*	2.576	27,2	2.525	28%	2.234	30%	2.503	33%	2.570	34%
	Klebsiella pneumoniae	1.627	17,2	1.416	16%	1.168	16%	1.172	16%	1.050	14%
	Pseudomonas aeruginosa	765	8,1	680	8%	621	8%	511	7%	516	7%
	Acinetobacter spp.	245	2,6	287	3%	195	3%	170	2%	232	3%
miceti	*Candida spp.*	880	9,3	716	8%	642	8,6%	541	7%	654	9%
	Totale	9.466		9.015		7.499		7.486		7.624	

ARS-SMART 2022

Staphylococcus aureus 2022: MRSA: 22.4%

Figura 1.6
Profilo di resistenza di *Stapylococcus aureus* nelle emocolture - Toscana 2022 - Fonte: ARS - Smart



MRSA infections

- Bacteremia
- Endocarditis (native, prosthetic valve)
- Pneumonia
- Osteomyelitis
- Prosthetic joint infection
- Septic arthritis
- ABSSSI

Recommendations for the treatment of MRSA

Indication	Vancomycin	Linezolid	Daptomycin
Complicated SSTI	AI	AI	AI
Osteomyelitis Septic arthritis	BII	BII	BII
Pneumonia	AII	AII	-
CNS infections	BII (+RFP)	BII	-
Bacteremia & IE, NV	AII	-	AI
PVE	BIII (GM+RFP)	-	-

IDSA Guidelines for MRSA; CID 2011; 52 (3) e18-e55

Drawbacks of the current therapeutic options for MRSA

Vancomycin

- Available for parenteral use only
- MIC creep
- Difficulties in attainement of therapeutic levels
- Emergence of VISA, hVISA, VRSA

Daptomycin

- Available for parenteral use only
- Not indicated for treatment of pneumonia

Linezolid

- Bacteriostatic
- Significant drug interactions
- Myelosuppressive

New anti gram-positives antibiotics

		cSSSi	CAP	HAP	VAP	notes
Ceftaroline *Zinforo*	Pfizer	X	X			No MRSA pneumonia 600 mg bid
Ceftobiprole *Mabelio*	Advanz Pharma		X	X		Not registered in US 500 mg bid
Telavancin *Vibativ*	Astellas	X		X	X	No more EMA approval OD 10 mg/Kg; No IR
Dalbavancin *Xydalba*	Angelini	X				IV single repeated dose 1500 mg dose
Oritavancin *Tenkasi*	Menarini	X				IV Single dose 1200 mg
Tedizolid *Sivextro*	MSD	X				200 mg IV/OS X 6 days
Delafloxacin *Quofenix*	Menarini	X	X			450 mg bid/OS 300 mg bid/IV

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March, 2021

JAC-Antimicrobial Resistance

Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): updated guidelines from the UK

Nicholas M. Brown[1]*, Anna L. Goodman[2,3], Carolyne Horner[4], Abi Jenkins[4] and Erwin M. Brown[4]

Skin and skin structure infections (1)

- (i) **For severe cellulitis/soft tissue infection caused by MRSA** use intravenous glycopeptides (vancomycin or teicoplanin) (strong recommendation).
- (ii) Use linezolid (oral or intravenous) or daptomycin (intravenous) as an alternative (strong recommendation).
- (iii) Consider tigecycline as an alternative when first- and second-line agents are contraindicated, and the isolate is susceptible (weak recommendation).

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Skin and skin structure infections (2)

- (iv) Consider clindamycin, co-trimoxazole, or doxycycline as oral agents (when the isolate is susceptible) for treatment of patients with **mild skin and soft tissue infection caused by MRSA, or for oral step-down therapy** (weak recommendation).
- (v) Consider recently licensed agents such as ceftaroline, delafloxacin, oritavancin, or telavancin as alternative options for treatment of cellulitis/soft tissue infection caused by MRSA (weak recommendation).
- (vi) No recommendations can be made on the use of ceftobiprole, dalbavancin and tedizolid over standard therapeutic agents in the treatment of SSTI caused by MRSA.

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Dalbavancin/Oritavancin

- Long-acting parenteral lipoglycopetide antibiotic
- Activity vs most G+ (VRE Oritavancin only)
- Bactericidal, MIC x Vanco, E-test
- Good PK profile (concentrations, long half-life, low potential for interactions)
  - 63% in bone similar to linezolid (60%)
- Good safety profile

In vitro Activity of New Gram-Positive Antibiotics

Table 1. *In vitro* Activity (MIC_{90} in µg/ml) of New Gram-Positive Agents[4,6-9, 29,30,36,37-39]

	Tedizolid[a]	Linezolid[b]	Dalbavancin[c]	Oritavancin[d]	Telavancin[e]	Vancomycin[f]
Coagulase-negative staphylococci	0.5	1-2	0.06 – 0.12	0.06	0.06	2
Vancomycin-susceptible *E. faecalis*	1	2	0.06	0.03	0.12	2
Vancomycin-resistant *E. faecalis*	0.5	2	>4	0.03, 0.5[†]	>2[€]	>32
Vancomycin-susceptible *E. faecium*	1	2-4	0.12	≤ 0.008	0.03	1
Vancomycin-resistant *E. faecium*	0.5	2	>4	≤ 0.008, 0.12[†]	2[€]	>32
Streptococcus pneumoniae	0.25	1	0.03	≤ 0.008	≤ 0.015	0.5
β-hemolytic *Streptococcus*	0.5	1	≤ 0.03	0.12	0.03	0.5
Viridans group *Streptococcus*	0.25	1	≤ 0.03	0.03, 0.06[‡]	0.03	1

Dosing and PK of of New Gram-Positive Antibiotics

Table 2. Dosing and Pharmacokinetics of New Gram-Positive Agents [5,17,18,27,40-42]

Drug	Tedizolid phosphate	Linezolid	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Drug Class	Oxazolidinone	Oxazolidinone	Lipoglycopeptide	Lipoglycopeptide	Lipoglycopeptide	Glycopeptide
Dosing	200 mg oral or intravenous daily	600 mg oral or intravenous every 12 hours	1000 mg intravenous followed one week later by 500 mg intravenous	1200 mg single intravenous infusion (over 3 hours)	10 mg/kg intravenous every 24 hours	1000 mg (or 15-20 mg/kg) intravenous every 12 hours
C_{max} (mcg/mL)	Oral: 2.0 Intravenous : 2.3	Oral: 12.7- 21.2 Intravenous : 12.9-15.1	287	138	93.6-108	63
T_{max} (hours)	Oral: 2.5 Intravenous : 1.1	Oral: 1.03- 1.28 Intravenous : 0.5	NR	Immediately following 3-hour infusion	NR	Immediately following 60-minute infusion
Half-life (hours)	12	4.6	346	245	8.0-8.1	4-6 hours
$AUC_{0\text{- infinity}}$ (mcg•h/m L)	Oral: 23.8 Intravenous : 26.6	Oral: 91.4- 138 Intravenous : 80.2-89.7	23,44	2,800	747	NR

Dosing and PK of of New Gram-Positive Antibiotics

Table 2. Dosing and Pharmacokinetics of New Gram-Positive Agents [5,17,18,27,40-42]						
Drug	Tedizolid phosphate	Linezolid	Dalbavancin	Oritavancin	Telavancin	Vancomycin
Drug Class	Oxazolidinone	Oxazolidinone	Lipoglycopeptide	Lipoglycopeptide	Lipoglycopeptide	Glycopeptide
Clearance (L/hour)	Oral: 6.9 Intravenous : 6.4	Oral: 4.8- 7.62 Intravenous : 7.38-8.28	0.0513	0.445	0.917-0.973	4.06
Volume of distribution (L)	67 – 80	40-50	7 – 13	87.6	9.3-10.2	60.5
Protein binding	70 – 90%	31%	93%	85%	90%	55%
Metabolism	Sulfation (liver)	Oxidation	No apparent metabolism	No apparent metabolism	No apparent metabolism	No apparent metabolism
Elimination	Urine: 18% Feces: 82%	Urine: 30% (additional 50% as metabolites) Feces: minimal	Urine: 33% unchanged 12% hydroxymetabolite Feces: 20%	Urine: < 5% Feces: < 1%	Urine: 76% Feces: < 1%	Urine: 75% over 24 hours

Journal Pre-proof

Expert Opinion on Dose Regimen and Therapeutic Drug Monitoring for Long-Term Use of Dalbavancin: Expert Review Panel

Eric Senneville , Guillermo Cuervo , Matthieu Gregoire , Carmen Hidalgo-Tenorio , Francois Jehl , Jose M. Miro , R Andrew Seaton , Bo Söderquist , Alex Soriano , Florian Thalhammer , Federico Pea

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DOI: https://doi.org/10.1016/j.ijantimicag.2023.1
Reference: ANTAGE 106960

Box 1: Type of complex infections eligible for off-label dalbavancin use.

- Infective endocarditis (IE)
- Bone and joint infections (BJIs)
- Prosthetic joint infections (PJIs)
- Vascular graft infections (VGIs)
- Catheter-related bacteraemia and other gram-positive biofilm-related infections

Key points

- Preliminary survey results and in-person presentations highlighted heterogeneity in dalbavancin use, confirming need for expert guidance.
- Experts suggest total dose 3,000mg dalbavancin in 4 weeks covers treatment for 4-6 weeks.
- Flexibility in dosing schedule is possible, depending on the healthcare setting.
- TDM should be used to guide the administration of a dose beyond 3,000mg and start between Day 28 and Day 35 where >6 weeks of dalbavancin treatment duration is expected.

Drugs - Real World Outcomes (2020) 7 (Suppl 1):S36–S40
https://doi.or

ORIGINA

A Two-
Analysi

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Warren E.

Key Points

Therapeutic concentrations of a novel oritavancin dosing regimen of 1200 mg and 800 mg administered 7 days apart were assessed in a pharmacokinetic model.

This dosing regimen achieved oritavancin concentrations above the susceptibility breakpoint (0.12 mg/L) for 8 weeks, and maintained a high AUC:MIC ratio for efficacy against organisms with MICs up to 0.25 mg/L.

Along with the observational clinical reports of success and safety with this dosing scheme, this study provides evidence for further evaluation of this approach when prolonged oritavancin treatment may be indicated.

Dalbavancin/Oritavancin:

place in therapy

- ABSSSi, Cellulitis (Diabetic foot infection due to susceptible organisms)
- Pts necessitating IV therapy who are not candidates for indwelling IV catheters or with a history of IV catheter-related complications;
- Pts in whom deferment of hospital admission is planned;
- Pts requiring continuation of therapy after hospital discharge;
- Pts who are candidates for OPAT where home health or frequent infusion center visits are not feasible;
- Pts with a history or risk for non-compliance with oral therapy.
- Shifting from a glycopeptide/daptomycin antibiotic to complete/continue prolonged antibiotic course
- Selected case of MSSA/MRSA endocarditis, vascular prosthetic infection, vertebral osteomyelitis for an earlier discharge from hospital

New Antimicrobials and New Therapy Strategies for Endocarditis: Weapons That Should Be Defended: Dalbavancin (1)

Table 3. Clinical studies investigating the treatment of infective endocarditis with dalbavancin.

Authors	Study Design	Endpoint	N° Patients/ IE Type	Pathogens	Dosage and Duration	Combination, Dosage	Outcomes	Safety
Bouza, E. et al., 2018 [128]	Multicentre retrospective study	Efficacy, tolerability, and cost reductions in people receiving DAL for various indications	69, mainly prosthetic joint infections (29%) and ABSSSI (21.7%) Previous therapy 97% 7 IE, type unspecified.	**IE subgroup:** CoNS (2), *Enterococcus* spp. (2), MRSA (1), *Streptococcus* spp. (1), negative culture (1)	Most common regimen: 1000 mg Day 1, then weekly 500 mg	Overall, 36.2%	Overall clinical success 84.1% and significant cost reduction **IE subgroup** Clinical success: 85.7%. Failure in 1 IE patient attributed to inadequate source control	Overall, AE in 13%. Most common AE: rash and tachycardia.
Tobudic, S. et al., 2018 [14]	Observational retrospective study DAL in IE mainly administered as OPAT	Clinical cure and safety	27 IE Previous therapy 88.9% 16 NVE, 6 PVE and 5 CIED-IE	*S. aureus* (33.3%), CoNS (22%), and *E. faecalis* (14.8%) main pathogens	Administered as twice-weekly regimen in 63.0% Median duration of 6 weeks (range, 1–30 weeks).	No	Clinical and microbiological success: 92.6%. Failure in 1 patient with MRSA CIED-IE and incomplete surgical control	2 AE: 1 nausea and vomiting after the second dose, therapy continued. 1 creatinine increase, resolved with dose reduction.
Bryson-Cahn, C. et al., 2019 [115]	Observational retrospective study on vulnerable patients *S. aureus* serious infection	Clinical response: any patient who had an FU visit within 1 year without evidence of on-going/relapsed infection	32 infections (BSI 40.6%, osteoarticular 28%) Previous therapy 100%. 9 IE tricuspid NVE	2 IE MSSA 7 IE MRSA	22 received a single 1000 mg dose, 7 received 2 weekly doses	No	**IE subgroup:** Clinical response 5/9 Lost to FU 4/9	No AE reported
Bork, J.T. et al., 2019 [116]	Multicentre retrospective study on vulnerable patients Invasive Gram-positive infections	Clinical cure	45 infections (osteomyelitis 45%, endovascular 25%) Previous therapy 100%. 6 IE, type unspecified	MRSA (29%) and MSSA (21%) main pathogens	Median of 3 doses prescribed	6 patients with concomitant oral fluoroquinolone.	Overall, 30 day cure was achieved by 50% of patients with endovascular infection; >25% loss to FU. IE subgroup unspecified.	AEs documented in 6.7% (2 acute kidney injuries and 1 rash)
Dinh, A. et al., 2019 [108]	Multicentre retrospective study French national cohort	Clinical cure	75 infections (most frequent bone and joint 64%, endocarditis 25%). Previous therapy 98.7% 19 IE: 9 NVE and 10 PVE	*S. aureus* (51.4%) and CoNS (44.4%) main pathogens	In IE most frequent regimen was 1500 mg single or double dose	Overall, 45.3%, mainly rifampicin, cotrimoxazole, quinolones and tetracyclines	Overall, clinical cure 79%. **IE subgroup** Clinical cure: 72.2%	Five AE in the cohort (6.7%) with no treatment discontinuation

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New Antimicrobials and New Therapy Strategies for Endocarditis: Weapons That Should Be Defended: Dalbavancin (2)

Authors	Study Design	Endpoint	N° Patients/ IE Type	Pathogens	Dosage and Duration	Combination, Dosage	Outcomes	Safety
Hidalgo-Tenorio, C. et al., 2023 [9]	Multicentre retrospective study DAL as consolidation treatment	Effectiveness of DAL as consolidation therapy	124 IE (46.8% native valve, 43.6% prosthetic valve and 9.6% pacemaker lead IE). Previous therapy 100%.	CoNS (38.7%), MSSA (22.6%) *E. faecalis* (19.4%) and Streptococcus species (9.7%) the most isolated pathogens	Single 1500 mg dose the most prescribed DAL regimen (33.3%)	No data reported	Clinical success in subjects that completed the 1 year follow-up: 95.9% Mean reduction in hospital stay: 14 days.	AE in 3.2%
Morrisette, T. et al., 2019 [107]	Multicentre retrospective study DAL or ORI in various infections	Clinical success	56 infections (ABSSSI 36%, osteomyelitis 27%), 40 DAL, 14 ORI and 2 both. Previous therapy 91% 5 IE, type unspecified.	MSSA (25%), MRSA (19%) and *E. faecalis* (11%) main pathogens	No data reported	30% of the whole cohort (drugs unspecified)	**IE subgroup** Clinical success: 100% among the 3 evaluable IE	Mild AE in 11%.
Wunsch, S. et al., 2019 [109]	Multicentre retrospective study DAL as sequential treatment	Clinical success	101 infections (prosthetic joint 31%, osteomyelitis 30%, IE 25%) Previous therapy 100% 25 IE: 15 NVE, 6 PVE, 4 CIED-IE	CoNS (33%), MSSA (16%), MRSA (9%) main pathogens	In IE, 9 single 1500 mg dose and 1000 mg dose followed by 500 mg 1 week apart.	Overall, 64% of the cohort, mainly rifampicin (64%) and fluoroquinolones (15%)	Overall, clinical success 89%. **IE subgroup** Clinical success: 92%	Three AE in the cohort (3%), requiring treatment discontinuation
Ajaka, L. et al., 2020 [117]	Observational retrospective study in people with barriers to SoC	Cure: lack of clinical or microbiological persis-tent/recurrent infection within 90 days or negative BCs within 90 days after completion of DAL	28 infections (24 BSI and 4 IE) Previous therapy 100%. PWID 67% 4 IE, type unspecified	MRSA (39%) and MSSA (17%) main pathogens	LD of 1500 mg followed by 1 maintenance dose	No	Overall, 44% clinical cure, 33% failed treatment, and 22% lost to FU.	No data reported
Bai, F. et al., 2020 [106]	Multicentre retrospective study DAL in various infections	Clinical cure	206 infections (124 ABSSSI, 82 other site infection) Previous therapy 77.8% 6 IE, type unspecified.	MRSA (29%), CoNS (35%) and MSSA (17%) in the non-ABSSSI group.	Overall, single 1500 mg dose in 60.2%	In 37.2% of non-ABSSSI patients, mainly fluoroquinolones, rifampicin, and tetracycline	Overall clinical cure in non-ABSSSI 75%. **IE subgroup** Clinical cure: 83.3%	5.4% had an AE, mainly dermatologic. One serious AE (Stevens–Johnson).

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New Antimicrobials and New Therapy Strategies for Endocarditis: Weapons That Should Be Defended: Dalbavancin (3)

Authors	Study Design	Endpoint	N° Patients/ IE Type	Pathogens	Dosage and Duration	Combination, Dosage	Outcomes	Safety
Núñez-Núñez, M. et al., 2020 [110]	Observational prospective study. DAL as sequential treatment	Clinical success	22 infections (osteoarticular 46%, BSI 23%). Previous therapy 100%. 3 IE, type unspecified.	*S. aureus* (55%), CoNS (27%)	63% of the whole cohort received 1000 mg followed by 500 mg	No data reported	Overall, clinical success 95%	AE 1 (4.5%), infusion site reaction
Veve, M.P. et al., 2020 [119]	Observational retrospective study DAL vs. SOC	Incidence of infection-related readmission within 90 d of hospital discharge or outpatient DAL administration	215 infections (most common BSI, osteoarticular and IE) 70 DAL vs. 145 SoC Previous therapy 100%. IE 54: 9 DAL vs. 45 SOC	MRSA 82%	Most frequent regimen 2: 1500 mg doses 1 week apart	in 13% of DAL treated.	Overall, DAL was associated with lower 90-day infection-related readmissions and shorter length of stay.	AE 2.9% in the DAL group, 1 required discontinuation.
Durante-Mangoni, E. et al., 2021 [111]	Observational single-centre retrospective study DAL in IE	Clinical and microbiological cure	10 IE: 3 NVE, 5 PVE, 2 CIED-IE At least 2 weeks previous therapy 100%	Mainly caused by staphylococci and enterococci.	Median of 2.5 DAL doses per patient	No data reported	Clinical and microbiological cure 70%	1 AE (rash after the third dose) with treatment withdrawal
Arrieta-Loitegui, M. et al., 2022 [112]	Observational retrospective study DAL as sequential treatment	Clinical and microbiological cure	102 infections (SSTI 30%, BSI 15.7%, IE 13.7%) Previous therapy 100%. 14 IE, type unspecified	*S. aureus* in 70.6%	IE patients, 1500 mg as LD followed by a range of 1–6: 1500 mg doses	16.7%, mainly moxifloxacin and linezolid	Overall, clinical and microbiological success: 93.7%. Median reduction in hospitalization 14 days (range 7–84).	AE in 3.9%, 1 patient discontinued.
Taylor, K. et al., 2022 [114]	Observational retrospective study DAL as sequential treatment	Clinical success	48 infections (osteomyelitis 54%, IE 23%, BSI 15%). 11 IE, type unspecified. Previous therapy 100%	MRSA (42%) and MSSA (19%) main pathogens	Most patients received 1500 mg doses 44% 1 dose, 52% 2 doses.	27%, mainly rifampin and quinolones	Overall clinical success 85%. **IE subgroup:** Clinical success at 90 days 82%.	No AE reported
Lueking, R. et al., 2023 [120]	Observational retrospective study Vulnerable people receiving DAL	Clinical failure (not defined)	40 infections (BSI 67.5%, ABSSSI 45%) Previous therapy 100%. 4 IE, type unspecified	MRSA (57.5%) and MSSA (30%) main pathogens	Most frequent regimen 1500 mg single dose	In 15% of the whole cohort.	**IE subgroup:** Clinical success in all patients	AE in 5%

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New Antimicrobials and New Therapy Strategies for Endocarditis: Weapons That Should Be Defended: Oritavancin

Table 4. Clinical studies investigating the treatment of infective endocarditis with oritavancin.

Authors	Study Design	Endpoint	N° Patients/ IE Type	Pathogens	Dosage and Duration	Combination, Dosage	Outcomes	Safety
Stewart, C.L. et al., 2017 [145]	Observational retrospective study ORI as an off-label indication	Clinical cure	10 infections (BSI 50%) 1 tricuspid NVE in a PWID with previous therapy: VAN (3 days), then CRO (4 days)	*Streptococcus agalactiae*	IE patient 1200 mg 1 dose and then discharged	No	Clinical failure with need for valve replacement 3 months after ORI administration	No AE reported
Ahiskali, A. et al., 2020 [143]	Observational retrospective study on a vulnerable population of PWID receiving ORI	Clinical cure	23 infections (BSI 50%) Previous therapy 100%. 2 IE, type unspecified	1 MSSA 1 MRSA	MSSA IE: single 1200 mg dose, MRSA IE: two 1200 mg doses	No	**IE subgroup:** Clinical cure 1 (MSSA), Clinical failure 1 (MRSA)	AE in 8.7%, mild
Brownell, L.E. et al., 2020 [11]	Multicentre observational retrospective study ORI as primary treatment	Clinical cure	75 infections (ABSSSI 49%) No previous treatment 4 IE, type unspecified	MSSA (31.5%) and MRSA (17.8%)	All patients included received initial 1200 mg dose followed by 1200 or 800 mg weekly	No data reported	**IE subgroup:** Clinical cure 75% Average hospital days avoided in IE: 18 d	AE in 12%, most commonly back pain with infusion. All resolved upon discontinuation
Salcedo, D.A.T. et al., 2018 [146]	Case series of Gram-positive IE in PWID	N/A	5 IE Previous therapy 100%.	MRSA (20%), MSSA (20%), *Streptococcus* (10%)	2 received 4 ORI doses, 3 received only 1 dose	No	Clinical cure: 3/5 Lost to FU: 2/5	AE in 1 patient (allergic reaction treated with oral prednisone)
Johnson, J.A. et al., 2015 [144]	Case report Limited treatment options	N/A	1 Aortic PVE	VR *E. faecium*.	1200 mg every other day for 3 doses, then weekly for 6 weeks, then 1200 mg biweekly for 10 weeks after recurrence and valve exchange	GEN for the first 4 days, discontinued due to renal toxicity	Recurrence after the first treatment course attributed to lack in source control. Clinical cure after valve exchange and a second prolonged course of ORI	Mild increase in transaminases

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Summary

- Overall, we analyzed 313 cases of IE treated with DAL (the most-used regimen was1500 mg single or repeated dose), caused mostly by *S. aureus* (with a slight predominance of MSSA), followed by CoNS.
- Native valves of the right side were predominantly involved but cases involving the left side, prosthetic valves, and CIEDs were reported as well.
- Previous antibiotic treatment before DAL was almost universal.
- Clinical and microbiological outcomes were generally positive although there was an elevated rate of patients lost to follow-up and the data are difficult to interpret because of high heterogeneity.
- Overall, we retrieved only 13 IE cases of various types that were treated with ORI 1200 mg single or repeated doses, which were caused by staphylococci for the most part and frequently affected people with reduced compliance. Results were commonly good.

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Dalbavancin in BJI & IAI (1)

Table 2. Main characteristics of the studies about the use of dalbavancin in implant-associated infection and bone and joint infections included in the review (arranged by publication year).

Authors (Year) [Bibliography Reference]	N of Patients	Infection(s) (n)	Pathogens (n)	Most Frequent Dosages	Duration/n of Doses	Success [a], n (%)	Adverse Event(s) (n)
Bouza et al. (2018) [20]	33	IAI (20), BJI (13)	*S. aureus* (9), CoNS (16), *Enterococcus* spp (3), other (6)	1000 mg once then 500 mg weekly	3 doses	28 (85)	Rash (2), tachycardia (2), reversible kidney injury (2), nausea (1), rectal bleeding (1), candidiasis (1)
Rappo et al., (2019) [34]	67	BJI (67)	*S. aureus* (42), CoNS (14), *Enterococcus* spp (8), other (33)	1500 mg weekly × 2	2 doses	65 (97)	IRR (1)
Morata et al., (2019) [35]	64	IAI (45), BJI (19)	*S. aureus* (14), CoNS (33), *Enterococcus* spp (9), other (22)	1000 mg once then 500 mg weekly	2–5 doses	45 (70)	Gastrointenstinal symptoms (3), rash (1), phlebitis (1), asthenia (1), reversible kidney injury (1)
Almangour et al., (2019) [36]	31	BJI (31)	*S. aureus* (27), CoNS (1), other (6)	1000 mg once then 500 mg weekly or 1500 mg weekly × 2	2–3 doses	28 (90)	None
Tobudic et al., (2019) [37]	46	IAI (8), BJI (38)	Not specified	1500 mg once then 1000 mg every 2 wk or 1000 mg once then 500 mg weekly or 1500 mg at day 1 and day 8	2–32 doses	30 (65)	Nausea (1), exanthema (2), hyperglycemia (1)

Siciliano, V.et al: Pathogens 2024, 13, 189.

Dalbavancin in BJI & IAI (2)

Authors (Year) [Bibliography Reference]	N of Patients	Infection(s) (n)	Pathogens (n)	Most Frequent Dosages	Duration/n of Doses	Success [a], n (%)	Adverse Event(s) (n)
Dinh et al., (2019) [24]	48	BJI (48)	Not specified	1500 mg once or 1500 mg once then 1500 mg every 2 wk	110 doses	35 (73)	Hypersensitivity (2), headache (1), eosinophilia (1), phlebitis (1)
Wunsch et al., (2019) [23]	62	IAI (32), BJI (30)	Not specified	1000 mg once then 500 mg weekly or 1500 mg once or 1500 mg twice	1–3 doses	58 (94)	Dyspnea (1), IRR (1), fatigue and vertigo (1)
Buzon-Martin et al., (2019) [38]	16	IAI (16)	*S. aureus* (6), CoNS (7), *Enterococcus* spp (6),	1500 mg once then 500 mg on day 7 and every 2 wk	6–12 wk	11 (69)	Leukopenia (1), rash (1)
Bork et al., (2019) [25]	15	Not specified	Not specified	Not specified	4 doses	7 (47)	AKI (2), rash (1)
Veve et al., (2020) [26]	49	Not specified	Not specified	1500 mg once or 1500 mg once then 1500 mg at day 7 or day 14	1–2 doses	N/R	Catheter infection (1), hypersensitivity (1)
Matt et al., (2021) [39]	17	IAI (17)	*S. aureus* (10), CoNS (10), *E. faecalis* (1), other (5)	1500 mg once or 1500 mg weekly ×2	1–2 doses	8 (47)	None
Cojutti et al., (2021) [40]	15	IAI (11), BJI (4)	*S. aureus* (5), CoNS (9), *E. faecalis* (1),	1500 mg weekly × 2	2 doses	12 (80)	None
Tuan et al., (2022) [28]	23	BJI (21), SA (2)	Staphylococci, streptococci, enterococci, *Corynebacterium* spp. MSSA, MRSA,	1500 mg once or 1500 mg at day 1 and 8	1–2 doses	21 (91.3)	Hepatotoxicity (1)

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Dalbavancin in BJI & IAI (3)

Taylor et al., (2022) [12]	30	IAI (4), BJI (26)	CoNS, *Corynebacterium* spp, *E. faecalis*	1500 mg every 14 days	1–4 doses	26 (87)	N/R
Cain et al., (2022) [41]	42	BJI (42)	*S. aureus* (23), other (19)	1500 mg once	1 dose	33 (78.6)	Nausea, IRR
Mazzitelli et al. (2022) [42]	15	Spondylodiscitis	MRSA	1500 mg at day 1 and 8, then 1500 mg every 28–35 days	3–14 doses	14 (93.3)	None
Lueking et al., (2023) [29]	20	BJI 16), SA (4)	MSSA, MRSA, CoNS, *Enterococcus* spp, streptococci	1500 mg once or 1125 mg once or 1500 mg at day 1 and 8	1–2 doses	18 (90)	Clostridioides difficile colitis (1), substernal chest pain during infusion (1).
Soderquist et al., (2023) [43]	1	IAI (1)	*Corynebacterium striatum*	1000 mg once then 500 mg every week	12 weeks	1(100)	N/R
Ruiz-Sancho et al., (2023) [31]	2	IAI (2)	*E. faecium* (1), *S. epidermidis* (1)	1000 mg once then 500 mg every week	N/R	1 (50)	None
Ioannou et al., (2023) [32]	55	IAI, SA (not specified)	*S. aureus*, Enterococci, streptococci, CoNS	1500 mg every two weeks	N/R	42 (76)	N/R
Doub et al. (2023) [44]	15	IAI (15)	*C.striatum* (2), MSSA (3), MRSA (3), CoNS (4), other (4)	1500 mg at day 1 and 8	2 doses	13 (86.6)	N/R

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Oritavancin (1)

Authors (Year) [Bibliography Reference]	*N* of Patients	Infection(s) (*n*)	Pathogens (*n*)	Most Frequent Dosages	Duration/n of Doses	Success [a], *n* (%)	Adverse Event(s) (*n*)
Bhavnani et al. (2006) [16]	55	Bacteremia (55)	*S. aureus* (55)	5–10 mg/kg/day	10–14 days	45 (78)	N/R
Johnson et al., (2015) [45]	1	PVE (1)	*E. faecium* VRE (1)	1200 mg weekly every 48 h × 3 doses, then 1200 mg × 6 wk, then 1200 mg biweekly	14 doses	1 (100)	Anorexia, nausea (1)
Stewart et al., (2017) [46]	8	Bacteremia (6), NVE (1) and bursitis (1)	MSSA (4), CoNS (1), *Enterococcus* spp (1), *S. agalactiae* (1)	1200 mg	1 dose	5 (62.5)	Hearing loss (1)
Foster et al., (2017) [47]	1	IAI (1)	*E. faecium* VRE (1)	1200 mg weekly	6 doses	1 (100)	None
Delaportas et al., (2017) [48]	1	Acute osteomyelitis (1)	MSSA (1)	1200 mg weekly	7 doses	1(100)	None
Ruggero et al., (2018) [49]	1	Acute osteomyelitis (1)	MRSA (1)	1200 mg every 2–4 wk	5 doses	1 (100)	N/R
Schulz et al., (2018) [50]	5	Bacteremia (1); acute and chronic osteomyelitis, septic arthritis, discitis (4)	MSSA (1), *E.faecium* VRE (1), other (3)	1200 mg then 800 mg weekly	2–8 doses	2 (40)	Anemia and leukopenia (1)
Datta et al., (2018) [51]	3	Bacteremia (3)	MRSA (1), *S. gallolyticus* (1), *Granulicatella adiacens* (1)	1200 mg	1 dose	3 (100)	N/R

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Oritavancin (2)

Authors (Year) [Bibliography Reference]	N of Patients	Infection(s) (n)	Pathogens (n)	Most Frequent Dosages	Duration/n of Doses	Success [a], n (%)	Adverse Event(s) (n)
Redell et al., (2019) [52]	32	Bacteremia (7); acute and chronic osteomyelitis, septic arthritis, IAI (25)	MRSA (2), MSSA (1), *S. epidermidis* (1), other (28)	1200 mg once or every 6–14 days	1–10 doses	26 (81.2%)	Not specified (29)
Dahesh et al., (2019) [53]	1	IAI (1)	*E.faecium* VRE (1)	1200 mg × 2 wk then 800 mg weekly	10 doses	1 (100)	N/R
Chastain and Davis, (2019) [54]	9	Chronic osteomyelitis	MRSA (5), other (4)	1200 mg once then 1200 mg every 13–52 days	2–6 doses	9 (100)	None
Brownell et al., (2020) [55]	20	Endocarditis (4); osteomyelitis, diabetic foot, IAI (16)	Not specified	1200 mg once then 800–1200 mg weekly	N/R	20 (100)	Not specified (3)
Van Hise et al., (2020) [18]	134	Acute osteomyelitis (134)	MSSA (35), MRSA (108), VISA (2), *E. faecium* VRE (7)	1200 mg once then 800 mg weekly	4–5 doses	118 (88.1)	Hypoglycemia (3), tachycardia (2)
Texidor et al., (2023) [17]	72	Bacteremia (72)	Polymicrobial (20), MRSA (12), MSSA (37), streptococci (19), *E. faecium* (3), *E. faecium* VRE (4), CoNS (6), other (4)	800–1200 mg once, followed by 800–1200 mg	1–2 doses	52 (81.2%), N/R for 8 patients	AKI (3), IRR (2)

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- The long-acting lipoglycopeptides (LGPs), dalbavancin and oritavancin, showed remarkable efficacy against Gram-positive pathogens, including MSSA, MRSA, CNS, streptococci, and VS *Enterococcus faecalis*.
- Dalbavancin may face limitations against enterococci with vanA-mediated resistance.
- Their bactericidal activity, including anti-bioflm activity, mediated by inhibiting cell-wall biosynthesis, makes them potent agents in combating infections.
- The extended half-life, (Dalbavancin, range from 149 to 250 h, Oritavancin from 200 to 300 h), allow for less frequent administration, offering advantages like earlier hospital discharge, reduced catheter residence time, and improved patient compliance.
- The current FDA approval is for ABSSSIs but the robust antimicrobial activity and prolonged half-life suggest their potential efficacy in more severe infections, including BJIs, implanted-associated infections, IE &BSI.

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- Both antibiotics demonstrate a prolonged selective pressure on bacteria due to their extended half-life, yet resistance remains uncommon in clinical practice.
- The reported adverse effects, predominantly mild, include nausea, headache, infusion site reactions, rash, and less frequently, *Clostridioides difficile* colitis, liver toxicity, and reversible AKI.
- Notably, LGPs may influence prothrombin time and international normalized ratio for up to 12 hrs
- Dalbavancin emerges as a promising therapeutic option in infective endocarditis, bloodstream infections, and implant-associated infections, showcasing high clinical and microbiological success rates.
- Oritavancin, though primarily FDA-approved for skin infections, demonstrates potential in treating bacteremia and bone/joint infections.
- However, the heterogeneity in dosing regimens and limited structured data highlight the need for further large-scale studies to establish standardized guidelines for optimal use.

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Oritavancin Versus Daptomycin for Osteomyelitis Treatment After Surgical Debridement

Nicholas W. Van Hise . Russell M. Petrak . Kairav Shah .Melina Diaz, Vishnu Chundi . Mark Redell

- OM is an acute or chronic inflammatory process involving the bone and bone structures. In the US 50,000 annual hospital admission occur.
- Weekly IV oritavancin (1200 mg plus 800 mg day 8) and daily daptomycin (6-8 mg/Kg) were compared in an outpatient setting following extensive surgical debridement for treating patients with osteomyelitis.
- Compared to oritavancin, patients prescribed daptomycin had higher rates of all-cause and infection-related readmission, and greater likelihood of repeat surgical debridement and need for antibiotics post-discontinuation of initial therapy.
- Compared to daptomycin, patients receiving oritavancin had greater clinical success, and lower all-cause and infection-related readmission, need for repeat surgical debridement, and requirement for additional antibiotics.

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Table 1 Baseline characteristics of study groups

	Oritavancin $N = 75$	Daptomycin $N = 75$	Total
Male, *n* (%)	36 (48.0)	40 (54.1)	76 (51)
Age, years[a]	63.7 ± 14.9	65.5 ± 11.7	64.6 + 13.4
Weight, kg[a]	101.1 ± 39.4	94.5 ± 31.1	97.8 + 35.5
Ethnicity, *n* (%)			
Asian	2 (2.7)	0 (0)	2 (1.3)
Black	3 (4.0)	7 (9.3)	10 (6.7)
Hispanic	7 (9.3)	3 (4.0)	10 (6.7)
White	63 (84.0)	65 (86.7)	128 (85.3)
Charlson Comorbidity Scores			
Mean	7.61	7.25	
Median	6.2	6.4	
Co-morbidities			
Mild liver disease	6/75 (8)	5/75 (6.7)	
Moderate-to-severe liver disease	0/75 (0)	2/75 (2.7)	
Peripheral vascular disease	17/75 (22.7)	12/75 (16)	
Diabetes with end-organ damage	19/75 (25)	16/75 (21)	
Chronic kidney disease	21/75 (28)	7/75 (9)	
Immunocompromised by malignancy	16/75 (21)	21/75 (28)	
Treatment received in office, *n* (%)	75 (100)	60 (80)	135 (90)

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Table 2 Culture results (bone, bone biopsy or contiguous wound site)

Pathogen (> 10 total isolates per species)	**Oritavancin** *N* = 75	**Daptomycin** *N* = 75
S. aureus		
MSSA	32	28
MRSA	24	21
S. aureus, no phenotype	9	4
Enterococcus species		
VRE	2	9
Monomicrobial Gram-positive	66	65
Mixed Gram-positives	7	4
No growth at baseline	2	3

MSSA methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRE* vancomycin-resistant *Enterococcus*

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Table 4 Outcome for each study group

Outcome	Oritavancin $N = 75$	Daptomycin $N = 75$	P value*
Clinical success	55 (73.3)	25 (33.3)	< 0.001
Clinical failure criteria			
Infection-related readmission	16 (21.3)	51 (68.0)	< 0.001
Need for repeat surgical debridement	16 (21.3)	51 (68.0)	< 0.001
Received antibiotics after study drug discontinuation	23 (30.7)	49 (65.3)	< 0.001
All-cause readmission	18 (24.0)	52 (69.3)	< 0.001
All-cause mortality rate	1 (1.3)	3 (4.0)	0.620
Incidence of *Clostridioides difficile* infection within 30 days following drug discontinuation	0	3 (4.0)	0.245
Adverse drug events during treatment	2 (2.7)	4 (5.4)	0.681
Discontinuation of drug	2 (2.7)	5 (6.7)	0.442

*Chi-square test or Fisher's exact test

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Conclusions

- Infections due to gram-positive MDR bugs may be challenging
- Drawbacks of old antibiotics
- LGPs: advantages in terms of bactericidal activity, long half-life, more cost
- Limited registered indications (ABSSSIs) but potential efficacy in IE & BSI, CR-BSI, BJIs, IAI
- Need for more evidence (RCTs ?) to have more indications
- Difficulties in managing an antimicrobial stewardship program with these new antibiotics (high acquisition cost, no registered indications)
- Need for re-thinking the access rules of AIFA
- Dalbavancin & Oritavancin: advantages in cost-effectiveness analysis

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TESSERAMENTO 2024

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