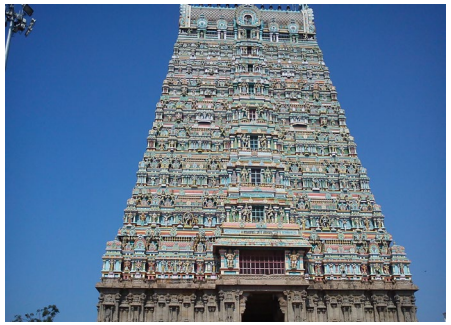


Sessione 6 | Le nuove armi per la terapia delle infezioni batteriche MDR

Moderatori: *I. Gentile, M. Tumbarello*

10:45 - 11:00 **Come ottimizzare l'uso dei nuovi BL/BLI** - *F. Pea*

11:00 - 11:15 **Si utilizzano i nuovi antibiotici in pediatria? Quali e perché?** *S. Esposito*

11:15 - 11:30 **Cefiderocol** - *M. Bassetti*

11:30 - 11:45 **Eravaciclina** - *A. Vena*

11:45 - 12:00 **BL/BLI** - *M. Tumbarello*

12:00 - 12:15 **Nuovi inibitori delle betalattamasi** - *D.R. Giacobbe*

12:15 - 12:30 **Azteronam/avibactam** - *M. Falcone*

12:30 - 12:45 **Delafloxacina** - *I. Gentile*

12:45 - 13:00 **Oritavancina** - *A. Cascio*

Oritavancin

Antonio Cascio

Università di Palermo

Il sottoscritto **Antonio Cascio**
in qualità di relatore

ai sensi dell’art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Gilead, ViiV, MSD, GSK, Tillots, Astra Zeneca, Angelini, Menarini, Pfizer, Viatris, Shionogi

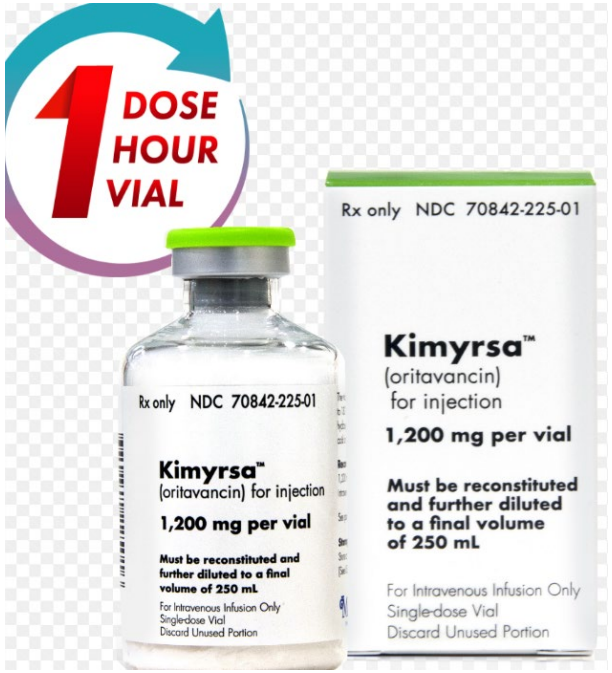
Open Forum Infectious Diseases

MAJOR ARTICLE

Kimyrsa, An Oritavancin-Containing Product: Clinical Study and Review of Properties

Randall K. Hoover,[1] Martin Krsak,[2] Kyle C. Molina,[2,3] Kairav Shah,[4] and Mark Redell[5]

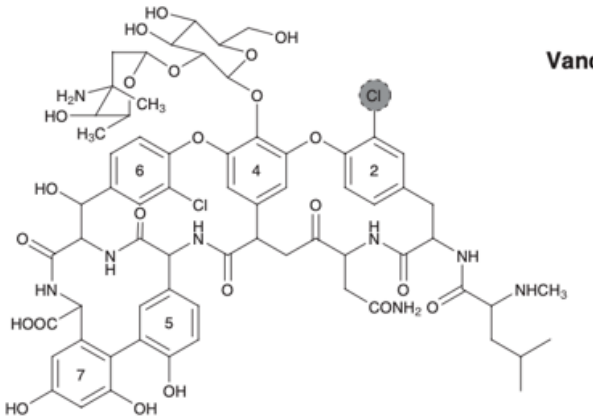
[1]Melinta Therapeutics, Dix Hills, New York, USA, [2]University of Colorado School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA, [3]University of Colorado Hospital, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, Colorado, USA, [4]Metro Infectious Disease Consultants, Stockbridge, Georgia, USA, [5]Medical Affairs, Melinta Therapeutics, Morristown, New Jersey, USA

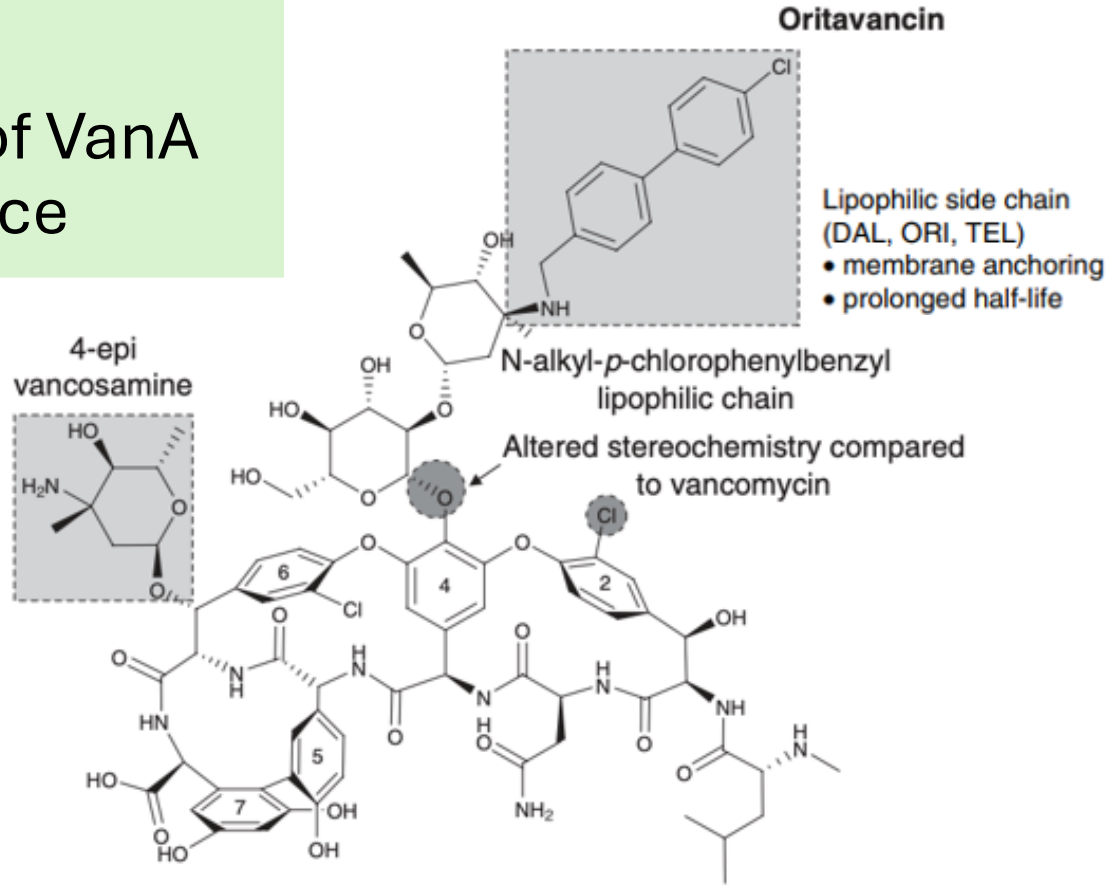


- Hoover et al. described Kimyrsa® a new formulation of oritavancin that can be infused in **250 mL of D5W or normal saline solution**.
- It was also developed to shorten **the time of infusion from 3 h to 1 h**.
- This new formulation, currently **not available in Europe** and available mainly in United States, simplifies the preparation of the solution and increases flexibility, especially in patients with congestive heart failure or insulin-dependent diabetes mellitus. Despite that, Kimyrsa® includes within the **excipients 2-hydroxypropyl-Beta-cyclodestrin**, which can increase the risk of **nephrotoxicity**.
- No dosage adjustment of Kimyrsa® is needed in patients with mild or moderate renal impairment and the pharmacokinetics in severe renal impairment have not been evaluated.

Characteristics of oritavancin

- Semisynthetic lipoglycopeptide, synthetic derivative of the naturally occurring **chloroeremomycin**
- Structurally similar to vancomycin
- May retain some activity in the presence of VanA and VanB-mediated vancomycin-resistance



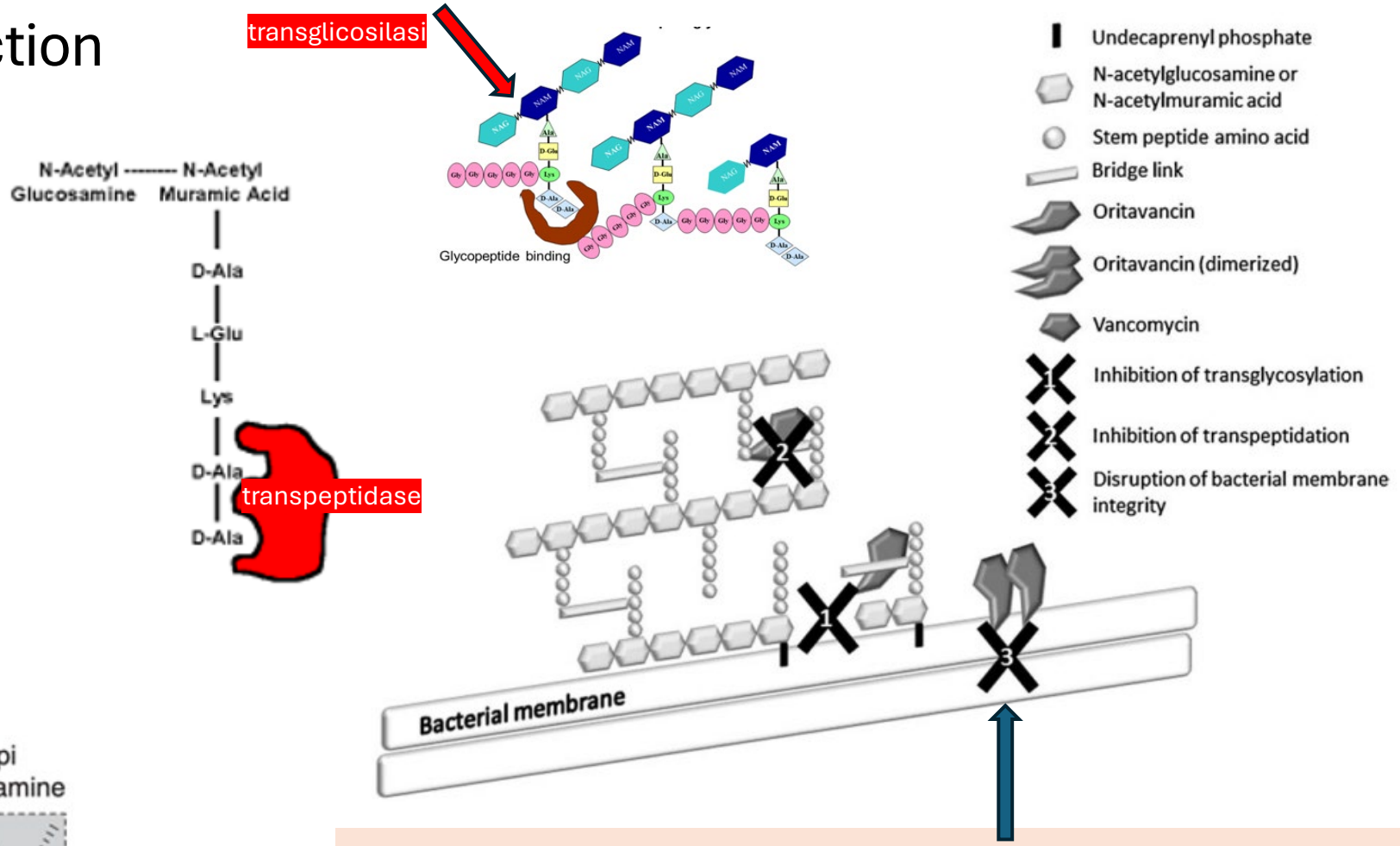


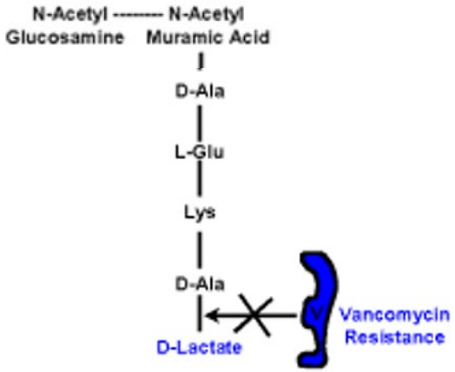
The binding pocket, between the hydrophobic tail group and the nearby 4-epi-vancosamine, is believed to interact with peptides near, but distinct from the terminal D-alanyl-D-alanine (or D-lactate) in both S. aureus and enterococci

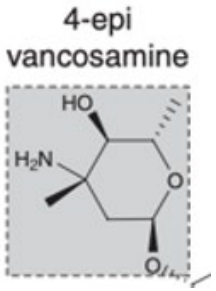
Brade KD, et al. Infect Dis Ther 2016; 5:1–15
Biavasco F, et al. Antimicrob Agents Chemother 1997; 41:2165–2172
Cooper RD, et al. J Antibiot (Tokyo) 1996; 49:575–581
Domenech O, et al. Biochim Biophys Acta 2009; 1788:1832–1840

Mechanism(s) of action

- **Inhibition of transglycosylation**
- **Inhibition of transpeptidation**
- **Membrane depolarization and permeabilization**

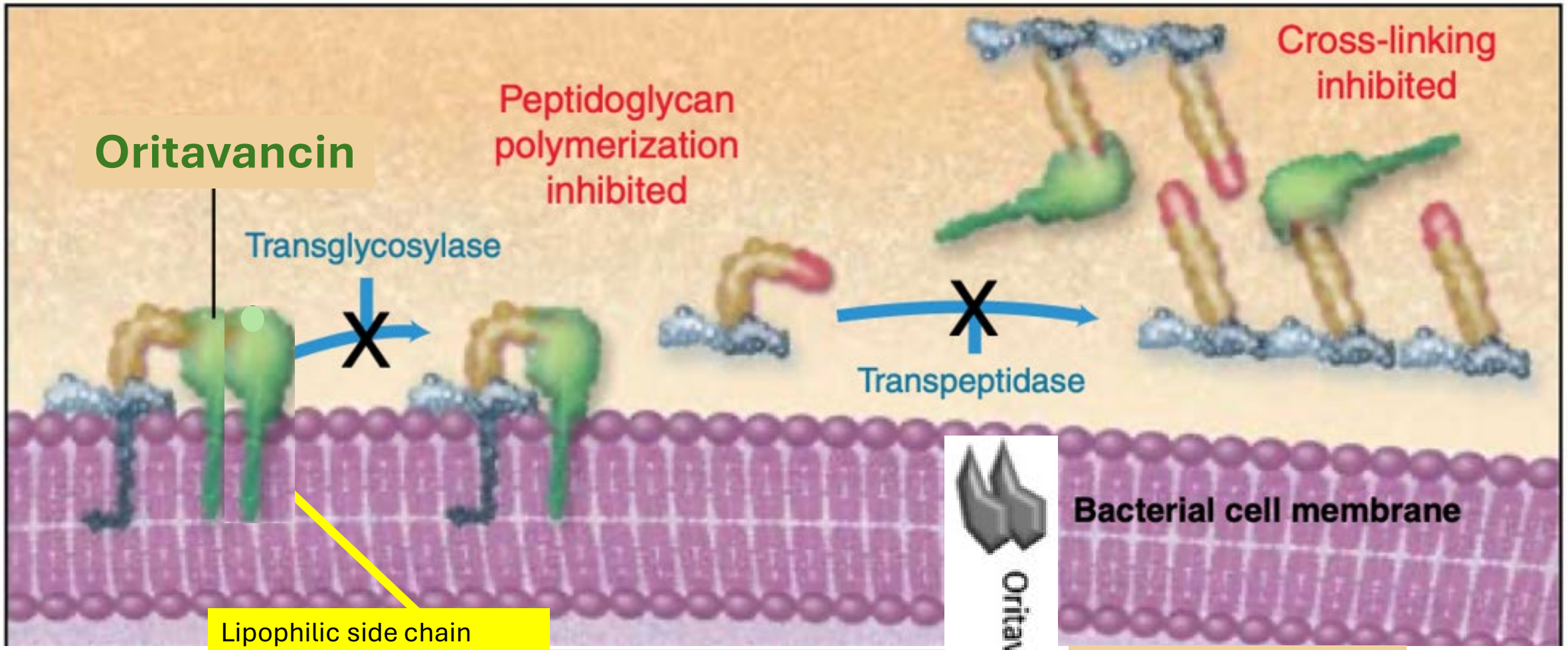






The membrane-targeted mechanism of action is proposed to be independent of cellular growth and division. This is supported by the rapid bactericidal activity of oritavancin against **stationary phase and biofilm-associated organisms**, both often more resilient to antimicrobial treatment

Zhanel GG, et al. Drugs 2010; 70:859–886
Munch D, et al. Antimicrob Agents Chemother 2015; 59:772–781
Zhanel GG, et al. Clin Infect Dis 2012; 54(Suppl 3):S214–S219



Lipophilic side chain

The lipophilic side chain in oritavancin anchors the compound to the cell membrane through hydrophobic interactions, and it stabilizes the oritavancin dimer

Membrane depolarization and permeabilization

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Clinical breakpoints and dosing of antibiotics

	S.aureus	CONS	Enterococcus spp	Streptococcus A,B,G	Streptococcus pneumoniae	Viridans group streptococci
Oritavancin	0.125		IE	0.125	IE	0.25
Dalbavancin	0.125	4	IE	0.125	IE	0.125
Vancomycin	2		IE	2	2	2
Teicoplanin	2	4	2	2	2	2

	Cephalosporins	Lipopeptides	Lipoglycopeptides			Oxazolidinones	
	Ceftaroline	Daptomycin	Telavancin	Dalbavancin	Oritavancin	Linezolid	Tedizolid
In vitro activity	MSSA, MRSA, CoNS, streptococci, some *Enterococcus faecalis* isolates	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*
No activity	*Enterococcus faecium*, VRE *vanA, vanB*		VRE *vanA*	VRE *vanA*			
Drug target	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Protein synthesis	Protein synthesis
FDA/EMA approved dosing regimen (for ABSSSI, unless otherwise mentioned)	600 mg b.i.d. IV	ABSSSI 4 mg/kg/day IVBSI/IE 6 mg/kg/day IV	10 mg/kg/day IV	1500 mg IV single doseAlternative: 1000 mg IV single dose at day 1, followed by 500 mg IV single dose at day 8	1200 mg IV single dose	600 mg b.i.d. IV / PO	200 mg q.d. IV / PO

Bloem, A.; Bax, H.I.; Yusuf, E.; Verkaik, N.J. New-Generation Antibiotics for Treatment of Gram-Positive Infections: A Review with Focus on Endocarditis and Osteomyelitis. J. Clin. Med. **2021**, 10, 1743. https://doi.org/10.3390/ jcm10081743

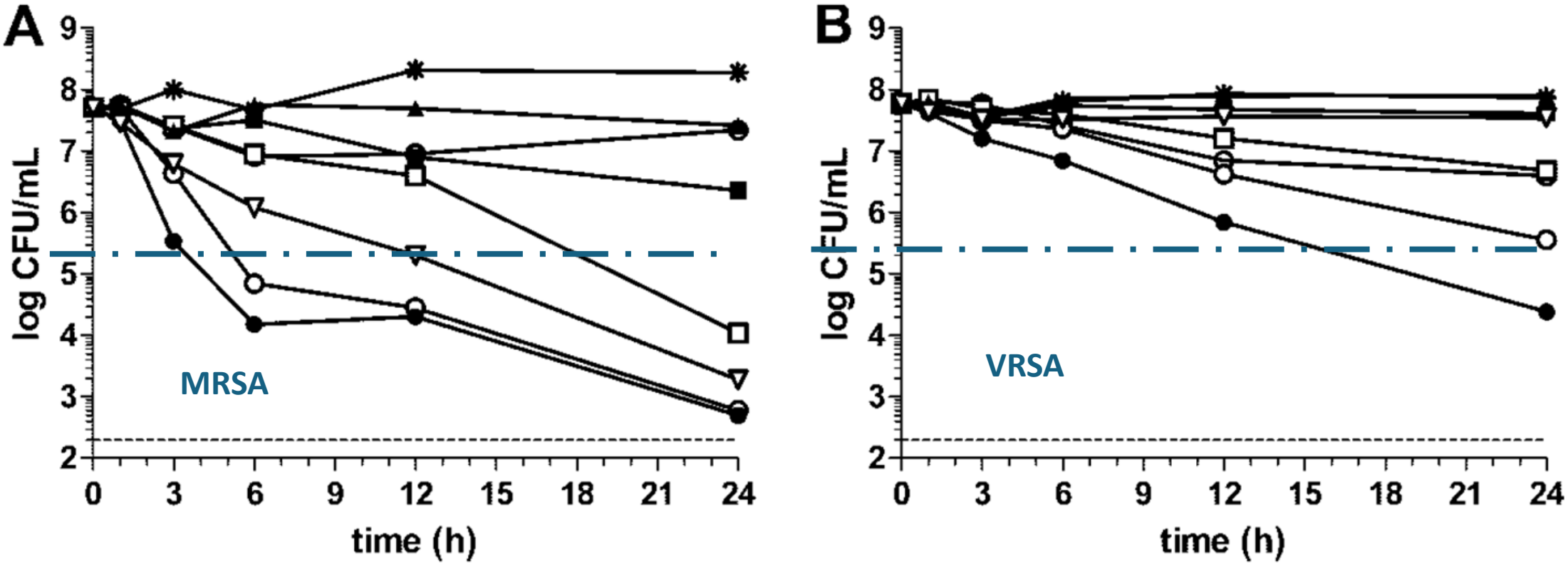
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2009, p. 918–925 Vol. 53, No. 3
0066-4804/09/$08.00+0 doi:10.1128/AAC.00766-08

Oritavancin Kills Stationary-Phase and Biofilm *Staphylococcus aureus* Cells In Vitro[▽]

Adam Belley,[1] Eve Neesham-Grenon,[1] Geoffrey McKay,[1] Francis F. Arhin,[1] Robert Harris,[2,3] Terry Beveridge,[2,4] Thomas R. Parr, Jr.,[1] and Gregory Moeck[1]*

Targanta Therapeutics Incorporated, 7170 Frederick Banting, St. Laurent, Quebec H4S 2A1, Canada[1]; MicroTEM Inc., P.O. Box 1107, 101 Chalmers St., Elora, Ontario N0B 1S0, Canada[2]; Guelph Regional Integrated Imaging Facility, New Science Complex, 488 Gordon St., University of Guelph, Guelph, Ontario N1G 2W1, Canada[3]; and Department of Molecular and Cellular Biology, New Science Complex, 488 Gordon St., University of Guelph, Guelph, Ontario N1G 2W1, Canada[4]

Received 12 June 2008/Returned for modification 19 October 2008/Accepted 11 December 2008



*, untreated control;; **θ,** 0,5 µg/ml **oritavancin**; **O**, 4 µg/ml **oritavancina**; ●, 16 µg/ml **oritavancina**; ■, 16 µg/ml **vancomycin**; □, 4 µg/ml **daptomycina**; ▲, 8 µg/ml **linezolid**; ∇, 2 µg/ml rifampina.

Belley A, et al. Oritavancin kills stationary-phase and biofilm Staphylococcus aureus cells in vitro. Antimicrob Agents Chemother. 2009 Mar;53(3):918-2

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2009, p. 918–925 Vol. 53, No. 3
0066-4804/09/$08.00+0 doi:10.1128/AAC.00766-08

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Received 12 June 2008/Returned for modification 19 October 2008/Accepted 11 December 2008

TABLE 1. Oritavancin exhibits antibiofilm activity in vitro against *S. aureus* strains of different resistance phenotypes[a]

Antimicrobial agent	MSSA ATCC 29213		MRSA ATCC 33591		VRSA VRS5	
	MIC (μg/ml)	MBEC (μg/ml)	MIC (μg/ml)	MBEC (μg/ml)	MIC (μg/ml)	MBEC (μg/ml)
Oritavancin[b]	2	2–4	0.5–4	0.5–4	2–8	2–8
Linezolid	8	>128	2–4	>128	4–8	>128
Rifampin	<0.02	4	<0.03	0.25–4	<0.03–0.06	4
Vancomycin	1	>128	1–2	≥128	>128	>128

[a] MICs (μg/ml) were determined using MBEC plates and represent the antibacterial activity against planktonic cells shed from the biofilms. MBECs (μg/ml) were determined according to the manufacturer's protocol.

[b] Oritavancin MICs and MBECs were determined in the absence of 0.002% polysorbate 80.

Belley A, et al. Oritavancin kills stationary-phase and biofilm Staphylococcus aureus cells in vitro. Antimicrob Agents Chemother. 2009 Mar;53(3):918-2

PK characteristics

Table III. Pharmacokinetic parameters for lipoglycopeptides at usual human doses.[23,57–60]

Parameter	Telavancin (10 mg/kg)	Oritavancin (1200 mg)	Dalbavancin (1 g on day 1, 500 mg on day 8)	Vancomycin (15 mg/kg BID)
C_{max}, mg/L	88–101	138	312	20–50
AUC, mg · h/L	776–858	1110	27,103	260
V_d, L/kg	0.1–0.12	1	0.11	0.3
Protein binding, %	93	86	90	10–55
Terminal half-life, h	7–9	245	187	4–8

- Prolonged terminal half-life of 200–300 hours
- Large Vd and high protein binding (85–90%)
- Elimination mainly through the reticuloendothelial system (no adjustments for kidney or hepatic failure)

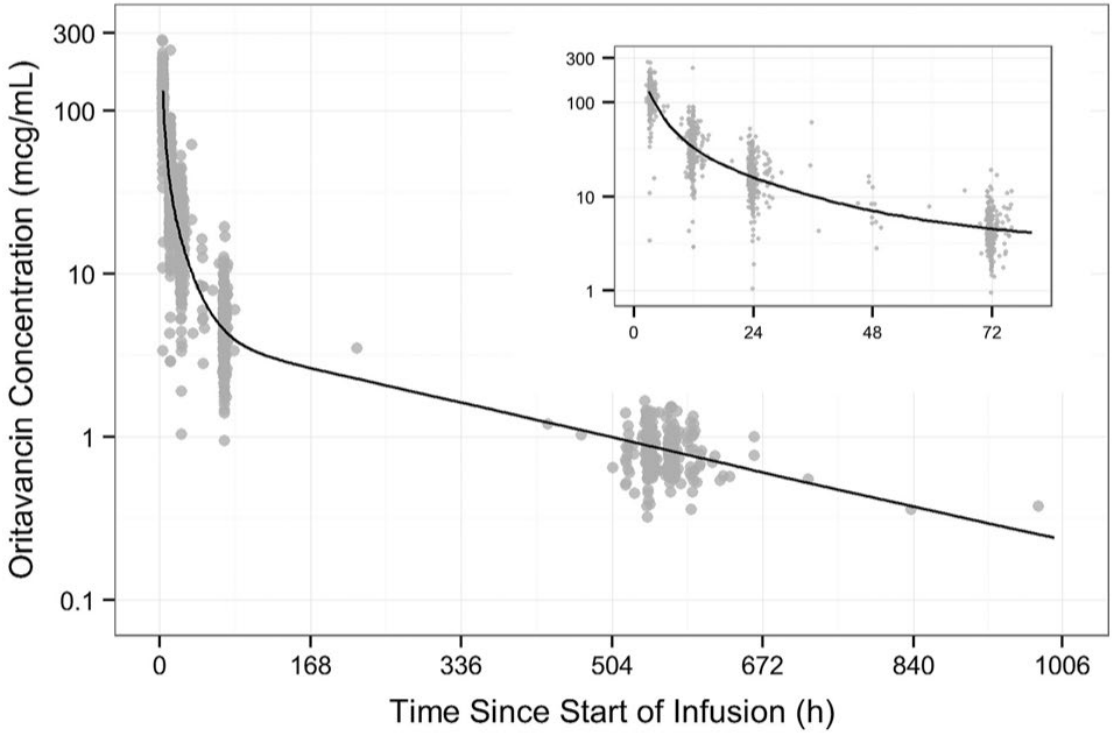
- Rubino CM, et al. Antimicrob Agents Chemother 2015; 59:3365–3372.
- Mitra S, et al. Infect Drug Resist 2015; 8:189–197
- Brade KD, et al. Infect Dis Ther 2016; 5:1–15
- Bassetti M, et al. Expert Opin Drug Saf 2019; 18:635–6
- Klinker KP, Borgert SJ. Beyond Vancomycin: The Tail of the Lipoglycopeptides. Clin Ther. 2015 Dec 1;37(12):2619-36

AAC Journals.ASM.org

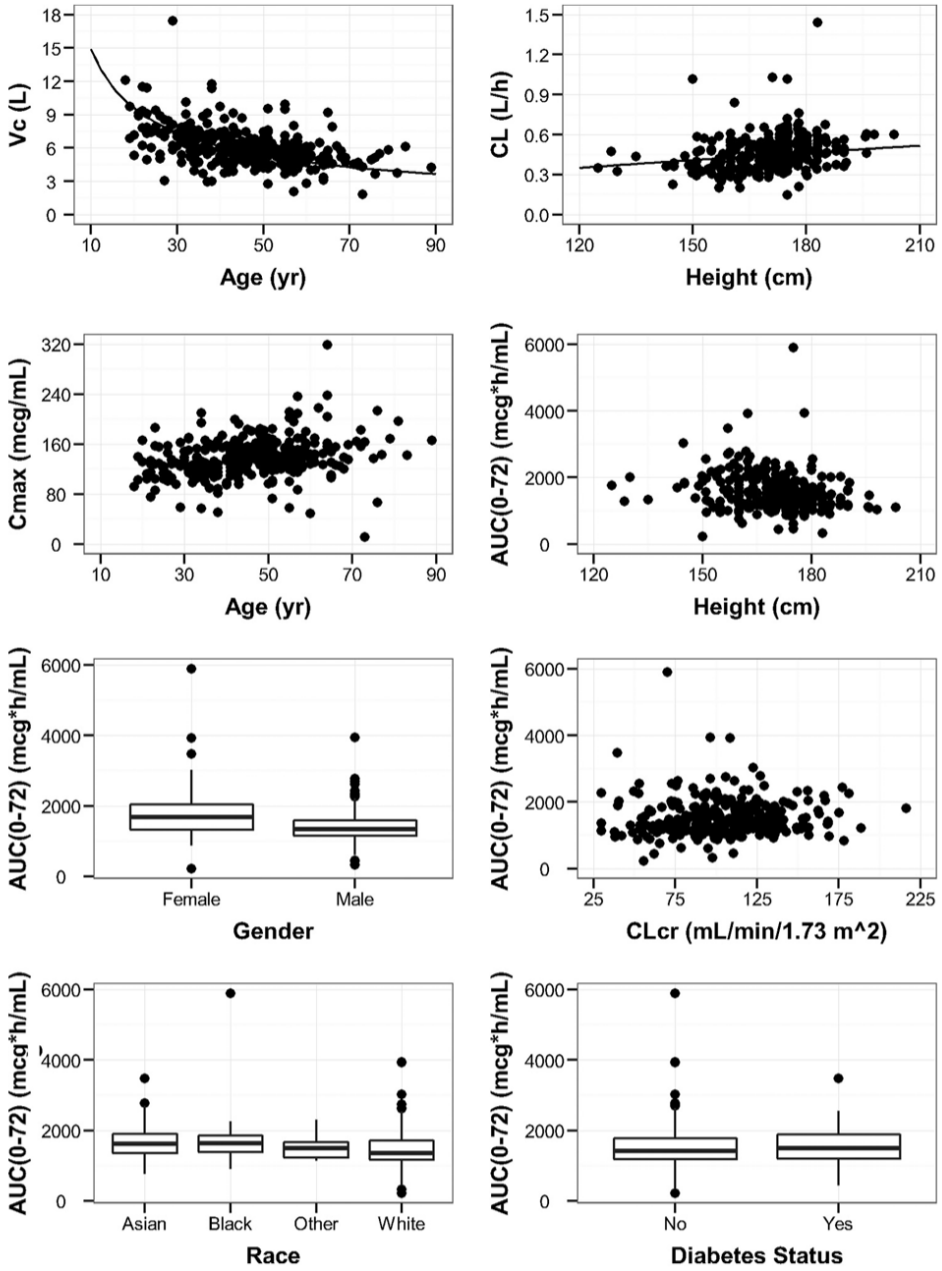
Population Pharmacokinetic Analysis for a Single 1,200-Milligram Dose of Oritavancin Using Data from Two Pivotal Phase 3 Clinical Trials

C. M. Rubino,[a] S. M. Bhavnani,[a] G. Moeck,[b] S. E. Bellibas,[b] P. G. Ambrose[a]

Institute for Clinical Pharmacodynamics, Latham, New York, USA[a]; The Medicines Company, Parsippany, New Jersey, USA[b]



Population means concentration-time profile following a single oritavancin dose of 1,200 mg i.v. administered over 3 hours, overlaid upon the observed concentration-time data.

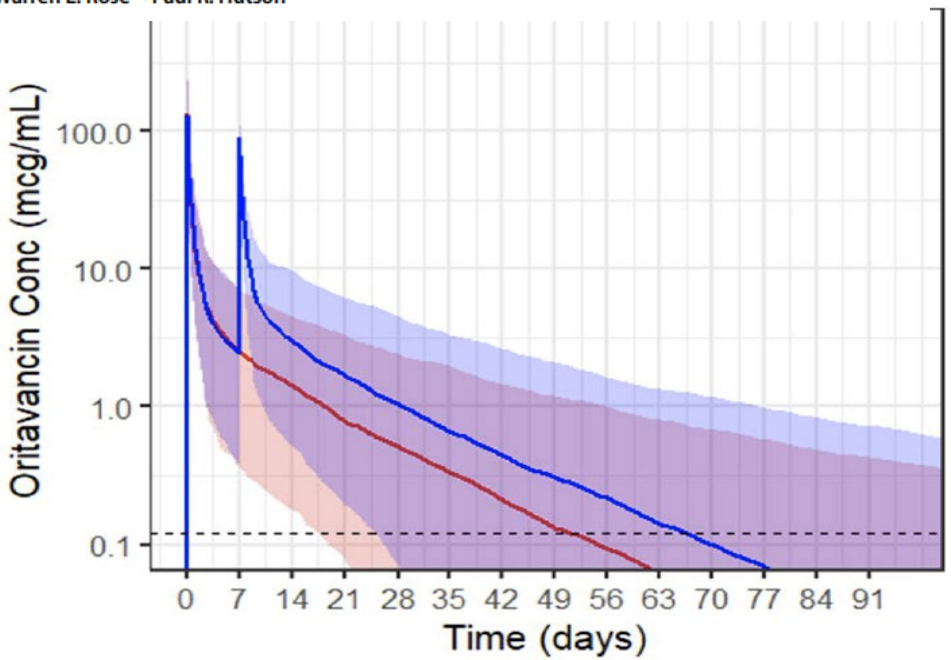


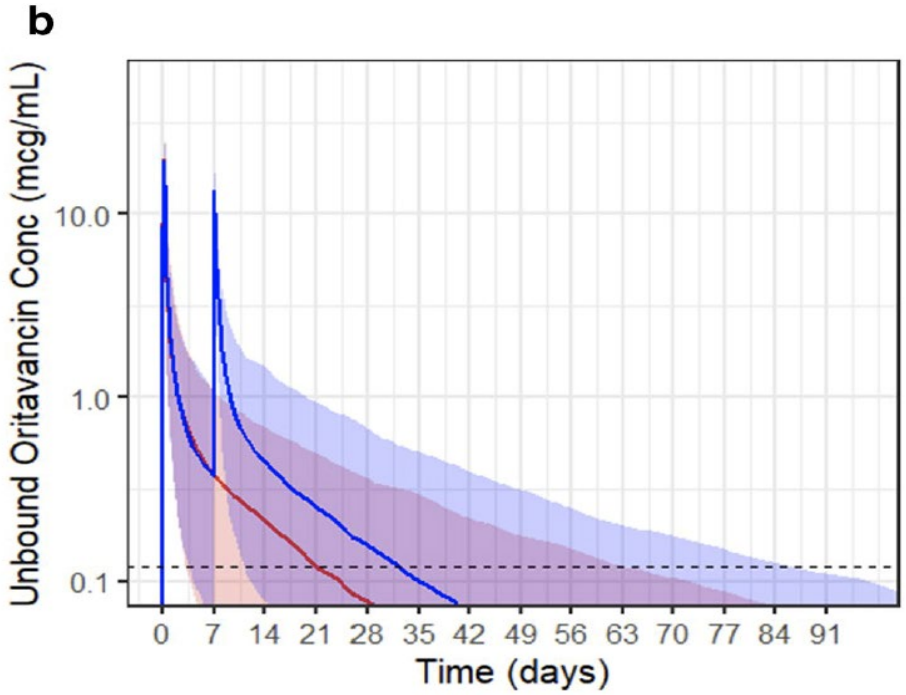
Drugs - Real World Outcomes (2020) 7 (Suppl 1):S36–S40
https://doi.org/10.1007/s40801-020-00188-6

ORIGINAL RESEARCH ARTICLE

A Two-Dose Oritavancin Regimen Using Pharmacokinetic Estimation Analysis

Warren E. Rose[1] · Paul R. Hutson[1]





The **blue line** displays the median plasma concentrations expected after **one 1200 mg dose followed by an 800 mg dose 1 week apart**,

the red line represents the **single 1200 mg dose**.

Methods A simulated oritavancin 1200 mg dose was infused over 3 h followed 7 days later by a simulated 800 mg dose infused over 3 h for pharmacokinetic estimation.
Results The oritavancin dosing displayed predictable linear pharmacokinetics and therapeutic concentrations. **The total and free oritavancin concentrations remained above the susceptibility breakpoint (0.12 mg/L) for 8 weeks and 4.6 weeks**, respectively, with the two-dose regimen.

Warren E. Rose, Paul R. Huston. Drugs - Real World Outcomes (2020) 7 (Suppl 1):S36–S40 https://doi.org/10.1007/s40801-020-00188-6

Drug interactions

- Oritavancin is a weak inhibitor of CYP2C9 and CYP2C19, and an inducer of CYP3A4 and CYP2D6
- Patients treated with warfarin and receiving oritavancin should be monitored for possible bleeding

Bassetti M, et al. Curr Opin Infect Dis 2021; 34:96-108

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Alteration of lab tests

Effects of Oritavancin on Coagulation Tests in the Clinical Laboratory

Adam Belley,[a] Richard Robson,[b] John L. Francis,[c] Dorothy M. Adcock,[d] Stefan Tiefenbacher,[d] Christopher M. Rubino,[e] Greg Moeck,[a] David Sylvester,[a] Michael N. Dudley,[a] Jeffery Loutit[a]

- Possible **alterations of some coagulation tests** in the first hours/days after oritavancin administration (e.g., prolonged PT and prolonged aPTT) because of interaction of oritavancin with the phospholipid reagent
- i.v. **unfractionated heparin sodium** is contraindicated for up to 5 days after oritavancin administration, owing to inability to reliably monitor coagulation tests
- The results of the chromogenic factor Xa and the thrombin time assays are not affected by oritavancin administration
- False increase in vancomycin concentrations

Bassetti M, et al. Curr Opin Infect Dis 2021; 34:96-108
Smelter FM, et al. J Clin Pharmacol 2022; 62:472-478
Belley A, et al. Antimicrob Agents Chemother 2017; 61:e01968–16

Oritavancin -Efficacy in RCTs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O'Riordan, M.D., for the SOLO I Investigators*

Single-Dose Oritavancin Versus 7–10 Days of Vancomycin in the Treatment of Gram-Positive Acute Bacterial Skin and Skin Structure Infections: The SOLO II Noninferiority Study

G. Ralph Corey,[1] Samantha Good,[2] Hai Jiang,[2] Greg Moeck,[2] Matthew Wikler,[2] Sinikka Green,[3] Paul Manos,[4] Richard Keech,[5] Rajesh Singh,[6] Barry Heller,[7] Natalia Bubnova,[8] and William O'Riordan[9]; for the SOLO II Investigators[a]

[1]Duke University Medical Center, Durham, North Carolina; [2]The Medicines Company, Parsippany, New Jersey; [3]Sharp Grossmont Hospital, San Diego; [4]Paradise Valley Hospital, Oceanside, and [5]Physician Alliance Research Center, Anaheim, California; [6]Government Medical College, Nagpur, India; [7]Novo Research, Long Beach, California; [8]St George the Martyr City Hospital, St Petersburg, Russia; and [9]Sharp Chula Vista Medical Center, California

Study [ref] (type of study)	Investigational drugs (dosage)	Comparator/s (dosage)	Primary endpoint	Disease and study population of the primary analysis	Cured/total (rates, %)	Percent difference (95% CI)
SOLO I [45] (noninferiority)	Oritavancin (1200 mg i.v. on day 1)	Vancomycin (15 mg/kg q12h i.v. for 7–10 days)	*Early clinical response* (cessation of spreading or a reduction in the size of the baseline lesion, the absence of fever, and the absence of a need for rescue antibiotic medication; assessed at 48–72-h)	ABSSSI *MITT population* Oritavancin Vancomycin	 391/475 (82.3) 378/479 (78.9)	 3.4 (−1.6 to 8.4) Reference
SOLO II [44] (noninferiority)	Oritavancin (1200 mg i.v. on day 1)	Vancomycin (15 mg/kg q12h i.v. for 7–10 days)	*Early clinical response* (cessation of spreading or reduction in the size of the baseline lesion, absence of fever, and no rescue antibiotic medication; assessed at 48–72-h)	ABSSSI *MITT population* Oritavancin Vancomycin	 403/503 (80.1) 416/502 (82.9)	 −2.7 (−7.5 to 2.0) Reference

Corey GR et al. N Engl J Med 2014; 370:2180–2190
Corey GR et al. Clin Infect Dis 2015; 60:254–262
Bassetti M et al. Curr Opin Infect Dis 2020; 33:110-120

Open Forum Infectious Diseases

MAJOR ARTICLE

Efficacy and Safety of Oritavancin Relative to Vancomycin for Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in the Outpatient Setting: Results From the SOLO Clinical Trials

Thomas P. Lodise,[1] Mark Redell,[2] Shannon O. Armstrong,[2] Katherine A. Sulham,[2] and G. Ralph Corey[3]

[1]Albany College of Pharmacy and Health Sciences, New York; [2]The Medicines Company, Parsippany, New Jersey; [3]Duke University Medical Center, Durham, North Carolina

- The SOLO I and SOLO II protocols were originally designed so that patients were hospitalized until assessments of early clinical evaluation (ECE) were completed at 48 to 72 hours after the initiation of treatment (primary endpoint).
- The protocols were amended (Amendment 2) 5 months into enrollment to allow US patients to complete their entire course of antimicrobial therapy in an outpatient setting at the discretion of the investigator.
- **The primary efficacy endpoint** was a composite clinical outcome at ECE at 48 to 72 hours that comprised (1) cessation of spreading or reduction in the size of the baseline lesion, (2) absence of fever, and (3) no rescue antibiotic medication. **The key secondary endpoints** were investigator-assessed clinical cure at posttherapy evaluation (PTE) and reduction in size of baseline lesion ≥20% at ECE.
- **The SOLO studies comprised 1987 randomized patients**.
- **The outpatient subgroup described in the current analysis consisted of 792 patients treated in the outpatient setting exclusively** (392 in the oritavancin arm and 400 in the vancomycin arm). The outpatient subgroup accounted for 74% of patients enrolled in the United States after Amendment 2

Open Forum Infectious Diseases

MAJOR ARTICLE

Efficacy and Safety of Oritavancin Relative to Vancomycin for Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) in the Outpatient Setting: Results From the SOLO Clinical Trials

Thomas P. Lodise,[1] Mark Redell,[2] Shannon O. Armstrong,[2] Katherine A. Sulham,[2] and G. Ralph Corey[3]

[1]Albany College of Pharmacy and Health Sciences, New York; [2]The Medicines Company, Parsippany, New Jersey; [3]Duke University Medical Center, Durham, North Carolina

- **Results:** 792(oritavancin, 392; vancomycin, 400) received entire course of treatment in the **outpatient setting**.
- Efficacy response rates at early clinical evaluation and posttherapy evaluation were similar (primary composite endpoint at ECE: 80.4% vs 77.5% for oritavancin and vancomycin, respectively) as was incidence of adverse events. Five patients (1.3%) who received oritavancin and 9 (2.3%) vancomycin patients were subsequently admitted to a hospital.
- **Conclusions:** Oritavancin provides a single-dose alternative to multidose vancomycin for treatment of ABSSSI in the outpatient setting.

Safety in RCTs

- Safety of oritavancin in the SOLO studies was similar to vancomycin (most common AEs were nausea and headache in both arms)
- SAE were 7.4% for oritavancin vs. 7.3% for vancomycin in SOLO I
- SAE were 4.4% for oritavancin vs. 4.6% for vancomycin in SOLO II

The post hoc analysis shows that a single dose of oritivancin has comparable efficacy outcomes to twice-daily IV vancomycin for 7–10 days in patients who were treated in the outpatient setting.
Oritavancin was generally well tolerated, with lower incidences of hypersensitivity reactions and pruritus relative to vancomycin.

Corey GR, et al., N Engl J Med 2014; 370:2180–2190
Corey GR, et al., Clin Infect Dis 2015; 60:254–262
Thomas P Lodise. Et al, Open Forum Infect Dis . 2017 Jan 19;4(1):ofw274

Journal of Global Antimicrobial Resistance 25 (2021) 380–389

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Review

Efficacy and safety of oritavancin for the treatment of acute bacterial skin and skin-structure infections: a systematic review and meta-analysis

Huan Zhang[a,b], Weiying Zhou[b], Jin Wang[a], Yun Cai[a,*]

[a] Centre of Medicine Clinical Research, Department of Pharmacy, PLA General Hospital, Beijing 100853, China
[b] College of Pharmacy, Chongqing Medical University, Chongqing 400016, China

PubMed, Cochrane Library and Embase were searched from database inception to 28 July 2020 to identify clinical studies assessing the efficacy and safety of ORI and comparator antibiotics for the treatment of ABSSSIs. Primary efficacy outcome, investigator-assessed clinical cure, lesion size reduction ≥20%, additional post-treatment antibiotics, and 30-day emergency room (ER) visits and readmission were assessed as efficacy outcomes. Adverse events (AEs) and mortality were assessed as safety outcomes. I^2 statistic was calculated for heterogeneity, and a fixed-effects or random-effects model was used for estimation of the risk ratio (RR).

- Results
- A total of **9213** patients from two RCTs and four cohort studies were included in this meta-analysis. ORI was statistically non-inferior to control agents in all efficacy and safety outcomes. Moreover, **ORI significantly reduced the occurrence of 30-day readmission (RR = 0.42; *P* = 0.0004) and drug-related AEs** (RR = 0.78; *P* = 0.002). In the subgroup analysis, ORI also had a lower rate of 30-day ER visits in the outpatient setting (RR = 0.34; *P* < 0.00001).
- ORI was not inferior to comparators for the treatment of ABSSSIs. Meanwhile, it showed advantages in reducing the rate of readmission and drug-related AEs. More high-quality and large-scale RCTs are required to further confirm the efficacy and safety of ORI. [Trial registration: PROSPERO ID: CRD42020201942]

› Am J Emerg Med. 2021 May:43:77-80. doi: 10.1016/j.ajem.2021.01.050. Epub 2021 Jan 26.

Effectiveness of oritavancin for management of skin and soft tissue infections in the emergency department: A case series

Drew Dretske [1], Lucas Schulz [2], Erin Werner [3], Brian Sharp [4], Michael Pulia [5]

Affiliations + expand

PMID: 33545550 DOI: 10.1016/j.ajem.2021.01.050

- In this case series, we describe the characteristics and outcomes of **ten patients with high-risk skin and soft tissue infections who received oritavancin and were discharged from the emergency department**

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
2023, VOL. 21, NO. 7, 703–721
https://doi.org/10.1080/14787210.2023.2214727

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REVIEW

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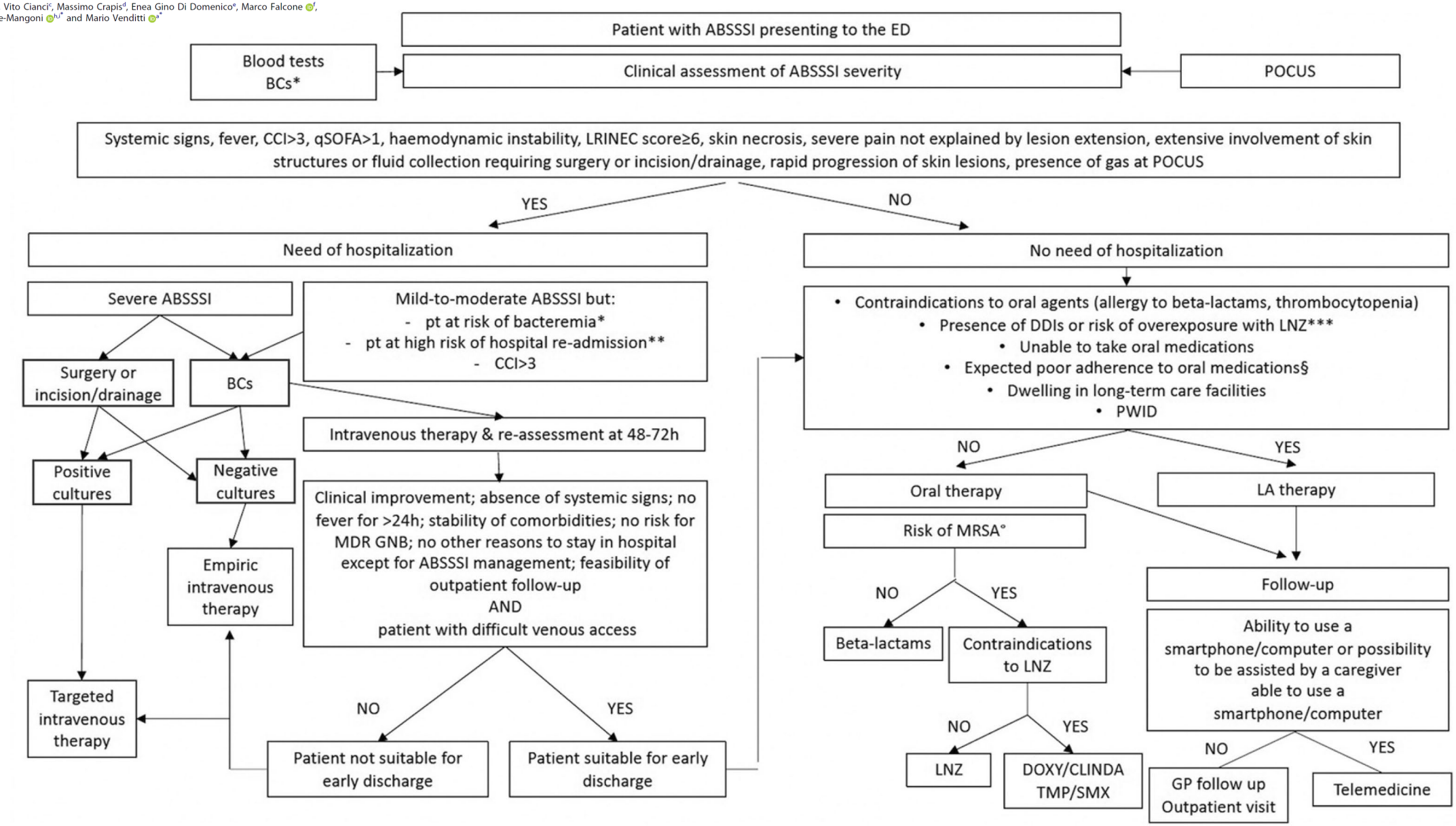
Direct or early Discharge of Acute Bacterial Skin and Skin Structure Infection patients from the Emergency Department/Unit: place in therapy of dalbavancin

Alessandra Oliva [a], Sergio Carbonara[b], Vito Cianci[c], Massimo Crapis[d], Enea Gino Di Domenico[e], Marco Falcone [f], Gioacchino Galardo[g], Emanuele Durante-Mangoni [h,i]* and Mario Venditti [a]*



Utilizzo di Oritavancina in indicazioni off-label

Infective Endocarditis

First Author et al. (Year) [Ref]	Type of Study	N. of Patients Treated, Type of Infection	Dosing and Interval	Pathogen (s)	Outcome	Adverse Effects
Johnson et al. (2015) [12]	Case Report	1 (1), PVE	1200 q48h × 3; 1200 twice weekly for 6 wks; After recurrence 2 wks twice weekly in combination with gentamicin (4 days) and then linezolid and tigecicline; 10 wks after surgery 1200 twice weekly (in the first ten days in addition with linezolid and tigecycline)	VRE	Favourable after surgical valve replacement	Increased aPTT; nausea and anorexia (during combination therapy with linezolid and tigecycline)
Stewart et al. (2017) [13]	Case Series	1 (10), NVE	1200 single dose (after 3 days of vancomycin and 4 days of ceftriaxone)	Group B Streptococcus	Failure due to the need for surgical intervention and hospital readmission 3 months later	None
Salcedo et al. (2018) [15]	Case Series	5 (5), NVE	1200 single dose in 3 patiens, 1200 weekly × 4 in 2 patients	2 MSSA, 2 MRSA and 1 GBS/GFS	3 favourable. 2 Not reported	One patients reported eosinophilia/ anaphylaxis
Brownell et al. (2020) [14]	Retrospective, observational	4 (75), Endocarditis not specified	NA	NA	Favourable in 100% of cases	NA
Morrisette et al. (2019) [16]	Retrospective, multicenter	1 (56), Endocarditis	1200 single dose, then lost to follow-up	*E. faecalis*	Lost to follow-up	NA
Ahiskali et al. (2020) [17]	Retrospective, observational	2 (24), Endocarditis not specified	1200 single dose in 1 patients, 1200 weekly × 2 in 1 patient	1 MSSA and 1 MRSA	Clinical cure (MSSA). Failure (complicated by spondylodiscitis and epidural abscess)	NA

Device-Related Infections

First Author et al. (Year) [Ref]	Type of Study	N. of Patients Treated	Dosing and Interval	Pathogen(s)	Outcome	Adverse Effects
Stewart et al. (2017) [13]	Case Series	1 (10), CLABSI	1200 single dose (after 4 days of vancomycin and 1 days of cefazoline)	MSSA	Favourable	Nausea
Shulz et al. (2018) [18]	retrospective, observational	1 (17), endovascular graft infection	1200 mg × 1; 800 mg/wk × 11 doses; 1200 mg × 1 following 11-day intervals; and 800 mg × 5/wk	*S. lugdunensis*	Palliative intent	NA
Morrisette et al. (2019) [16]	Retrospective, multicenter	2 (56), CLABSI	NA	NA	NA	NA
Co et al. (2018) [19]	Retrospective, observational	7 (67), cardiac device infection	NA	NA	NA	NA
Brownell et al. (2020) [14]	Retrospective, observational	2 (75), Line infection	NA	NA	Favourable in 100% of cases	NA
Redell et al. (2019) [20]	Retrospective, observational	2 (440), 1 exit site infection, 1 Spinal Hardware	1200 single dose	NA	NA	NA

Blood-Stream Infections

First Author et al. [Ref]	Type of Study	N. of Patients Treated	Dosing and Interval	Pathogen(s)	Outcome	Adverse Effects
Stewart et al. (2017) [13]	Case Series	6 (10), isolated BSI	1200 single dose	4 MSSA, 1 enterococcus (Ampicillin-susceptible) and 1 CoNS	4 Favourable, 1 Failure and 1 Not evaluable	None
Ahiskali et al. (2020) [17]	Retrospective, observational	3 (24), isolated BSI	1200 single dose in 5 patients, 1200 weekly × 2 in 2 patient, 1200 weekly × 4 in 1 patient	5 MRSA and 4 MSSA	3 complete cure, 4 incomplete cure, 2 lost at FUP	NA
Redell et al. (2019) [20]	Retrospective, observational	7 (440), isolated BSI	1200 single dose	NA	NA	NA

Prosthetic Joint Infections

First Author et al. [Ref]	Type of Study	N. of Patients Treated	Dosing and Interval	Pathogen(s)	Outcome	Adverse Effects
Van Hise et al. (2020) [21]	multicenter, retrospective, descriptive	134 ostheomyelitis, of which 24 prosthetic	1200 mg, then 800 mg weekly (4 to 5 doses)	71.9% MRSA	88.1% clinical success at the end of therapy	3 hypoglycemia, 1 tachycardia, 1 tachycardia with chest pain
Redell et al. (2019) [20]	retrospective, observational	438, of which 18 osteomyelitis and 3 prosthetic	1200 mg every 6–14 days (1–10 doses)	74% *S. aureus* of which 59.3% MRSA	93.8% cure or 30-days improvement	6.6% of patients reported an adverse event
Shulz et al. (2018) [18]	retrospective, observational	17 including osteomyelitis	1200 mg (2–18 doses)	NA	100% clinical success or improvement	24% of patients reported an adverse event
Delaportas et al. (2017) [22]	case report	1 ostheomyelitis	1200 mg weekly (6 doses)	MSSA	clinical cure	NA
Chastain et al. (2018) [23]	case series	9 chronic ostheomyelitis	1200 mg—variable time between doses (2–6 doses)	5 MRSA	100% clinical cure at 6-months follow up	None
Nguyen et al. (2020) [24]	case report	1 prosthetic joint infection	daptomycin plus ampicillin 10 days, then 1200 mg weekly (6 doses)	vancomycin sensitive *E. faecalis*	clinical cure	NA
Dahesh et al. (2019) [25]	case report	1 prosthetic vertebral ostheomyelitis	1200 mg weekly (2 doses), then 800 mg weekly (8 doses) plus ampicillin	vancomycin-resistant *E. faecium*	clinical cure	NA

Abbreviations: Ref: references; BSI: bloodstream infections; CLABSI: central-line-associated BSI; NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant Staphylococcus aureus; GBS: Group B Streptococcus; GFS: Group F Streptococcus; NA: not available; VRE: vancomycin-resistant enterococcus; PTT: prothrombin time.

Lupia T. et al. Life 2023, 13, 959. https://doi.org/10.3390/life13040959

Macrophage Killing of Bacterial and Fungal Pathogens Is Not Inhibited by Intense Intracellular Accumulation of the Lipoglycopeptide Antibiotic Oritavancin

Beverlie Baquir, Sandrine Lemaire, Françoise Van Bambeke, Paul M. Tulkens, Lin Lin, Brad Spellberg

Clinical Infectious Diseases, Volume 54, Issue suppl_3, April 2012, Pages S229–S232,
https://doi.org/10.1093/cid/cir921
Published: 15 April 2012

The ability of 2 macrophage cell lines (HL-60; RAW 264.7) to kill archetypal Gram-positive (*Staphylococcus aureus*), Gram-negative (*Acinetobacter baumannii*), and fungal (*Candida albicans*) pathogens was tested following exposure of the macrophages to the lipoglycopeptide antibiotic oritavancin. Oritavancin did not affect killing of *C. albicans* but markedly enhanced killing of *S. aureus* by both macrophages. Oritavancin modestly reduced killing of *A. baumannii* by HL-60 cells but not by RAW 264.7 cells. Thus, macrophage killing of microbes remains intact despite substantial intracellular accumulation with a lipoglycopeptide antibiotic.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae241

Journal of Antimicrobial Chemotherapy

Comparative *in vitro* efficacy of antibiotics against the intracellular reservoir of *Staphylococcus aureus*

Brent Beadell [1], Joe Yamauchi[1] and Annie Wong-Beringer [1,2]*

[1]*Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences, University of Southern California, Los Angeles, CA, USA;*
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Objectives We assessed antimicrobial activity at phagolysosome-mimicking pH, intracellular penetration, and SA eradication within Kupffer cells *in vitro* for clinically prescribed antistaphylococcal agents alone or in combination: vancomycin, daptomycin, ceftaroline, ceftobiprole, oritavancin, oxacillin, cefazolin; rifampin and fosfomycin.

- **Methods** pH-adjusted broth microdilution assays, intracellular bioaccumulation assays, and intracellular killing assays against clinical bloodstream isolates were performed using a murine KC line with study agents.
- **Results** Rifampin and β-lactams exhibited enhanced activity [2- to 16-fold minimum inhibitory concentrations (MIC) decrease] at phagolysosomal pH while vancomycin, oritavancin, daptomycin and fosfomycin demonstrated reduced activity (2- to 32-fold MIC increase in order of least to greatest potency reduction). All agents evaluated had poor to modest intracellular to extracellular concentration ratios (0.024–7.8), with exceptions of rifampin and **oritavancin (intracellular to extracellular ratios** of 17.4 and **78.2, respectively**). Finally, we showed that the first-line treatment for SA bacteraemia (SAB), vancomycin, performed worse than all other tested antibiotics in eradicating intracellular SA at human C_{max} concentration (0.20 log cfu decrease), while oritavancin performed better than all other agents alone (2.05 versus 1.06–1.36 log cfu decrease).

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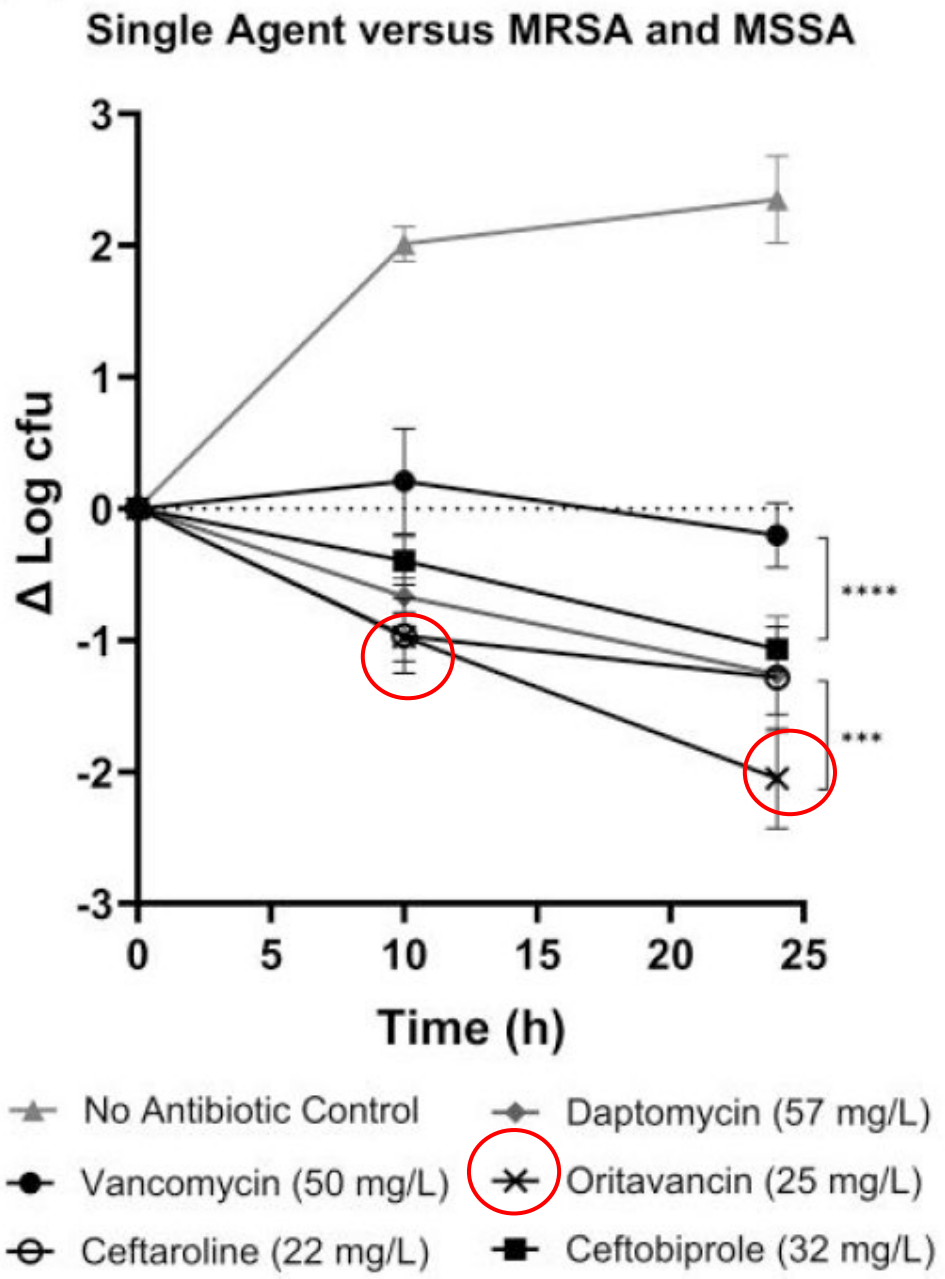
Differential antimicrobial activity against intracellular SA in Kupffer cells.

Oritavancin exposure resulted in the greatest reduction in cfu count by 24 h when compared to all other tested agents alone (−2.05, $P < 0.001$ compared to ceftaroline), approaching the limit of quantitation (LOQ) of our assay (−2.89).



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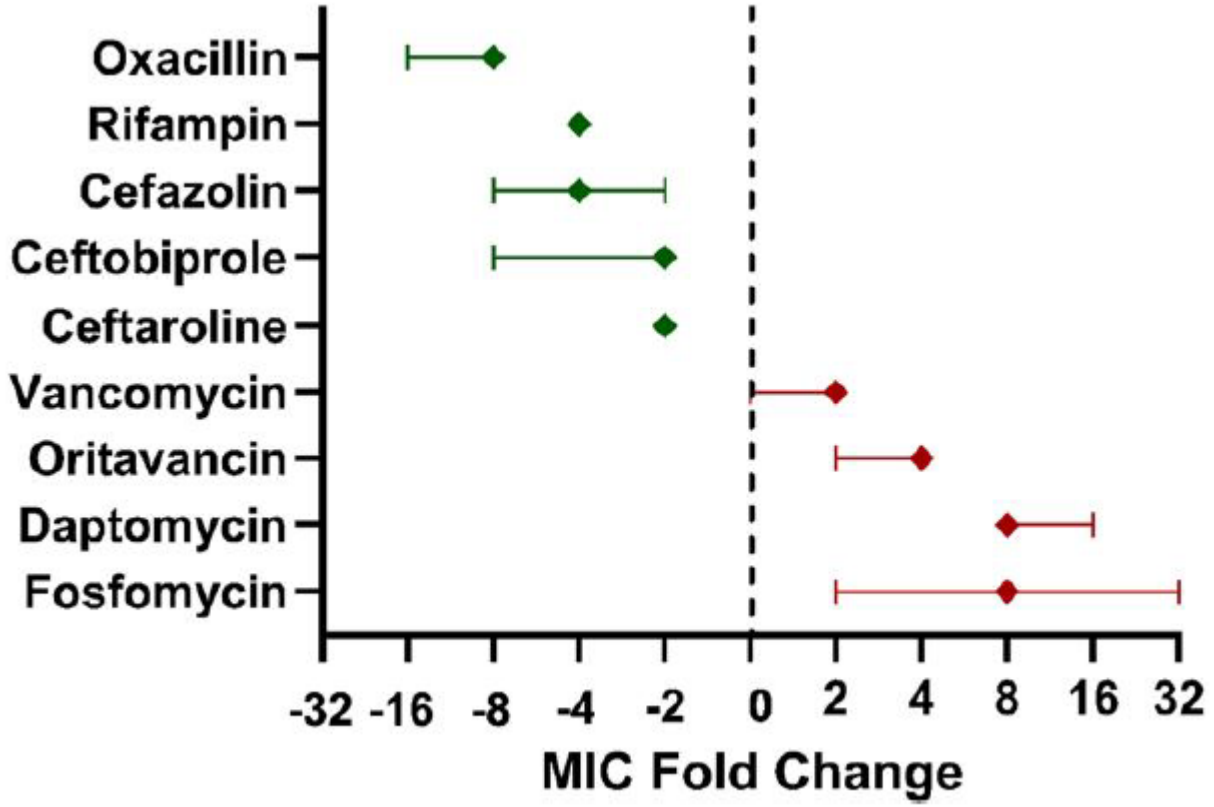

Antibiotic MIC fold change in phagolysosome-mimicking low-pH environment relative to physiological pH.

- MICs were performed according to CLSI guidelines, with supplementation of Ca2+ to CAMHB to achieve 50 mg/L total Ca2+ for daptomycin assays, supplementation of 25 mg/L glucose-6-phosphate for fosfomycin assays and 0.002% Tween-80 (*v/v*) for oritavancin assays.
- Diamonds indicate the median MIC fold change for all tested isolates and control strains, with bars representing the range of MIC fold change

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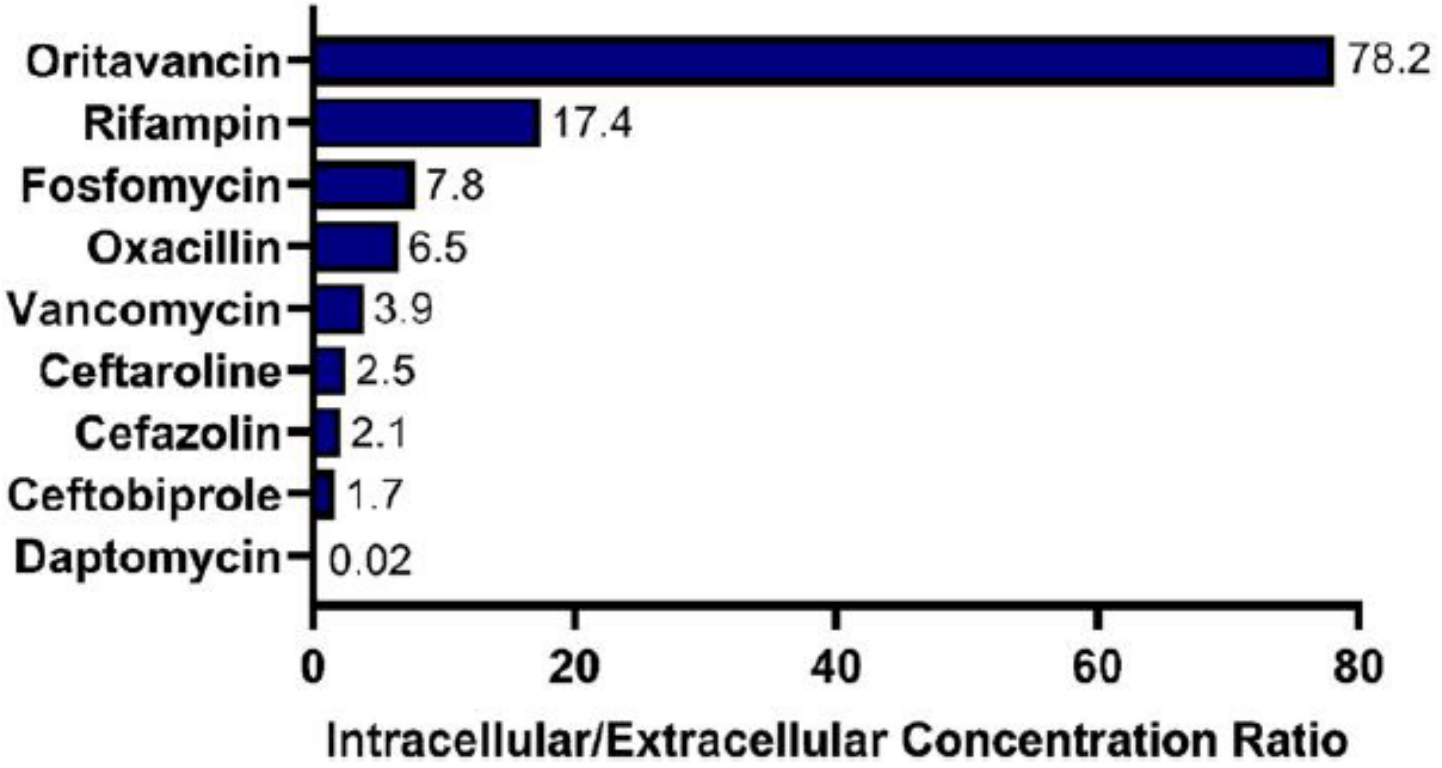

- Differential antibiotic intracellular penetration.
- Kupffer cells were exposed to study agents at human *C*max for 24 h: oritavancin (25 mg/L), rifampin (18 mg/L), fosfomycin (29 mg/L), oxacillin (86 mg/L), vancomycin (50 mg/L), ceftaroline (22 mg/L), cefazolin (188 mg/L), ceftobiprole (32 mg/L) or daptomycin (57 mg/L).

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October 2015 Volume 59 Number 10

Oritavancin Pharmacokinetics and Bone Penetration in Rabbits

Dario Lehoux, Valerie Ostiguy, Cordelia Cadieux, Mireille Malouin, Odette Belanger, Adel Rafai Far, Thomas R. Parr, Jr.

The Medicines Company, St. Laurent, Quebec, Canada

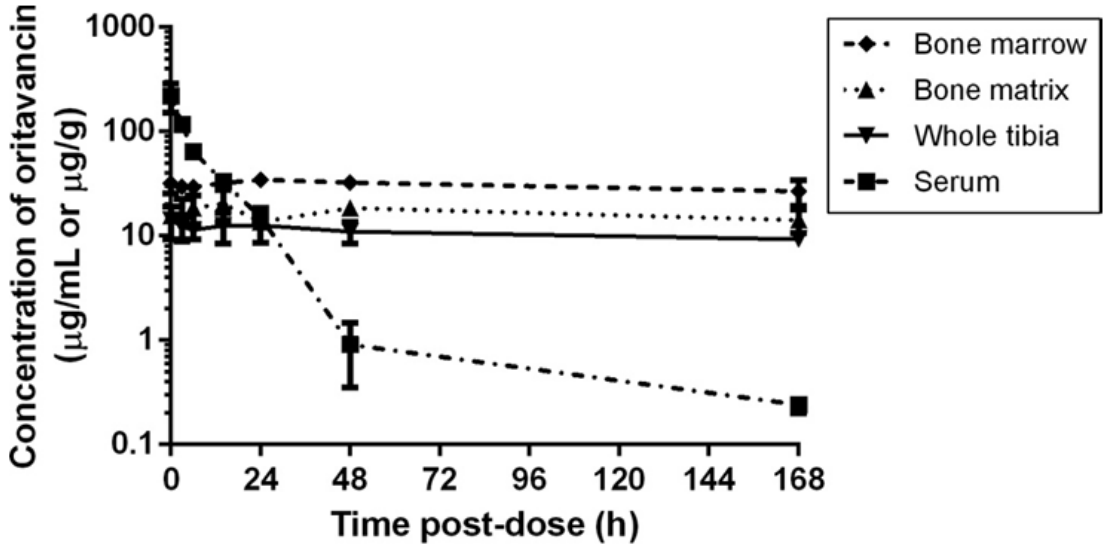


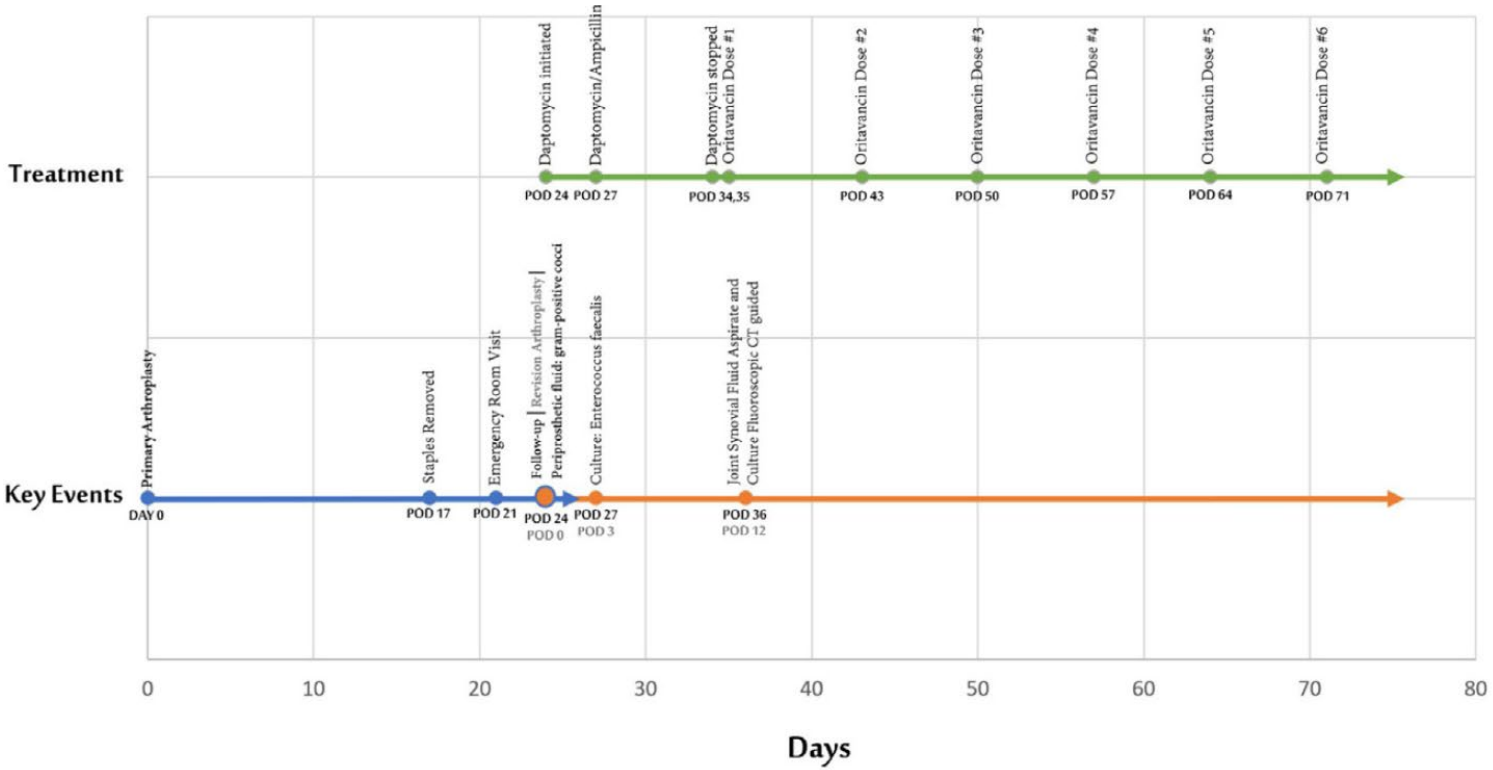
FIG 2 Mean (± SD) oritavancin concentration-versus-time curves for serum, whole tibia, bone matrix, and bone marrow from rabbits administered a 20-mg/kg intravenous dose; $n = 3$ rabbits/time point. The y axis has a logarithmic scale.

- Oritavancin has been shown to rapidly penetrate osseous tissues in rabbit tibia models and drug levels are maintained for greater than 168 h.
- The active ratio of oritavancin in bone is still unknown;
- in this animal model, bone penetration, defined as the tissue to serum AUC 0-168 ratio into bone matrix and bone marrow, was 1.7 and 3.1, respectively, which is higher than that of linezolid, vancomycin, teicoplanin, and dalbavancin.

IDCases 22 (2020) e00949

Case report

Successful treatment of a prosthetic hip infection due to *Enterococcus faecalis* with sequential dosing of oritavancin and prosthesis preservation without prosthetic joint surgical manipulation



- A patient with a prosthetic joint infection complicated with deep surgical site infection due to vancomycin-susceptible Enterococcus faecalis.
- The initial treatment consisted of 10 days with daptomycin plus ampicillin. The hip prosthesis was retained and salvaged with six outpatient sequential doses of oritavancin 1200 mg every seven days without intra-articular irrigation or other surgical interventions.
- The patient was ambulating independently without symptoms after ten months of the last treatment of oritavancin.

Drugs - Real World Outcomes (2020) 7 (Suppl 1):S46–S54
https://doi.org/10.1007/s40801-020-00194-8

REVIEW ARTICLE

Real-World Use of Oritavancin for the Treatment of Osteomyelitis

Patrick J. Scoble[1] · Joseph Reilly[2] · Glenn S. Tillotson[3]

Published online: 25 June 2020

- This article reviews the occurrence and outcomes of off-label oritavancin use for the treatment of osteomyelitis as described in case reports. Analysis included **23 patients treated for osteomyelitis with single- or multiple-dose oritavancin**.
- Overall, clinical **cure or improvement was achieved in 87% of patients**, and adverse events were mild and reported in only two patients.
- Clinical efficacy was demonstrated in 81.8% of methicillin-resistant Staphylococcus aureus (MRSA), 71.4% of methicillin-sensitive S. aureus (MSSA), 50% of vancomycin-resistant Enterococcus (VRE), and in the single case of Streptococcus pyogenes.

Table 1 Patients receiving oritavancin to treat culture-positive osteomyelitis—results per pathogen, methicillin-resistant *Staphylococcus aureus*

Reference	Sex/age (years)	Site of infection	Antimicrobials prior to oritavancin	Oritavancin dosing regimen	Concomitant antimicrobials	Outcome	Time of follow-up	Adverse events
Chastain et al. [44]	M/65	Right great toe	None	1200 mg × 2; on days 1 and 13	Doxycycline × 3 months	Clinical cure	6 months	None reported
	M/31	Left distal metatarsal	Clindamycin × 1 week	1200 mg × 3 on days 1, 52, and 90	None	Clinical cure	6 months	None reported
	M/47	Right distal first metatarsal	Clindamycin × 1 week, then doxycycline × 3 months	1200 mg × 2; on days 1 and 72	None	Clinical cure	6 months	None reported
	F/89	Left lateral malleolus	None	1200 mg × 4; on days 1, 36, 73, and 147	None	Clinical cure	6 months	None reported
	M/62	Right calcaneus	None	1200 mg × 6; on days 1, 14, 28, 70, 84, and 113	None	Clinical cure	6 months	None reported
Ruggero et al. [41]	M/46	Native, vertebral osteomyelitis	Aztreonam, vancomycin, metronidazole, doxycycline, TMP/SMX	1200 mg every 2 weeks × 4 doses, then 1200 mg 1 month later	TMP/SMX	Clinical improvement	5 months, and 1 year	None reported
CHROME Registry [46]	F/47	Not specified	TMP/SMX	1200 mg × 1	None	Failure	N/A	None reported
	F/70	Not specified	None	1200 mg × 10 doses every 7–8 days	None	Clinical improvement	N/A	None reported
	F/46	Skull	Vancomycin	1200 mg × 6 doses every 7–14 days	None	Clinical cure	N/A	None reported
	M/58	Left foot	Minocycline, vancomycin	1200 mg × 1, then in 14 days, AE occurred with second dose	Linezolid	Clinical improvement	N/A	Infusion discontinued; moderate, not serious infusion-related reaction; sent to ED for observation
	F/47	Not specified	None	1200 mg × 2 doses every 9 days	TMP/SMX	Failure	N/A	None reported

Table 2 Patients receiving oritavancin to treat culture-positive osteomyelitis—results per pathogen, methicillin-sensitive *Staphylococcus aureus*

Reference	Sex/age (years)	Site of infection	Antimicrobials prior to oritavancin	Oritavancin dosing regimen	Concomitant antimicrobials	Outcome	Time of follow-up	Adverse events
Schulz et al. [40]	F/76	Not specified	None	1200 mg twice a week × 2 doses	Transitioned to doxycycline × 10 days	Clinical improvement	2 weeks	Anemia and leukopenia in 1 patient
Stewart et al. [42]	F/26	Sacral joint	Cefazolin; pip/tazo	1200 mg × 1 dose	None	Failure	6 weeks	None reported
Delaportas et al. [39]	F/49	Right tibia	None	1200 mg weekly × 6 doses	None	Clinical success	1, 4, 8, 12, 24, and 40 weeks	None reported
CHROME registry [46]	M/60	Not specified	Amox/clav, vancomycin, cefazolin/cephalexin	1200 mg × 1	None	Clinical cure	N/A	None reported
	F/98	Not specified	Ceftriaxone, levofloxacin	1200 mg × 1 (did not finish)	Ciprofloxacin	Clinical cure	N/A	None
	M/46	Not specified	Amoxicillin	1200 mg × 6 doses every 6–8 days	None	Clinical cure	N/A	None
	F/36	Not specified	Amp/sul, ceftriaxone, TMP/SMX, vancomycin, cefazolin, cephalexin	1200 mg × 3 doses every 14 days	None	Clinical cure	N/A	None

F female, M male, TMP/SMX trimethoprim/sulfamethoxazole, [illegible] amoxicillin/clavulanic acid, [illegible] ampicillin/sulbactam, [illegible]

Table 3 Patients receiving oritavancin to treat culture-positive osteomyelitis—results per pathogen, vancomycin-resistant *Enterococcus* (daptomycin non-susceptible)

Reference	Sex/age (years)	Site of infection	Antimicrobials prior to oritavancin	Oritavancin dosing regimen	Concomitant antimicrobials	Outcome	Time of follow-up	Adverse events
Foster et al. [45]	M/57	Hip	Daptomycin, ciprofloxacin	1200 mg once weekly × 6 weeks	Ciprofloxacin	Clinical success	9.5 months, and 14.5 months	None
Dahesh et al. [43]	M/57	Vertebral	Tigecycline, quinupristin-dalfopristin	1200 mg weekly × 2 doses, then 800 mg weekly × 8 doses	Ampicillin	Clinical improvement	N/A	None
CHROME registry [46]	F/50	Not specified	None	1200 mg × 1	None	Clinical cure	N/A	None
	F/50	Not specified	None	1200 mg × 1	None	Clinical improvement	N/A	None

Drugs - Real World Outcomes (2020) 7 (Suppl 1):S41–S45
https://doi.org/10.1007/s40801-020-00195-7

ORIGINAL RESEARCH ARTICLE

Treatment of Acute Osteomyelitis with Once-Weekly Oritavancin: A Two-Year, Multicenter, Retrospective Study

Nicholas W. Van Hise[1] · Vishnu Chundi[1] · Vishal Didwania[1] · Michael Anderson[1] · David McKinsey[2] · Ingrid Roig[3] · Akhilesh Sharma[4] · Russell M. Petrak[1]

Methods This was a 2-year, multicenter, retrospective, descriptive study of patients treated for acute osteomyelitis with weekly doses of oritavancin. End of therapy evaluation (ETE) was defined as evaluation at 7–10 days after the last dose of oritavancin, and post-therapy assessment (PTE) was at 3 months and 6 months. At ETE and PTE, patients were interviewed via telephone for clinical outcomes, using a standard questionnaire. Electronic medical record review was also conducted.

- Results **134 patients** were treated with oritavancin for acute osteomyelitis across 20 different Metro Infectious Disease Consultants infusion centers in six states. Of total positive cultures, 71.9% (92/128) were methicillin-resistant Staphylococcus aureus (MRSA) from deep wounds, bone, or joint culture; an additional nine (6.7%) of 134 patients presented with concomitant MRSA bacteremia.
- Oritavancin was administered via intravenous catheter; patients received an initial treatment of **1200 mg and then 800 mg weekly** thereafter for a **total number of doses of four (n = 118) or five (n = 16)**. 118 patients (88.1%) of the baseline 134 patients achieved clinical success at the ETE timepoint. 130 patients were available for PTE at 3 months and **6 months**.
- Overall, relapse or persistent infection was diagnosed in 13/134 (9.7%) patients. Nine (6.7%) of 134 patients were admitted to the hospital during the follow-up period but none for osteomyelitis. Adverse events were reported in five (3.7%) patients including hypoglycemia-related symptoms (three patients), tachycardia (one patient), and tachycardia with chest pain (one patient).

Drugs - Real World Outcomes (2020) 7 (Suppl 1):S41–S45
https://doi.org/10.1007/s40801-020-00195-7

ORIGINAL RESEARCH ARTICLE

Treatment of Acute Osteomyelitis with Once-Weekly Oritavancin: A Two-Year, Multicenter, Retrospective Study

Nicholas W. Van Hise[1] · Vishnu Chundi[1] · Vishal Didwania[1] · Michael Anderson[1] · David McKinsey[2] · Ingrid Roig[3] · Akhilesh Sharma[4] · Russell M. Petrak[1]

	No. of patients, *n* (%)	Clinical cure, *n* (%)
Clinical success ETE	134	118 (88.1)
Clinical success PTE	130	104 (80.0)
Subgroups evaluated at ETE		
Four-dose regimen	118 (88.1)	107 (90.7)
Five-dose regimen	16 (11.9)	11 (68.8)
MRI-proven infection	128 (95.5)	113 (90.4)
Diabetes	51 (38.1)	43 (84.3)
Prosthetic device	24 (17.9)	20 (88.3)
Heart failure	25 (18.7)	21 (84)
Previous antibiotic therapy	18 (13.4)	14 (77.8)
Malignancy on immunosuppression	12 (9)	11 (91.7)

ETE end of the last dose, *MRI* magnetic resonance imaging, *PTE* post-treatment

European Journal of Clinical Microbiology & Infectious Diseases (2024) 43:1503–1504
https://doi.org/10.1007/s10096-024-04844-5

LETTER TO THE EDITOR

Oritavancin use in patients with recurrent bone infections by methicillin-resistant *Staphylococcus aureus* with monitoring of concentrations

Marco Bongiovanni[1,3] · Paul Thoueille[2,3] · Beatrice Barda[1,3] · Thomas Mercier[2,3] · Catia Marzolini[2,3] · Niccolò Ramponi[1,3] · Eva Choong[2,3] · Marco Cantù[3,4] · Laurent A. Decosterd[2,3] · Enos Bernasconi[1,3,5,6]

Received: 29 February 2024 / Accepted: 3 May 2024 / Published online: 14 May 2024

- Case-1 A 84-year-old man was hospitalized for fever and back lumbar pain since one week, with a magnetic resonance imaging (MRI) showing **L4 spondylodiscitis**.
- Blood cultures (BC) and surgical drainage were positive for **MRSA** (strain was resistant to penicillin and derivatives, cephalosporins, ciprofoxacin, clindamycin, co-trimoxazole and gentamycin) which prompted treatment with **vancomycin** 25 mg/kg (loading dose) followed by 15 mg/kg b.i.d. At day 6, vancomycin was replaced by **daptomycin** (8 mg/kg/daily for 6 weeks) for **acute kidney failure**. One week after stopping daptomycin, the patient developed septic shock with BC again positive for MRSA; MRI showed a progression of the abscess with L5 involvement. Despite surgical drainage and targeted antibiotic treatment with daptomycin (8 mg/kg/daily), the fever persisted for>2 weeks and BC remained positive for fve days. Therefore, oritavancin (MIC: 0.125 mg/L) was started at a dose of 1200 mg, followed by **800 mg every 10 days for 4 total times**. The patient was clinically cured and remained asymptomatic during 15 months of follow-up. MRI, repeated 6 months after stopping oritavancin, showed complete resolution of spondylodiscitis. The Cmin prior each administration of oritavancin were 2.2, 1.9 and 2.3 mg/L, respectively,>2 times higher than the MIC when adjusting for the protein binding.

European Journal of Clinical Microbiology & Infectious Diseases (2024) 43:1503–1504
https://doi.org/10.1007/s10096-024-04844-5

LETTER TO THE EDITOR

Oritavancin use in patients with recurrent bone infections by methicillin-resistant *Staphylococcus aureus* with monitoring of concentrations

Marco Bongiovanni[1,3] · Paul Thoueille[2,3] · Beatrice Barda[1,3] · Thomas Mercier[2,3] · Catia Marzolini[2,3] · Niccolò Ramponi[1,3] · Eva Choong[2,3] · Marco Cantù[3,4] · Laurent A. Decosterd[2,3] · Enos Bernasconi[1,3,5,6]

Received: 29 February 2024 / Accepted: 3 May 2024 / Published online: 14 May 2024

- Case-2 A 61-year-old man with **osteomyelitis due to diabetic foot involving the right III, IV, and V metatarsal bones** was hospitalized for fever and worsening of ulcerative lesions. BC were positive (4/4 bottles) for **MRSA (strain was resistant to penicillins and derivatives, cephalosporin, ciprofoxacin and co-trimoxazole**). The first episode was treated with **vancomycin** 25 mg/kg as loading dose, then 15 mg/kg twice daily, then reduced after one week to 750 mg/daily due to kidney impairment (e-GFR 42 ml/min); treatment was administered for 4 weeks. Two weeks after stopping vancomycin, the patient was hospitalized for fever with BC again positive for MRSA. **Daptomycin** (8 mg/kg/ daily) was started and administered for 4 weeks. One month later, the patient was hospitalized again for fever and septic shock, with BC again positive for MRSA that remained positive for up to 4 days despite initiation of vancomycin (25 mg/kg as loading dose, then 750 mg/daily because of e-GFR 46 ml/min). Patient refused amputation of the right foot, therefore, after 7 days of vancomycin treatment, **oritavancin (MIC: 0.06 mg/L) was started (dose of 1200 mg every 10 days for 5 times**). The patient maintained asymptomatic and no clinical relapse was observed during 9 months of follow-up; MRI of the right foot showed complete resolution of osteomyelitis foci. The Cmin of oritavancin measured prior each administration were 2.1, 2.5, 3.3 and 4.4 mg/L, respectively,>5 times higher than the MIC when adjusting for the protein binding.

IDCases 38 (2024) e02105

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journal homepage: www.elsevier.com/locate/idcases

Case report

Long-term oritavancin therapy for shoulder prosthetic joint infection: A case guided by therapeutic drug monitoring (TDM)

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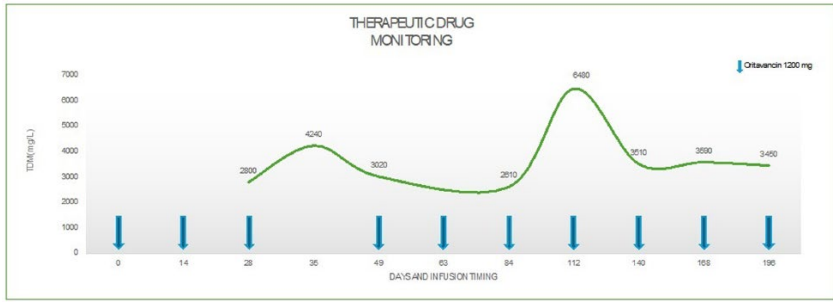
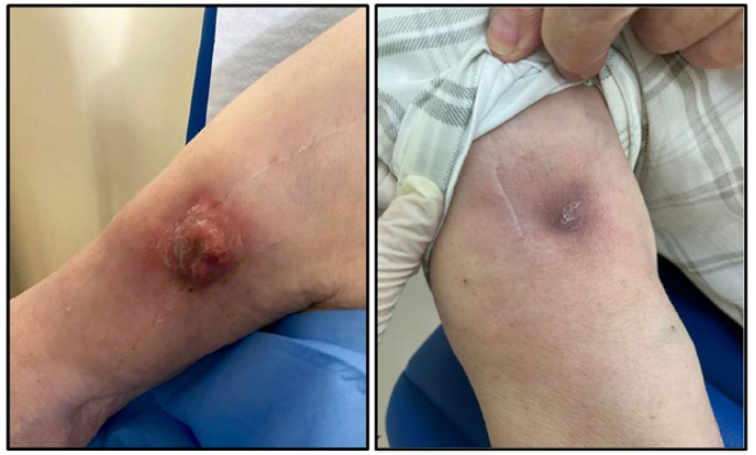


We reported a case of a man in his eighties with a late shoulder PJI caused by methicillin resistant *Staphyloccus epidermidis* (MRSE) with contraindications for surgical replacement and few oral therapeutic options for a long term suppressive antibiotic therapy. The prosthesis was retained, and the patient received **ten outpatient sequential doses of 1200 mg of oritavancin for 28 weeks**, based on therapeutic drug monitoring (TDM) as a guide for correct timing of administration of each dose.

During oritavancin administration, the patient achieved clinical cure, with disappearance of the pain and regaining pre-infection joint mobility, with no side effects reported and no further surgery or hospitalization needed. The treatment is ongoing as a long-lasting suppressive antimicrobial therapy.

Oritavancin could represent an excellent solution for treating PJI caused by MR organism, especially in patients who need a long-term suppressive therapy.



Infect Dis Ther (2024) 13:535–547
https://doi.org/10.1007/s40121-024-00925-2

ORIGINAL RESEARCH

Oritavancin Versus Daptomycin for Osteomyelitis Treatment After Surgical Debridement

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

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

- Retrospective, observational study of patients diagnosed with acute osteomyelitis
- Patients received a first dose of **1200 mg** intravenous (IV) of oritavancin (as Orbativ , Melinta Therapeutics) **followed by 800 mg** IV on day 8 or IV **daptomycin daily 6–8 mg/kg** based on ideal body weight or adjusted body weight if obese, renally dose adjusted, and for **4–6weeks.**

Infect Dis Ther (2024) 13:535–547
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ORIGINAL RESEARCH

Oritavancin Versus Daptomycin for Osteomyelitis Treatment After Surgical Debridement

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

- **Results:**
- Consecutive outpatients (n = 150) with acute osteomyelitis who were treated with oritavancin or daptomycin (1:1) following extensive surgical debridement were identified.
- Compared to oritavancin, patients prescribed daptomycin had higher rates of all-cause readmission [odds ratio (OR) 2.89; p < 0.001], more infection-related readmission (OR 3.19; p < 0.001), and greater likelihood of receiving antibiotics post-discontinuation of initial therapy (OR 2.13; p < 0.001). Repeat surgical debridement was required for 68.0% with daptomycin vs. 23.1% with oritavancin (p < 0.001).

Conclusions: Oritavancin demonstrated a significantly higher rate of clinical success compared to daptomycin, with lower all-cause and infection-related readmissions, reduced need for repeat surgical debridement, and fewer additional antibiotic requirements.

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

in vivo *38*: 3106-3111 (2024)
doi:10.21873/invivo.13795

Management of Recurrent Vancomycin-resistant *Enterococcus faecium* Bacteremia With Oritavancin: A Case Report

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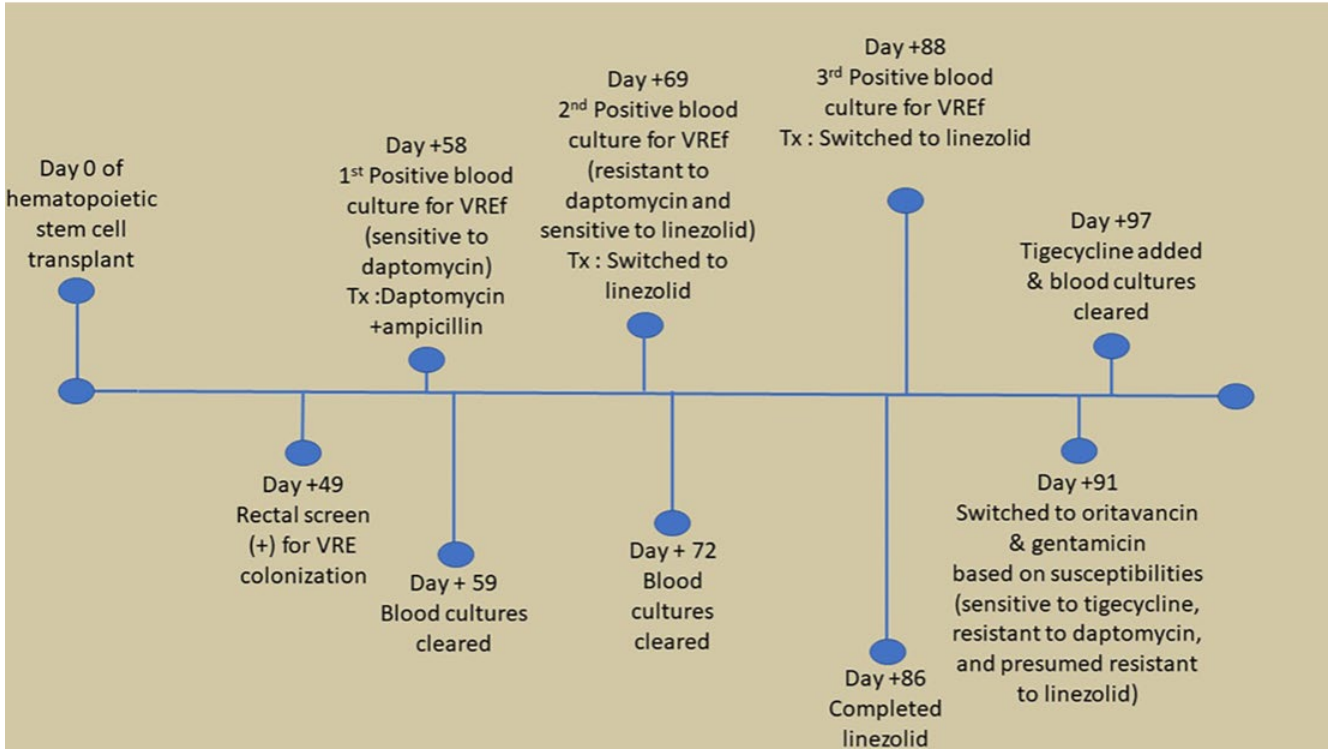
[2]*Department of Pharmacy, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, U.S.A.*

- We report the case of a 48-year-old male with hematological malignancy and graft failure post hematopoietic stem cell transplantation complicated by dialysis-dependent acute kidney injury and recurrent neutropenic fevers due to vancomycin-resistant Enterococcus faecium (VREf) bacteremia.
- Despite central line changes and strict aseptic precautions, the bacteremia returned, showing resistance to daptomycin and linezolid after the second recurrence. As a final effort, using limited clinical data and in vitro studies, we utilized oritavancin off-label as salvage therapy for refractory VREf bacteremia, with subsequent clearance of blood cultures.



The patient was given intravenous oritavancin at **1200 mg every 48 hours (total of three doses)**, with a single dose of gentamycin at 3 mg/kg. Blood cultures eventually cleared on day +97 and remained negative. **Weekly oritavancin was continued at 1,200 mg through day +128**. Unfortunately, despite clearance of bacteremia, a repeat bone marrow biopsy on day +125 revealed ongoing primary graft failure

Ahiskali and Rhodes *BMC Pharmacology and Toxicology* (2020) 21:73
https://doi.org/10.1186/s40360-020-00452-z

BMC Pharmacology and Toxicology

RESEARCH ARTICLE Open Access

Oritavancin for the treatment of complicated gram-positive infection in persons who inject drugs

Aileen Ahiskali[1] and Heather Rhodes[2*]

- Methods: Retrospective chart review of adult PWID who received at least one dose of oritavancin for a gram-positive infection between 1/1/17 and 6/30/19 at a large safety net hospital.
- Results: 23 PWID received 24 courses of at least one dose of oritavancin for a gram-positive infection; 16 were experiencing homelessness at the time of diagnosis.
- MRSA was the most common infecting pathogen and bone or joint the most frequent infection site.
- 19 encounters resulted in clinical cure, including 5 whose conditions improved despite non-adherence to their prescribed regimen. Three patients experienced a non-favorable outcome. Two patients experienced mild adverse drug reactions that did not interfere with therapy; no patients died while on therapy.
- Conclusion: Oritavancin may be a clinically effective treatment option for the management of complicated gram-positive infections in PWID and patients experiencing homelessness. Further studies should be performed to validate these results

› Clin Microbiol Infect. 2024 Apr;30(4):556-557. doi: 10.1016/j.cmi.2024.01.008. Epub 2024 Jan 20.

Successful treatment of complicated infective endocarditis due to Enterococcus faecium in a patient with substance use disorder using oritavancin as sequential maintenance therapy

Gabriele Giuliano [1], Sara Benedetti [2], Margherita Sambo [3], Fabio Pierguidi [2], Mario Tumbarello [4]

Affiliations + expand

PMID: 38253314 DOI: 10.1016/j.cmi.2024.01.008

35-year-old man, who was addicted to **heroin intravenously**

Fever and dyspnoea. Blood tests documented leukocytosis and increased levels of inflammatory markers, such as C-reactive protein. A chest X-ray showed lung consolidation with ground glass opacities, and blood cultures were positive for ***Enterococcus faecium*** **resistant to ampicillin, high-level resistant to gentamicin, and susceptible to glycopeptides and oxazolidinones**. Vancomycin therapy was promptly initiated, and a transthoracic echocardiographic examination revealed pedunculated and strongly mobile vegetation of the tricuspid valve, 0.6 × 0.5 cm in diameter, causing double jet valve insufficiency with a Coandă effect (i.e. blood flow adhering to the atrial wall) which was estimated to be moderate. The findings were confirmed by transoesophageal echocardiography.

A total body computed tomography scan revealed numerous pulmonary nodules suggestive of septic emboli and the presence of a left coxofemoral joint effusion suggestive of septic arthritis. Finally, due to reported breast pain, an ultrasound examination of skin and soft tissue was performed, which showed the presence of a septic collection in the left mammary gland, interpreted as further embolic-septic localization.

Forty-eight hours after the start of vancomycin therapy, control blood cultures were negative, and therapy was continued for 4 weeks, during which the patient experienced significant improvement in clinical symptoms, stable defervescence, and a reduction in inflammatory markers. No surgical procedure involving drainage of the septic collections was performed.

Case Series

DOI: 10.29011/2574-7754/100102

Oritavancin for the Treatment of Infective Endocarditis due to Gram-positive Organism

David A. Terrero Salcedo*, Rima El-Herte, Michele Granada

adult PWID

	Age	Gender	Organism	Diagnosis	Inpatient Antibiotic	Doses of Oritavancin	Vanco MIC	Adverse Reaction	Cure
1	44	M	MSSA	MV Endocarditis	Cefazolin	4	2	None	Yes
2	30	M	MRSA	TV Endocarditis	Vancomycin/Ceftaroline**	1	2	None	ND
3	24	F	MRSA	MV Endocarditis with embolization	Daptomycin	1	2	Eosinophilia/Anaphylaxis	Yes
4	36	M	GAS/GFS	TV Endocarditis / Skin Abscesses	Cefazolin	4	NR	None	Yes
5	32	F	MSSA	TV Endocarditis with embolization	Cefazolin/Vancomycin**	1	2	None	ND

**: First antimicrobial agent represents the initial choice which was later switched to a second agent.

Abbreviations: M: Male, F: Female, MV: Mitral Valve, TV: Tricuspid Valve, MSSA: Methicillin-Sensitive Staphylococcus aureus, MRSA: Methicillin-Resistant *Staphylococcus aureus*, GAS: Group A *Streptococcus*, GFS: Group F *Streptococcus*, NR: Not Reported, ND: Not Determined.

Texidor *et al. BMC Infectious Diseases* (2024) 24:127
https://doi.org/10.1186/s12879-023-08725-8

BMC Infectious Diseases

RESEARCH Open Access

Oritavancin as sequential therapy for Gram-positive bloodstream infections

Williams Monier Texidor[1,2†], Matthew A. Miller[1,3,4*†], Kyle C. Molina[1,2,4†], Martin Krsak[4], Barbara Calvert[1], Caitlin Hart[1], Marie Storer[1] and Douglas N. Fish[1]

- **Methods** We conducted a retrospective cohort study evaluating adult patients admitted to University of Colorado Hospital from March 2016 to January 2022 who received ≥ 1 oritavancin dose for treatment of Gram-positive BSI.
- Patients were excluded if the index culture was drawn at an outside facility or were > 89 years of age.
- The primary outcome was a 90-day composite failure (clinical or microbiological failure) in those with 90-day follow-up. Secondary outcomes included individual components of the primary outcome, acute kidney injury (AKI), infusion-related reactions (IRR), and institutional cost avoidance.

Table 1 Patient demographics and treatment details

Variable	N = 72
Age (years), mean (SD)	54 (16)
Male sex, n (%)	44 (61)
Race, n (%)	
White	46 (64)
Hispanic	15 (21)
Black	5 (7)
Body mass index (kg/m^2), mean (SD)	28 (8)
Charlson Comorbidity Index, median (IQR)	3 (1–5)
Index organism(s), n (%)	
S. aureus	49 (68)
Methicillin-resistant	12 (17)
Streptococcus spp.	19 (26)
Beta-hemolytic	13 (18)
Viridans group & other *Streptococcus* spp.[a]	6 (8)
Enterococcus spp.	7 (10)
Vancomycin-resistant	4 (6)
Coagulase-negative *Staphylococcus* spp.	6 (8)
Other[b]	4 (6)
Infectious diseases consult, n (%)	71 (99)
Prior antibiotics therapy, n (%)	
Vancomycin	64 (89)
Ceftriaxone	36 (50)
Cefazolin	35 (49)
Linezolid	18 (25)
Ampicillin	10 (14)
Ceftaroline	7 (10)
Daptomycin	6 (8)
Days of antibiotics prior to oritavancin dose, median (IQR)	11 (5–17)
Bloodstream infection clearance prior to oritavancin administration[c], n (%)	69 (99)
Oritavancin dose, n (%)	
800 mg once	4 (6)
1200 mg once	53 (74)
1200 mg, followed by 1200 mg	5 (7)
1200 mg, followed by 800 mg	10 (14)
Hospital LOS, median (IQR)	17 (8–24)

Texidor et al. BMC Infectious Diseases (2024) 24:127
https://doi.org/10.1186/s12879-023-08725-8

BMC Infectious Diseases

RESEARCH Open Access

Oritavancin as sequential therapy for Gram-positive bloodstream infections

Williams Monier Texidor[1,2†], Matthew A. Miller[1,3,4*†], Kyle C. Molina[1,2,4†], Martin Krsak[4], Barbara Calvert[1], Caitlin Hart[1], Marie Storer[1] and Douglas N. Fish[1]

Conclusions The use of oritavancin may be an effective sequential therapy for Gram-positive BSI to facilitate early discharge resulting in institutional cost avoidance.

- **Results** Overall, 72 patients were included. Mean ± SD age was 54 ± 16 years, 61% were male, and 10% had IE. Organisms most commonly causing BSI were *Staphylococcus aureus* (68%, 17% methicillin-resistant), followed by *Streptococcus* spp. (26%), and *Enterococcus* spp. (10%).
- Patients received standard-of-care antibiotics before oritavancin for a median (IQR) of 11 (5–17) days. Composite failure in the clinically evaluable population (n = 64) at 90-days occurred in 14% and was composed of clinical and microbiological failure, which occurred in 14% and 5% of patients, respectively. Three patients (4%) experienced AKI after oritavancin, and two (3%) experienced an IRR.
- Oritavancin utilization resulted in earlier discharge for 94% of patients corresponding to an institutional cost-avoidance of $3,055,804 (mean $44,938/patient) from 1,102 hospital days saved (mean 16 days/patient).

Table 2 Effectiveness in clinically evaluable patients and secondary outcomes at 90-days

Primary Outcome	
Composite failure at 90-days[a], n (%)	9 (14)
Secondary Outcomes	
Clinical failure[a], n (%)	9 (14)
All-cause mortality	8 (13)
Initiation of Gram-positive antibiotic for presumed failure	1 (2)
Index Infection-related readmission	1 (2)
Microbiological failure[a], n (%)	3 (5)
Infection-related readmission[b], n (%)	8 (11)
Acute Kidney Injury[b], n (%)	19 (26)
Prior to Oritavancin administration	19 (26)
AKI after Oritavancin administration	3 (4)
Infusion-related reactions[b], n (%)	2 (3)
Loss to follow-up[b], n (%)	8 (11)

antibiotics

MDPI

Systematic Review

The Clinical Efficacy of Multidose Oritavancin: A Systematic Review

Antibiotics **2023**, *12*, 1498. https://doi.org/10.3390/antibiotics12101498

Giammarco Baiardi [1,2,†], Michela Cameran Caviglia [1,2,†], Fabio Piras [1,2,†], Fabio Sacco [1,2,†], Roberta Prinapori [3], Maria Luisa Cristina [4,5], Francesca Mattioli [1,2,*,‡], Marina Sartini [4,5,‡] and Emanuele Pontali [3,‡]

- We extracted data concerning clinical response, bacteriologic response, mortality and adverse events (AEs).
- From the 16 included papers, 301 cases of treatment with multidose ORIs were identified.
- Multidose regimens comprised an initial ORI dose of 1200 mg followed by 1200 mg or 800 mg subsequent doses with a varying total number and frequency of reinfusions.
- The most often treated infections and isolates were osteomyelitis (148; 54.4%), ABSSSI (35; 12.9%) and cellulitis (14; 5.1%); and MRSA (121), MSSA (66), CoNS (17), E. faecalis (13) and E. faecium (12), respectively.
- Clinical cure and improvement by multidose ORI regimens were observed in 85% (231/272) and 8% (22/272) patients, respectively.
- Multidose ORI was safe and well tolerated; the most frequent AEs were infusion-related reactions and hypoglycemia.

JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlae174

JAC-Antimicrobial Resistance

Experience with expanded use of oritavancin in a tertiary hospital: indications, tolerability and outcomes

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- Objectives: This study describes the clinical outcomes and adverse reactions related to oritavancin.
- Retrospective study conducted over a 5 year period
- 95 adult patients were included in this study and were followed for 1 year after the last dose of oritavancin

- Results: The most common indication for oritavancin at our institution was osteomyelitis, followed by ABSSI. Other indications were vertebral infection, hardware-associated infection, bacteraemia and infective endocarditis.
- 14% (13/95) of patients developed an adverse reaction to oritavancin during the study period.
- Cure with no recurrence up to 1 year after the last dose of oritavancin was achieved in 74% (53/71) of patients, and the treatment failure rate was 19% (14/71 patients).

Indications	Number of patients	Percentage	Notes
Diabetic foot infection without osteomyelitis	4	4.2	1 *Coryne* sp., 1 MSSA/GBS, 1 GBS/aerobic GP, 1 CoNS
Diabetic foot infection with osteomyelitis	8	8.4	3 polymicrobial (MSSA/GBS/*C. striatum*/CoNS/mixed GP), 1 MRSA, 2 MSSA, 1 MSSA/*C. striatum*, 1 MSSA/mixed GP
Osteomyelitis	19	20	2 MSSA, 2 CoNS, 2 no culture data, 1 MSSA/*C. striatum*, 1 MSSA/GBS, 11 polymicrobial
Vertebral osteomyelitis (with and without hardware)	10	10.5	
Vertebral infection without HW	5	5.2	1 MRSA, 1 MSSA, 2 no culture data, 1 *C. striatum*
Vertebral osteomyelitis with HW	5	5.2	1 CoNS (MRSE), 2 MRSA, 1 VRE, 1 no culture data
HW-associated infection (other than PJI and HW-associated vertebral infection)	7	7.3	2 CoNS, 1 MRSA, 1 MSSA, 1 CoNS/*Coryne* sp., 1 culture negative, 1 no culture data
Prosthetic joint infection	5	5.2	2 CoNS, 1 *Corynebacterium striatum*, 1 *E. faecalis* and *Coryne* sp., 1 *Cutibacterium acnes*
Skin and soft tissue infection	19	20	7 no culture data, 3 MRSA, 1 GBS, 1 MSSA, 1 MRSA/GBS, 1 *C. striatum*/mixed, 3 polymicrobial, 1 MRSA/CoNS, 1 *Cutibacterium acnes*
Bacteraemia	10	10.5	3 MRSA, 6 MSSA (2/6 had polymicrobial with MSSA), 1 GBS
Infective endocarditis (total)	7	7.3	
Native valve endocarditis	4	4.2	3 MSSA (1/3 also with CoNS), 1 MRSA
Prosthetic valve endocarditis	3	3.1	1 *E. faecalis* (susceptible to vancomycin and ampicillin), 1 MSSA, 1 *Coryne* sp.
Other infections (MRSA LVAD drive line infection, postoperative finger infection due to MRSE and MSSA, recurrent abdominal wall abscess due to CoNS and mixed Gram-positive organisms, MSSA, abdominal mesh abscess, MRSA penile implant infection, MSSA deep-brain stimulator generator infection, MSSA wound dehiscence at hip arthroplasty site, breast abscess with culture positive for *Actinomyces*)	8	8.4	1 MSSA/CoNS, 1 MRSA, 1 CoNS/mixed GP, 4 MSSA, 1 *Actinomyces*
Total	95[a]		

Table 4. Adverse reactions

Age	Sex	Diagnosis	Oritavancin doses	Premedication	Reaction during infusion	Management
83	F	Thoracic abscess	1200 mg (2nd dose)	DPH 50 mg PO	Chest and back pain, dyspnoea, dry heaves, chills itching	Admitted Given IV DPH 25 mg
30	M	Endocarditis	1200 mg (2nd dose)	DPH 25 mg PO	Numbness in back radiating to legs, nausea, light-headedness, tachycardia	IV fluid, DPH 50 mg, ondansetron 4 mg, famotidine 20 mg Infusion stopped, discharged home
56	F	PJI	1200 mg (1st dose)	None	Itching, hives, throat swelling	DPH 25 mg IV Infusion stopped
62	M	Foot hardware infection	1200 mg (2nd dose)	None	Dizziness, nausea, light-headed, itching, hives	DPH 25 mg IV, ondansetron 4 mg Infusion stopped
60	F	PJI	1200 mg (3rd dose)	DPH 50 mg, ondansetron 4 mg	Rash—did not occur during the infusion	Topical steroids after biopsy by dermatology for persistent rash
58	F	Vertebral OM	1200 mg (2nd dose)	DPH 50 mg PO	Back and chest pain	DPH 25 mg IV Infusion stopped, discharged home
57	M	Foot infection	1200 mg (2nd dose)	DPH 50 mg PO	Shaking chills, nausea	IV hydrocortisone 100 mg, famotidine 20 mg, ondansetron 4 mg, DPH 25 mg Infusion stopped
71	M	OM frontal bone	1200 mg (1st dose)	DPH 25 mg IV	Facial flushing/redness (2nd dose—leg cramping/spasm, involuntary movements)	DPH 50 mg PO, 25 mg IV DPH Sent to ED, observation
46	F	PJI	3 (1200 mg then 800 mg × 2)	DPH 50 mg PO	Shaking, felt cold, vomited, back pain	Infusion stopped Hydrocortisone 100 mg, DPH 50 mg IV, famotidine 20 mg, ondansetron 4 mg
51	M	Foot OM	2 (1200 mg)	DPH 50 mg PO	Shaking, vomiting, headache, elevated BP	DPH 50 mg, ondansetron 4 mg ER
45	M	Elbow hardware infection	2 (1200 mg)	DPH 50 mg PO	R arm, chest wall pain	50 mg DPH, ondansetron 4 mg Infusion stopped Admitted
60	M	OM toe	2 (1200 mg)	DPH 50 mg PO, acetaminophen 650 mg	Itching	25 mg DPH IV
61	M	Lumbar skin soft tissue infection with hardware	2 (1200, 800 mg)	DPH 50 mg	Phlebitis	

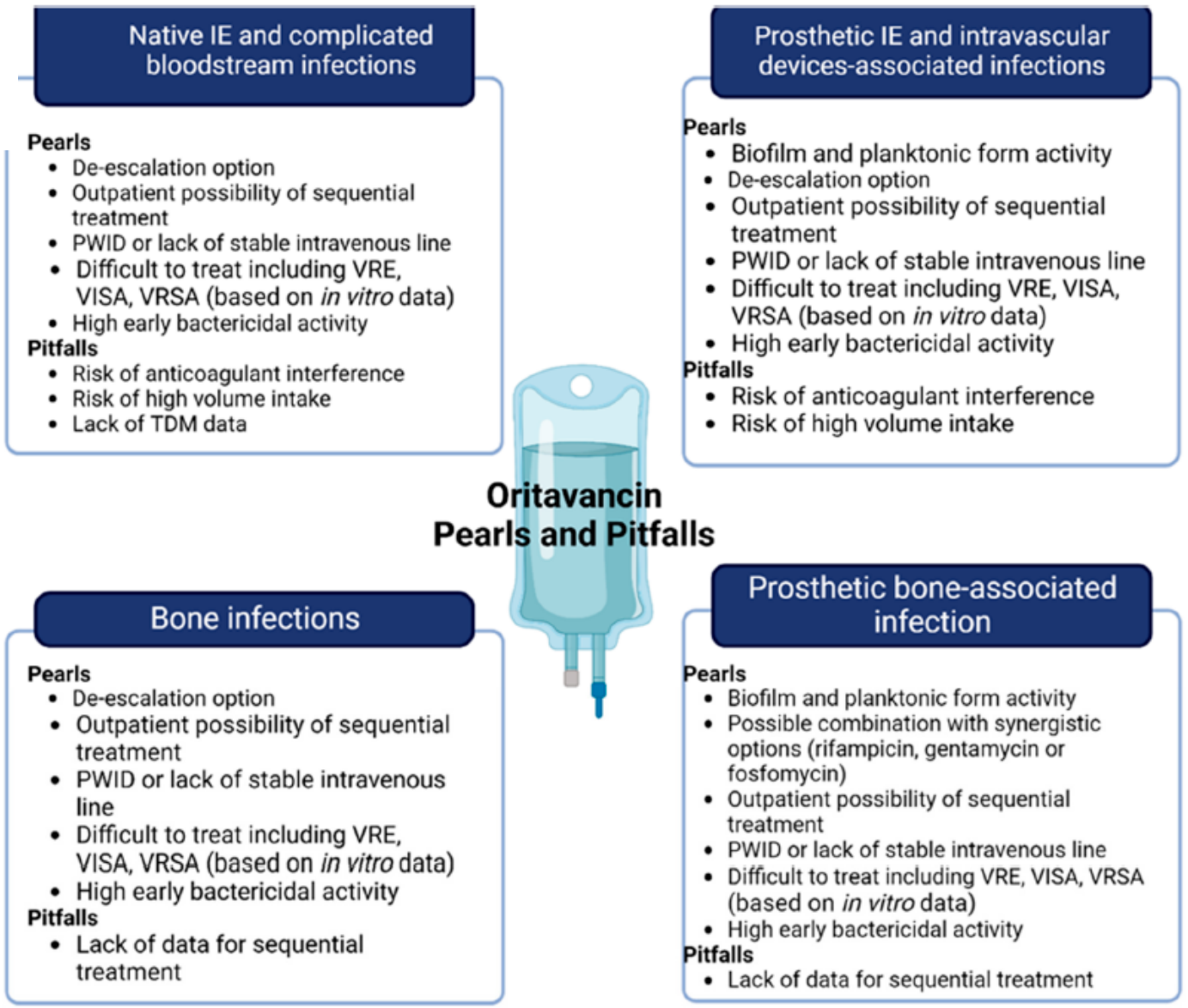
life

MDPI

Review

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

Tommaso Lupia [1,*], Ilaria De Benedetto [2], Roberta Bosio [2], Nour Shbaklo [2], Francesco Giuseppe De Rosa [1,2] and Silvia Corcione [2,3]



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Review

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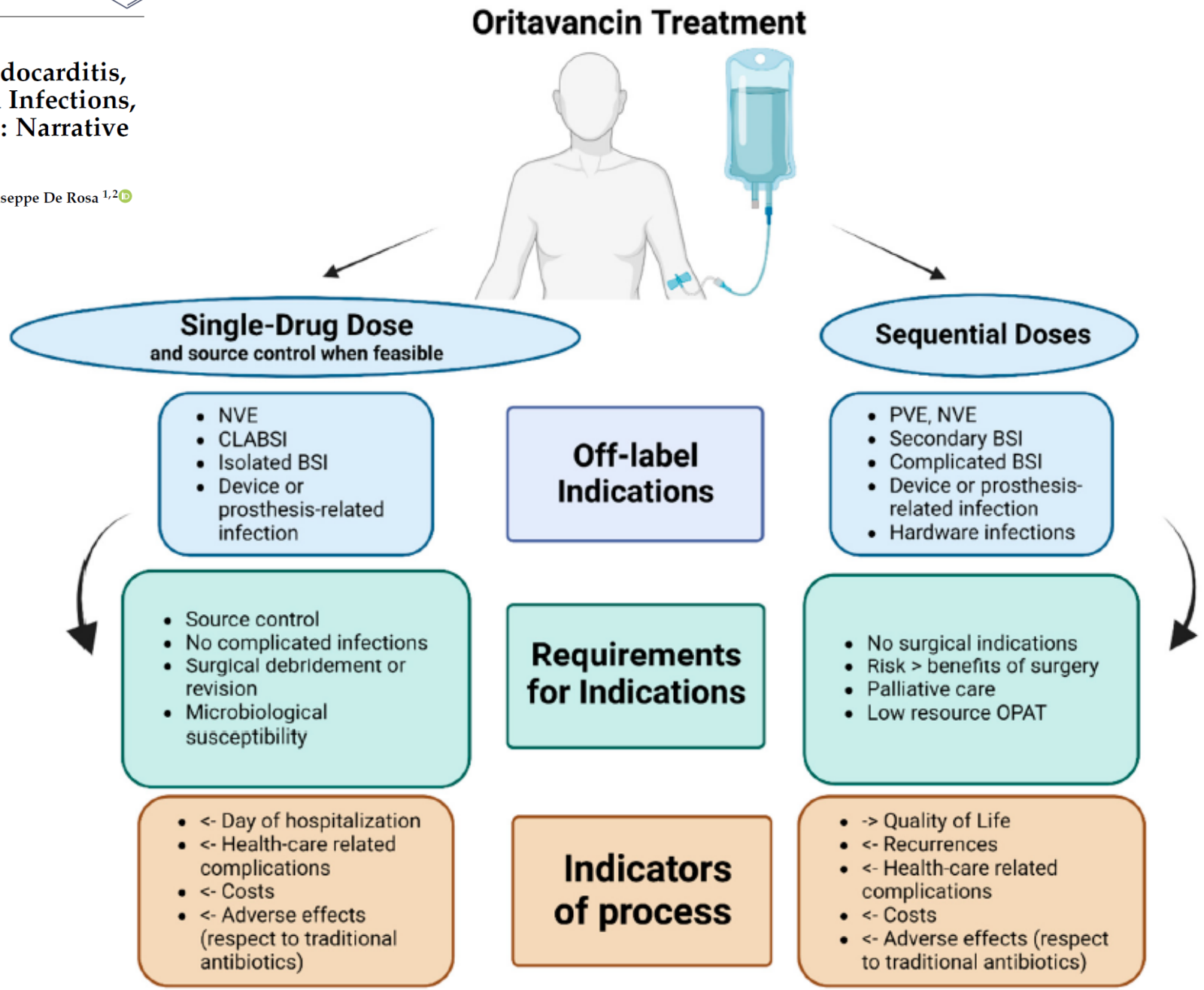

Grazie

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