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Activity of Oritavancin against Gram-Positive Pathogens Causing Bloodstream Infections in the United States over 10 Years: Focus on Drug-Resistant Enterococcal Subsets (2010–2019)

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ABSTRACT Oritavancin displayed potent and stable activity (MIC_{90} range of 0.06 to 0.5 mg/L) over a 10-year period (2010 to 2019) against Gram-positive pathogens that cause bloodstream infections (BSI), including methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant subsets of *Enterococcus* spp. Daptomycin and linezolid were also active against methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* (VRE). Only oritavancin and linezolid remained active against *Enterococcus faecium* isolates displaying an elevated daptomycin MIC (i.e., 2 to 4 mg/L). Proportions of methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus* within the respective *S. aureus* and enterococcal populations decreased over this period.

KEYWORDS lipoglycopeptides, *E. faecium*, VRE, VanA, VanB, vancomycin resistance, daptomycin resistance

Bloodstream infections (BSI) are a major cause of morbidity and mortality among healthcare- and community-associated infections. In this scenario, the emergence and global spread of multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), and carbapenem-resistant *Enterobacterales* imposes a serious challenge for treating BSI caused by these pathogens (1–3).

Oritavancin is a lipoglycopeptide agent with a prolonged half-life and concentration-dependent bactericidal activity against clinically relevant Gram-positive pathogens (4). Previous studies have demonstrated that, in addition to acting against methicillin-susceptible *S. aureus* (MSSA), streptococci, and vancomycin-susceptible enterococci isolates, oritavancin shows potent activity against resistant isolates, such as MRSA and VRE (5–8).

The efficacy and safety of a single 1,200-mg dose of oritavancin over a 3-h infusion (Orbactiv) was demonstrated previously in clinical trials (SOLO I and SOLO II studies) for treating patients with acute bacterial skin and skin structure infection (ABSSSI) (4, 9, 10). More recently, the same oritavancin dose (1,200 mg) with a shorter infusion duration time (1 h; Kimyrsa) was approved by the US FDA (11, 12), providing additional flexibility in treating patients with moderate or severe ABSSSI. This study evaluated the activity of oritavancin against a collection of Gram-positive pathogens and resistant subsets causing BSI in US medical during a 10-year (2010 to 2019) period. This study expands on a previous analysis of oritavancin activity against US and European *Enterococcus* species isolates during 2011 to 2014 (5).

Throughout 2010 to 2019, 15,403 Gram-positive bacterial pathogens causing BSI (1 per patient episode) were collected from 36 medical centers across all 9 US Census Divisions. Bacterial confirmatory identification was performed by JMI Laboratories (North Liberty, IA) using matrix-assisted light desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and standard microbiology methods, such as bile

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solubility and susceptibility to optochin (see the Table 1 footnotes for a list of all isolates included in the study). Susceptibility testing was performed by broth microdilution following CLSI methods (13), using either dry-form (2010 to 2014) (Thermo Fisher; Bedford, MA) or frozen-form (2015 to 2019) panels (JMI Laboratories). MIC interpretations were based on CLSI criteria (14).

S. aureus (48.7%) alone comprised almost half of Gram-positive pathogens. The proportion of methicillin resistance among *S. aureus* varied from 46.6% to 42.3%, and these rates appeared to trend lower over time (Table 2). This trend was also noted in other regional and national surveillance programs during the 2000s, likely as a result of an increasing emphasis on hospital infection prevention, stewardship programs, and activities directed toward healthcare quality improvement (2, 15–18). Similarly, a progressive decrease in the rate of methicillin resistance among coagulase-negative *Staphylococcus* (MRCoNS) BSI was noted. Oritavancin MIC_{50} values against *S. aureus* ranged from 0.015 to 0.03 mg/L, and MIC_{90} values were 0.06 mg/L irrespective of methicillin susceptibility (Table 1). Oritavancin susceptibility rates of >99.5% were observed during this period for *S. aureus* (99.5% in 2010 to 2011). Oritavancin displayed MIC_{50} values of 0.03 to 0.06 mg/L against CoNS. Oritavancin inhibited 98.4% to 100.0% of CoNS isolates at ≤0.12 mg/L, except during 2018 to 2019 (95.3% susceptible). Oritavancin susceptibility remained stable (>95%) across the years against MSSA, MRSA, methicillin-susceptible CoNS, and MRCoNS, and was comparable to vancomycin, daptomycin, and linezolid (see Table S1 in the supplemental material).

Enterococcus spp. comprised 18.8% (2,895 out of 15,403) of Gram-positive pathogens causing BSI, where *E. faecalis* was the most common species (59.0%), followed by *E. faecium* (37.4%). VRE rates within *E. faecalis* decreased over time, from 4.5% (2010 to 2011) to 2.2% (2018 to 2019). Likewise, vancomycin resistance (from 79.6% to 62.8%) and ampicillin resistance (from 92.6% to 79.2%) decreased in *E. faecium* (Table 2). Ampicillin resistance and VRE phenotypes were displayed by most *E. faecium* (87.3% were ampicillin resistant and 72.5% were VRE), whereas only 3.6% of *E. faecalis* were resistant to vancomycin and none were resistant to ampicillin (Table S2). The decline in VRE as a proportion of total enterococcal infections may be due to the same reasons as described above for MRSA (2, 19). The past increase in VRE in the US was mostly due to the expansion of *E. faecium* clonal complex 17 (20). The increase in ampicillin and vancomycin susceptibility may indicate a change in the epidemiology of *E. faecium* causing BSI in the United States. However, this epidemiology information was not captured for this large collection.

Oritavancin activity against *E. faecalis* and *E. faecium* was stable between 2010 and 2019. Consistent MIC_{50} values of 0.015 mg/L and MIC_{90} values of 0.03 to 0.06 mg/L were observed in all years against *E. faecalis*. Oritavancin inhibited 96.2% (in 2010 to 2011) to 99.1% (in 2016 to 2017) of *E. faecalis* at ≤0.12 mg/L (Table 1). *E. faecium* displayed MIC_{50}/MIC_{90} values of 0.03/0.12 mg/L during the 2010–2011 and 2012–2013 periods, whereas MIC_{50}/MIC_{90} values of 0.015/0.06 mg/L were seen during the 2016–2017 and 2018–2019 periods. Oritavancin susceptibility rates remained stable against *E. faecium* across all time periods (97.6% to 98.6%). Many antimicrobials showed activity (>95%) against *E. faecalis*, such as ampicillin, daptomycin, linezolid, vancomycin, and oritavancin, while only daptomycin, linezolid, and oritavancin remained active against *E. faecium* (Table S2).

Oritavancin inhibited 97.7% of VanA and 100% of VanB *E. faecium* at ≤0.12 mg/L. In contrast, only 32.7% of *E. faecalis* isolates displaying the VanA phenotype were inhibited by oritavancin at ≤0.12 mg/L. VRE *E. faecalis* showed oritavancin MIC_{50} values ranging from 0.12 to 0.25 mg/L, whereas MIC_{50} values ranged from 0.015 to 0.03 mg/L against VRE *E. faecium*. The greater activity of oritavancin against *E. faecium* compared to *E. faecalis* is not well understood. Expression of *vanZ* or changes in LiaS sensor kinase were reported as possible explanations (21).

Almost half (49.9%) of *E. faecium* displayed daptomycin MICs of 2 to 4 mg/L, and 9 (0.8%) isolates were resistant (MIC, ≥8 mg/L; Table 1). The rates of *E. faecium* displaying elevated daptomycin MICs showed a progressive decrease over the study years,

TABLE 1 Oritavancin activity and occurrence of resistance phenotypes among Gram-positive isolates that cause BSI in US medical centers (2010 to 2019)[a]

Organism or organism group (no. of isolates)	Oritavancin MIC_{50}/MIC_{90} (mg/L) and % susceptible (CLSI[b]) per yr group												
	2010–2011		2012–2013		2014–2015		2016–2017		2018–2019		All yrs		
	MIC_{50}/MIC_{90}	%S	MIC_{50}/MIC_{90}	%S	MIC_{50}/MIC_{90}	%S	MIC_{50}/MIC_{90}	%S	MIC_{50}/MIC_{90}	%S	MIC_{50}/MIC_{90}	%S	MIC range (mg/L)
S. aureus (7,498)	0.03/0.06	99.5	0.03/0.06	100.0	0.015/0.06	99.9	0.015/0.06	99.9	0.03/0.06	99.9	0.03/0.06	99.8	≤0.008–0.25
MRSA (3,226)	0.03/0.06	99.8	0.03/0.06	100.0	0.015/0.06	99.8	0.015/0.06	99.7	0.03/0.06	100.0	0.03/0.06	99.8	≤0.008–0.25
MSSA (4,272)	0.03/0.06	99.2	0.03/0.06	100.0	0.015/0.06	100.0	0.015/0.06	100.0	0.03/0.06	99.9	0.03/0.06	99.8	≤0.008–0.25
CoNS[c] (1,872)	0.03/0.06	99.4	0.03/0.06	100.0	0.03/0.06	99.8	0.03/0.12	98.5	0.06/0.12	95.3	0.03/0.12	98.4	≤0.008–1
MRCoNS (1,163)	0.03/0.06	99.5	0.03/0.06	100.0	0.03/0.06	99.6	0.03/0.12	97.5	0.06/0.12	94.0	0.03/0.12	97.9	≤0.008–0.5
MSCoNS (709)	0.015/0.06	99.2	0.015/0.06	100.0	0.03/0.06	100.0	0.03/0.06	100.0	0.03/0.06	97.0	0.03/0.06	99.2	≤0.008–1
VGS[d] (921)	0.015/0.12	100.0	≤0.008/0.06	100.0	0.015/0.06	100.0	0.015/0.25	99.3	0.015/0.25	93.8	0.015/0.12	98.7	≤0.008–0.5
BHS[e] (1,394)	0.03/0.12	100.0	0.03/0.12	99.1	0.03/0.12	98.6	0.06/0.25	97.1	0.06/0.25	98.2	0.03/0.25	98.5	≤0.008–1
Enterococcus spp. (2,895)	0.015/0.06	97.0	0.015/0.03	98.0	0.015/0.06	98.1	0.015/0.03	99.4	0.015/0.06	98.1	0.015/0.06	97.9	≤0.008–0.5
E. faecalis (1,709)	0.015/0.06	96.2	0.015/0.03	97.4	0.015/0.03	98.3	0.015/0.03	99.1	0.015/0.03	97.8	0.015/0.06	97.5	≤0.008–0.5
Vancomycin-NS (≥8 mg/L) (62)	0.25/0.5	33.3	0.25/-	28.6	0.12/-	50.0	0.12/0.25	75.0	0.25/-	12.5	0.25/0.5	40.3	0.008–0.5
VanA phenotype (53)	0.25/0.5	25.0	0.25/-	16.7	0.25/-	20.0	0.12/0.25	75.0	0.25/-	12.5	0.25/0.5	32.7	0.015–0.5
VanB phenotype (9)	0.015/-	100.0	0.015	100.0	0.015/-	100.0	-	-	-	-	0.015/-	100.0	0.008–0.25
Daptomycin-NS (≥4 mg/L) (8)	0.03/-	100.0	0.03/-	100.0	0.015/-	100.0	0.03	100.0	-	-	0.03/-	100.0	0.008–0.06
Linezolid-NS (≥4 mg/L) (2)	≤0.008	100.0	-	-	-	-	-	-	0.008	100.0	≤0.008/-	100.0	≤0.008
E. faecium (1,082)	0.03/0.12	98.0	0.03/0.12	98.6	0.015/0.12	97.6	0.015/0.06	100.0	0.015/0.06	98.4	0.03/0.06	98.4	≤0.008–0.5
Vancomycin-NS (≥8 mg/L) (784)	0.03/0.12	97.5	0.03/0.12	98.2	0.03/0.12	96.5	0.03/0.06	100.0	0.03/0.06	97.4	0.03/0.12	97.8	≤0.008–0.5
VanA phenotype (755)	0.03/0.12	97.5	0.03/0.12	98.2	0.03/0.12	96.3	0.03/0.06	100.0	0.03/0.06	97.4	0.03/0.12	97.0.8	≤0.008–0.5
VanB phenotype (29)	≤0.008/≤0.008	100.0	≤0.008/-	100.0	≤0.008/-	100.0	-	-	≤0.008/-	100.0	≤0.008/0.03	100.0	≤0.008–0.06
Daptomycin-R (≥8 mg/L) (9)	≤0.008/-	100.0	-	-	≤0.008/-	100.0	0.015/-	100.0	0.06/-	66.7	0.015/-	88.9	≤0.008–0.25
Daptomycin MIC, 2–4 mg/L (540)	0.03/0.12	97.2	0.03/0.12	98.9	0.03/0.12	97.5	0.015/0.06	100.0	0.015/0.06	96.6	0.03/0.12	97.8	≤0.008–0.5
Linezolid-NS (≥4 mg/L) (13)	≤0.008/-	100.0	0.03	100.0	0.12	100.0	0.015/-	100.0	≤0.008/-	100.0	0.015/0.06	100.0	≤0.008–0.12
Ampicillin-R (≥16 mg/L) (945)	0.03/0.12	97.9	0.03/0.12	98.5	0.03/0.12	97.2	0.015/0.06	100.0	0.03/0.06	97.9	0.03/0.12	98.2	≤0.008–0.5
Other *Enterococcus* spp.[f] (104)	≤0.008/0.015	100.0	≤0.008	100.0	≤0.008/0.03	100.0	≤0.008/0.015	100.0	≤0.008/0.015	100.0	≤0.008/0.015	100.0	≤0.008–0.06

[a]MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; MRCoNS, methicillin-resistant coagulase-negative *Staphylococcus*; MSCoNS, methicillin-susceptible coagulase-negative *Staphylococcus*; VGS, Viridans group streptococci; BHS, beta-hemolytic streptococci; R, resistant; NS, nonsusceptible.

[b]Using CLSI (14) breakpoints. The oritavancin-susceptible breakpoint for *S. aureus* was applied to CoNS. The oritavancin-susceptible breakpoint for vancomycin-susceptible *E. faecalis* was applied to all *Enterococcus* species isolates.

[c]Organisms included: *Staphylococcus arlettae* (1), *S. auricularis* (14), *S. capitis* (115), *S. caprae* (10), *S. cohnii* (10), *S. condimenti* (1), *S. epidermidis* (1,133), *S. haemolyticus* (80), *S. hominis* (220), *S. intermedius* (1), *S. lugdunensis* (64), *S. pasteuri* (2), *S. pettenkoferi* (21), *S. pseudintermedius* (3), *S. saprophyticus* (10), *S. schleiferi* (4), *S. sciuri* (1), *S. simulans* (15), *S. warneri* (36), and *Staphylococcus* spp. (131).

[d]Organisms included: *Streptococcus alactolyticus* (2), *S. anginosus* group (89), *S. australis* (6), *S. bovis* group (28), *S. constellatus* (11), *S. cristatus* (7), *S. equinus* (1), *S. gallolyticus* (41), *S. gordonii* (23), *S. infantarius* (1), *S. infantis* (5), *S. intermedius* (12), *S. lutetiensis* (10), *S. mitis* group (393), *S. mutans* (12), *S. parasanguinis* (61), *S. salivarius* group (75), *S. sanguinis* (52), *S. sinensis* (1), *S. vestibularis* (9), and viridans group *Streptococcus* spp. (82).

[e]Organisms included: *Streptococcus agalactiae* (747), *S. canis* (7), *S. dysgalactiae* (143), *S. equi* (1), and *S. pyogenes* (496).

[f]Organisms included: *Enterococcus avium* (15), *E. casseliflavus* (23), *E. durans* (9), *E. gallinarum* (33), *E. hirae* (8), *E. raffinosus* (12), and *Enterococcus* spp. (4).

TABLE 2 Evolution of resistance phenotypes of *Staphylococcus* spp. *and Enterococcus* species isolates from BSI in US medical centers[a]

	Rates of resistance (%) per study period[b]					
Resistance phenotype	**2010–2011**	**2012–2013**	**2014–2015**	**2016–2017**	**2018–2019**	**All yrs**
MRSA	46.6	40.1	43.7	40.4	42.3	43.0
MRCoNS	64.3	62.9	64.7	61.4	58.3	62.1
E. faecalis						
VRE (≥8 mg/L)	4.5	3.6	3.4	3.7	2.2	3.6
VanA phenotype	81.5	85.7	62.5	100.0	100.0	85.5
VanB phenotype	18.5	14.3	37.5	0.0	0.0	14.5
E. faecium						
VRE (≥8 mg/L)	79.6	77.4	67.7	66.5	62.8	72.5
VanA phenotype	96.6	98.2	95.5	96.7	93.9	96.3
VanB phenotype	3.4	1.8	4.5	3.3	6.1	3.7
Daptomycin-R (≥8 mg/L)	0.5	0.0	1.2	1.1	1.6	0.8
Daptomycin MIC, 2–4 mg/L	62.4	60.3	48.2	33.5	31.7	49.9
Linezolid-NS (≥4 mg/L)	1.7	0.7	0.6	1.1	1.1	1.2
Ampicillin-R (≥16 mg/L)	92.6	90.4	87.2	81.3	79.2	87.3

[a]MRSA, methicillin-resistant *Staphylococcus aureus*; MRCoNS, methicillin-resistant coagulase-negative *Staphylococcus*; VRE, vancomycin-resistant *Enterococcus;* R, resistant; NS, nonsusceptible.
[b]Using CLSI (14) breakpoints.

ranging from 62.4% (in 2010 to 2011) to 31.7% (in 2018 to 2019) (Table 2). Oritavancin activity against *E. faecium* with elevated MIC values against daptomycin (2 to 4 mg/L) remained stable throughout the study (MIC_{50}/MIC_{90}, 0.015 to 0.03/0.06 to 0.12 mg/L). Oritavancin inhibited >97% of VRE, linezolid-nonsusceptible, and *E. faecium* displaying elevated daptomycin MICs (2 to 4 mg/L) at ≤0.12 mg/L. Recent pharmacokinetic (PK) analysis provide evidence that multiple oritavancin doses may be beneficial in treating severe infections and can achieve serum concentrations above the *E. faecalis* susceptibility breakpoint of 0.12 mg/L, for over 4 weeks (22, 23). However, clinical studies are needed to evaluate the relationship between PK and clinical outcomes with oritavancin treatment. Another study conducted by Belley and colleagues on the pharmacodynamic activity of oritavancin against daptomycin-nonsusceptible VRE *E. faecium* suggested that a multiple-dose strategy with oritavancin may be effective against daptomycin-nonsusceptible vancomycin-resistant *E. faecium* (24).

Viridans group *Streptococcus* isolates displayed oritavancin MIC_{50}/MIC_{90} values of ≤0.008 to 0.015/0.06 to 0.25 mg/L and susceptibility rates of 93.8% to 100.0% over the study period, while beta-hemolytic *Streptococcus* showed oritavancin MIC_{50}/MIC_{90} values of 0.03 to 0.06/0.12 to 0.25 mg/L and susceptibility rates of 97.1% to 100.0%. The activity of oritavancin and comparator agents against Viridans group *Streptococcus* and beta-hemolytic *Streptococcus* are displayed in the supplemental material (Table S1).

In conclusion, we noted encouraging decreasing trends in MRSA and VRE rates. Oritavancin showed potent and consistent activity against Gram-positive pathogens that cause BSI in US from 2010 to 2019, including multidrug-resistant pathogens such as MRSA, MRCoNS, VRE, and *E. faecium* with elevated daptomycin MIC and reduced susceptibility to linezolid and daptomycin. Further studies are warranted to identify appropriate oritavancin dosing strategies and the role of oritavancin in the armamentarium against either susceptible or multidrug-resistant Gram-positive isolates causing BSI and other severe infections.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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