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Analysis of Oritavancin *In Vitro* Activity against Enterococcal Isolates from US Medical Centers and Resistant Subsets

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Introduction

- Enterococcal infections remain a clinical challenge due to the efficiency of these pathogens at attaining antimicrobial resistance
- Enterococci represent the second and third most common pathogen across all healthcare-associated infections (HAI) in the United States and Europe, respectively. This is also the single most common pathogen among central line-associated bloodstream infection (CLABSIs) in the United States based on the Centers for Disease Control and Prevention's 2011-2014 report
- The vast majority of enterococcal infections are caused by *Enterococcus faecalis* and *Enterococcus faecium*, and *E. faecium*-caused HAIs have become nearly as prevalent as *E. faecalis*-caused HAIs
  - This change in epidemiology is of paramount clinical importance, since *E. faecium* isolates often display a multidrug-resistance (MDR) phenotype
- The lipoglycopeptide oritavancin possesses long-acting activity against Gram-positive bacteria
  - Oritavancin possesses multiple mechanisms of action and a rapid concentration-dependent bactericidal activity
  - Oritavancin inhibits transpeptidation and transglycosylation by binding to the peptidic cross-linking portion of the cell wall and to the peptidoglycan precursor, respectively
  - In addition, oritavancin appears to cause membrane depolarization and permeabilization
- The *in vitro* activities of oritavancin and comparator agents were assessed against *E. faecalis* and *E. faecium* from US hospitals and a global challenge set of enterococci, including vancomycin-nonsusceptible, linezolid-nonsusceptible, and daptomycin-nonsusceptible isolates

Materials and Methods

Bacterial isolates

- A total of 391 *E. faecalis* and 179 *E. faecium* isolates recovered from US hospitals during 2017 were studied
- Isolates were responsible for bloodstream (43.7%), urinary tract (18.1%), skin and skin structure (18.8%) and intra-abdominal infections (18.4%)
- Isolates originated from 31 sites located in 21 states in 9 US census divisions and were submitted to JMI Laboratories (North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program
- A worldwide challenge set of 12 daptomycin-nonsusceptible *E. faecium* isolates were tested, as well as 97 molecularly characterized linezolid-nonsusceptible isolates, including 24 *optrA*-carrying *E. faecalis*
- Isolates were initially identified by the participating laboratory, and identifications were confirmed at JMI Laboratories using matrix assisted laser desorption ionization time of flight technology mass spectrometry (Bruker Daltonics, Bremen, Germany) and/or genome sequencing

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07 (2018) document
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories and contained cation-adjusted Mueller-Hinton broth (CAMHB)
  - Polysorbate-80 (0.002%) was included in the CAMHB when testing oritavancin, while calcium (Ca^{2+}) supplementation (50 mg/L) was used for testing daptomycin
- Quality assurance was performed by concurrently testing the CLSI-recommended quality control reference strain *E. faecalis* ATCC 29212
- Breakpoint criteria for comparator agents were from the CLSI M100 (2018) document
- Screening for gentamicin and streptomycin high-level (HL) resistance used EUCAST methods and criteria
- *E. faecalis* and *E. faecium* displaying vancomycin and teicoplanin MIC results of ≥4 mg/L and ≥8 mg/L, respectively, were classified as VanA phenotype
- *E. faecalis* and *E. faecium* isolates with vancomycin MIC results of ≥4 mg/L and teicoplanin MIC results of ≤8 mg/L were classified as VanB phenotype

Results

- Oritavancin inhibited all *E. faecalis* and *E. faecium* isolates from US medical centers, including those displaying a VanA phenotype, at the susceptible breakpoint for vancomycin-susceptible *E. faecalis* (≤0.12 mg/L) (Table 1)
- Oritavancin (MIC_{50}, 0.015 mg/L) had similar MIC_{50} values against a US collection of vancomycin-susceptible (Table 1) and a global collection of linezolid-nonsusceptible *E. faecalis* (Table 2), including a subset carrying *optrA*
  - In contrast, the MIC_{50} values against vancomycin-nonsusceptible *E. faecalis* were 8-fold higher than that of vancomycin-susceptible, albeit an MIC_{100} value of 0.12 mg/L was noted (Table 1)
- Isolates displaying gentamicin HL resistance phenotype were more common among *E. faecalis* (25.8%) than *E. faecium* (12.8%), but streptomycin HL resistance was more frequent among *E. faecium* (33.0% vs. 16.6% *E. faecalis*) (Table 3)
- Oritavancin ($MIC_{50/90}$, 0.004/0.008 mg/L) showed low MIC_{50} and MIC_{90} values against vancomycin-susceptible *E. faecium*, while oritavancin MIC results ($MIC_{50/90}$, 0.03/0.06 mg/L) were 8-fold higher against VanA-type *E. faecium* (Table 1)
- All *E. faecium* isolates were inhibited by oritavancin at ≤0.12 mg/L
- Similar MIC_{50} results were obtained for oritavancin when tested against daptomycin-nonsusceptible ($MIC_{50/90}$, 0.03/0.25 mg/L) or linezolid-nonsusceptible ($MIC_{50/90}$, 0.015/0.12 mg/L) *E. faecium* (Table 2)
- VanA *E. faecium* showed a multidrug-resistance phenotype in which linezolid and daptomycin remained active (100.0% susceptible) (Table 3)

Conclusions

- Oritavancin showed potent *in vitro* activity against *E. faecalis* and *E. faecium* isolates causing infections, including against VanA phenotype pathogens, in hospitalized patients in US medical centers
- Oritavancin also displayed potent *in vitro* activity against a worldwide challenge set of nonsusceptible isolates
  - All isolates but 1 were inhibited by oritavancin at ≤0.25 mg/L (Table 2)
- Overall, *E. faecalis* isolates remained susceptible to ampicillin, linezolid, daptomycin (100%), and vancomycin (96.9%); however, 25.8% of *E. faecalis* showed gentamicin HL resistance, which may compromise the standard empiric β-lactam-aminoglycoside combination approach for serious invasive infections (Table 3)
- High vancomycin resistance rates were observed among *E. faecium* isolates, and only oritavancin, linezolid, tigecycline, and daptomycin remained active *in vitro* against those isolates (Table 3)
- The potent *in vitro* activity of oritavancin reported against vancomycin-resistant *E. faecium* isolates and linezolid-nonsusceptible isolates suggests that this agent may be considered as part of the therapeutic options against highly resistant *E. faecium*

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Table 1 MIC distribution of oritavancin against *Enterococcus* spp. clinical isolates collected from US medical centers

Organism (no. of isolates)	Number and cumulative % of isolates inhibited at MIC (mg/L) of:								MIC_{50}	MIC_{90}
	0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12		
E. faecalis (391)			7 1.8	74 20.7	179 66.5	101 92.3	20 97.4	10 100.0	0.015	0.03
Vancomycin-susceptible (379)			7 1.8	74 21	179 68.6	99 94.7	17 99.2	3 100.0	0.015	0.03
VanA (11)						1 9.1	3 36.4	7 100.0	0.12	0.12
E. faecium (179)	1 0.6	6 3.9	40 26.3	42 49.7	24 63.1	42 86.6	17 96.1	7 100.0	0.015	0.06
Vancomycin-susceptible (62)		5 8.1	34 62.9	23 100.0					0.004	0.008
VanA (107)			2 1.9	15 15.9	24 38.3	42 77.6	17 93.5	7 100.0	0.03	0.06

Table 2 MIC distribution of oritavancin against a global subset of multidrug-resistant *Enterococcus* spp. clinical isolates

Organism (no. of isolates)	Number and cumulative % of isolates inhibited at MIC (mg/L) of:								MIC_{50}	MIC_{90}
	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	
E. faecalis										
Linezolid-nonsusceptible (33)		7 21.2	15 66.7	5 81.8	1 84.8	2 90.9	2 97.0	0 97.0	1 100.0	0.015	0.12
optrA (24)		5 20.8	13 75.0	4 91.7	1 95.8	1 100.0				0.015	0.03
E. faecium										
Daptomycin-nonsusceptible (12)		1 8.3	3 33.3	2 50.0	1 58.3	1 66.7	4 100.0			0.03	0.25
Linezolid-nonsusceptible (64)		22 34.4	10 50.0	12 68.8	8 81.2	9 95.3	3 100.0			0.015	0.12

Table 3 Activity of oritavancin and comparator antimicrobial agents when tested against *Enterococcus* spp. clinical isolates from US medical centers in the 2017 SENTRY Program

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
E. faecalis (391)									
Oritavancin[b]	0.015	0.03	0.004 to 0.12	100.0					
Ampicillin	1	1	≤0.12 to 4	100.0		0.0	100.0	0.0	0.0
Daptomycin	0.5	1	≤0.25 to 4	100.0					
Linezolid	1	2	0.25 to 2	100.0	0.0	0.0	100.0		0.0
Gentamicin HL[c]							74.2		25.8
Streptomycin HL[c]							83.4		16.6
Tigecycline	0.06	0.12	≤0.015 to 0.25				100.0	0.0	0.0
Teicoplanin	0.5	0.5	≤0.12 to >16	97.2	0.0	2.8	97.2		2.8
Vancomycin	1	2	0.25 to >16	96.9	0.0	3.1	96.9		3.1
VanA *E. faecalis* (11)									
Oritavancin[b]	0.12	0.12	0.03 to 0.12	100.0					
Ampicillin	1	1	0.5 to 1	100.0		0.0	100.0	0.0	0.0
Daptomycin	0.5	0.5	≤0.25 to 0.5	100.0					
Linezolid	1	2	0.5 to 2	100.0	0.0	0.0	100.0		0.0
Gentamicin HL[c]							27.3		72.7
Streptomycin HL[c]							27.3		72.7
Tigecycline	0.06	0.12	0.03 to 0.12				100.0	0.0	0.0
Teicoplanin	>16	>16	>16 to >16	0.0	0.0	100.0	0.0		100.0
Vancomycin	>16	>16	>16 to >16	0.0	0.0	100.0	0.0		100.0
E. faecium (179)									
Oritavancin	0.015	0.06	0.001 to 0.12						
Ampicillin	>16	>16	≤0.12 to >16	19.6		80.4	17.9	1.7	80.4
Daptomycin	1	2	≤0.25 to 4	100.0					
Linezolid	1	2	0.25 to 2	100.0	0.0	0.0	100.0		0.0
Gentamicin HL[c]							87.2		12.8
Streptomycin HL[c]							67.0		33.0
Tigecycline	0.06	0.12	≤0.015 to 0.5				98.3	1.7	0.0
Teicoplanin	>16	>16	≤0.12 to >16	40.2	6.1	53.6	37.4		62.6
Vancomycin	>16	>16	0.5 to >16	34.6	0.0	65.4	34.6		65.4
VanA *E faecium* (107)									
Oritavancin	0.03	0.06	0.004 to 0.12						
Ampicillin	>16	>16	≤0.12 to >16	0.9		99.1	0.9	0.0	99.1
Daptomycin	1	2	≤0.25 to 4	100.0					
Linezolid	1	2	0.5 to 2	100.0	0.0	0.0	100.0		0.0
Gentamicin HL[c]							83.2		16.8
Streptomycin HL[c]							53.3		46.7
Tigecycline	0.06	0.12	≤0.015 to 0.5				98.1	1.9	0.0
Teicoplanin	>16	>16	16 to >16	0.0	10.3	89.7	0.0		100.0
Vancomycin	>16	>16	>16 to >16	0.0	0.0	100.0	0.0		100.0

HL, high level
[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[b] Breakpoint applied to all *E. faecalis* isolates, but approved for vancomycin-susceptible isolates only.
[c] Screening for gentamicin and streptomycin HL resistance applied EUCAST methods and criteria.