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Current Assessment of Oritavancin Activity against Multidrug-Resistant Enterococcal Clinical Isolates

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Introduction

- Enterococci represent the second and third most frequently observed pathogens responsible for healthcare-associated infections (HAI) in the United States and Europe, respectively
- The vast majority of enterococcal infections are caused by *Enterococcus faecalis* and *Enterococcus faecium*, and until a few decades ago, *E. faecalis* comprised 80%–90% of the isolates
  - Although the prevalence of each enterococcal species can vary, *E. faecium*-causing HAIs have become nearly as prevalent as *E. faecalis*
  - This change in epidemiology is of paramount clinical importance, since *E. faecium* isolates often display a multidrug-resistance (MDR) phenotype
- More recently, reports have described the emergence and dissemination of *E. faecium* isolates resistant to both glycopeptides (VRE) and/or aminoglycosides, which precludes using this combination as a standard therapy
- Although linezolid remains the only anti-Gram-positive agent approved by regulatory agencies for treatment of VRE infections, daptomycin has become a first-line option in these cases
- The lipoglycopeptide oritavancin possesses long-acting activity against Gram-positive bacteria
  - Oritavancin inhibits the cell wall synthesis and causes perturbation of the membrane barrier function
- The *in vitro* activities of oritavancin and comparator agents were assessed against a challenge set of enterococci, including vancomycin-nonsusceptible enterococci and isolates exhibiting high-level (HL) aminoglycoside resistance causing infections in US medical centers

Materials and Methods

Bacterial isolates

- A total of 1,138 *E. faecalis* and 457 *E. faecium* collected from US medical centers during 2016–2017 were included
- Isolates were responsible for the following infections:
  - Urinary tract (30.3%)
  - Bloodstream (30.0%)
  - Skin and skin structure (24.7%)
  - Intra-abdominal (10.8%)
  - Other (4.3%)
- Isolates originated from 81 sites located in 36 states in 9 US census divisions and were submitted to JMI Laboratories (North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program
- 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)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines in the Clinical and Laboratory Standards Institute (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 µg/mL) 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, and screening for gentamicin and streptomycin HL resistance used EUCAST methods and criteria

Results

- Overall, oritavancin inhibited 98.9% of all *E. faecalis* at the susceptible breakpoint (≤0.12 µg/mL) for vancomycin-susceptible isolates
  - Oritavancin also inhibited 95.2%–99.6% of *E. faecalis* isolates, regardless of the aminoglycoside phenotype (Table 1)
- A vancomycin-nonsusceptible phenotype was detected in 3.4% of *E. faecalis*, while 29.6% and 14.6% of *E. faecalis* showed gentamicin or streptomycin HL resistance phenotypes (Table 1)
  - All isolates were susceptible to ampicillin (data not shown)
- Equivalent MIC_{50} results (0.015 µg/mL) were obtained for oritavancin, irrespective of the aminoglycoside phenotype
  - In contrast, the MIC_{50} values against vancomycin-nonsusceptible *E. faecalis* were 8-fold higher than that of vancomycin-susceptible (Table 1)
- All but 1 *E. faecium* isolate were inhibited by oritavancin at the susceptible breakpoint for vancomycin-susceptible *E. faecalis* (≤0.12 µg/mL), and oritavancin MIC_{50} and MIC_{90} values were similar when tested against isolates with distinct aminoglycoside phenotypes (Table 2)

Table 1 MIC distribution of oritavancin tested against *E. faecalis* pathogens causing infections in US medical centers

Phenotype (no. of isolates)	No. of isolates and cumulative % inhibited at MIC (µg/mL) of:									MIC_{50}	MIC_{90}
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5		
All (1,138)		32 (2.8)	313 (30.3)	529 (76.8)	182 (92.8)	40 (96.3)	29 (98.9)	9 (99.6)	4 (100.0)	0.015	0.03
Gentamicin-HL-susceptible (800)		30 (3.8)	251 (35.1)	357 (79.8)	122 (95.0)	26 (98.3)	11 (99.6)	3 (100.0)		0.015	0.03
Gentamicin-HL-resistant (337)		2 (0.6)	61 (18.7)	172 (69.7)	60 (87.5)	14 (91.7)	18 (97.0)	6 (98.8)	4 (100.0)	0.015	0.06
Streptomycin-HL-susceptible (771)		21 (2.7)	195 (28.0)	359 (74.6)	146 (93.5)	29 (97.3)	17 (99.5)	4 (100.0)		0.015	0.03
Streptomycin-HL-resistant (166)		2 (1.2)	32 (20.5)	82 (69.9)	23 (83.7)	9 (89.2)	10 (95.2)	4 (97.6)	4 (100.0)	0.015	0.12
Vancomycin-susceptible (1,099)		32 (2.9)	313 (31.4)	527 (79.3)	180 (95.7)	33 (98.7)	12 (99.8)	2 (100.0)		0.015	0.03
Vancomycin-nonsusceptible (38)				1 (2.6)	2 (7.9)	7 (26.3)	17 (71.1)	7 (89.5)	4 (100.0)	0.12	0.5

Screening for gentamicin and streptomycin HL resistance used EUCAST methods and criteria

- The oritavancin MIC_{50} and MIC_{90} values against vancomycin-nonsusceptible *E. faecium* ($MIC_{50/90}$, 0.03/0.06 µg/mL) were 8-fold higher than those obtained against vancomycin-susceptible isolates ($MIC_{50/90}$, 0.004/0.008 µg/mL) (Table 2)
- MIC_{50} and MIC_{90} values of 0.03 and 0.06 µg/mL, respectively, were obtained for oritavancin when tested against vancomycin-nonsusceptible *E. faecium* that showed a susceptible phenotype to gentamicin and streptomycin HL (Table 3)
- Daptomycin ($MIC_{50/90}$, 1/2 µg/mL) and linezolid ($MIC_{50/90}$, 1/2 µg/mL) were active (99.3%–99.6% susceptible) against vancomycin-nonsusceptible *E. faecium* that displayed a susceptible phenotype to gentamicin and streptomycin HL (Table 3)

Table 2 MIC distribution of oritavancin tested against *E. faecium* pathogens causing infections in US medical centers

Phenotype (no. of isolates)	No. of isolates and cumulative % inhibited at MIC (µg/mL) of:									MIC_{50}	MIC_{90}
	≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25		
All (457)	2 (0.4)	12 (3.1)	101 (25.2)	86 (44.0)	72 (59.7)	115 (84.9)	55 (96.9)	13 (99.8)	1 (100.0)	0.015	0.06
Gentamicin-HL-susceptible (406)	2 (0.5)	12 (3.4)	92 (26.1)	79 (45.6)	59 (60.1)	100 (84.7)	50 (97.0)	11 (99.8)	1 (100.0)	0.015	0.06
Gentamicin-HL-resistant (51)			9 (17.6)	7 (31.4)	13 (56.9)	15 (86.3)	5 (96.1)	2 (100.0)		0.015	0.06
Streptomycin-HL-susceptible (293)	1 (0.3)	11 (4.1)	71 (28.3)	58 (48.1)	42 (62.5)	68 (85.7)	34 (97.3)	7 (99.7)	1 (100.0)	0.015	0.06
Streptomycin-HL-resistant (100)		1 (1.0)	12 (13.0)	19 (32.0)	19 (51.0)	29 (80.0)	17 (97.0)	3 (100.0)		0.015	0.06
Vancomycin-susceptible (150)		11 (7.3)	94 (70.0)	40 (96.7)	5 (100.0)					0.004	0.008
Vancomycin-nonsusceptible (307)	2 (0.7)	1 (1.0)	7 (3.3)	46 (18.2)	67 (40.1)	115 (77.5)	55 (95.4)	13 (99.7)	1 (100.0)	0.03	0.06

Screening for gentamicin and streptomycin HL resistance used EUCAST methods and criteria

Table 3 Activity of oritavancin and comparator antimicrobial agents when tested against vancomycin-nonsusceptible *E. faecium* pathogens causing serious infections in US

Phenotype (no. tested) Antimicrobial agent	MIC (µg/mL)		Range	CLSI[a]		
	50%	90%		%S	%I	%R
Gentamicin-susceptible (270)						
Oritavancin	0.03	0.06	0.001–0.25			
Ampicillin	>16	>16	≤0.5–>16	3.0		97.0
Daptomycin	1	2	≤0.25–>8	99.6		
Linezolid	1	2	0.25–8	99.3	0.4	0.4
Streptomycin HL	≤512	>1024	≤512–>1024	68.1		31.9
Streptomycin-susceptible (176)						
Oritavancin	0.03	0.06	0.001–0.25			
Ampicillin	>16	>16	≤0.5–>16	3.3		96.7
Daptomycin	1	2	≤0.25–>8	99.5		
Gentamicin HL	≤128	>512	≤128–>512	88.1		11.9
Linezolid	1	2	0.25–4	99.5	0.5	0.0

[a] Criteria as published by CLSI (2018). Screening for gentamicin and streptomycin HL resistance used EUCAST methods and criteria

Conclusions

- The aminoglycoside HL resistance phenotype did not seem to affect the oritavancin *in vitro* activity; however, a vancomycin-resistance phenotype increased the oritavancin MIC values 8-fold
  - All *E. faecium* and *E. faecalis* isolates were inhibited by oritavancin at ≤0.25 µg/mL and ≤0.5 µg/mL, respectively
- Overall, *E. faecalis* isolates remained susceptible to ampicillin and vancomycin; however, approximately 30% of *E. faecalis* isolates showed a gentamicin HL resistance phenotype, which may compromise the standard empiric β-lactam-aminoglycoside combination approach for serious invasive infections
- While *E. faecium* isolates were more likely than *E. faecalis* isolates to show a vancomycin-nonsusceptible phenotype, only 11.2% of *E. faecium* isolates showed a gentamicin HL resistance phenotype, suggesting that oritavancin may be an option for combination therapy with aminoglycosides against vancomycin-nonsusceptible and gentamicin-HL-susceptible *E. faecium*
- Combination therapy of oritavancin and aminoglycosides for treating severe infections caused by vancomycin-nonsusceptible enterococci in patients hospitalized in US medical centers deserves further investigation

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