Tedizolid In Vitro Activity against a Contemporary Challenge Collection of Multidrug-Resistant Enterococcal Clinical Isolates

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Introduction

- Enterococci are important opportunistic pathogens and common causes of hospital-associated infections (HAIs), resulting in substantial morbidity and mortality
- These pathogens can display a variety of mechanisms for acquired and intrinsic resistance
- The majority of enterococcal infections are caused by *Enterococcus faecalis* and *Enterococcus faecium* and, although *E. faecalis* isolates remain largely susceptible to clinically available agents, this species may cause serious high-inoculum infections, such as infective endocarditis
  - –However, E. faecium-causing HAIs have become nearly as prevalent as E. faecalis HAIs and commonly exhibit multidrug-resistance (MDR) phenotypes
- Tedizolid is an oxazolidinone antibiotic approved by the Food and Drug Administration (2014) for acute bacterial skin and skin structure infections (ABSSSIs) and is currently undergoing a clinical trial for the treatment of pneumonia
- The in vitro activity of tedizolid and comparator agents was assessed against a challenge set of enterococci, including vancomycin-resistant enterococci (VRE) and isolates exhibiting high-level aminoglycoside (gentamicin and streptomycin) resistance (HLAR)

Materials and Methods

Bacterial isolates

- A total of 2,218 enterococci (1,443 *E. faecalis* and 775 *E. faecium*) were collected from US and European (and adjacent) regions during 2016–2017
- Isolates were responsible for the following infections:
  - –Bloodstream (44.8%)
  - –Skin and skin structure (24.0%)
  - –Intra-abdominal (15.6%)
  - –Urinary tract (13.4%)
- Isolates originated from 65 sites located in 15 countries 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 bacterial 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)
  - –Calcium (Ca^{2+}) supplementation (50 mg/L) was included in the CAMHB when testing daptomycin
- Quality assurance was performed by concurrently testing the CLSI-recommended quality control reference strain *E. faecalis* ATCC 29212

Table 1. Antimicrobial activity of tedizolid tested against *E. faecalis* and *E. faecium* clinical isolates recovered from US and European medical centers (2016–2017)

Organism (no. of isolates)[a]	No. and cumulative % of isolates inhibited at MIC (mg/L) of:							MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1		
All *Enterococcus* spp. (2,218)		4 0.2	66 3.2	796 39.0	1,207 93.5	142 99.9	3 100.0	0.25	0.25
VSE (1,886)		1 0.1	44 2.4	653 37.0	1059 93.2	127 99.9	2 100.0	0.25	0.25
VSE-HLAS (1,077)			19 1.8	335 32.9	621 90.5	102 100.0		0.25	0.25
VSE-HLAR (242)			8 3.3	92 41.3	132 95.9	8 99.2	2 100.0	0.25	0.25
VRE (329)		3 0.9	22 7.6	141 50.5	147 95.1	15 99.7	1 100.0	0.12	0.25
VRE-HLAS (136)		2 1.5	15 12.5	54 52.2	61 97.1	4 100.0		0.12	0.25
VRE-HLAR (60)		1 1.7	1 3.3	28 50.0	27 95.0	3 100.0		0.12	0.25
E. faecalis (1,443)		1 0.1	26 1.9	480 35.1	843 93.6	93 100.0		0.25	0.25
VSE (1,413)			25 1.8	467 34.8	829 93.5	92 100.0		0.25	0.25
VSE-HLAS (877)			16 1.8	259 31.4	521 90.8	81 100.0		0.25	0.25
VSE-HLAR (301)			5 1.7	106 36.9	183 97.7	7 100.0		0.25	0.25
VRE (30)		1 3.3	1 6.7	13 50.0	14 96.7	1 100.0		0.12	0.25
VRE-HLAS (4)				3 75.0	0 75.0	1 100.0		0.12	
VRE-HLAR (23)		1 4.3	1 8.7	10 52.2	11 100.0			0.12	0.25
E. faecium (775)		3 0.4	40 5.5	316 46.3	364 93.3	49 99.6	3 100.0	0.25	0.25
VSE (473)		1 0.2	19 4.2	186 43.6	230 92.2	35 99.6	2 100.0	0.25	0.25
VSE-HLAS (200)			3 1.5	76 39.5	100 90.0	21 100.0		0.25	0.25
VSE-HLAR (78)			7 9.0	25 41.0	38 89.7	6 97.4	2 100.0	0.25	0.5
VRE (299)		2 0.7	21 7.7	128 50.5	133 95.0	14 99.7	1 100.0	0.12	0.25
VRE-HLAS (69)		2 2.9	4 8.7	18 34.8	43 97.1	2 100.0		0.25	0.25
VRE-HLAR (36)				18 50.0	15 91.7	3 100.0		0.12	0.25

[a] VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci; HLAS, screen-negative results for gentamicin and streptomycin high-level resistance; HLAR, screen-positive results for gentamicin and streptomycin high-level resistance.

- Breakpoint criteria for comparator agents were from the CLSI M100 (2018) document
- Screening for HLAR used EUCAST methods and criteria (gentamicin and streptomycin)

Results

- Overall, tedizolid inhibited all but 3 *E. faecium* isolates at ≤0.5 mg/L (susceptible breakpoint for vancomycin-susceptible *E. faecalis*) (Table 1)
- Similar MIC_{50} and MIC_{90} results (0.12–0.25 mg/L) were obtained for tedizolid against vancomycin-susceptible enterococci (VSE) and VRE, regardless of species (Tables 1 and 2)
- VRE isolates were more frequently observed among *E. faecium* isolates from the United States (64.8%) than Europe (19.1%); however, HLAR were higher among enterococci from Europe (52.9%) than those recovered from US medical centers (35.6%) (data not shown)
- Linezolid and daptomycin also displayed similar MIC_{50} and MIC_{90} values (1–2 mg/L) against enterococci, regardless of vancomycin susceptibility, but daptomycin MIC_{50} values were slightly lower against *E. faecalis* (0.5 mg/L) than *E. faecium* (1.0 mg/L) (Table 2)
- *E. faecalis* remained highly susceptible (≥99.9%) to tedizolid, linezolid, daptomycin, vancomycin, and ampicillin (Table 2)
- Overall, daptomycin and linezolid (96.2–99.7% susceptible) were active against *E. faecium*, while tedizolid ($MIC_{50/90}$, 0.25/0.25 mg/L) inhibited 99.6% of all *E. faecium* isolates at ≤0.5 mg/L
- A total of 4.6% of *E. faecium* showed a VRE and HLAR phenotype, and similar tedizolid MIC results were obtained against different patterns ($MIC_{50/90}$, 0.12-0.25/0.25-0.5 mg/L)
- The daptomycin MIC_{50} results against the HLAR *E. faecium* population was 2-fold higher than that observed for the HLAS group, regardless of the vancomycin resistance pattern (Table 1)

Conclusions

- Tedizolid showed potent in vitro activity against both *E. faecalis* and *E. faecium* isolates from US and European medical centers
- Similar tedizolid activity was observed among enterococcal isolates exhibiting different vancomycin and/or aminoglycoside resistance patterns
- These results indicate that tedizolid may be considered for treating serious enterococcal infections, including MDR enterococci

Table 2. MIC_{50}, MIC_{90}, and susceptibility rates of tedizolid and comparators against *Enterococcus* spp. clinical isolates according to vancomycin and high-level aminoglycoside resistance patterns

Organism (no. tested)	Tedizolid			Linezolid			Daptomycin			Ampicillin		
	MIC (mg/L)		%S[b]	MIC (mg/L)		%S[b]	MIC (mg/L)		%S[b]	MIC (mg/L)		%S[b]
Phenotype[a]	50%	90%		50%	90%		50%	90%		50%	90%	
All *Enterococcus spp.* (2,218)	0.25	0.25	—	1	2	99.7	1	2	99.9	1	>16	70.2
VSE (1,886)	0.25	0.25	—	1	2	99.7	1	2	100.0	1	>16	80.6
VSE-HLAS (1077)	0.25	0.25	—	1	2	99.9	1	2	100.0	1	16	90.0
VSE-HLAR (242)	0.25	0.25	—	1	2	98.3	1	2	100.0	1	>16	70.2
VRE (329)	0.12	0.25	—	1	2	99.4	1	2	99.4	>16	>16	10.9
VRE-HLAS (136)	0.12	0.25	—	1	2	99.3	1	2	99.3	>16	>16	5.1
VRE-HLAR (60)	0.12	0.25	—	1	2	100.0	1	2	98.3	>16	>16	38.3
E. faecalis (1,443)	0.25	0.25	100.0	1	2	99.9	0.5	1	100.0	1	2	100.0
VSE (1,413)	0.25	0.25	100.0	1	2	99.9	0.5	1	100.0	1	2	100.0
VSE-HLAS (877)	0.25	0.25	100.0	1	2	99.9	1	1	100.0	1	1	100.0
VSE-HLAR (301)	0.25	0.25	100.0	1	2	99.7	0.5	1	100.0	1	2	100.0
VRE (30)	0.12	0.25	100.0	1	2	100.0	0.5	1	100.0	1	2	100.0
VRE-HLAS (4)	0.12		100.0	0.5		100.0	0.5		100.0	1		100.0
VRE-HLAR (23)	0.12	0.25	100.0	1	1	100.0	0.5	1	100.0	1	2	100.0
E. faecium (775)	0.25	0.25	—	1	2	99.4	1	2	99.7	>16	>16	14.7
VSE (473)	0.25	0.25	—	1	2	99.4	1	2	100.0	>16	>16	22.8
VSE-HLAS (200)	0.25	0.25	—	1	2	100.0	1	2	100.0	>16	>16	46.0
VSE-HLAR (78)	0.25	0.5	—	1	2	96.2	2	2	100.0	>16	>16	7.7
VRE (299)	0.12	0.25	—	1	2	99.3	1	2	99.3	>16	>16	2.0
VRE-HLAS (69)	0.25	0.25	—	1	2	100.0	1	2	100.0	>16	>16	1.4
VRE-HLAR (36)	0.12	0.25	—	1	2	100.0	2	2	97.2	>16	>16	0.0

[a] VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci; HLAS, screen-negative results for gentamicin and streptomycin high-level resistance; HLAR, screen-positive results for gentamicin and streptomycin high-level resistance.
[b] %S, percentage susceptible (CLSI, 2018). "-" breakpoint not available

Acknowledgements

This study was supported by Merck & Co, Inc., Kenilworth, NJ USA.

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Presented at ASM-ESCMID 2018, Lisbon, Portugal, Sept. 4–7, 2018