Activity of Tedizolid and Comparators against *Enterococcus* spp. that Include Multidrug-Resistant Clinical Isolates from European and US Medical Centres (2016–2018)

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Introduction

- Tedizolid is an oxazolidinone-class antimicrobial with potent *in vitro* activity against gram-positive organisms, including vancomycin-resistant enterococci (VRE)
- Tedizolid is approved by the European Medicines Agency and the United States Food and Drug Administration for the treatment of skin and skin structure infections
- Tedizolid is currently under investigation for serious infections, such as pneumonia and bone and joint infections
- *Enterococcus* spp. pathogens are the second most common cause of gram-positive hospital-associated infections with significant mortality rates
- VRE isolates, mainly *Enterococcus faecium*, commonly exhibit a multidrug-resistance phenotype, causing infections with limited treatment options
- This study assessed the *in vitro* activity of tedizolid and comparators against a contemporary collection of enterococci, including VRE and isolates exhibiting high-level aminoglycoside resistance (HLAR)

Materials and Methods

Organism collection

- A total of 3,953 enterococci were collected from US (1,829 isolates) and European (and adjacent) medical centres (2,124 isolates) during 2016–2018
- The isolates were recovered from 73 medical centres, including 33 sites from the United States and 40 sites from Europe and surrounding countries; Figure 1 lists total isolates per participating country
- The most frequent pathogens were *E. faecalis* (*n* = 2,525; 63.9%), followed by *E. faecium* (*n* = 1,300; 32.9%), and other *Enterococcus* spp. (*n* = 128; 3.2%), including *E. avium* (*n* = 39; 1,0%), 37 *E. gallinarum* (*n* = 37; 0.9%), *E. casseliflavus* (*n* = 26; 0.7%), *E. raffinosus* (*n* = 10; 0.3%), *E. hirae* (*n* = 9; 0.2%) and *E. durans* (*n* = 7; 0.2%)
  - *Enterococcus* spp. distribution in Europe and the United States are shown in Figure 1
- Enterococcal isolates determined to be significant by local criteria as the probable cause of bloodstream infection (BSI); pneumonia in hospitalized patients (PIHP); intra-abdominal infection (IAI); skin and skin structure infection (SSTI); and urinary tract infection (UTI) are shown in Figure 2
- Only 1 isolate per patient infection episode was included
- Bacterial identification was confirmed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (Bruker Daltonics, Massachusetts, USA) following the manufacturer's instructions

Antimicrobial susceptibility testing

- Susceptibility (S) testing was performed by broth microdilution according to European Committee of Antimicrobial Susceptibility Testing (EUCAST) methods using 96-well panels manufactured by JMI Laboratories (North Liberty, Iowa, USA)
- Quality assurance was performed by concurrently testing EUCAST quality control (QC) reference strains (*Staphylococcus aureus* ATCC 29213 and *E. faecalis* ATCC 29212)
  - All QC results were within published acceptable ranges
- Susceptibility determinations and HLAR screenings were based on EUCAST breakpoint criteria (2019)

Results

- Overall, tedizolid ($MIC_{50/90}$, 0.25/0.25 mg/L) inhibited all but 6 enterococci at MIC of ≤0.5 mg/L (Table 1)
- Isolates with VRE and/or HLAR phenotypes showed similar tedizolid MIC_{50} (0.25 mg/L) and MIC_{90} results (0.25-0.5 mg/L), regardless of enterococcal species (Table 1)
- Although VRE isolates were more frequently observed in the US hospitals than in European hospitals (66.8% vs.18.3% of *E. faecium* and 3.3% vs. 0.7% of *E. faecalis*, respectively), tedizolid MIC_{50} and MIC_{90} results remained at 0.25 mg/L and 0.25/0.5 mg/L, respectively, against enterococci from US and European hospitals (Figure 1)
- *E. faecalis* showed high S rates (≥98.0%S) to linezolid, vancomycin, and ampicillin, and these agents, except vancomycin, remained active against the combined VRE and HLAR subset (1.6% of all *E. faecalis;* Table 1)
- Tedizolid ($MIC_{50/90}$, 0.25/0.25 mg/L) exhibited MIC results 4- to 8-fold lower than those of linezolid ($MIC_{50/90}$, 1/2 mg/L; 99.7%S) when tested against *E. faecium* (Table 1)
- A total of 8.7% of *E. faecium* isolates were highly resistant (VRE and HLAR), and similar tedizolid MIC results were obtained against the VRE, HLAR, and VRE/HLAR subsets ($MIC_{50/90}$, 0.25/0.25 mg/L; Table 1)
- Five linezolid non-S isolates (MIC, >4 mg/L) were observed, and 4 of those isolates were inhibited by tedizolid at ≤1 mg/L
- Two VRE isolates that showed elevated daptomycin MIC results (MIC >4 mg/L) were inhibited by tedizolid at ≤0.5 mg/L

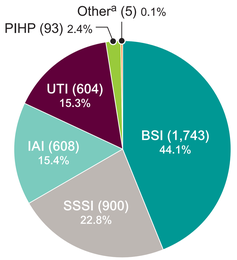
Table 1 Activity of tedizolid and comparators against *Enterococcus* spp. isolates by resistant phenotype

Organism (no. tested) Phenotype	$MIC_{50/90}$ (%S, EUCAST[a])				
	Tedizolid	Linezolid	Daptomycin	Ampicillin	Vancomycin
All (3,953)	0.25/0.25 (-)	1/2 (99.9)	1/2 (-)	1/>16 (71.1)	1/>16 (85.4)
E. faecalis (2,525)	0.25/0.25 (-)	1/2 (>99.9)	0.5/1 (-)	1/1 (100)	1/2 (98.1)
HLAR (754)	0.25/0.25 (-)	1/2 (99.9)	0.5/1 (-)	1/2 (100)	1/1 (94.7)
VRE (48)	0.25/0.25 (-)	1/2 (100)	0.5/1 (-)	1/2 (100)	-
HLAR and VRE (40)	0.25/0.25 (-)	1/2 (100)	0.5/1 (-)	1/2 (100)	-
E. faecium (1,300)	0.25/0.25 (-)	1/2 (99.7)	1/2 (-)	>16/>16 (12.9)	1/>16 (60.6)
HLAR (345)	0.25/0.25 (-)	1/2 (99.4)	1/2 (-)	>16/>16 (3.2)	1/>16 (67.2)
VRE (512)	0.25/0.25 (-)	1/2 (99.8)	1/2 (-)	>16/>16 (1.0)	-
HLAR and VRE (113)	0.25/0.25 (-)	1/2 (100)	1/2 (-)	>16/>16 (0.0)	-
Other *Enterococcus* spp. (128)	0.25/0.5 (-)	1/2 (100)	0.5/1 (-)	≤0.5/2 (92.2)	1/8 (86.7)
Vancomycin non-S (17)	0.25/0.5 (-)	1/2 (100)	1/4 (-)	1/2 (100)	-

HLAR, high-level aminoglycoside resistance; VRE, vancomycin-resistant *Enterococcus*; S, susceptible; -, VRE selected isolates.

[a] Susceptibility rate based on EUCAST v.9.0 (2019) criteria.

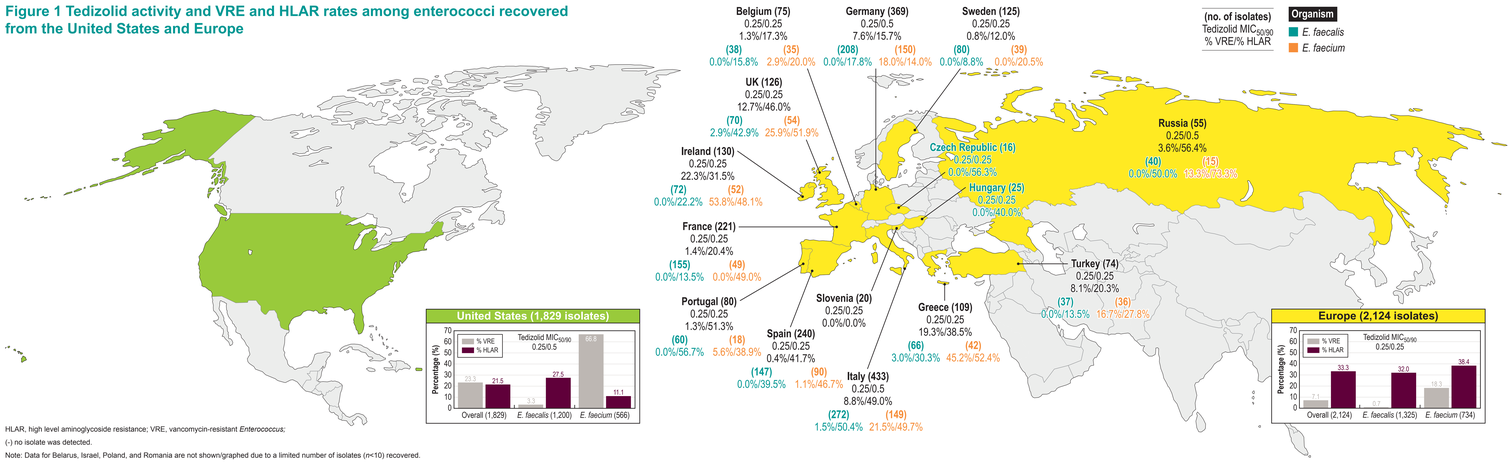
Figure 2 Distribution of enterococci isolates by infection type



[a] Other sites include genital tract (2) and unspecified body site (3).

BSI, bloodstream infection; SSSI, skin and skin structure infection; IAI, intra-abdominal infection; UTI, urinary tract infection; PIHP, pneumonia in hospitalized patient.

Figure 1 Tedizolid activity and VRE and HLAR rates among enterococci recovered from the United States and Europe

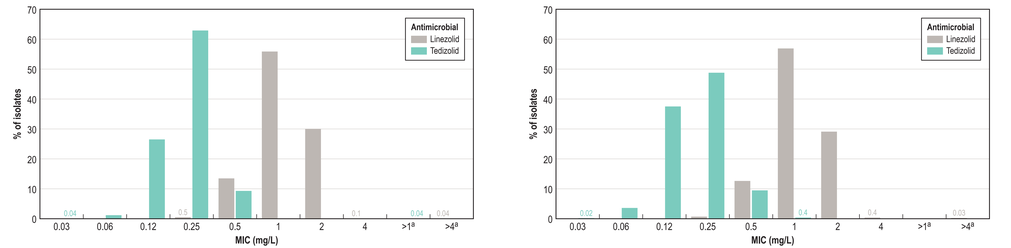


HLAR, high level aminoglycoside resistance; VRE, vancomycin-resistant *Enterococcus*;

(-) no isolate was detected.

Note: Data for Belarus, Israel, Poland, and Romania are not shown/graphed due to a limited number of isolates (*n*<10) recovered.

Figure 3. MIC distribution of oxazolidinones against (A.) *E. faecalis* (*n* = 2,525) and (B.) *E. faecium* (*n* = 1,300) isolates



[a] Greater than the highest concentration tested for linezolid (>4 mg/L) and tedizolid (>1 mg/L)

Conclusions

- Tedizolid showed good activity ($MIC_{50/90}$, 0.25/0.25 mg/L) against this 2016-2018 US and European collection of *Enterococcus* spp. isolates responsible for BSI, PIHP, IAI, SSSI, and UTI
- Overall, tedizolid remained potent against this challenge set of enterococcal clinical isolates, regardless of resistance phenotype (HLAR or VRE)
- Tedizolid was 4- to 8-fold more active than linezolid against both *E. faecalis* and *E. faecium* isolates, regardless of resistance phenotype
- Tedizolid may be considered for treating serious enterococcal infections, granted clinical approval

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The database used for this poster was amended to include the entire 2018 collection.

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