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Activity of Oritavancin and Comparators against a Contemporary Collection of *Enterococcus* spp. Clinical Isolates from Europe (2015–2019)

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Introduction

- *Enterococcus faecalis* is the fourth and *Enterococcus faecium* the seventh most reported bacteria species to the European Antimicrobial Resistance Surveillance Network (EARS-Net) in 2019.
- *E. faecalis* and *E. faecium* may cause difficult-to-treat infections due to their intrinsic and acquired resistance to many antimicrobials.
- Oritavancin is a semisynthetic lipoglycopeptide antibiotic with long-acting activity against Gram-positive microorganisms, including *E. faecalis* and *E. faecium* and vancomycin-resistant strains (VRE).
- Oritavancin was approved by the US-FDA (1- and 3-hours infusion) and the EMA (3-hour infusion) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults, as a single dose of 1200 mg IV.
- Oritavancin holds multiple mechanisms of action: inhibition of the transglycosylation (polymerization), transpeptidation (crosslinking) and disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and rapid cell death.
- This study evaluated the activity of oritavancin and comparator agents against a contemporary (2015–2019) collection of *Enterococcus* spp. clinical isolates from European medical centres.

Materials and Methods

Bacterial isolates

- A total of 3,596 consecutive and non-duplicated *Enterococcus* clinical isolates were collected from 37 medical centres in Western Europe (W-EU; n=3,114; 10 countries) and Eastern Europe (E-EU; n=482; 5 countries) during 2015–2019 (Table 1).
- These isolates were collected from patients with bloodstream infections (BSIs; 1,554 isolates; 43.2%), skin and soft tissue infections (SSTIs; 886 isolates; 24.6%), intra-abdominal infections (IAIs; 545; 15.2%), urinary tract infections (UTIs; 482, 13.4%), and other infection types (129; 3.6%), according to a common surveillance design.
- Only isolates determined to be clinically significant by local criteria as the reported probable cause of infection were included in the program.
- Bacteria were identified at the participant medical centres and confirmed by JMI using standard microbiology methods and/or MALDI-TOF.

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution method according to CLSI guidelines (M07-A11) using 96-well panels manufactured by JMI Laboratories (North Liberty, Iowa, USA).
- Oritavancin minimal inhibitory concentrations (MICs) were determined in the presence of polysorbate-80 (0.002%).
- Susceptibility determinations were based on EUCAST (2021) breakpoint criteria, except for oritavancin (the breakpoint for vancomycin-susceptible *E. faecalis* was applied to all isolates) and daptomycin, which used CLSI (2021) criteria.

Resistant subsets

- *In vitro* activities were evaluated against the following resistance subsets: vancomycin-resistant, ampicillin-resistant, linezolid non-susceptible, daptomycin non-susceptible, and isolates with elevated daptomycin MIC values (2-4 mg/L; *E. faecium* only).
- Vancomycin resistance phenotypes (VanA and VanB) were determined by EUCAST (2021) criteria:
  - VanA: vancomycin MIC >4 mg/L and teicoplanin MIC >2 mg/L
  - VanB: vancomycin MIC >4 mg/L and teicoplanin MIC ≤2 mg/L

Results

- *E. faecalis* (n=2,182) and *E. faecium* (n=1,304) comprised >95% of the collection.
- VRE phenotype was noted in 0.9% of the *E. faecalis* and 19.6% of the *E. faecium* isolates (Figure 1A).
- Overall, the VRE rate was higher in E-EU (13.7%) than W-EU (7.1%).
  - VanA was the most common VRE phenotype (78.7% of all VREs), regardless of species or geographic region.
  - VanB phenotype was more frequently observed among VRE-*E. faecium* isolates from W-EU (n=45, 23.1%; Figure 1B) than E-EU (n=4, 6.6%; Figure 1C).
    - Only 2 (10.5%) *E. faecalis* met the criteria for a VanB phenotype (Figure 1A).
    - 49 *E. faecium* (19.1%; Figure 1A) met the criteria for a VanB phenotype.
- Oritavancin was active against *E. faecalis* isolates ($MIC_{50/90}$, 0.015/0.03 mg/L, 99.3% susceptible), including 57.9% (11/19) of VRE isolates (Table 2).
- *E. faecalis* displayed high susceptibility to ampicillin (100%), linezolid (99.9%), daptomycin (99.6%, using CLSI breakpoints), and vancomycin (99.1%; Table 2).
  - In this setting of multi-resistant pathogens, oritavancin was active against 100.0% of both daptomycin non-susceptible (n=9) and linezolid-resistant (n=2) *E. faecalis* subsets.
- Oritavancin ($MIC_{50/90}$, 0.004/0.015 mg/L) inhibited 99.9% of *E. faecium* isolates at ≤0.12 mg/L, including 99.6% of VRE (n=256) isolates and 75% of linezolid-resistant (n=4) *E. faecium* subset isolates (Table 3).
- Linezolid (99.7%) and daptomycin (100% susceptible dose-dependent using CLSI breakpoints) remained active against *E. faecium* isolates (Table 3).
- Oritavancin inhibited 96.0% of enterococci displaying VanA and 100.0% of enterococci displaying VanB phenotypes at a MIC of ≤0.12 mg/L (Figure 2).

Table 1. Participant countries and the respective occurrence of VRE phenotypes in each European region

Participant country by region	Total no. of isolates contributed	VRE phenotype VanA	VanB
W-EU			
Belgium	158	2	1
France	364		1
Germany	638	13	38
Ireland	201	49	
Italy	796	64	12
Portugal	154	4	2
Spain	398	1	
Sweden	182	1	
Switzerland	5		
UK	218	20	2
E-EU			
Greece	177	29	2
Israel	22	1	3
Poland	24	8	4
Russia	99	3	
Turkey	160	11	4

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against *E. faecalis* isolates from European hospitals.

Antimicrobial agent (No. of isolates)	mg/L MIC_{50}	mg/L MIC_{90}	EUCAST[a] %S	%R
All *E. faecalis (2,182)*				
Oritavancin	0.015	0.03	99.3 [b]	
Ampicillin	1	1	100.0	0.0
Daptomycin	0.5	1	99.6 [d]	0.0
Levofloxacin	1	>4	75.0 [c]	25.0
Linezolid	1	2	99.9	0.1
Teicoplanin	≤2	≤2	99.2	0.8
Vancomycin	1	2	99.1	0.9
VRE (19)				
Oritavancin	0.12	0.25	57.9 [b]	
Ampicillin	1	2	100.0	0.0
Daptomycin	0.5	1	100.0 [d]	0.0
Levofloxacin	>4	>4	10.5 [c]	89.5
Linezolid	0.5	2	100.0	0.0
Teicoplanin	>16	>16	10.5	89.5
Vancomycin	>16	>16	0.0	100.0
VanA (17)				
Oritavancin	0.12	0.25	52.9 [b]	
Ampicillin	1	2	100.0	0.0
Daptomycin	0.5	1	100.0 [d]	0.0
Levofloxacin	>4	>4	5.9 [c]	94.1
Linezolid	0.5	2	100.0	0.0
Teicoplanin	>16	>16	0.0	100.0
Vancomycin	>16	>16	0.0	100.0

Abbreviations: VRE, vancomycin-resistant *Enterococcus*.
[a] Criteria as published by CLSI (2021) and EUCAST (2021).
[b] Using CLSI breakpoint approved for vancomycin-susceptible *E. faecalis* isolates.
[c] Uncomplicated UTI only.
[d] Using CLSI breakpoints.

Table 3. Antimicrobial activity of oritavancin and comparator agents tested against *E. faecium* isolates from European hospitals.

Antimicrobial agent (No. of isolates)	mg/L MIC_{50}	mg/L MIC_{90}	EUCAST[a] %S	%R
All *E. faecium* (1,304)				
Oritavancin	0.004	0.015	99.9 [d]	
Ampicillin	>8	>8	10.0	89.6
Daptomycin	1	2	100.0[b]	0.0
Levofloxacin	>4	>4	11.6 [c]	88.4
Linezolid	1	2	99.7	0.3
Teicoplanin	≤2	>16	84.1	15.9
Vancomycin	≤0.5	>16	80.4	19.6
VRE (256)				
Oritavancin	0.015	0.06	99.6 [d]	
Ampicillin	>8	>8	0.0	100.0
Daptomycin	1	2	100.0[b]	0.0
Levofloxacin	>4	>4	0.0 [c]	100.0
Linezolid	1	2	99.2	0.8
Teicoplanin	>16	>16	19.1	80.9
Vancomycin	>16	>16	0.0	100.0
VanA (207)				
Oritavancin	0.015	0.06	99.5 [d]	
Ampicillin	>8	>8	0.0	100.0
Daptomycin	1	2	100.0[b]	0.0
Levofloxacin	>4	>4	0.0 [c]	100.0
Linezolid	1	2	99.0	1.0
Teicoplanin	>16	>16	0.0	100.0
Vancomycin	>16	>16	0.0	100.0
VanB (49)				
Oritavancin	0.004	0.008	100.0 [d]	
Ampicillin	>8	>8	0.0	100.0
Daptomycin	1	2	100.0[b]	0.0
Levofloxacin	>4	>4	0.0 [c]	100.0
Linezolid	1	2	100.0	0.0
Teicoplanin	≤2	≤2	100.0	0.0
Vancomycin	>16	>16	0.0	100.0
Ampicillin-R (1,168)				
Oritavancin	0.004	0.015	99.9 [d]	
Ampicillin	>8	>8	0.0	100.0
Daptomycin	1	2	100.0[b]	0.0
Levofloxacin	>4	>4	3.3 [c]	96.7
Linezolid	1	2	99.7	0.3
Teicoplanin	≤2	>16	82.3	17.7
Vancomycin	≤0.5	>16	78.1	21.9
Daptomycin MIC, 2-4 mg/L (544)				
Oritavancin	0.004	0.015	99.8 [d]	
Ampicillin	>8	>8	8.3	91.2
Daptomycin	2	2	100.0[b]	0.0
Levofloxacin	>4	>4	9.4 [c]	90.6
Linezolid	1	2	99.4	0.6
Teicoplanin	≤2	>16	86.4	13.6
Vancomycin	≤0.5	>16	83.6	16.4

Abbreviations: VRE, vancomycin-resistant *Enterococcus*; R, resistant.
[a] Criteria as published by EUCAST (2021).
[b] *Enterococcus faecium* susceptible based on a dosage regimen of 8-12 mg/kg (CLSI 2021).
[c] Uncomplicated UTI only.
[d] CLSI breakpoint for vancomycin-susceptible *E. faecalis* have been applied to all *E. faecium*.

Figure 1. Distribution of *Enterococcus* spp. isolates stratified by vancomycin phenotypes and European region (2015–2019)

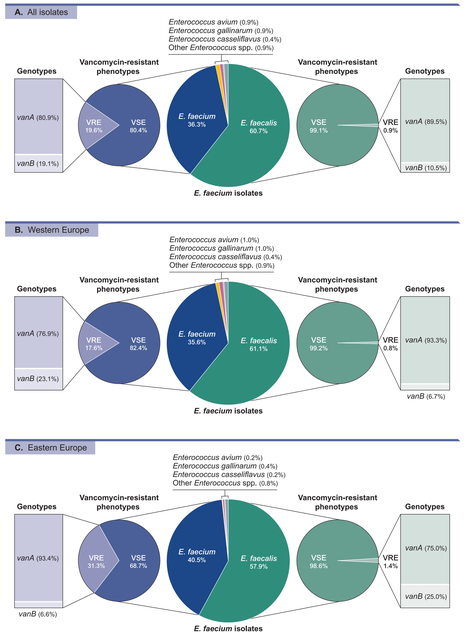
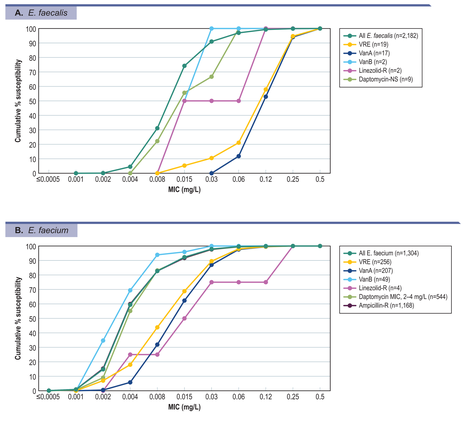


Figure 2. Cumulative MIC distributions of oritavancin tested against *Enterococcus* spp. isolates from European medical centres stratified by resistant subsets (2015–2019)



Abbreviations: VRE, vancomycin-resistant *Enterococcus*; NS, nonsusceptible; R, resistant.

Conclusions

- Rates of VRE phenotype varied among enterococci from W-EU and E-EU, but this phenotype was more frequently observed in *E. faecium* isolates from E-EU.
- Although VanA remains the most common phenotype across all regions, VanB phenotype seems to be mostly detected in W-EU.
- Oritavancin was very active against this contemporary collection of *Enterococcus* isolates from Europe, including isolates non-susceptible to daptomycin and/or resistant to ampicillin, linezolid, and vancomycin.

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