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Trend Analysis of Oritavancin and Comparator Agents' Activities against *Enterococcus* species Causing Infections in US Medical Centers between 2017–2019 and 2022

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Introduction

- *Enterococcus* infections, mainly caused by *E. faecium* and *E. faecalis* species, remain challenging because of intrinsic resistance to various antimicrobials and acquisition of resistance traits.
- Oritavancin is a lipoglycopeptide agent with a prolonged half-life and concentration-dependent bactericidal activity against clinically relevant Gram-positive pathogens, including *Enterococcus*.
- A new formulation of oritavancin (Kimyrsa™) that can be infused over 1 hour as a single dose for the treatment of acute bacterial skin and skin structure infections (ABSSSI) was approved in 2021 by the US FDA.
- Currently, oritavancin is indicated for the treatment of adult patients with infections caused or suspected to be caused by susceptible isolates of designated Gram-positive microorganisms, including vancomycin-susceptible *Enterococcus faecalis*.
- The activity of oritavancin and its comparators against *Enterococcus* spp. and resistant subsets from US medical centers was evaluated comparatively between 2017–2019 and 2022.

Methods

- 2,344 Enterococcus were consecutively collected (1/patient) from 34 US medical centers in 2017–2019 and 2022 periods—28/34 sites were included in both periods.
- Organisms included 1,283 and 246 *E. faecalis,* 573 and 148 *E. faecium*, and 80 and 14 other *Enterococcus* spp. from 2017–2019 and 2022 periods, respectively (Figure 1A).
- *Enterococcus* isolates were collected mainly from bloodstream infections in both periods (Figure 1B).
- Isolates were identified by MALDI-TOF MS and standard microbiology tests then were susceptibility tested by CLSI broth microdilution.
- CLSI clinical breakpoints and VanA/VanB phenotypes were used, as follows:
 - VanA: isolates non-susceptible (NS) to teicoplanin and vancomycin
 - VanB: isolates susceptible (S) to teicoplanin and vancomycin-NS
- Oritavancin breakpoints against vancomycin-susceptible *E. faecalis* were applied to all *Enterococcus*.

Results

All *Enterococcus*

- Overall, oritavancin activity against *Enterococcus* spp. from 2017–2019 ($MIC_{50/90}$, 0.015/0.06 mg/L) was similar to 2022 ($MIC_{50/90}$, 0.015/0.03 mg/L; Table 1).
- At the vancomycin *E. faecalis* susceptible breakpoint (≤0.12 mg/L), oritavancin inhibited 98.9% and 97.5% of all *Enterococcus* spp. isolates from 2017–2019 and 2022, respectively (Table 2).
- Vancomycin and linezolid inhibited 78.6%/76.2% and 99.6%/99.0% of *Enterococcus* spp. from 2017–2019/2022, at the respective breakpoints (Table 2).

E. faecalis

- Oritavancin, vancomycin, linezolid and daptomycin showed stable susceptibility rates (>96%) against *E. faecalis* (Table 2).
- Vancomycin-resistant (VAN-R) *E. faecalis* rates were low in both periods—only 2.5% in 2017–2019 and 2.8% in 2022.
- Oritavancin remained active against 53.1% and 57.1% of VAN-R *E. faecalis* from 2017–2019 and 2022, respectively (Table 2).
 - VanA rates in *E. faecalis* were 2.3% in 2017–2019 and 2.4% in 2022.
 - Oritavancin inhibited the 3 VanB *E. faecalis* isolates at ≤0.03 mg/L.
 - Linezolid and daptomycin remained active against VAN-R *E. faecalis* (100%).

E. faecium

- Notably, an increase in the number of VanB-*E. faecium* isolates was observed in 2022 (18 isolates) compared to an average of 10 isolates per year in 2017–2019 (29 isolates total).
- Overall, similar activity was noted for oritavancin against *E. faecium* from 2017–2019 ($MIC_{50/90}$, 0.015/0.06 mg/L) and 2022 ($MIC_{50/90}$, 0.008/0.06 mg/L; Table 1).
- The susceptibility rates to oritavancin (using VAN-S *E. faecalis* breakpoints) and linezolid remained stable between 2017–2019 (99.1%/99.6%) and 2022 (98.6%/98.0%, respectively), as well as rates of daptomycin susceptible dose-dependent (SDD; 99.5% in 2017–2019 and 96.6% in 2022; Table 2 and Figure 2).
- The highest oritavancin MIC value displayed by *E. faecium* was 0.5 mg/L in 2017–2019 and 0.25 mg/L in 2022, only 1–2 dilutions above the susceptible clinical breakpoint for vancomycin-S *E. faecalis* (≤0.12 mg/L).
- The *E. faecium* susceptibility rate to vancomycin was 35.1% in 2017–2019 and 39.2% in 2022 (Table 2).
 - The VanB phenotype increased from 7.8% in 2017–2019 to 20.0% in 2022.
 - Oritavancin inhibited all VanB and 97.2–98.5% of VanA *E. faecium* at ≤0.12 mg/L.
 - Linezolid inhibited 99.4%/98.6% of VanA *E. faecium* isolates in 2017–2019/2022, respectively.
- The daptomycin-SDD rate decreased against VanA *E. faecium* between 2017–2019 (99.7%) and 2022 (93.1%; Table 2).

Other *Enterococcus* spp.

- Oritavancin (100%S in 2017–2019 and 2022) and comparators (87.5%–100%S in 2017–2019 and 100%S in 2022) were active against other species of *Enterococcus* (Table 2).

Conclusions

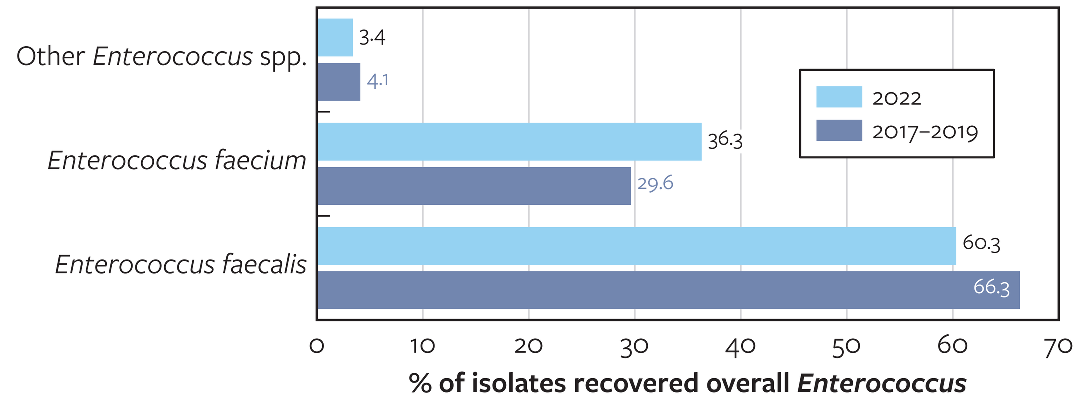
- Oritavancin exhibited potent and stable activity against *Enterococcus* clinical isolates, including VAN-R *E. faecium* and *E. faecalis* in US medical centers.
- Van-R *E. faecalis* rates remain very low in US medical centers (<3%), while Van-R *E. faecium* rates are >60%.
- An increase in VanB *E. faecium* phenotype and a slight decrease in the daptomycin-SDD rates in VAN-R *E. faecium* subsets were noted over time.
- Oritavancin may represent a valuable treatment option for infections caused by *Enterococcus* including VAN-R strains.

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Figure 1. Characterization of *Enterococcus* isolates causing infection in US medical centers (2017–2019 and 2022)

A. By species


Other Enterococcus spp.
Enterococcus faecium
Enterococcus faecalis
3.4
4.1
36.3
29.6
60.3
66.3
2022
2017–2019
0
10
20
30
40
50
60
70
% of isolates recovered overall Enterococcus

B. By infection type

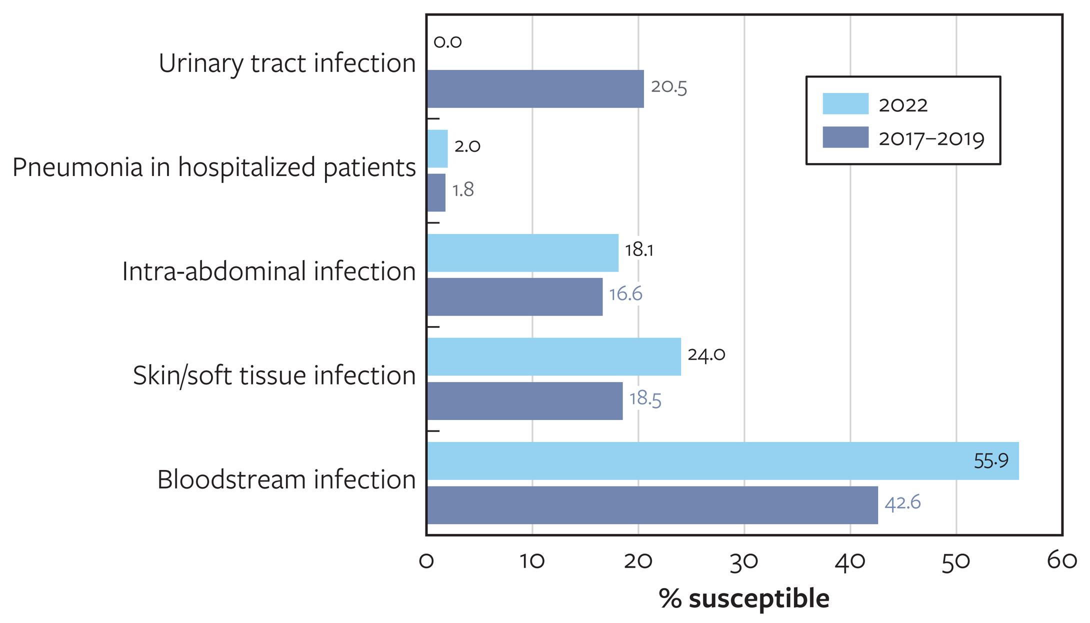
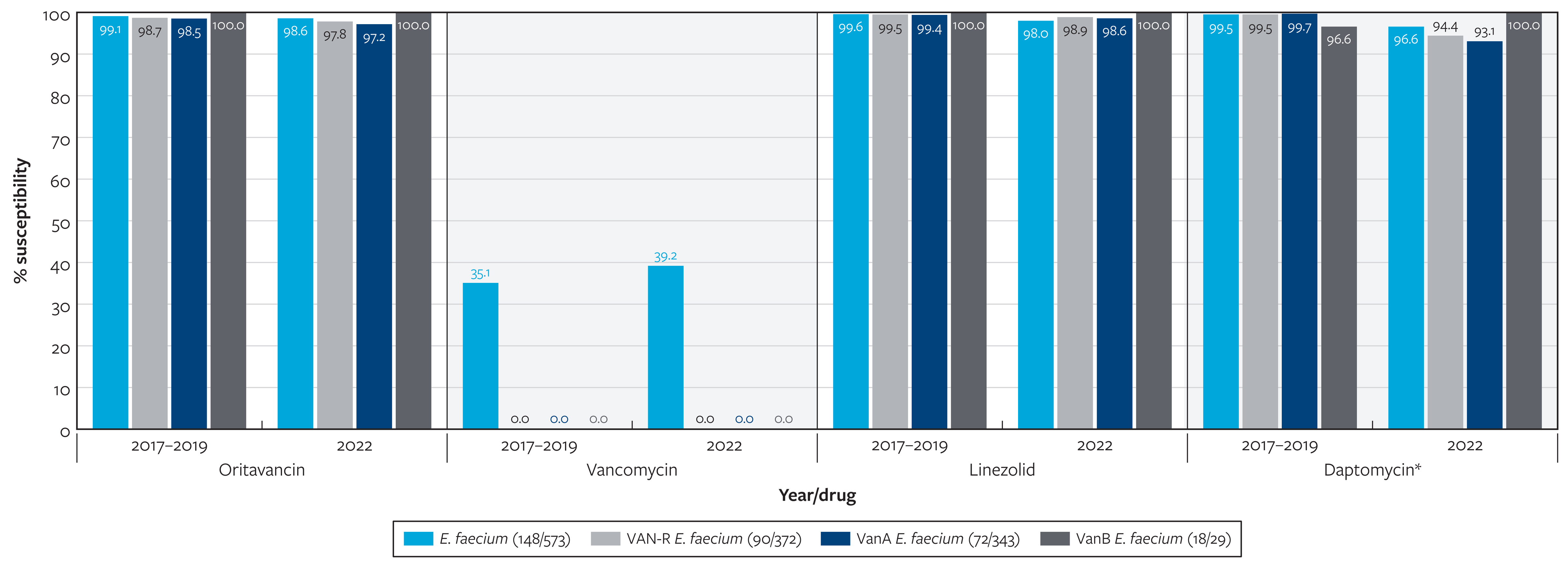

Urinary tract infection
Pneumonia in hospitalized patients
Intra-abdominal infection
Skin/soft tissue infection
Bloodstream infection
0.0
20.5
2.0
1.8
18.1
16.6
24.0
18.5
55.9
42.6
2022
2017–2019
0
10
20
30
40
50
60
% susceptible

Figure 2. Activity of oritavancin and comparator agents against *E. faecium* and resistant subgroups (2017–2019 and 2022)


% susceptibility
100
90
80
70
60
50
40
30
20
10
0
99.1
98.7
98.5
100.0
98.6
97.8
97.2
100.0
35.1
0.0
0.0
0.0
39.2
0.0
0.0
0.0
99.6
99.5
99.4
100.0
98.0
98.9
98.6
100.0
99.5
99.5
99.7
96.6
96.6
94.4
93.1
100.0
2017–2019
2022
Oritavancin
Vancomycin
Linezolid
Daptomycin*
Year/drug
E. faecium (148/573)
VAN-R E. faecium (90/372)
VanA E. faecium (72/343)
VanB E. faecium (18/29)

* Daptomycin bars represent the susceptible-dose dependent (SDD) category of MIC values ≤4 mg/L.

Table 1. Activity of oritavancin and comparator agents against *Enterococcus* spp collected from US medical centers in 2017–2019 and 2022

Organism group (no. of isolates 2017–2019/2022)	2017–2019								2022							
	Oritavancin		Vancomycin		Linezolid		Daptomycin		Oritavancin		Vancomycin		Linezolid		Daptomycin	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Enterococcus spp. (1,936/408)	0.015	0.06	1	>16	1	2	1	2	0.015	0.03	1	>16	1	2	1	2
E. faecalis (1,283/246)	0.015	0.03	1	2	1	2	0.5	1	0.015	0.03	1	2	1	2	1	1
VAN-R *E. faecalis* (32/7)	0.12	0.5	>16	>16	1	2	0.5	1	0.12	—	>16	—	1	—	0.5	—
VanA *E. faecalis* (30/6)	0.12	0.5	>16	>16	1	2	0.5	1	0.12	—	>16	—	1	—	0.5	—
VanB *E. faecalis* (2/1)	0.015	—	>16	—	1	—	0.5	—	0.015	—	>16	—	0.5	—	0.5	—
E. faecium (573/148)	0.015	0.06	>16	>16	1	2	1	2	0.008	0.06	>16	>16	1	2	1	2
VAN-R *E. faecium* (372/90)	0.03	0.06	>16	>16	1	2	1	2	0.015	0.06	>16	>16	1	2	1	2
VanA *E. faecium* (343/72)	0.03	0.06	>16	>16	1	2	1	2	0.03	0.06	>16	>16	1	2	1	2
VanB *E. faecium* (29/18)	0.008	0.03	>16	>16	1	2	1	2	0.004	0.015	>16	>16	1	1	1	2
Other *Enterococcus* spp. (80[a]/14[b])	0.008	0.015	0.5	8	1	2	1	2	0.004	0.015	0.5	4	1	2	0.5	0.5

[a] Organisms include in 2017–2019: *Enterococcus avium* (31), *E. casseliflavus* (16), *E. gallinarum* (17), *E. hirae* (3), and *E. raffinosus* (13).
[b] Organisms include in 2022: *Enterococcus avium* (8), *E. casseliflavus* (1), *E. gallinarum* (2), and *E. raffinosus* (3).

Table 2. Oritavancin and comparator agents' susceptibility rates against *Enterococcus* spp. and subgroups

Organism group (no. of isolates 2017–2019/2022)	2017–2019				2022			
	CLSI[a] %S				CLSI[a] %S			
	ORI[c]	VAN	LZD	DAP	ORI[c]	VAN	LZD	DAP
Enterococcus spp. (1,936/408)	98.9	78.6	99.6	[b]	97.5	76.2	99.0	[b]
E. faecalis (1,283/246)	98.7	97.5	99.8	99.4	96.7	97.2	99.6	99.2
VAN-R *E. faecalis* (32/7)	53.1	0	100	100	57.1	0	100	100
VanA *E. faecalis* (30/6)	50	0	100	100	50	0	100	100
VanB *E. faecalis* (2/1)	100	0	100	100	100	0	100	100
E. faecium (573/148)	99.1	35.1	99.6	99.5[d]	98.6	39.2	98.0	96.6[d]
VAN-R *E. faecium* (372/90)	98.7	0	99.5	99.5[d]	97.8	0	98.9	94.4[d]
VanA *E. faecium* (343/72)	98.5	0	99.4	99.7[d]	97.2	0	98.6	93.1[d]
VanB *E. faecium* (29/18)	100	0	100	96.6[d]	100	0	100	100.0[d]
Other *Enterococcus* spp. (80[e]/14[f])	100	87.5	100	97.5	100	100	100	100

Abbreviations: ORI, oritavancin; VAN, vancomycin; LZD, linezolid; DAP, daptomycin
[a] Criteria as published by CLSI (2023).
[b] Values are not shown because breakpoints are different among organism species (CLSI 2023).
[c] Vancomycin-susceptible *E. faecalis* breakpoints have been applied to all *Enterococcus*.
[d] Using daptomycin susceptible-dose dependent (SDD) category of MIC values ≤4 mg/L.
[e] Organisms include in 2017–2019: *Enterococcus avium* (31), *E. casseliflavus* (16), *E. gallinarum* (17), *E. hirae* (3), and *E. raffinosus* (13).
[f] Organisms include in 2022: *Enterococcus avium* (8), *E. casseliflavus* (1), *E. gallinarum* (2), and *E. raffinosus* (3).

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