

Vancomycin Resistance in *Enterococcus faecium* Clinical Isolates Responsible for Bloodstream Infections in US Hospitals Over Ten Years (2010–2019) and Activity of Oritavancin

CG Carvalhaes; HS Sader; J Streit; M Castanheira; RE Mendes
JMI Laboratories, North Liberty, Iowa, USA

Introduction

- Enterococcus* spp. are among the 5 most common causes of bacteremia worldwide. The CDC 2019 report on antimicrobial resistant pathogens considered vancomycin-resistant *Enterococcus* spp. (VRE), mainly *E. faecium*, a serious threat.
- Due to intrinsic and acquired resistance factors, *E. faecium* frequently challenges empirical and targeted antimicrobial therapy by forcing clinicians to seek alternative treatments for patients with serious infections.
- Oritavancin is a lipoglycopeptide antimicrobial agent that has activity against *Enterococcus* spp., including *vanA*-containing VRE.
 - Oritavancin impairs membrane barrier function and inhibits cell wall synthesis mechanisms.
 - Oritavancin was approved in the United States (2014) and Europe (2015) to treat adults with acute bacterial skin and skin structure infections (ABSSSI) caused by Gram-positive pathogens.
 - Oritavancin displays a rapid concentration-dependent bactericidal activity and prolonged half-life that allows for single-dose treatment against vancomycin-susceptible *E. faecalis* isolates causing ABSSSI.
- This study evaluated the vancomycin resistance rates over time and the activity of oritavancin against a collection of *E. faecium* causing bloodstream infection (BSI) in US medical centers.

Materials and Methods

Bacterial isolates

- This study included a total of 1,081 *E. faecium* isolates causing BSI.
- Isolates were collected from 36 US medical centers in a prevalence mode design during 2010–2019.
- Isolates were determined to be clinically significant based on local guidelines and then were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program.
- Isolates initially were identified by the participating laboratory. Bacterial identifications were confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI-TOF MS (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution (BMD) following guidelines in the CLSI M07 (2018) with testing performed using 96-well dry-form panels (2010–2014) manufactured by Thermo Fisher Scientific (Bedford, MA) or frozen-form (2015–2019) panels manufactured by JMI Laboratories.
 - Polysorbate-80 (0.002%) was included in the BMD panels when testing oritavancin, while calcium (Ca²⁺) supplementation (50 mg/L) was used for testing daptomycin.
- Quality assurance was performed by concurrently testing CLSI-recommended QC reference strains *Staphylococcus aureus* ATCC 29213 and *E. faecalis* ATCC 29212.
 - All QC results were within published acceptable ranges.
- Breakpoint criteria for oritavancin and comparator agents were those criteria published in the CLSI M100 (2020). For comparison, the oritavancin breakpoint for vancomycin-susceptible *E. faecalis* was applied to *E. faecium*.
- In vitro* activities were evaluated against resistant subsets, including vancomycin-resistant, ampicillin-resistant, linezolid non-susceptible, daptomycin-resistant, and daptomycin elevated MIC values (2–4 mg/L).
 - Isolates were characterized as *VanA* (i.e., vancomycin and teicoplanin MIC, >4 and >8 mg/L, respectively) or *VanB* (i.e., vancomycin and teicoplanin MIC, >4 and ≤8 mg/L, respectively) phenotypes based on their susceptibility to vancomycin and teicoplanin.
 - The *VanB* phenotype was confirmed by screening of *vanB* by PCR and/or whole genome sequencing and *in silico* analysis.

Results

- Overall, 72.3% (782/1,081) of *E. faecium* were vancomycin-resistant (Table 1; Figure 1).
- The vancomycin-resistance rates decreased from 81.8% in 2010 to 58.7% in 2019 (Figure 2).
 - VanA* was the most common phenotype (97.7%; 764/782).
 - A total of 18 (2.3%) isolates exhibited a *VanB* phenotype (teicoplanin MIC, 0.5–8 mg/L); however, the *vanB* gene only was confirmed in 9 *E. faecium* isolates (teicoplanin MIC, 0.5–1 mg/L), which were all collected in 2010–2012 (Tables 2 and 3).
 - The remaining 9 (50.0%) *VanB*-phenotype *E. faecium* isolates carried a *vanA* gene (teicoplanin MIC, 4–8 mg/L; Table 3).
- Oritavancin was very active against vancomycin-susceptible *E. faecium* (MIC_{50/90}, ≤0.008/≤0.008 mg/L), *VanA* (MIC_{50/90}, 0.03/0.12 mg/L; MIC₉₀, 0.5 mg/L), and *VanB* (MIC_{50/90}, ≤0.008/0.015 mg/L; MIC₁₀₀, 0.03 mg/L) subsets (Tables 2 and 3).
- Only linezolid and oritavancin (MIC, ≤0.12 mg/L) showed >90.0% susceptibility against all *E. faecium* and vancomycin-resistant subsets.
- Daptomycin resistance rarely was observed (0.8%), but it was noted more frequently in the last 5 surveillance years (Table 1).
 - However, 50.0% (540/1,081) of *E. faecium* isolates showed elevated daptomycin MICs (2–4 mg/L), requiring an increase on the daptomycin dosage regimen (8–12 mg/Kg).
- Oritavancin inhibited 97.8% and 100.0% of daptomycin-resistant and linezolid-nonsusceptible *E. faecium* isolates at ≤0.12 mg/L, respectively (Table 4).

Conclusions

- Vancomycin-resistance rates among *E. faecium* causing BSI in the US decreased during 2010–2019.
- VanA* remains the most common phenotype, likely due to the continued clonal expansion of multidrug-resistant isolates associated with clonal complex 17.
 - vanB*-carrying isolates became almost nonexistent in later years.
- Half of *VanB*-phenotype isolates determined based on the CLSI teicoplanin breakpoint susceptibility criterion demonstrated a *vanA* genotype.
 - These findings indicate that the CLSI breakpoint for teicoplanin is not optimal for categorizing a *VanB* phenotype.
 - The EUCAST resistant breakpoint for teicoplanin (>2 mg/L) would provide a more accurate categorization for *VanA* and *VanB* phenotypes.
- Oritavancin was very active against *E. faecium* causing BSI, including isolates resistant to vancomycin, daptomycin, and/or nonsusceptible to linezolid.
- The *in vitro* potency of oritavancin against BSI isolates of *E. faecium* support further investigations into treatment of infections due to this pathogen.

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Table 1 Oritavancin activity and occurrence of resistance phenotypes among *E. faecium* isolates causing BSI in US medical centers (2010–2019)

<i>E. faecium</i> Resistant subset (No. of isolates)	Occurrence (%) per study year										
	2010 (n=269)	2011 (n=138)	2012 (n=76)	2013 (n=70)	2014 (n=74)	2015 (n=90)	2016 (n=92)	2017 (n=90)	2018 (n=90)	2019 (n=92)	All years (n=1081)
Oritavancin MIC _{50/90} (mg/L)	0.03/0.06	0.03/0.12	0.03/0.12	0.03/0.06	0.015/0.06	0.03/0.12	0.015/0.03	0.015/0.06	0.015/0.06	0.015/0.06	0.03/0.06
VRE (782)	81.8	74.6	78.9	75.7	68.9	66.7	65.2	67.8	66.7	58.7	72.3
<i>VanA</i> phenotype (764)	97.3	97.1	98.3	100.0	94.1	98.3	100.0	98.4	96.7	98.1	97.7
<i>VanB</i> phenotype (18)	2.7	2.9	1.7	0.0	5.9	1.7	0.0	1.6	3.3	1.9	2.3
<i>vanB</i> genotype (9)	2.7	1.9	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2
Daptomycin-R (9)	0.0	1.4	0.0	0.0	0.0	2.2	2.2	0.0	0.0	3.3	0.8
Daptomycin MIC, 2–4 mg/L (540)	63.9	59.4	64.5	55.7	71.6	28.9	43.5	23.3	35.6	28.3	50.0
Linezolid-NS (13)	2.2	0.7	0.0	1.4	1.4	0.0	2.2	0.0	2.2	0.0	1.2
Ampicillin-R (944)	93.3	91.3	90.8	90.0	91.9	83.3	77.2	85.6	81.1	77.2	87.3

R, resistant; NS, nonsusceptible.

Figure 1 *E. faecium* isolates and vancomycin-resistant phenotypes causing BSI in US medical centers (2010–2019)

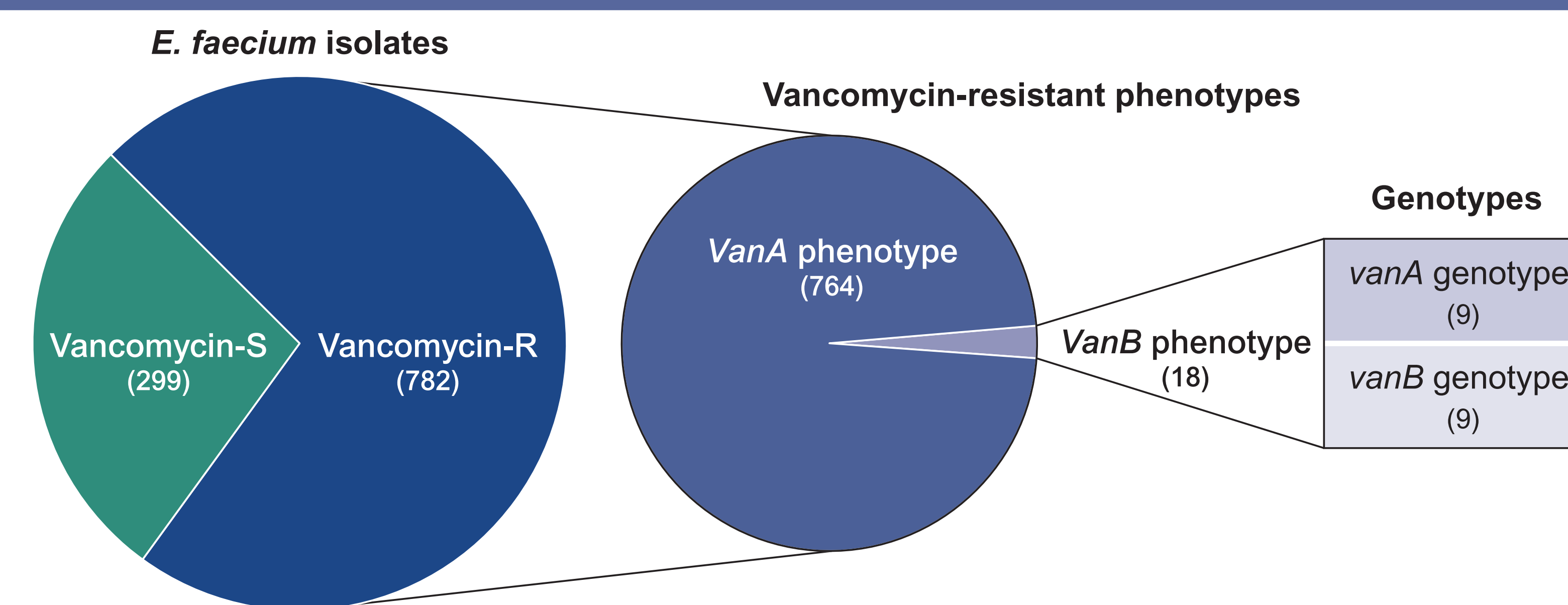


Figure 2 VRE rates and proportions of *VanA* and *VanB* phenotypes among *E. faecium* isolates causing BSI in US medical centers

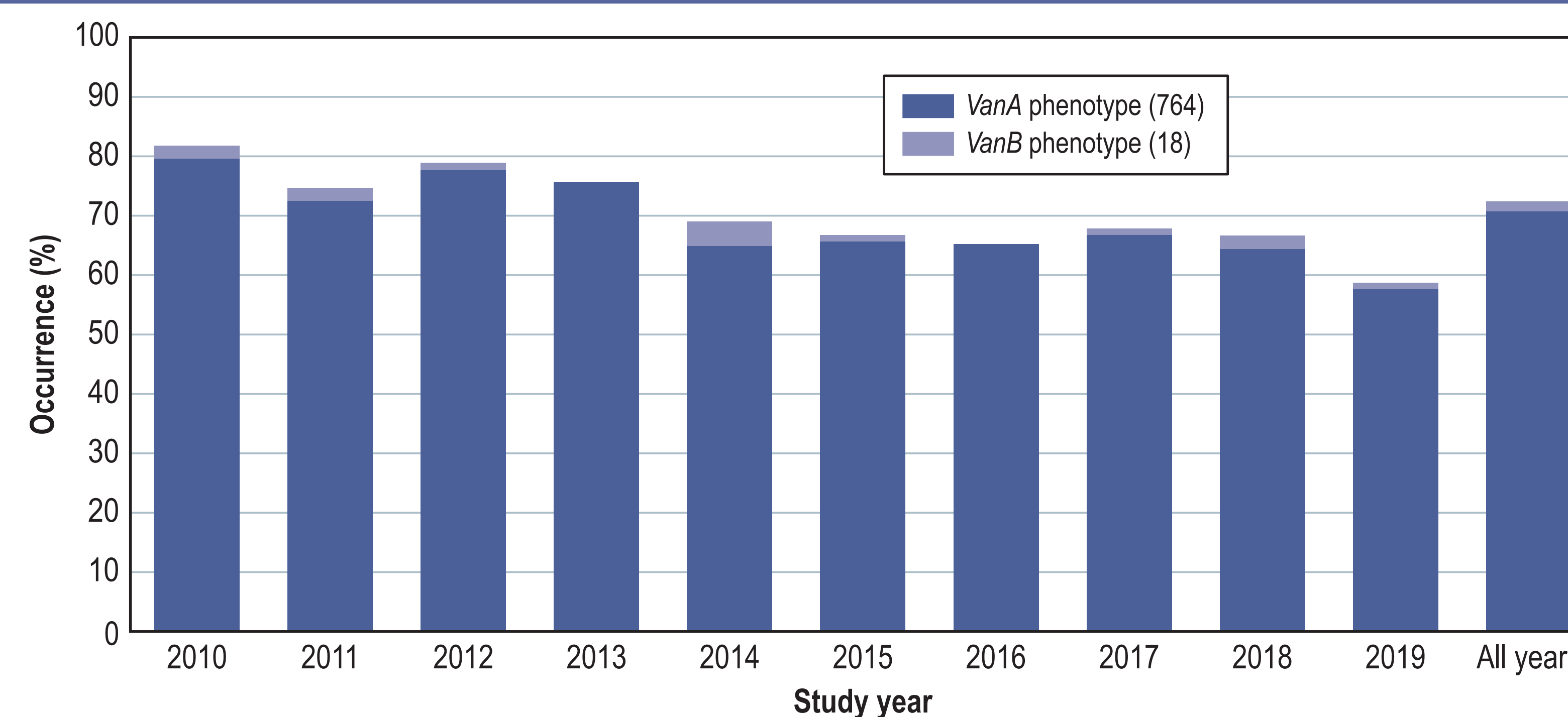


Table 2 Activity of oritavancin and comparators against *E. faecium* isolates and vancomycin-resistant subsets causing BSI in US medical centers (2010–2019)

Antimicrobial agent (No. of isolates)	mg/L		CLSI ^a			EUCAST ^a		
	MIC ₅₀	MIC ₉₀	%S	%I	%R	%S	%I	%R
All <i>E. faecium</i> (1,081)								
Oritavancin ^c	0.03	0.06	98.4					
Ampicillin	>8	>8	12.7		87.3	11.8	0.8	87.3
Daptomycin	2	2	^b 99.2	0.8				
Linezolid	1	2	98.8	0.7	0.5	99.5		0.5
Teicoplanin	>8	>8	30.2	3.9	46.3	28.7		71.3
Vancomycin	>16	>16	27.6	0.2	72.2	27.6		72.4
Vancomycin-susceptible (299)								
Oritavancin ^c	≤0.008	≤0.008	100					
Ampicillin	>8	>8	44.1		55.9	41.8	2.3	55.9
Daptomycin	2	2	^b 98.7	1.3				
Linezolid	1	2	98.7	0.7	0.7	99.3		0.7
Teicoplanin	≤2	≤2	100	0	0	99.7		0.3
Vancomycin	≤0.5	1	99.7	0.3	0	99.7		0.3

Antimicrobial agent (No. of isolates)	mg/L		CLSI ^a			EUCAST ^a		
	MIC ₅₀	MIC ₉₀	%S	%I	%R	%S	%I	%R
<i>VanA</i> phenotype (764)								
Oritavancin ^c	0.03	0.12	97.8					
Ampicillin	>8	>8	0.4		99.6	0.3	0.1	99.6
Daptomycin	1	2	^b 99.3	0.7				
Linezolid	1	2	99.0	0.7	0.4	99.6		0.4
Teicoplanin	>8	>8	1.2	5.5	65.4	0		100
Vancomycin	>16	>16	0	0	100	0		100
<i>VanB</i> phenotype (18)								
Oritavancin ^c	≤0.008	0.015	100					
Ampicillin	>8	>8	11.1		88.9	5.6	5.6	88.9
Daptomycin	1	2	^b 100	0				
Linezolid	1	1	94.4	5.6	0	100		0
Teicoplanin	≤2	8	100	0	0	66.7		33.3
Vancomycin	>16	>16	0	5.6	94.4	0		100

^a Criteria as published by CLSI (2020) and EUCAST (2020).
^b Non-resistant interpreted as susceptible-dose dependent (CLSI 2020).
^c Vancomycin-susceptible *E. faecalis* breakpoint applied to *E. faecium* (CLSI 2020).

Table 3 Characterization of 18 *VanB*-phenotype *E. faecium* isolates causing BSI in US medical centers

Isolate no.	Year	US Census Division	VRE genotype	MIC (mg/L)						
				Oritavancin	Ampicillin	Daptomycin	Linezolid	Teicoplanin	Vancomycin	
550011	2010	Mountain	<i>vanB</i>	0.008	>8	1	1	0.5	128	
550597	2010	West North Central	<i>vanB</i>	0.015	>8	1	0.5	0.5	256	
554317	2010	Pacific	<i>vanB</i>	0.008	>8	2	1	0.5	128	
554318	2010	Pacific	<i>vanB</i>	0.008	>8	2	1	0.5	256	
563299	2010	Mountain	<i>vanB</i>	0.008	>8	2	1	0.5	256	
568769	2010	Mid-Atlantic	<i>vanB</i>	0.008	>8	1	4	0.5	16	
656250	2011	West South Central	<i>vanB</i>	0.008	>8	0.5	1	0.5	128	
661484	2011	West North Central	<i>vanB</i>	0.008	>8	1	1	0.5	32	
709139	2012	West North Central	<i>vanB</i>	0.004	>8	0.12	0.5	1	8	
675410	2011	West North Central	<i>vanA</i>	0.06	>8	1	1	4	64	
835648	2014	West South Central	<i>vanA</i>	0.015	>8	2	0.5	4	128	
850957	2014	Pacific	<i>vanA</i>	0.06	>8	2	1	4	128	
861280	2014	East North Central	<i>vanA</i>	0.06	>8	0.5	1	8	256	
910300	2015	Pacific	<i>vanA</i>	0.06	>8	1	0.5	8	64	
1011197	2017	East North Central	<i>vanA</i>	0.03	>8	1	1	8	128	
1045354	2018	Mid-Atlantic	<i>vanA</i>	0.06	>8	0.5	0.5	8	128	
1068730	2018	West South Central	<i>vanA</i>	0.12	>8	≤0.25	1	8	256	
1096556	2019	West South Central	<i>vanA</i>	0.12	>8	0.5	0.5	4	128	

Table 4 Activity of oritavancin and comparators against *E. faecium* isolates and resistant subsets causing BSI in US medical centers (2010–2019)

Antimicrobial agent (No. of isolates)	mg/L		CLSI ^a			EUCAST ^a		
	MIC ₅₀	MIC ₉₀	%S	%I	%R	%S	%I	%R
AMP-R <i>E. faecium</i> (944)								
Oritavancin ^c	0.03	0.12	98.2					
Daptomycin	2	2	^b 99.0	1.0				
Linezolid	1	2	98.6	0.8	0.5	99.5		0.5
Teicoplanin	>8	>8	20.3	4.4	52.6	18.9		81.1
Vancomycin	>16	>16	17.6	0.2	82.2	17.6		82.4
LZD-NS <i>E. faecium</i> (13)								
Oritavancin ^c	0.015	0.06	100					
Ampicillin	>8	>8	0.0		100	0.0		100
Daptomycin	2	4	^b 92.3	7.7				
Teicoplanin	>8	>8	38.5		38.5	38.5		61.5
Vancomycin	>16	>16	30.8	7.7	61.5	30.8		69.2
DAP MIC 2–4 mg/L <i>E. faecium</i> (540)								
Oritavancin ^c	0.03	0.12	97.8					
Ampicillin	>8	>8	13.3		86.7	12.4	0.9	86.7
Linezolid	1	2	98.5	0.7	0.7	99.3		0.7
Teicoplanin	>8	>8	31.3	2.8	41.7	30.9		69.1
Vancomycin	>16	>16	29.8	0.2	70.0	29.8		70.2
DAP-R <i>E. faecium</i> (9)								
Oritavancin ^c	0.015	—	77.8					
Ampicillin	>8	—	0.0		100	0.0		100
Linezolid	2	—	88.9	11.1	0.0	100		0.0
Teicoplanin	8	—	55.6		44.4	44.4		55.6
Vancomycin	>16	—	44.4		55.6	44.4		55.6

^a Criteria as published by CLSI (2020) and EUCAST (2020).
^b Non-resistant interpreted as susceptible-dose dependent (CLSI 2020).
^c Vancomycin-susceptible *E. faecalis* breakpoint applied to *E. faecium* (CLSI 2020).
Abbreviations. AMP, ampicillin; R, resistant; LZD, linezolid; NS, non-susceptible; DAP, daptomycin.

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