IDWEEK 2020 | Poster Number: 1629

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

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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 (Ca^{2+}) 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; MIC_{100}, 0.5 mg/L), and *VanB* ($MIC_{50/90}$, ≤0.008/0.015 mg/L; MIC_{100}, 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 criterium 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.

Acknowledgements

This study was supported by Melinta Therapeutics. Melinta was involved in the design and decision to present these results, and JMI Laboratories received compensation for services in relation to preparing this presentation. Melinta Therapeutics had no involvement in the collection, analysis, and interpretation of data.

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

E. faecium 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
VanA phenotype (764)	97.3	97.1	98.3	100.0	94.1	98.3	100.0	98.4	96.7	98.1	97.7
VanB phenotype (18)	2.7	2.9	1.7	0.0	5.9	1.7	0.0	1.6	3.3	1.9	2.3
vanB 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)

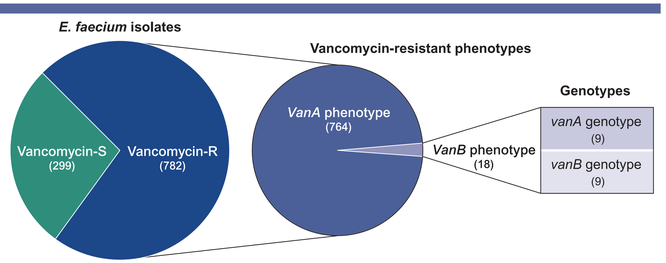

Figure 2 VRE rates and proportions of *VanA* and *VanB* phenotypes among *E. faecium* isolates causing BSI in US medical centers

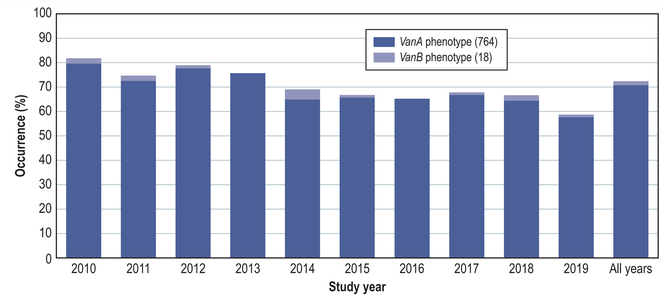

Table 2 Activity of oritavancin and comparators against *E. faecium* isolates and vancomycin-resistant subsets causing BSI in US medical centers (2010–2019)

Antimicrobial agent (No. of isolates)	mg/L		CLSI[a]			EUCAST[a]		
	MIC_{50}	MIC_{90}	%S	%I	%R	%S	%I	%R
All *E. faecium* (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
VanA 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
VanB 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	*vanB*	0.008	>8	1	1	0.5	128
550597	2010	West North Central	*vanB*	0.015	>8	1	0.5	0.5	256
554317	2010	Pacific	*vanB*	0.008	>8	2	1	0.5	128
554318	2010	Pacific	*vanB*	0.008	>8	2	1	0.5	256
563299	2010	Mountain	*vanB*	0.008	>8	2	1	0.5	256
568769	2010	Mid-Atlantic	*vanB*	0.008	>8	1	4	0.5	16
656250	2011	West South Central	*vanB*	0.008	>8	0.5	1	0.5	128
661484	2011	West North Central	*vanB*	0.008	>8	1	1	0.5	32
709139	2012	West North Central	*vanB*	0.004	>8	0.12	0.5	1	8
675410	2011	West North Central	*vanA*	0.06	>8	1	1	4	64
835648	2014	West South Central	*vanA*	0.015	>8	2	0.5	4	128
850957	2014	Pacific	*vanA*	0.06	>8	2	1	4	128
861280	2014	East North Central	*vanA*	0.06	>8	0.5	1	8	256
910300	2015	Pacific	*vanA*	0.06	2	1	0.5	8	64
1011197	2017	East North Central	*vanA*	0.03	>8	1	1	8	128
1045354	2018	Mid-Atlantic	*vanA*	0.06	8	0.5	0.5	8	128
1068730	2018	West South Central	*vanA*	0.12	>8	≤0.25	1	8	256
1096556	2019	West South Central	*vanA*	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 *E. faecium* (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 *E. faecium* (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 *E. faecium* (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 *E. faecium* (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.

References

CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

Clinical and Laboratory Standards Institute (2018). M07-A11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—eleventh edition. Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2020). M100-S30. Performance standards for antimicrobial susceptibility testing: 30th informational supplement. Wayne, PA: CLSI.

Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, Jones RN. The Microbiology of Bloodstream Infection: 20-Year Trends from the SENTRY Antimicrobial Surveillance Program. Antimicrob Agents Chemother. 2019;63:e00355-19.

EUCAST (2020). Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0, July 2020. Available at https://eucast.org/clinical_breakpoints/. Accessed July 2020.

Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients, 2012–2017. N Engl J Med. 2020;382(14):1309–1319.

Orbactiv™ package insert (EMA). Available at https://www.ema.europa.eu/en/documents/product-information/orbactiv-epar-product-information_en.pdf. Accessed July 2020.

Orbactiv™ package insert (US-FDA). Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206334s000lbl.pdf. Accessed July 2020.

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