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Oritavancin Activity Against Methicillin-Resistant *S. aureus* (MRSA) Isolates Causing Skin and Skin Structure Infections in US Hospitals (2017–2019)

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Introduction

- MRSA strains are an important cause of community (CO) and nosocomial (NO)-onset skin and skin structure infection (SSSI).
- Oritavancin is a long-acting lipoglycopeptide with prolonged tissue exposure at the site of infection and antimicrobial activity against *S. aureus*, including MRSA and multidrug-resistant (MDR) strains.
- Oritavancin was approved for clinical use by the US FDA to treat acute bacterial SSSI with a single 1,200 mg infusion over 3 hours (Orbactiv) and as of March 2021 as a 1 hour infusion of the same dose (Kimyrsa).
- This study evaluated the activity of oritavancin and comparator agents against MRSA isolates causing SSSI in US medical centers.

Materials and Methods

Bacterial isolates

- A total of 3,792 *S. aureus* isolates were consecutively collected from patients with SSSI between 2017 and 2019.
- Only isolates (1 per patient per infection episode) determined to be clinically significant by local criteria as the probable cause of infection were included.
- The isolates were recovered from 31 medical centers located in all 9 US Census Divisions and 22 states (Figure 1).
- Among 1,582 (41.7%) MRSA, 1,379 (87.2%) isolates were reported by the participant sites to be the causative pathogens of CO infections and 203 (12.8%) as NO infections (Figure 2).
- Bacterial isolates were identified by standard microbiology methods and/or MALDI-TOF.

Susceptibility testing

- Broth microdilution method was conducted according to CLSI M07 (2018) guidelines using frozen-form panels containing cation-adjusted Mueller-Hinton broth manufactured by JMI Laboratories (North Liberty, Iowa, USA).
- Oritavancin minimal inhibitory concentrations (MICs) were determined in the presence of polysorbate-80 (0.002%), while calcium (Ca^{2+}) supplementation (50 mg/L) was used for testing daptomycin.
- Quality assurance was performed by concurrently testing the CLSI-recommended quality control reference strains *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212.
- Susceptibility determinations were based on CLSI M100 (2021) breakpoint criteria.
- Oritavancin and comparator activities against MRSA were evaluated by the infection onset criteria (CO-MRSA vs. NO-MRSA). The CO-MRSA group was also split among clindamycin-resistant, levofloxacin-resistant, multi-drug resistant (MDR), and extensively drug-resistant (XDR) subsets.
- Although by Magiorakos *et al*. criteria (2012), MRSA isolates are always considered as MDR, herein, isolates were categorized as MDR and XDR, when MDR = nonsusceptible to at least 1 agent in at least 3 antimicrobial classes and XDR = nonsusceptible to at least 1 agent in all but 2 or fewer antimicrobial classes.
- Antimicrobial classes used in this study to categorize *S. aureus* isolates into the MDR and XDR categories were: β-lactams (oxacillin), fluoroquinolone (levofloxacin), macrolide (erythromycin), tetracycline, trimethoprim-sulfamethoxazole, lincosamide (clindamycin), oxazolidinone (linezolid), and glycopeptide (vancomycin).

Results

- Oritavancin was active against *S. aureus* isolates ($MIC_{50/90}$, 0.03/0.03 mg/L, 99.9%S) regardless of the US Census Division ($MIC_{50/90}$ range, 0.015-0.03/0.03-0.06 mg/L).
- Oritavancin was equally active against MSSA ($MIC_{50/90}$, 0.03/0.03 mg/L, 99.9%S) and MRSA ($MIC_{50/90}$, 0.03/0.03 mg/L, 100%S) isolates (Table 1).
  - Only 2 MSSA isolates (MIC, 0.25 mg/L) displayed an oritavancin MIC value above the FDA/CLSI published susceptible breakpoint (i.e. ≤0.12 mg/L).
- Oritavancin showed similar activity against CO-MRSA ($MIC_{50/90}$, 0.03/0.03 mg/L, 100%S) and NO-MRSA isolates ($MIC_{50/90}$, 0.03/0.06 mg/L, 100%S; Figure 3).
- Susceptibility rates were generally comparable between NO-MRSA and CO-MRSA isolates for comparator agents such as linezolid ($MIC_{50/90}$, 1/2 mg/L, 100%S), daptomycin ($MIC_{50/90}$, 0.25/0.25 mg/L, 100%S), and vancomycin ($MIC_{50/90}$, 1/1 mg/L, 100%S; Table 1).
  - Slightly lower susceptibility rates were observed for NO-MRSA compared to CO-MRSA for clindamycin (71.9%S vs. 79.1%S), levofloxacin (31.0%S vs. 39.4%S), and trimethoprim-sulfamethoxazole (91.1%S vs. 96.9%S; Table 1).
- Oritavancin and linezolid remained active (100%S) against all CO-MRSA subsets, including the clindamycin-resistant, levofloxacin-resistant, MDR, and XDR subsets (Table 2).
  - Limited activity against CO-MRSA resistant subsets was displayed by clindamycin (69.9%S) and levofloxacin (13.1%S), whereas trimethoprim-sulfamethoxazole showed >90% susceptibility for all MSSA, MRSA, and resistant subsets, except XDR (66.0%; Tables 1 and 2).

Conclusions

- Oritavancin exhibited potent *in vitro* activity against MRSA, regardless of the infection origin or resistant subset.
- Oritavancin *in vitro* activity against MRSA remains stable (>99.7%S) over time when compared to previous reports.
- In contrast, clindamycin and levofloxacin demonstrated limited *in vitro* activity against both CO-MRSA and NO-MRSA.
- This potent *in vitro* activity coupled with prolonged tissue exposure suggests oritavancin as a favorable and flexible alternative for treating SSSI caused by MSSA and MRSA, including MDR and XDR strains in the US.

Acknowledgements

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References

Stevens DL, Bisno AL, Chambers HF, Dellinger EP Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52.

Bassetti M, Labate L, Vena A, Giacobbe DR. Role of oritavancin and dalbavancin in acute bacterial skin and skin structure infections and other potential indications. Curr Opin Infect Dis. 2021 Apr 1;34(2):96-108.

Kimyrsa™ package insert (US-FDA). Available at: https://kimyrsa.com/wp-content/uploads/2021/03/kimyrsa-us-prescribing-information.pdf. Accessed Jul 2021.

Orbactiv™ package insert (US-FDA). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206334s000lbl.pdf. Accessed Jul 2021.

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 (2021). M100-S31. Performance standards for antimicrobial susceptibility testing: 31st informational supplement. Wayne, PA: CLSI.

Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3):268-81.

Pfaller MA, Sader HS, Flamm RK, Castanheira M, Mendes RE. Oritavancin in vitro activity against gram-positive organisms from European and United States medical centers: results from the SENTRY Antimicrobial Surveillance Program for 2010-2014. Diagn Microbiol Infect Dis. 2018 Jun;91(2):199-204.

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Figure 1. Distribution of *S. aureus* isolates causing SSSI in US Census Divisions (2017–2019)

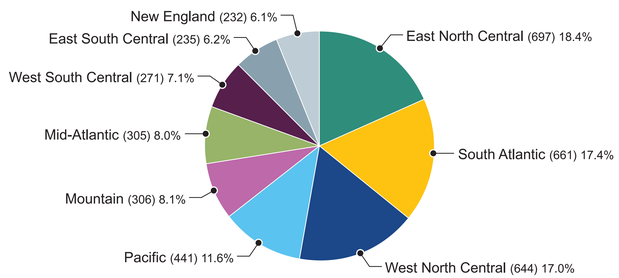
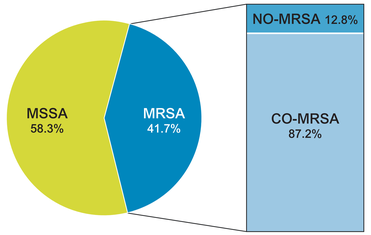


Figure 2. Percentage of MRSA isolates causing SSSI in US medical centers and reported infection onset (2017–2019)



Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CO-MRSA, community-onset methicillin-resistant *S. aureus*; NO-MRSA, nosocomial-onset methicillin-resistant *S. aureus*

Figure 3. Antimicrobial activity of oritavancin and comparator agents against CO-MRSA and NO-MRSA isolates causing SSSI in US medical centers (2017–2019)

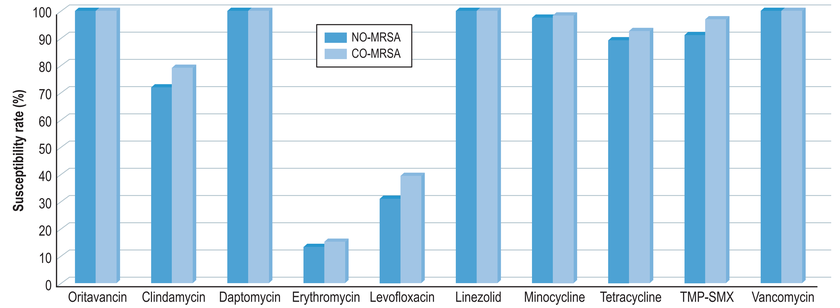


Table 1. Antimicrobial activity of oritavancin and comparator agents tested against *S. aureus* isolates causing SSSI in US medical centers (2017–2019)

Antimicrobial agent	CO-MRSA (*n*=1,379)			NO-MRSA (*n*=203)			All MRSA (*n*=1,582)			All MSSA (*n*=2,210)		
	MIC (mg/L)		CLSI[a]	MIC (mg/L)		CLSI[a]	MIC (mg/L)		CLSI[a]	MIC (mg/L)		CLSI[a]
	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S
Oritavancin	0.03	0.03	100.0	0.03	0.06	100.0	0.03	0.03	100.0	0.03	0.03	99.9
Clindamycin	0.06	>2	79.1	0.06	>2	71.9	0.06	>2	78.2	0.06	0.06	95.8
Daptomycin	0.25	0.25	100.0	0.25	0.25	100.0	0.25	0.25	100.0	0.25	0.25	100.0
Erythromycin	>8	>8	15.2	>8	>8	13.3	>8	>8	15.0	0.25	>8	66.0
Levofloxacin	4	>4	39.4	4	>4	31.0	4	>4	38.4	0.25	1	90.3
Linezolid	1	2	100.0	1	2	100.0	1	2	100.0	1	2	100.0
Minocycline	0.06	0.12	98.3	0.06	0.25	97.5	0.06	0.12	98.2	0.12	0.12	98.9
Tetracycline	≤0.5	1	92.6	≤0.5	8	89.2	≤0.5	1	92.2	≤0.5	≤0.5	94.4
TMP-SMX	≤0.5	≤0.5	96.9	≤0.5	≤0.5	91.1	≤0.5	≤0.5	96.1	≤0.5	≤0.5	99.3
Vancomycin	1	1	100.0	1	1	100.0	1	1	100.0	1	1	100.0

Abbreviations: CO-MRSA, community-onset methicillin-resistant *S. aureus*; NO-MRSA, nosocomial-onset methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole
[a] Criteria as published by CLSI (2021).

Table 2. Antimicrobial activity of oritavancin and comparator agents tested against CO-MRSA and NO-MRSA resistant subsets causing SSSI in US medical centers (2017–2019)

Antimicrobial agent	CO-MRSA (no. of isolates)				NO-MRSA (no. of isolates)			
	MIC (mg/L)		CLSI[a]		MIC (mg/L)		CLSI[a]	
	MIC_{50}	MIC_{90}	%S	%R	MIC_{50}	MIC_{90}	%S	%R
CLI-R	**(n=283)**				**(n=57)**			
Oritavancin	0.03	0.03	100.0	—[b]	0.03	0.06	100.0	—[b]
Clindamycin	>2	>2	0.0	100.0	>2	>2	0.0	100.0
Daptomycin	0.25	0.25	100.0	—[b]	0.25	0.25	100.0	—[b]
Erythromycin	>8	>8	0.0	100.0	>8	>8	0.0	100.0
Levofloxacin	>4	>4	13.1	86.9	>4	>4	3.5	96.5
Linezolid	1	2	100.0	0.0	1	2	100.0	0.0
Minocycline	0.12	0.5	92.9	4.2	0.12	0.5	93.0	7.0
Tetracycline	≤0.5	>8	84.5	15.5	≤0.5	>8	84.2	15.8
TMP-SMX	≤0.5	≤0.5	95.8	4.2	≤0.5	16	84.2	15.8
Vancomycin	1	1	100.0	0.0	1	1	100.0	0.0
LEV-R	**(n=831)**				**(n=140)**			
Oritavancin	0.03	0.03	100.0	—[b]	0.03	0.06	100.0	—[b]
Clindamycin	0.06	>2	69.9	29.6	0.06	>2	60.7	39.3
Daptomycin	0.25	0.5	100.0	—[b]	0.25	0.25	100.0	—[b]
Erythromycin	>8	>8	11.0	86.2	>8	>8	9.3	89.3
Levofloxacin	>4	>4	0.0	100.0	>4	>4	0.0	100.0
Linezolid	1	2	100.0	0.0	1	2	100.0	0.0
Minocycline	0.06	0.25	97.8	1.1	0.06	0.25	96.4	2.9
Tetracycline	≤0.5	1	93.1	6.6	≤0.5	2	90.7	9.3
TMP-SMX	≤0.5	≤0.5	94.9	5.1	≤0.5	16	87.1	12.9
Vancomycin	1	1	100.0	0.0	1	1	100.0	0.0

Antimicrobial agent	CO-MRSA (no. of isolates)				NO-MRSA (no. of isolates)			
	MIC (mg/L)		CLSI[a]		MIC (mg/L)		CLSI[a]	
	MIC_{50}	MIC_{90}	%S	%R	MIC_{50}	MIC_{90}	%S	%R
MDR	**(n=816)**				**(n=138)**			
Oritavancin	0.03	0.03	100.0	—[b]	0.03	0.06	100.0	—[b]
Clindamycin	0.06	>2	64.7	34.7	0.06	>2	58.7	41.3
Daptomycin	0.25	0.25	100.0	—[b]	0.25	0.25	100.0	—[b]
Erythromycin	>8	>8	1.6	95.5	>8	>8	0.7	97.8
Levofloxacin	>4	>4	7.5	92.2	>4	>4	7.2	92.8
Linezolid	1	2	100.0	0.0	1	2	100.0	0.0
Minocycline	0.06	0.25	97.2	1.7	0.06	0.25	96.4	2.9
Tetracycline	≤0.5	8	89.0	9.3	≤0.5	>8	84.1	13.8
TMP-SMX	≤0.5	≤0.5	94.7	5.3	≤0.5	16	87.0	13.0
Vancomycin	1	1	100.0	0.0	1	1	100.0	0.0
XDR	**(n=47)**				**(n=17)**			
Oritavancin	0.03	0.06	100.0	—[b]	0.03	0.06	100.0	—[b]
Clindamycin	>2	>2	6.4	91.5	>2	>2	5.9	94.1
Daptomycin	0.25	0.5	100.0	—[b]	0.25	0.5	100.0	—[b]
Erythromycin	>8	>8	0.0	97.9	>8	>8	0.0	100.0
Levofloxacin	>4	>4	0.0	100.0	>4	>4	0.0	100.0
Linezolid	1	2	100.0	0.0	1	2	100.0	0.0
Minocycline	0.5	>8	66.0	14.9	0.12	>8	76.5	23.5
Tetracycline	>8	>8	19.1	80.9	>8	>8	47.1	52.9
TMP-SMX	≤0.5	16	66.0	34.0	16	>16	41.2	58.8
Vancomycin	1	1	100.0	0.0	1	1	100.0	0.0

Abbreviations: CO-MRSA, community-onset methicillin-resistant *S. aureus*; NO-MRSA, nosocomial-onset methicillin-resistant *S. aureus*; CLI-R, clindamycin-resistant; LEV-R, levofloxacin-resistant; MDR, multi-drug resistant; XDR, extensively drug-resistant; TMP-SMX, trimethoprim-sulfamethoxazole
[a] Criteria as published by CLSI (2021).
[b] CLSI oritavancin and daptomycin resistant breakpoints not available