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Oritavancin Activity against *Staphylococcus aureus* Isolates Causing Bone and Joint Infection in European Hospitals (2010–2019)

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Introduction

- Bone and joint infections (BJI) frequently are caused by *Staphylococcus aureus*.
  - Methicillin-resistant *S. aureus* (MRSA) narrows antimicrobial options for treating osteomyelitis and other forms of BJI in children and adults.
- Oritavancin belongs to the lipoglycopeptide class of antimicrobial agents that act by inhibiting cell wall synthesis via three mechanisms of action which include membrane permeability and two sequential steps inhibiting cell wall synthesis.
  - It 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 has activity against *Staphylococcus* spp., including MRSA, *Streptococcus* spp., and most *Enterococcus* spp., including activity against *vanA*- and *vanB*-containing vancomycin-resistant enterococci (VRE).
  - The ABSSSI indication was approved as a single-dose treatment due to its prolonged half-life. US-FDA approved a single-dose treatment for ABSSSI caused by *S. aureus*, including MRSA, *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*.
- This study evaluates the activity of oritavancin and comparator agents against *S. aureus* isolates causing BJI in European (EU) hospitals.

Materials and Methods

Bacterial isolates

- A total of 575 *S. aureus* isolates causing BJI were included in this study.
- Isolates were collected from 41 European medical centers located in 15 countries during 2010–2019 (Figure 1).
- Isolates were determined to be clinically significant based on local guidelines and 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 following guidelines in the CLSI M07 document with testing performed using 96-well dry-form panels (2010–2014) manufactured by ThermoFisher Scientific (Bedford, MA) or frozen-form (2015–2019) panels manufactured by JMI Laboratories.
  - Polysorbate-80 (0.002%) was included in the frozen-form 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 (*S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212).
  - All QC results were within published acceptable ranges.
- Interpretation of susceptibility results was performed following current CLSI and EUCAST guidelines. The activities of oritavancin and comparators were evaluated across the years and by either western Europe (W-EU; 491 isolates) or eastern Europe/Mediterranean region (E-EU; 84 isolates).

Results

- MRSA was observed in 20.5% of *S. aureus* (Table 1) and this phenotype was more frequent in E-EU (32.1%) than W-EU (18.5%).
- MRSA rates decreased from 31.1% in 2011 to 14.6% in 2016. MRSA rates were slightly lower between 2016–2019 (14.6%–19.2%) than 2011–2013 (24.4%–31.1%) (Table 2).
- Oritavancin exhibited 100.0% susceptibility (per both CLSI and EUCAST criteria) across the entire *S. aureus* collection (Table 1).
  - Oritavancin yearly MIC_{50} and MIC_{90} variations were within 1 doubling dilution (MIC_{50} and MIC_{90}, 0.015–0.03 mg/L and 0.03–0.06 mg/L, respectively), regardless of the MRSA phenotype or European region (Figure 2).
- All *S. aureus* isolates also were susceptible to daptomycin, linezolid, teicoplanin, and vancomycin per CLSI and EUCAST criteria (Figure 3).
- Oritavancin MIC results ($MIC_{50/90}$, 0.03/0.06 mg/L) against all *S. aureus* were ≥8-fold lower compared to daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), linezolid ($MIC_{50/90}$, 1/2 mg/L), and vancomycin ($MIC_{50/90}$, 1/1 mg/L).
- Ceftaroline and clindamycin showed susceptibility rates of 98.0%/98.0% and 92.9%/92.7% (CLSI/EUCAST), respectively, against *S. aureus* (Table 1).

Table 1 Activity of oritavancin and comparator agents against *S. aureus* isolates causing BJI by European region (2010–2019)

Antimicrobial agent	*S. aureus* susceptibility[a] (n=575)			MRSA susceptibility[a] (n and % within *S. aureus*)				MSSA susceptibility[a] (n and % within *S. aureus*)			
				W-EU (n=91; 18.5%)		E-EU (n=27; 32.1%)		W-EU (n=400; 81.5%)		E-EU (n=57; 67.9%)	
	MIC_{50} / MIC_{90}	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI	EUCAST
Oritavancin	0.03 / 0.06	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Ceftaroline[b]	0.25 / 1	98.0	98.0	90.6	90.6	83.3	83.3	100.0	100.0	100.0	100.0
Clindamycin	≤0.25 / ≤0.25	92.9	92.7	74.7	74.7	44.4	44.4	99.2	99.2	100.0	98.2
Daptomycin	0.25 / 0.5	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Erythromycin	≤0.25 / >4	73.2	73.6	46.2	47.3	37.0	37.0	79.8	80.0	87.7	87.7
Levofloxacin	≤0.5 / >4	80.5	80.5[c]	14.3	14.3[c]	22.2	22.2[c]	96.7	96.7[c]	100.0	100.0[c]
Linezolid	1 / 2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Oxacillin	0.5 / >2	79.5	79.5	0.0	0.0	0.0	0.0	100.0	100.0	100.0	100.0
Teicoplanin	≤2 / ≤2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Tetracycline	≤0.5 / ≤0.5	93.9	93.6	89.0	87.9	66.7	66.7	97.8	97.8	87.7	86.0
TMP-SMX	≤0.5 / ≤0.5	99.5	99.5	97.8	97.8	100.0	100.0	99.8	99.8	100.0	100.0
Vancomycin	1 / 1	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[a] Criteria as published by CLSI (2020) and EUCAST (2020).
[b] Ceftaroline was tested against isolates from 2016–2019 only.
[c] Represents percentage of isolates that were characterized as susceptible under increased dosing regimens per EUCAST (2020).
Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

Figure 1 Distribution of *S. aureus* isolates causing BJI recovered from European countries (2010–2019)

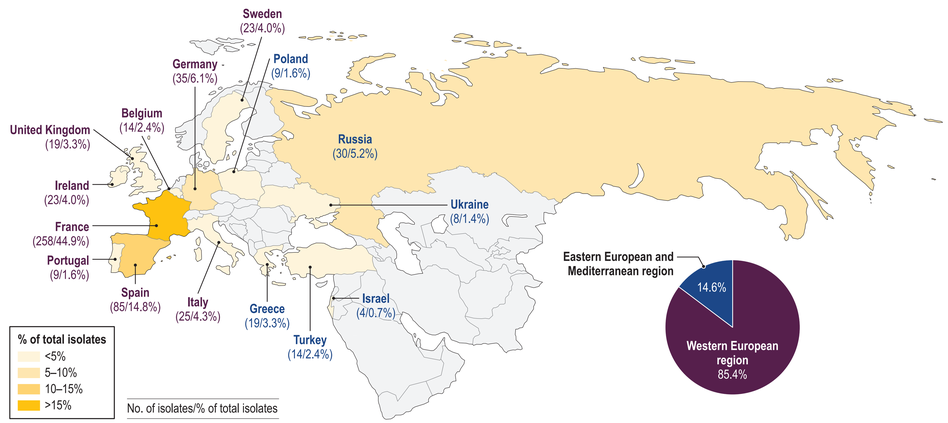


Figure 2 Evaluation of oritavancin and vancomycin MIC_{50} and MIC_{90} values across 2010–2019 against all *S. aureus*

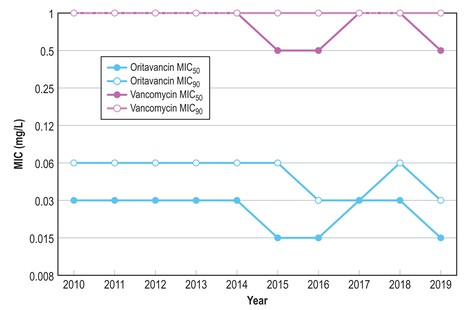
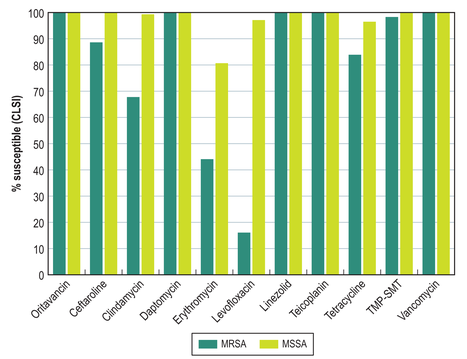


Figure 3 Oritavancin and comparators' susceptibility rates against MRSA and MSSA isolates recovered from patients with BJI from European medical centers



Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 2 Activity of oritavancin and comparators against MRSA isolates causing BJI in European medical centers per study year (2010–2019)

Antimicrobial agent	% of MRSA susceptible[a] by year (n and % within *S. aureus*)									
	2010 (n=8; 16.7)	2011 (n=14; 31.1)	2012 (n=12; 24.5)	2013 (n=10; 24.4)	2014 (n=14; 17.7)	2015 (n=16; 23.5)	2016 (n=7; 14.6)	2017 (n=12; 18.8)	2018 (n=15; 19.2)	2019 (n=10; 18.2)
Oritavancin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Ceftaroline[b]	—	—	—	—	—	—	85.7	75.0	100.0	90.0
Clindamycin	50.0	42.9	50.0	60.0	78.6	75.0	85.7	66.7	86.7	80.0
Daptomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Erythromycin	25.0	28.6	33.3	60.0	64.3	31.2	57.1	33.3	53.3	60.0
Levofloxacin	12.5	7.1	0.0	0.0	21.4	18.8	14.3	50.0	6.7	30.0
Linezolid	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Teicoplanin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Tetracycline	87.5	78.6	75.0	90.0	100.0	75.0	71.4	66.7	93.3	100.0
TMP-SMX	87.5	100.0	100.0	100.0	100.0	100.0	100.0	91.7	100.0	100.0
Vancomycin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[a] Criteria as published by CLSI (2020).
[b] Ceftaroline was tested against isolates from 2016–2019 only.
Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; MRSA, methicillin-resistant *S. aureus*.

- Clindamycin (>99.0% susceptible [CLSI and EUCAST]) and levofloxacin (>95.0% susceptible [CLSI]) were active against methicillin-susceptible *S. aureus*, but less active against MRSA (67.8% [CLSI and EUCAST] and 16.1% susceptible [CLSI], respectively; Table 1 and Figure 3).
- E-EU MRSA isolates displayed lower susceptibility rates than W-EU MRSA isolates for ceftaroline (83.3% for E-EU vs. 90.6% for W-EU), clindamycin (44.4% vs. 74.7%) and tetracycline (66.7% vs. 89.0%) (Table 1).

Conclusions

- MRSA rates among isolates causing BJI varied between European regions, with a trend toward decreasing MRSA rates from 2010 to 2019.
- Reduced susceptibility of many agents was observed for MRSA causing BJI compared to MSSA isolates.
- Oritavancin showed *in vitro* activity against the entire collection of European *S. aureus* isolates, and oritavancin MIC values remained stable over the 10-year study period.
- The *in vitro* activity presented here could support clinical studies of oritavancin use in BJI.

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