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# Comprehensive In Vitro Assessment of Oritavancin Activity Tested against *Staphylococcus aureus* causing Invasive Disease (2008 – 2009)

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## Abstract

**Background**: We provide an evaluation of oritavancin activity tested against *S. aureus* collected from patients with bloodstream infection in the USA and Europe. This analysis includes categorization of methicillin-resistant *S. aureus* (MRSA) based on resistance patterns.

**Methods**: 2,813 and 1,939 *S. aureus* were collected from USA (29 sites) and European (30 sites) hospitals, respectively. Identification was performed by standard algorithms and Vitek 2. *S. aureus* were tested for susceptibility by CLSI methods (M07-A8 and M100-S20-U) and EUCAST. Oritavancin was evaluated based on resistance patterns. MRSA isolates displaying resistance to at least four classes of drugs were considered multidrug-resistant (MDR).

**Results**: Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was eight- to 64-fold more active than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; 99.8% susceptible), vancomycin ($MIC_{50/90}$, 1/1 μg/mL; 100% susceptible) and linezolid ($MIC_{50/90}$, 2/2 μg/mL; >99.9% susceptible). Trimethoprim/sulfamethoxazole ($MIC_{50/90}$, ≤0.5/≤0.5 μg/mL; 98.4% susceptible) also showed a good coverage against *S. aureus*. Four main resistance patterns were noted among MRSA and 41.2% were MDR (Table). Oritavancin showed modal and $MIC_{50}$ values of 0.03 μg/mL across several resistance patterns, including MDR. The activity of daptomycin ($MIC_{50}$, 0.25 μg/mL), vancomycin ($MIC_{50}$, 1 μg/mL) and linezolid ($MIC_{50}$, 1 – 2 μg/mL) against these resistance subsets were equivalent to those noted against methicillin-susceptible *S. aureus*. Oritavancin showed higher MIC against MRSA with vancomycin MIC = 2 μg/mL (48.7% inhibited at ≤0.03 μg/mL) compared to strains with vancomycin MIC ≤1 μg/mL (84.1% inhibited at ≤0.03 μg/mL), although oritavancin $MIC_{90}$ values (0.06 μg/mL) were equivalent for both groups.

**Conclusions**: Oritavancin activity was stable against these *S. aureus*, regardless of resistance phenotype. The clinical impact, if any, of the two-fold oritavancin $MIC_{50}$ shift against MRSA with vancomycin MIC of 2 μg/mL is unknown.

## Introduction

Glycopeptides (vancomycin) have been the most commonly used antimicrobial agent in numerous medical care facilities in the United States (USA). This has been driven by a high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the nosocomial settings, and more recently the emergence and spread of a MRSA clonal lineage (i.e. USA300) in the community and hospital environments. However, recent evidence has suggested that serious infections caused by MRSA isolates with elevated vancomycin MIC values (1 – 2 μg/mL) do not respond to treatment as well as those infections caused by isolates with MIC at ≤0.5 μg/mL.

## Introduction-continued

The observations described above prompted the introduction of several anti-gram-positive drugs (e.g. linezolid, daptomycin, telavancin, tigecycline) into clinical practice and the antimicrobial pipeline contains additional agents at advanced development stages. Among the latter is oritavancin, a semisynthetic bactericidal lipoglycopeptide for treatment of serious infections caused by several Gram-positive organisms, including multidrug-resistant (MDR) staphylococci, enterococci and streptococci. This study was conducted to evaluate the oritavancin activity against *S. aureus* collected from bloodstream infections in the USA and Europe. Furthermore, this analysis includes an evaluation of oritavancin activity when tested against MRSA displaying a variety of resistance patterns.

## Methods

**Bacterial strain collection**. A total of 2,813 and 1,939 *S. aureus* were collected from USA (29 sites) and European (30 sites) medical centers, respectively. Isolates were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) as part of the SENTRY Antimicrobial Surveillance Program. The primary medical center provided the species identification and the monitoring laboratory confirmed the speciation using BactiStaph® latex and tube coagulase agglutination tests (Remel, Lenxa, Kansas, USA), and the Vitek® 2 Microbial Identification Systems (bioMérieux, Hazelwood, Missouri, USA), when necessary.

**Antimicrobial susceptibility testing**. Isolates were tested for susceptibility by the reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI; M07-A8, 2009) recommendations. Susceptibility testing was performed by using commercially prepared and validated panels (TREK Diagnostic Systems, Cleveland, Ohio, USA) in cation-adjusted Mueller-Hinton broth. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains: *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213. Interpretation of comparator (ten) MIC results was in accordance with published CLSI (M100-S20-U) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2010) criteria. Analysis of oritavancin activity was performed against groups of *S. aureus* displaying different antibiogram resistance patterns (intermediate susceptibility was grouped as resistant using CLSI criteria). Among these patterns, a set of MDR (i.e. isolates displaying resistance to at least three classes of drugs in addition to β-lactams [oxacillin]) and a group of strains with elevated vancomycin MIC results (2 μg/mL) were included.

## Results-1

- Overall, oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL; modal MIC, 0.03 μg/mL) demonstrated consistent antimicrobial activity when tested against *S. aureus,* regardless of geographic origin and across several resistance phenotypes (Table 1).
- Oritavancin showed slightly higher MIC results when tested against MRSA with vancomycin MIC of 2 μg/mL (48.7% inhibited at ≤0.03 μg/mL) compared to strains with vancomycin MIC at ≤1 μg/mL (84.1% inhibited at ≤0.03 μg/mL). However, oritavancin $MIC_{90}$ values (0.06 μg/mL) were equivalent for both analysis groups (Table 1).
- Methicillin-susceptible *S. aureus* (MSSA) recovered from USA and European medical centers exhibited similar susceptibility profiles, except for levofloxacin, which was less active against USA isolates ($MIC_{50/90}$, ≤0.5/4 μg/mL; 88.4% susceptible) compared to European MSSA ($MIC_{50/90}$, ≤0.5/≤0.5 μg/mL; 93.2% susceptible; Table 2).
- Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) was eight- to 64-fold more active than daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/mL; ≥99.4% susceptible), vancomycin ($MIC_{50/90}$, 1/1 μg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 2/2 μg/mL; ≥99.9% susceptible) when tested against either USA or European MRSA clinical isolates (Table 2).
- Equivalent antimicrobial susceptibility patterns were observed between USA and European MRSA, except that isolates from the USA were more susceptible to tetracycline ($MIC_{50/90}$, ≤2/≤2 μg/mL; 93.8 – 95.3% susceptible) when compared to those from Europe ($MIC_{50/90}$, ≤2/>8 μg/mL; 78.9 – 79.5% susceptible; Table 2).
- Isolates displaying resistance to at least three classes of drugs in addition to β-lactams (oxacillin) were categorized as MDR. Oritavancin ($MIC_{50/90}$, 0.03/0.06 μg/mL) tested against strains exhibiting a MDR phenotype was as active as when tested against MSSA ($MIC_{50/90}$, 0.03/0.06 μg/mL, Tables 1 and 2).
- Vancomycin (100.0% susceptible), teicoplanin (≥97.9% susceptible), daptomycin (99.1% susceptible), linezolid (99.9% susceptible) and trimethoprim/sulfamethoxazole (95.3% susceptible) also demonstrated good *in vitro* antimicrobial coverage when tested against MDR strains (Table 2).

## Results-2

**Table 1. MIC frequency distribution for oritavancin tested against *S. aureus* and resistant subsets of MRSA isolates submitted as part of the 2008 – 2009 international surveillance program.**

| Resistance pattern[a] (no. tested/% of total) | MIC (μg/mL) | | Number (cumulative %) inhibited at MIC (μg/mL) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 50% | 90% | ≤0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 |
| All *S. aureus* (4,752) | 0.03 | 0.06 | 217(4.6) | 1505(36.2) | **2267(83.9)** | 681(98.3) | 73(99.8) | 8(>99.9) | 1(100.0) |
| *S. aureus* USA (2,813) | 0.03 | 0.06 | 153(5.4) | 961(39.6) | **1292(85.5)** | 366(98.5) | 35(99.8) | 6(100.0) | – |
| *S. aureus* Europe (1,939) | 0.03 | 0.06 | 64(3.3) | 544(31.4) | **975(81.6)** | 315(97.9) | 38(99.8) | 2(>99.9) | 1(100.0) |
| MSSA (2,910/61.2) | 0.03 | 0.06 | 137(4.7) | 965(37.9) | **1366(84.8)[b]** | 404(98.7) | 35(99.9) | 3(100.0) | – |
| MRSA (1,842/38.8) | 0.03 | 0.06 | 80(4.3) | 540(33.7) | **901(82.6)** | 277(97.6) | 38(99.7) | 5(99.9) | 1(100.0) |
| OX, LE, CL, ER (621/33.7) | 0.03 | 0.06 | 15(2.4) | 149(26.4) | **328(79.2)** | 109(96.8) | 15(99.2) | 4(99.8) | 1(100.0) |
| OX, LE, ER (613/33.3) | 0.03 | 0.06 | 34(5.5) | 196(37.5) | **300(86.5)** | 77(99.0) | 6(100.0) | – | – |
| OX, ER (196/10.6) | 0.03 | 0.06 | 13(6.6) | 70(42.3) | **81(83.7)** | 26(96.9) | 6(100.0) | – | – |
| OX, LE, (123/6.7) | 0.03 | 0.06 | 8(6.5) | 40(39.0) | **59(87.0)** | 13)97.6) | 3(100.0) | – | – |
| OX (75/4.1) | 0.03 | 0.06 | 2(2.7) | 26(37.3) | **31(78.7)** | 16(100.0) | – | – | – |
| OX, LE, CL, ER, TC (64/3.5) | 0.03 | 0.06 | 2(3.1) | 17(29.7) | **35(84.4)** | 7(95.3) | 3(100.0) | – | – |
| OX, TC (26/1.4) | 0.03 | 0.06 | 2(7.7) | 4(23.1) | 9(57.7) | **11(100.0)** | – | – | – |
| OX, LE, ER, TC (24/1.3) | 0.03 | 0.06 | 1(4.2) | 6(29.2) | **10(70.8)** | 6(95.8) | 1(100.0) | – | – |
| MDR (758/41.2) | 0.03 | 0.06 | 19(2.5) | 186(27.0) | **397(79.4)** | 130(96.6) | 20(99.2) | 5(99.9) | 1(100.0) |
| VA MIC ≤1 μg/mL (1,764/95.8) | 0.03 | 0.06 | 80(4.5) | 536(34.9) | **867(84.1)** | 243(97.8) | 34(99.8) | 3(99.9) | 1(100.0) |
| VA MIC = 2 μg/mL (78/4.2) | 0.06 | 0.06 | 0(0.0) | 4(5.1) | **34(48.7)** | **34(92.3)** | 4(97.4) | 2(100.0) | – |

a. MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*. Most prevalent resistance patterns noted among MRSA. Intermediate and resistant results grouped as resistant. Criteria for susceptibility were those published by CLSI (2010). CL, clindamycin; ER, erythromycin; LE, levofloxacin; OX, oxacillin; VA, vancomycin; and TC, tetracycline. MDR = resistance to at least three classes of drugs in addition to β-lactams (oxacillin).
b. Modal MIC values are shown in bold.

**Table 2. Antimicrobial activity of oritavancin and comparator antimicrobial agents tested against *S. aureus* from USA and European hospitals (2008 – 2009).**

| Organism (no. tested)/ Antimicrobial agent | MIC (μg/mL) | | | % Susceptible / % Resistant[a] | |
|---|---|---|---|---|---|
| | 50% | 90% | Range | CLSI | EUCAST |
| MSSA USA (1,479) | | | | | |
| Oritavancin | 0.03 | 0.06 | ≤0.008 – 0.25 | –[b] / – | – / – |
| Vancomycin | 1 | 1 | 0.25 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Teicoplanin | ≤2 | ≤2 | ≤2 – 4 | 100.0 / 0.0 | 99.6 / 0.4 |
| Erythromycin | ≤0.25 | >2 | ≤0.25 – >2 | 66.4 / 32.4 | 67.1 / 32.4 |
| Clindamycin | ≤0.25 | ≤0.25 | ≤0.25 – >2 | 94.0 / 5.9 | 93.6 / 6.0 |
| Tetracycline | ≤2 | ≤2 | ≤2 – >8 | 96.1 / 2.8 | 95.7 / 4.3 |
| Levofloxacin | ≤0.5 | 4 | ≤0.5 – >4 | 88.4 / 11.1 | 88.4 / 11.1 |
| Daptomycin | 0.25 | 0.5 | 0.12 – 1 | 100.0 / - | 100.0 / 0.0 |
| Linezolid | 2 | 2 | 0.25 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | ≤0.5 – >2 | 98.3 / 1.7 | 98.3 / 1.7 |
| MSSA Europe (1,431) | | | | | |
| Oritavancin | 0.03 | 0.06 | ≤0.008 – 0.25 | – / – | – / – |
| Vancomycin | 1 | 1 | 0.5 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Teicoplanin | ≤2 | ≤2 | ≤2 – 4 | 100.0 / 0.0 | 99.7 / 0.3 |
| Erythromycin | ≤0.25 | >2 | ≤0.25 – >2 | 86.7 / 12.2 | 87.4 / 12.2 |
| Clindamycin | ≤0.25 | ≤0.25 | ≤0.25 – >2 | 98.1 / 1.6 | 97.6 / 1.9 |
| Tetracycline | ≤2 | ≤2 | ≤2 – >8 | 93.7 / 5.9 | 93.4 / 6.6 |
| Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5 – >4 | 93.2 / 6.3 | 93.2 / 6.3 |
| Daptomycin | 0.25 | 0.5 | ≤0.06 – 1 | 100.0 / – | 100.0 / 0.0 |
| Linezolid | 2 | 2 | 0.5 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | ≤0.5 – >2 | 99.2 / 0.8 | 99.2 / 0.8 |
| MRSA USA (1,334) | | | | | |
| Oritavancin | 0.03 | 0.06 | ≤0.008 – 0.25 | – / – | – / – |
| Vancomycin | 1 | 1 | 0.25 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Teicoplanin | ≤2 | ≤2 | ≤2 – 8 | 100.0 / 0.0 | 99.3 / 0.7 |
| Erythromycin | >2 | >2 | ≤0.25 – >2 | 7.1 / 92.3 | 7.3 / 92.3 |
| Clindamycin | ≤0.25 | >2 | ≤0.25 – >2 | 58.8 / 40.7 | 58.1 / 41.2 |
| Tetracycline | ≤2 | ≤2 | ≤2 – >8 | 95.3 / 4.2 | 93.8 / 6.2 |
| Levofloxacin | >4 | >4 | ≤0.5 – >4 | 19.9 / 79.3 | 19.9 / 79.3 |
| Daptomycin | 0.25 | 0.5 | 0.12 – 4 | 99.4 / – | 99.4 / 0.6 |
| Linezolid | 2 | 2 | 0.5 – >8 | 99.9 / 0.1 | 99.9 / 0.1 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | ≤0.5 – >2 | 97.9 / 2.1 | 97.9 / 2.1 |
| MRSA Europe (508) | | | | | |
| Oritavancin | 0.03 | 0.06 | ≤0.008 – 0.5 | – / – | – / – |
| Vancomycin | 1 | 1 | 0.25 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Teicoplanin | ≤2 | ≤2 | ≤2 – 8 | 100.0 / 0.0 | 97.6 / 2.4 |
| Erythromycin | >2 | >2 | ≤0.25 – >2 | 29.9 / 68.5 | 31.3 / 68.5 |
| Clindamycin | ≤0.25 | >2 | ≤0.25 – >2 | 62.4 / 36.8 | 61.4 / 37.6 |
| Tetracycline | ≤2 | >8 | ≤2 – >8 | 79.5 / 19.7 | 78.9 / 21.1 |
| Levofloxacin | >4 | >4 | ≤0.5 – >4 | 12.8 / 85.8 | 12.8 / 85.8 |
| Daptomycin | 0.25 | 0.5 | 0.12 – 1 | 100.0 / – | 100.0 / 0.0 |
| Linezolid | 2 | 2 | 0.25 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | 1 | ≤0.5 – >2 | 97.4 / 2.6 | 97.4 / 2.6 |
| MDR MRSA (758) | | | | | |
| Oritavancin | 0.03 | 0.06 | ≤0.008 – 0.5 | – / – | – / – |
| Vancomycin | 1 | 1 | 0.25 – 2 | 100.0 / 0.0 | 100.0 / 0.0 |
| Teicoplanin | ≤2 | ≤2 | ≤2 – 8 | 100.0 / 0.0 | 97.9 / 2.1 |
| Erythromycin | >2 | >2 | 0.5 – >2 | 0.1 / 99.2 | 0.7 / 99.2 |
| Clindamycin | >2 | >2 | ≤0.25 – >2 | 4.6 / 94.2 | 4.5 / 95.4 |
| Tetracycline | ≤2 | >8 | ≤2 – >8 | 85.1 / 14.1 | 83.1 / 26.9 |
| Levofloxacin | >4 | >4 | ≤0.5 – >4 | 0.7 / 98.7 | 0.7 / 98.7 |
| Daptomycin | 0.25 | 0.5 | 0.12 – 4 | 99.1 / – | 99.1 / 0.9 |
| Linezolid | 1 | 2 | 0.25 – >8 | 99.9 / 0.1 | 99.9 / 0.1 |
| Trimethoprim/sulfamethoxazole | ≤0.5 | ≤0.5 | ≤0.5 – >2 | 95.3 / 4.7 | 95.3 / 4.7 |

MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug-resistant.
a. Criteria for susceptibility as published by the CLSI (M100-S20-U; Update June 2010) and EUCAST (2010).
b. –, no breakpoint available.

## Conclusions

- Overall, oritavancin demonstrated the greatest potency when tested against this contemporary collection of *S. aureus* causing invasive disease. Oritavancin was eight- to 64-fold more potent than daptomycin, vancomycin and linezolid when tested against MRSA, including MDR phenotypes.
- Oritavancin activity was minimally affected (two-fold in the $MIC_{50}$ value) when tested against MRSA exhibiting elevated vancomycin MIC values (2 μg/mL) compared with those with lower MIC results (≤1 μg/mL); yet inhibiting all strains at ≤0.5 μg/mL.
- This *in vitro* activity update for oritavancin demonstrates that this investigational compound continues to be a promising therapeutic option for treating serious infections caused by *S. aureus*.

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