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# Telavancin *In Vitro* Activity against a Collection of Methicillin-Resistant *Staphylococcus aureus* Isolates, Including Resistant Subsets, from the United States

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**Telavancin had $MIC_{50}$, $MIC_{90}$, and $MIC_{100}$ values of 0.03, 0.06, and 0.12 μg/ml, respectively, against methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and non-multidrug-resistant (non-MDR) and MDR subsets. MRSA with elevated MIC values for vancomycin (2 to 4 μg/ml) or daptomycin (1 to 2 μg/ml) had telavancin $MIC_{50}$ (0.06 μg/ml) values 2-fold higher than those of isolates with lower MIC results ($MIC_{50}$, 0.03 μg/ml). However, telavancin had $MIC_{90}$ and $MIC_{100}$ results of 0.06 and 0.12 μg/ml (100% susceptible), respectively, regardless of the MRSA subset.**

Methicillin-resistant *Staphylococcus aureus* (MRSA) has remained a major public health problem worldwide and challenges the management of infections caused by this pathogen (1). Multiple factors have been implicated with this therapeutic challenge, including the dynamic epidemiology of MRSA lineages (2). Infection rates of MRSA rise and fall in epidemic waves, with several waves occurring in the past decades and the emergence of community-acquired (CA) MRSA being the latest and one of the still-present waves (2). CA-MRSA isolates, primarily those associated with the USA300 lineage, are responsible for the vast majority of skin and skin structure infections (SSSIs) in the United States (3). Moreover, the emergence of CA-MRSA is reflected in the nosocomial epidemiology of *S. aureus*, and the USA300 clone has also been implicated as a cause of invasive infections among hospitalized patients (4–6).

The treatment of invasive MRSA infections has relied significantly on vancomycin. However, several studies have reported increased treatment failures against isolates displaying elevated vancomycin MIC results (i.e., 2 μg/ml) but still considered susceptible based on current breakpoints (7). Interestingly, recent investigations have identified treatment failures in infections caused by both MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates exhibiting elevated MIC values for vancomycin, regardless of treatment with vancomycin or another β-lactam agent (8–10). This suggests that increasing vancomycin MICs may reflect a yet-to-be-identified marker of host or organism. Recent consensus guidelines recommend alternative therapeutic agents for the management of infections due to MRSA strains with reduced susceptibility to vancomycin (11, 12).

Telavancin is a lipoglycopeptide antibiotic with potent *in vitro* bactericidal activity against Gram-positive bacteria, including MSSA, MRSA, vancomycin-intermediate *S. aureus* (VISA), heterogeneous VISA (hVISA), and multidrug-resistant (MDR) streptococci and enterococci (13, 14). Early in 2014, the Food and Drug Administration (FDA) approved a revised broth microdilution

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**TABLE 1** Antimicrobial activity and MIC distribution for telavancin against a contemporary (2011 to 2013) U.S. collection of *S. aureus* clinical isolates using a recently approved and revised susceptibility testing method

| *S. aureus* category[a] (no. of isolates tested) | MIC (μg/ml) | | No. (cumulative %) of isolates inhibited by telavancin at indicated MIC (μg/ml)[b] | | | |
|---|---|---|---|---|---|---|
| | 50% | 90% | ≤0.015 | 0.03 | 0.06 | 0.12 |
| All (9,610) | 0.03 | 0.06 | 364 (3.8) | **6,210 (68.4)** | 3,012 (99.8) | 24 (100.0) |
| MSSA (4,959) | 0.03 | 0.06 | 242 (4.9) | **3,272 (70.9)** | 1,437 (99.8) | 8 (100.0) |
| MRSA (4,651) | 0.03 | 0.06 | 122 (2.6) | **2,938 (65.8)** | 1,575 (99.7) | 16 (100.0) |
| Vancomycin MIC, ≤1 μg/ml (4,561) | 0.03 | 0.06 | 119 (2.6) | **2,930 (66.8)** | 1,502 (99.8) | 10 (100.0) |
| Vancomycin MIC, 2–4 μg/ml (90) | 0.06 | 0.06 | 3 (3.3) | 8 (12.2) | **73 (93.3)** | 6 (100.0) |
| Daptomycin MIC, ≤0.5 μg/ml (4,607) | 0.03 | 0.06 | 122 (2.6) | **2,928 (66.2)** | 1,545 (99.7) | 12 (100.0) |
| Daptomycin MIC, 1–2 μg/ml (43) | 0.06 | 0.06 | 0 (0.0) | 9 (20.9) | **30 (90.7)** | 4 (100.0) |
| MDR (1,371) | 0.03 | 0.06 | 37 (2.7) | **749 (57.3)** | 574 (99.2) | 11 (100.0) |
| Non-MDR (3,280) | 0.03 | 0.06 | 85 (2.6) | **2,189 (69.3)** | 1,001 (99.8) | 5 (100.0) |

[a] MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug resistant.
[b] Data representing modal MICs are shown in bold.

**TABLE 2** Antimicrobial activity of telavancin and comparator agents tested against a contemporary (2011 to 2013) U.S. collection of clinical isolates using a recently approved and revised susceptibility testing method

| Organism category[a] (no. tested) and antimicrobial agent | MIC (μg/ml) | | % susceptible/% intermediate/% resistant[b] | | |
|---|---|---|---|---|---|
| | 50% | 90% | FDA | CLSI | EUCAST |
| MSSA (4,959) | | | | | |
| Telavancin | 0.03 | 0.06 | 100.0/-[c]/- | -/-/- | -/-/- |
| Vancomycin | 1 | 1 | | 100.0/0.0/0.0 | 100.0/0.0/0.0 |
| Daptomycin | 0.25 | 0.5 | | >99.9/-/- | >99.9/0.0/<0.1 |
| Linezolid | 1 | 1 | | >99.9/0.0/<0.1 | >99.9/0.0/<0.1 |
| Levofloxacin | 0.25 | 4 | | 88.8/0.9/10.3 | 88.8/0.9/10.3 |
| Erythromycin | 0.25 | >16 | | 65.6/3.7/30.7 | 66.0/1.3/32.7 |
| Clindamycin | ≤0.25 | ≤0.25 | | 95.2/0.1/4.7 | 94.8/0.4/4.8 |
| Gentamicin | ≤1 | ≤1 | | 99.2/0.2/0.6 | 99.0/0.0/1.0 |
| Tetracycline | ≤0.25 | ≤0.25 | | 96.2/0.7/3.1 | 95.3/0.2/4.5 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 99.5/0.0/0.5 | 99.5/0.1/0.4 |
| MRSA (4,651) | | | | | |
| Telavancin | 0.03 | 0.06 | 100.0/-/- | -/-/- | 100.0/-/- |
| Vancomycin | 1 | 1 | | >99.9/<0.1/0.0 | >99.9/0.0/<0.1 |
| Daptomycin | 0.25 | 0.5 | | >99.9/-/- | >99.9/0.0/<0.1 |
| Linezolid | 1 | 1 | | 99.9/0.0/0.1 | 99.9/0.0/0.1 |
| Levofloxacin | 4 | >4 | | 31.3/2.2/66.5 | 31.3/2.2/66.5 |
| Erythromycin | >16 | >16 | | 10.4/1.9/87.7 | 10.6/0.5/88.9 |
| Clindamycin | ≤0.25 | >2 | | 70.5/0.1/29.4 | 70.2/0.3/29.5 |
| Gentamicin | ≤1 | ≤1 | | 96.8/0.1/3.1 | 96.5/0.0/3.5 |
| Tetracycline | ≤0.25 | 1 | | 94.9/0.4/4.7 | 92.6/2.0/5.4 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 97.8/0.0/2.2 | 97.8/0.2/2.0 |
| MRSA with vancomycin MIC 2–4 μg/ml (4,651) | | | | | |
| Telavancin | 0.06 | 0.06 | 100.0/-/- | -/-/- | 100.0/-/- |
| Vancomycin | 2 | 2 | | 98.9/1.1/0.0 | 98.9/0.0/1.1 |
| Daptomycin | 0.5 | 1 | | 97.8/-/- | 97.8/0.0/2.2 |
| Linezolid | 1 | 2 | | 98.9/0.0/1.1 | 98.9/0.0/1.1 |
| Levofloxacin | >4 | >4 | | 14.4/0.0/85.6 | 14.4/0.0/85.6 |
| Erythromycin | >16 | >16 | | 5.6/1.1/93.3 | 5.6/1.1/93.3 |
| Clindamycin | >2 | >2 | | 36.7/0.0/63.3 | 36.7/0.0/63.3 |
| Gentamicin | ≤1 | 2 | | 91.1/0.0/8.9 | 88.9/0.0/11.1 |
| Tetracycline | ≤0.25 | 2 | | 95.6/1.1/3.3 | 88.9/6.7/4.4 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 97.8/0.0/2.2 | 97.8/1.1/1.1 |
| MDR MRSA (1,371) | | | | | |
| Telavancin | 0.03 | 0.06 | 100.0/-/- | -/-/- | 100.0/-/- |
| Vancomycin | 1 | 1 | | 99.9/0.1/0.0 | 99.9/0.0/0.1 |
| Daptomycin | 0.25 | 0.5 | | 99.9/-/- | 99.9/0.0/0.1 |
| Linezolid | 1 | 1 | | 99.7/0.0/0.3 | 99.7/0.0/0.3 |
| Levofloxacin | >4 | >4 | | 0.9/0.3/98.8 | 0.9/0.3/98.8 |
| Erythromycin | >16 | >16 | | 0.5/0.4/99.1 | 0.5/0.1/99.4 |
| Clindamycin | >2 | >2 | | 6.3/0.0/93.7 | 6.3/0.0/93.7 |
| Gentamicin | ≤1 | 4 | | 90.2/0.2/9.6 | 89.9/0.0/10.1 |
| Tetracycline | ≤0.25 | >8 | | 88.6/0.2/11.2 | 82.4/6.1/11.5 |
| Trimethoprim-sulfamethoxazole | ≤0.5 | ≤0.5 | | 93.9/0.0/6.1 | 93.9/0.7/5.4 |

[a] MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MDR, multidrug resistant.
[b] Telavancin breakpoint criteria for *S. aureus* according to the labeling supplement for the product (Vibativ) and EUCAST (MRSA only) at ≤0.12 μg/ml for susceptibility.
[c] -, breakpoint not available.

susceptibility testing method for telavancin that was published in a labeling supplement for a package insert for a commercially produced formulation of telavancin (Vibativ) (15). This revised method was also published in the Clinical and Laboratory Standards Institute (CLSI) M100-S24 document (16) Briefly, this revised method follows the current CLSI guidelines for water-insoluble agents and includes the addition of polysorbate-80 (P-80; 0.002%) to the test medium (15–17). The latter constitutes an approach similarly used for other members of the lipoglycopeptide class (18, 19). These modifications were shown to improve the drug solubility during panel preparation and drug availability in the 96-well plastic plates, resulting in a more accurate *in vitro* assessment of telavancin MIC determinations (17). This study was conducted to assess and update the activity of telavancin against a recent (2011 to 2013) collection of *S. aureus* clinical isolates and resistant subsets collected from U.S. medical centers using the recently approved broth microdilution method.

As part of the SENTRY Antimicrobial Surveillance Program

for the United States, a total of 9,610 *S. aureus* clinical isolates collected from 28 U.S. sites were included in this analysis. These isolates were recovered from blood (1,937 isolates; 20.2%) and SSSI (4,851; 50.5%) and from patients with hospital-acquired bacterial pneumonia (2,283; 23.8%), urinary tract infections (163; 1.7%), and other less prevalent or undetermined infection sources (376; 3.9%). Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA). Isolates were initially identified by the participating laboratory, and identification was confirmed by the reference monitoring laboratory by standard algorithms and supported by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany).

Isolates were tested for susceptibility by broth microdilution following CLSI guidelines (20). Telavancin was tested using dry-form panels manufactured by Thermo Fisher Scientific (Cleveland, Ohio, USA). These panels provide telavancin MIC results (dilution range applied, 0.015 to 2 μg/ml) equivalent to those approved by the FDA (15) and published by the CLSI (16, 17). The quality of the MIC values was ensured by concurrent testing of *S. aureus* (ATCC 29213) and *Enterococcus faecalis* (ATCC 29212). Telavancin MIC interpretations for *S. aureus* applied the recently approved breakpoint criterion (≤0.12 μg/ml for susceptible) appropriate for the revised testing method (15, 21). CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint criteria were applied for comparator agents (16, 21). MRSA isolates were categorized according to the vancomycin MIC (≤1 versus 2 to 4 μg/ml) and daptomycin MIC (≤0.5 versus 1 to 2 μg/ml) results, and group of isolates with MIC values at the upper end of the MIC distributions were compared with those having lower MIC values (10, 22). In addition, *S. aureus* strains showing a phenotype of resistance to methicillin and at least additional three classes of antimicrobial agents were defined as multidrug resistant (MDR).

Overall, telavancin demonstrated $MIC_{50}$ and $MIC_{90}$ values of 0.03 and 0.06 μg/ml against *S. aureus* (100.0% susceptible), respectively, and equivalent values were observed against the MSSA, MRSA, non-MDR and MDR subsets (Table 1). Tested against the MRSA subset displaying vancomycin MIC results of 2 to 4 μg/ml or daptomycin MIC values of 1 to 2 μg/ml, the telavancin $MIC_{50}$ value (0.06 μg/ml) was 2-fold higher than that ($MIC_{50}$, 0.03 μg/ml) obtained from MRSA isolates with lower MIC values for vancomycin (≤1 μg/ml) or daptomycin (≤0.5 μg/ml). All MRSA subsets had potent telavancin $MIC_{90}$ results (0.06 μg/ml). *In vitro* activity comparison analysis resulted in telavancin ($MIC_{50/90}$, 0.03/0.06 μg/ml) showing MIC values 8-fold lower than the values for daptomycin ($MIC_{50/90}$, 0.25/0.5 μg/ml) and 16-fold to 32-fold lower than the values for vancomycin ($MIC_{50/90}$, 1/1 μg/ml) or linezolid ($MIC_{50/90}$, 1/1 μg/ml) against MSSA, the overall MRSA group, and the MDR subset (Table 2). Gentamicin, tetracycline, and trimethoprim-sulfamethoxazole also had antimicrobial coverage (>90.0% susceptible) in tests against MRSA, while these agents and clindamycin were active against MSSA.

Daptomycin MIC results ($MIC_{50/90}$, 0.5/1 μg/ml) obtained against MRSA isolates with elevated vancomycin MIC values (2 to 4 μg/ml) were 2-fold higher than those obtained against MRSA with vancomycin MIC data points at ≤1 μg/ml ($MIC_{50/90}$, 0.25/0.5 μg/ml; data not shown). Daptomycin ($MIC_{50/90}$, 0.5/1 μg/ml) and linezolid ($MIC_{50/90}$, 1/2 μg/ml) remained active (97.8% to 98.9% susceptible) against MRSA isolates with vancomycin MIC values of 2 to 4 μg/ml; however, telavancin had MIC results 8-fold to 32-fold lower than the MIC results determined for these comparators. Gentamicin, tetracycline, and trimethoprim-sulfamethoxazole also remained active *in vitro* against the MRSA subset showing vancomycin MIC values of 2 to 4 μg/ml, whereas gentamicin and trimethoprim-sulfamethoxazole exhibited *in vitro* activity against the MDR subset.

In this *in vitro* study, telavancin exhibited potent activity against *S. aureus*, including isolates with decreased susceptibility to comparator agents, maintaining $MIC_{90}$ and $MIC_{100}$ results of 0.06 and 0.12 μg/ml, respectively, regardless of the MRSA subset (100.0% susceptible). In addition, the telavancin potency observed was at least 8-fold greater than that seen with the tested comparators. These results confirm the telavancin activity against a recent collection of *S. aureus* clinical isolates and also update the drug activity with respect to applying a recently approved broth microdilution susceptibility testing method. Moreover, these results confirm the more potent activity of telavancin compared with that seen in previous studies (13, 14, 23), which underestimated the potency of drug due to solubility and availability issues during susceptibility testing (17).

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