# Telavancin Activity Against Uncommonly Isolated Gram-Positive Pathogens Responsible for Documented Infections in Hospitals Worldwide (2011–2013) When Using A Revised Susceptibility Testing Method

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## ABSTRACT

**Objectives**: To assess the activity of telavancin when tested against a worldwide collection of rarely isolated clinical pathogens using a revised broth microdilution method. This revised method for telavancin utilises dimethyl sulphoxide as solvent and diluent for stock solution preparation and dilution, following the CLSI guidelines for water-insoluble agents, and incorporates polysorbate-80 (or Tween; 0.002%) in the test medium. Like other lipoglycopeptides, addition of P-80 was deemed necessary for more accurate and reproducible telavancin MIC determinations.

**Methods**: A total of 1656 coagulase-negative staphylococci (CoNS), 1939 viridans group streptococci, 157 ß-haemolytic streptococci, and other 69 Gram-positive isolates (three genera) collected over a 3-year period were evaluated (SENTRY Antimicrobial Surveillance Programme, 2011–2013). Isolates were submitted to a central laboratory and identification was performed by standard algorithms and MALDI-TOF. Susceptibility testing for comparator agents was performed by CLSI methods (M07-A9). Quality assurance applied MIC QC ranges from CLSI M100-S24. Interpretation of MIC results for telavancin used the updated US-FDA criteria, while comparator agents were guided by current EUCAST (2014) and CLSI (2014) breakpoint criteria.

**Results**: Isolates were recovered primarily from bacteraemia (44%), skin and soft-tissue (28%), and respiratory tract infections (8%). Only 27.6% of CoNS were susceptible to oxacillin. Telavancin was highly active against all CoNS ($MIC_{50/90}$, 0.03/0.06 mg/L) with $MIC_{50}$ values of 0.06 mg/L among tested species, with slightly lower MIC results noted for *S. hominis* ($MIC_{50}$, ≤0.015 mg/L), *S. lugdunensis* ($MIC_{50}$, ≤0.015 mg/L), and *S. simulans* ($MIC_{50}$, 0.03 mg/L; **Table 1**). Vancomycin ($MIC_{50}$, 0.5–1 mg/L), daptomycin ($MIC_{50}$, 0.12–1 mg/L), and linezolid ($MIC_{50}$, 0.25–1 mg/L) showed $MIC_{50}$ results at least four-fold higher than telavancin when tested against these CoNS species. Overall, vancomycin (100.0% susceptible), teicoplanin (91.3% susceptible), daptomycin (99.8% susceptible), and linezolid (99.6% susceptible) were active against CoNS. Streptococcal isolates exhibited $MIC_{50}$ values of ≤0.015 mg/L for telavancin, except for *S. bovis/gallolyticus* and *S. mutans* ($MIC_{50}$, 0.03 mg/L for both). Other Gram-positive isolates such as *Micrococcus* spp., *Listeria* spp., and *Corynebacterium* spp. were inhibited by telavancin at ≤0.015, ≤0.03, and ≤0.06 mg/L, respectively.

**Conclusions:** Telavancin exhibited potent *in vitro* activity when tested against less common pathogens recovered from human clinical specimens. These results were obtained using a revised broth microdilution method; therefore, providing new baseline MIC results for telavancin. In addition, this investigation confirms the spectrum and potency of telavancin against less commonly encountered Gram-positive species.

## INTRODUCTION

- Telavancin is a lipoglycopeptide antibiotic approved in the United States and Canada for the treatment of patients with complicated skin and skin structure infections due to susceptible Gram-positive pathogens, and in the United States and Europe for the treatment of hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (HABP/VABP) due to susceptible isolates of *Staphylococcus aureus* (methicillin-resistant strains [MRSA] only in Europe), when alternative medicines are unsuitable.[1,2]
- Telavancin has demonstrated potent antimicrobial activity *in vitro* against a broad range of other Gram-positive organisms.[3,4]
- That potency appears derived from a concentration-dependent bactericidal activity due to a dual mechanism of action combining inhibition of cell-wall synthesis and disruption of bacterial cell membrane function.[5]
- Recently, the broth microdilution (BMD) susceptibility testing method for telavancin was revised to accommodate modifications associated with dilution of the drug stock solution, which now follows the current Clinical and Laboratory Standards Institute (CLSI) guidelines for water-insoluble agents.[2,6]
- Moreover, this revised method encompasses the addition of polysorbate-80 (P-80; 0.002%) to the test medium (see Poster #P1579 for additional information).[2,6]
- This revised BMD method provides minimum inhibitory concentration (MIC) results for telavancin that are lower than the previously established methodology.
- Therefore, this study was performed to assess the activity of telavancin when tested against a worldwide collection of rarely isolated clinical pathogens using a revised BMD method (CLSI, 2014).[6]

## MATERIALS AND METHODS

### Bacterial strain collection

- A total of 3821 consecutive, non-duplicate Gram-positive clinical isolates were included in this study, which were collected from medical centres located in 12 countries in the Asia-Western Pacific region (35 sites), 21 countries in Europe and Israel (53 sites), 11 countries in Latin America (21 sites), and two countries in North America (110 sites).
- These isolates were recovered primarily from bacteraemia (44%), skin and soft-tissue (28%), and respiratory tract infections (8%) and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Programme for 2011–2013.
- Isolates were initially identified by the participating laboratory and the identification was confirmed by the reference monitoring laboratory (JMI Laboratories) by standard algorithms and supported by Vitek® 2 (bioMérieux, Hazelwood, Missouri, USA), and MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

### Antimicrobial susceptibility test methods

- Isolates were tested for susceptibility by BMD following the CLSI M07-A9 document method.[7]
- Testing was performed using dry-form panels manufactured by ThermoFisher Scientific (Cleveland, Ohio, USA). These panels were previously validated and shown to provide MIC results equivalent to the Food and Drug Administration (FDA) and CLSI-approved revised BMD method (supplemented with 0.002% P-80) described above.
- Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event.
- Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619).[6]
- Telavancin MIC ranges when tested against ATCC strains were those established during a QC study conducted according to the CLSI M23-A3 (2008) guideline document using the revised BMD method.[6]
- The MIC QC ranges for telavancin are available in the current M100-S24 document, as follows: *S. aureus* ATCC 29213 (0.03–0.12 mg/L); *E. faecalis* ATCC 29212 (0.03–0.12 mg/L); and *S. pneumoniae* ATCC 49619 (0.004–0.015 mg/L).[6]
- All QC results were within published acceptable ranges.
- The European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2014) breakpoint criteria were applied for comparator agents, as available.[8]

## RESULTS

- Only 27.6% of coagulase-negative staphylococci (CoNS) isolates were susceptible to oxacillin. Telavancin was similarly active against methicillin-susceptible ($MIC_{50/90}$, 0.03/0.06 mg/L) and -resistant ($MIC_{50/90}$, 0.06/0.06 mg/L) CoNS isolates.

**Table 1. Antimicrobial activity and MIC distribution for telavancin when tested against 3821 contemporary (2011–2013) and worldwide collection of clinical isolates**

| Genus / Group / Species (no. tested) | MIC (mg/L) 50% | MIC (mg/L) 90% | Number (cumulative %) inhibited at telavancin MIC (mg/L) ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 |
|---|---|---|---|---|---|---|---|
| *Staphylococcus* spp. (1656) | | | | | | | |
| *Staphylococcus capitis* (214) | 0.06 | 0.06 | 24 (11.2) | 72 (44.9) | 114 (98.1) | 3 (99.5) | 1 (100.0) |
| *Staphylococcus caprae* (42) | 0.06 | 0.06 | 1 (2.4) | 12 (31.0) | 28 (97.6) | 1 (100.0) | |
| *Staphylococcus cohnii* (27) | 0.06 | 0.06 | 1 (3.7) | 12 (48.1) | 13 (96.3) | 1 (100.0) | |
| *Staphylococcus haemolyticus* (425) | 0.06 | 0.06 | 24 (5.6) | 126 (35.3) | 262 (96.9) | 13 (100.0) | |
| *Staphylococcus hominis* (414) | ≤0.015 | 0.06 | 228 (55.1) | 127 (85.7) | 58 (99.8) | 1 (100.0) | |
| *Staphylococcus intermedius* (11) | ≤0.015 | ≤0.015 | 10 (90.9) | 1 (100.0) | | | |
| *Staphylococcus lugdunensis* (258) | ≤0.015 | 0.03 | 147 (57.0) | 98 (95.0) | 13 (100.0) | | |
| *Staphylococcus pettenkoferi* (18) | 0.06 | 0.12 | 0 (0.0) | 8 (44.4) | 4 (66.7) | 6 (100.0) | |
| *Staphylococcus saprophyticus* (106) | 0.06 | 0.12 | 3 (2.8) | 4 (6.6) | 58 (61.3) | 39 (98.1) | 2 (100.0) |
| *Staphylococcus simulans* (48) | 0.03 | 0.06 | 0 (0.0) | 24 (50.0) | 21 (93.8) | 3 (100.0) | |
| *Staphylococcus warneri* (93) | 0.06 | 0.06 | 4 (4.3) | 31 (37.6) | 51 (92.5) | 7 (100.0) | |
| Viridans group streptococci (1939) | | | | | | | |
| *Streptococcus anginosus* group (627) | ≤0.015 | 0.03 | 371 (59.2) | 238 (97.1) | 18 (100.0) | | |
| *Streptococcus anginosus* (434) | ≤0.015 | 0.03 | 227 (52.3) | 195 (97.2) | 12 (100.0) | | |
| *Streptococcus constellatus* (157) | ≤0.015 | 0.03 | 119 (75.8) | 36 (98.7) | 2 (100.0) | | |
| *Streptococcus intermedius* (36) | ≤0.015 | 0.06 | 25 (69.4) | 7 (88.9) | 4 (100.0) | | |
| *Streptococcus mitis* group (1039) | ≤0.015 | 0.03 | 604 (58.1) | 388 (95.5) | 46 (99.9) | 1 (100.0) | |
| *Streptococcus gordonii* (37) | 0.03 | 0.06 | 15 (40.5) | 18 (89.2) | 4 (100.0) | | |
| *Streptococcus mitis/oralis* (788) | ≤0.015 | 0.03 | 488 (61.9) | 268 (95.9) | 31 (99.9) | 1 (100.0) | |
| *Streptococcus parasanguinis* (101) | 0.03 | 0.03 | 43 (42.6) | 53 (95.0) | 5 (100.0) | | |
| *Streptococcus sanguinis* (113) | ≤0.015 | 0.03 | 58 (51.3) | 49 (94.7) | 6 (100.0) | | |
| Other viridans group streptococci (273) | | | | | | | |
| *Streptococcus bovis/gallolyticus* (126) | 0.03 | 0.03 | 61 (48.0) | 59 (94.5) | 6 (100.0) | | |
| *Streptococcus mutans* (14) | 0.03 | 0.06 | 3 (21.4) | 9 (85.7) | 2 (100.0) | | |
| *Streptococcus salivarius* (123) | ≤0.015 | 0.03 | 77 (62.6) | 38 (93.5) | 7 (99.2) | 1 (100.0) | |
| *Streptococcus vestibularis* (10) | ≤0.015 | ≤0.015 | 9 (90.0) | 1 (100.0) | | | |
| ß-haemolytic streptococci (157) | | | | | | | |
| *Streptococcus dysgalactiae* (143) | ≤0.015 | 0.03 | 109 (76.2) | 28 (95.8) | 5 (99.3) | 1 (100.0) | |
| *Streptococcus equisimilis* (14) | ≤0.015 | 0.06 | 7 (50.0) | 5 (85.7) | 2 (100.0) | | |
| Other Genus groups (69) | | | | | | | |
| *Corynebacterium* spp. (34) | ≤0.015 | 0.03 | 29 (82.9) | 4 (94.3) | 1 (100.0) | | |
| *Listeria* spp. (24) | ≤0.015 | 0.03 | 21 (87.5) | 3 (100.0) | | | |
| *Micrococcus* spp. (11) | ≤0.015 | ≤0.015 | 11 (100.0) | | | | |

- A total of 99.7% of CoNS isolates exhibiting vancomycin MIC results at ≥2 mg/L were inhibited by telavancin ($MIC_{50/90}$, 0.06/0.06 mg/L) at ≤0.12 mg/L (data not shown).
- In general, telavancin showed modal MIC and $MIC_{50}$ values of 0.06 mg/L among tested CoNS species. Slightly lower MIC results were noted for *S. hominis* ($MIC_{50}$, ≤0.015 mg/L), *S. lugdunensis* ($MIC_{50}$, ≤0.015 mg/L), and *S. simulans* ($MIC_{50}$, 0.03 mg/L; **Table 1**).
- Vancomycin (100.0% susceptible), teicoplanin (91.3% susceptible), daptomycin (99.8% susceptible), and linezolid (99.6% susceptible) demonstrated wide antimicrobial coverage against CoNS. However, telavancin ($MIC_{50}$, ≤0.015–0.06 mg/L) had $MIC_{50}$ results at least four-fold lower than vancomycin ($MIC_{50}$, 0.5–1 mg/L), daptomycin ($MIC_{50}$, 0.12–1 mg/L), and linezolid ($MIC_{50}$, 0.25–1 mg/L) against these CoNS species (data not shown).
- Streptococcal isolates exhibited $MIC_{50}$ values of ≤0.015 mg/L for telavancin. Exceptions were observed for *S. parasanguinis* ($MIC_{50/90}$, 0.03/0.03 mg/L), *S. bovis/gallolyticus* ($MIC_{50/90}$, 0.03/0.03 mg/L), *S. gordonii* ($MIC_{50/90}$, 0.03/0.06 mg/L), and *S. mutans* ($MIC_{50/90}$, 0.03/0.06 mg/L; **Table 1**).
- Other Gram-positive isolates such as *Micrococcus* spp., *Listeria* spp., and *Corynebacterium* spp. were also inhibited by telavancin MICs at ≤0.015, ≤0.03, and ≤0.06 mg/L, respectively.

## CONCLUSIONS

- Telavancin exhibited potent *in vitro* activity when tested against less common pathogens recovered from human clinical specimens. In addition, this investigation confirms the spectrum and potency of telavancin against these less commonly encountered Gram-positive species.
- The results presented here were obtained using a revised CLSI reference BMD method for telavancin that replaces the previously established susceptibility testing methodology. Therefore, this study provides new, markedly lower baseline MIC results for telavancin when tested against these less common pathogens.

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