Analysis of Vancomycin Susceptibility Testing Results for Presumptive Categorization of Telavancin

Short running title: Vancomycin to predict telavancin susceptibility

Intended category: Short-form

Rodrigo E. Mendes1*, David J. Farrell1, Robert K. Flamm1, Helio S. Sader1, and Ronald N. Jones1

JMI Laboratories, North Liberty, Iowa, USA

*Corresponding author: Rodrigo E. Mendes, Ph.D.
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
E-mail: rodrigo-mendes@jmilabs.com
Scattergrams between vancomycin and telavancin demonstrated susceptibility agreement rates of 99.96, 99.65 and 100.00\% for *Staphylococcus aureus*, *Enterococcus faecalis* and streptococci, respectively. A single very major error was obtained against *E. faecalis*, while vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant and teicoplanin-susceptible (VanB-phenotype) *E. faecalis* were responsible for the major and minor errors. These results support the use of vancomycin to infer telavancin susceptibility among indicated pathogens, except VISA, which should be tested for telavancin susceptibility.

Keywords: Susceptibility; Lipoglycopeptide; Surrogate.
Telavancin is a lipoglycopeptide antibiotic with potent in vitro bactericidal activity against Gram-positive bacteria including methicillin-susceptible (MSSA) and methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-intermediate S. aureus (VISA), heterogeneous (h)VISA, and multidrug-resistant (MDR) streptococci and enterococci (1). In 2014, the Food and Drug Administration (FDA) approved and published a revised broth microdilution susceptibility testing method for telavancin in a labeling supplement for the VIBATIV® (telavancin) package insert (2). This revised method was also published in the Clinical and Laboratory Standards Institute (CLSI) M100-S24 document (3), and breakpoint criteria for the revised method are available in the FDA package insert and European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2, 4).

Validated commercial susceptibility testing products/systems are not always available for all antimicrobial agents utilized in clinical practice, but when available, delays between drug regulatory approval and availability of respective testing device often occurs. Therefore, clinical microbiology laboratories have frequently applied the use of a “surrogate” agent to predict susceptibility of organisms to another, yet similar antimicrobial agent. This strategy minimizes the number of agents to be tested against a certain species or group of organisms, and/or provides susceptibility results for a given drug when a validated commercial product is not yet available (3). The revision of the telavancin broth microdilution method provided additional challenges for the availability of commercial susceptibility testing products. In fact, only Etest (research use only) and dry-form plates produced by ThermoFisher Scientific (FDA-approved device) were available at the time this article was written. This study evaluated the potential use of vancomycin for predicting telavancin susceptibility results.

As part of the SENTRY Antimicrobial Surveillance Program for the USA, Europe and adjacent regions, a total of 15,314 S. aureus (including six vancomycin-resistant [VRSA], six vancomycin-intermediate [VISA] strains and ten heterogeneous vancomycin-intermediate [hVISA]), 1,991 Enterococcus faecalis (44 vancomycin-resistant [VRE]), 1,155 viridans group streptococci (VGS), and 2,424 β-hemolytic streptococci (BHS) were included in this study. The challenge set of VRSA, hVISA and VISA isolates (one originated from the SENTRY Program) was provided by the Network on Antimicrobial Resistance in S. aureus (NARSA) or other JMI collections. Identification of clinical isolates was initially performed by the participating laboratory
and confirmed by the reference monitoring laboratory by standard algorithms and supported by MALDI-TOF-MS (Bruker Daltonics, Bremen, Germany).

Isolates were tested for susceptibility by broth microdilution following CLSI guidelines (5). Telavancin was tested using the revised method according to CLSI (6) and product package insert (2). The minimum inhibitory concentration (MIC) values were quality assured by concurrent testing of *S. aureus* (ATCC 29213) and *E. faecalis* (ATCC 29212) (3). The following telavancin MIC interpretations were applied: *S. aureus* at ≤0.12 μg/ml for susceptible; *E. faecalis* (vancomycin-susceptible) at ≤0.25 μg/ml for susceptible; *Streptococcus pyogenes* and *Streptococcus agalactiae* at ≤0.12 μg/ml for susceptible; and *Streptococcus anginosus* group at ≤0.06 μg/ml for susceptible (2). The CLSI M100-S25 (2015) breakpoint criteria were applied for vancomycin and teicoplanin (3).

Data analysis followed the intermethod comparison guidelines found in CLSI documents (M23-A3), and scattergrams and error rates were generated (7). As there is no intermediate or resistant category for telavancin, non-susceptible results were considered as resistant to meet the error’s definition for the purpose of this analysis. Therefore, errors were defined as very major (vancomycin-susceptible and telavancin-resistant [or any non-susceptible]); major (vancomycin-resistant and telavancin-susceptible); and minor (vancomycin-intermediate and telavancin-susceptible or vancomycin-intermediate and telavancin-resistant [or any non-susceptible]). A categorical agreement rate of ≥90.0%, and very major, major and minor error rates of ≤1.5, ≤3.0 and 5.0% were considered acceptable, respectively (7).

Table 1 shows a summary of categorical agreement results and error rates obtained when performing an intermethod comparison analysis between telavancin and vancomycin tested against a recent collection of Gram-positive isolates. Telavancin was active against all 15,302 vancomycin-susceptible *S. aureus*, including hVISA (telavancin MIC, 0.06 – 0.12 μg/ml; vancomycin MIC, 1 – 2 μg/ml). Telavancin MIC results of 0.12 – 0.25 and ≥1 μg/ml were obtained against VISA and VRSA isolates, respectively (Figure 1A). These MIC results provided an overall categorical agreement rate of 99.96% for *S. aureus*. Minor errors (0.04%) occurred against six VISA isolates, which were susceptible or resistant (non-susceptible) to telavancin (Table 1 and Figure 1A).

When tested against *E. faecalis*, categorical agreement rates of 99.65% or 99.95% were obtained against all isolates or the vancomycin-susceptible set (Table 1). A single (0.05%) very major error (a
confirmed false-susceptibility result; vancomycin-susceptible and telavancin-non-susceptible) was observed.

Other major (7.3%) and minor (0.15%) errors were noted for six VRE isolates displaying a VanB-phenotype. These VanB-type isolates were susceptible to telavancin (when applying the breakpoint for vancomycin-susceptible E. faecalis) and intermediate (MIC, 8 – 16 μg/ml) or resistant (MIC, ≥32 μg/ml) to vancomycin and teicoplanin-susceptible (MIC, ≤8 μg/ml; Table 1 and Figure 1B). All streptococcal isolates included in this investigation were telavancin- and vancomycin-susceptible, and these comparison analyses resulted in absolute categorical agreement rates (Table 1 and Figures 1C – E).

Overall, high categorical agreement rates were observed between telavancin and vancomycin. However, the data presented here has limitations. The number of isolates resistant (or non-susceptible) to telavancin (and vancomycin) was limited due to the in vitro potent characteristic of the drug(s), especially against streptococci (8, 9). The results suggest that susceptibility to vancomycin does predict susceptibility to telavancin, and non-susceptibility to vancomycin does predict non-susceptibility to telavancin against E. faecalis and S. aureus, including hVISA and VRSA. The only exceptions were noted against VISA and VanB-phenotype E. faecalis (not an indicated species in the prescribing information) (2), due to greater activity of telavancin compared to vancomycin. Moreover, telavancin and vancomycin non-susceptible isolates remain non-existent, and precludes from susceptibility testing. As vancomycin remains widely available (in commercial products/systems) and tested in microbiology laboratories, these results show that it can be utilized as a surrogate marker for reporting telavancin susceptibility (>99.99% accuracy). VISA isolates require susceptibility testing for telavancin using the reference broth microdilution or other validated testing method. Alternatively, the isolate should be forwarded to a reference laboratory.
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Table 1. Summary of categorical agreement results and error rates between telavancin and vancomycin where tested against Gram-positive isolates.

<table>
<thead>
<tr>
<th>Pathogena (no. tested)</th>
<th>Error rate (number of errors)</th>
<th>% CAc</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Very major</td>
<td>Major</td>
</tr>
<tr>
<td>S. aureus (15,314)</td>
<td>0.00 (0)</td>
<td>0.00 (0)</td>
</tr>
<tr>
<td>MRSA (5,985)</td>
<td>0.00 (0)</td>
<td>0.00 (0)</td>
</tr>
<tr>
<td>E. faecalisd (1,991)</td>
<td>0.05 (1)</td>
<td>7.3 (3)</td>
</tr>
<tr>
<td>Vancomycin-susceptible (1,947)</td>
<td>0.05 (1)</td>
<td>NA</td>
</tr>
<tr>
<td>BHS (2,424)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>VGS (1,155)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

a. MRSA = methicillin-resistant S. aureus; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
b. Very major = vancomycin-susceptible and telavancin-resistant (or non-susceptible for the purpose of this analysis); Major = vancomycin-resistant and telavancin-susceptible; Minor = vancomycin-intermediate and telavancin-susceptible or telavancin-resistant (or non-susceptible). NA = not applicable due to absence non-susceptible isolates.
c. CA = Categorical agreement rate.
d. A single (0.05%) very major error (false-susceptibility) and a 99.95% agreement rate if only vancomycin-susceptible isolates were analyzed.
Figure 1A. Scattergram comparing the telavancin and vancomycin MIC results tested against 15,314 S. aureus isolates. The horizontal darker line represents FDA-approved telavancin susceptible breakpoint (≤0.12 μg/ml) for S. aureus, while vertical darker lines represent the vancomycin breakpoints (≤2 μg/ml for susceptible; 4 – 8 μg/ml for intermediate; and ≥16 μg/ml for resistant). * Isolates considered telavancin-resistant for the purpose of this analysis.

Figure 1B. Scattergram comparing the telavancin and vancomycin MIC results tested against 1,991 E. faecalis isolates. The horizontal darker line represents FDA-approved telavancin susceptible breakpoint vancomycin-susceptible E. faecalis (≤0.25 μg/ml), while vertical darker lines represent the vancomycin breakpoints (≤4 μg/ml for susceptible; 8 – 16 μg/ml for intermediate; and ≥32 μg/ml for resistant) for E. faecalis. * Isolates considered telavancin-resistant for the purpose of this analysis.
Table 1.

<table>
<thead>
<tr>
<th>Telavancin MIC (μg/ml)</th>
<th>Vancomycin MIC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>37 12</td>
</tr>
<tr>
<td>0.03</td>
<td>15 349 76</td>
</tr>
<tr>
<td>≤0.015</td>
<td>8 89 492 77</td>
</tr>
<tr>
<td>≤0.12</td>
<td>8 89 492 77</td>
</tr>
<tr>
<td>0.25</td>
<td>0.5 1 2 4 8 16 &gt;16</td>
</tr>
<tr>
<td>0.5</td>
<td>0.25 0.5 1 2 4 8 16 &gt;16</td>
</tr>
<tr>
<td>1</td>
<td>0.25 0.5 1 2 4 8 16 &gt;16</td>
</tr>
<tr>
<td>2</td>
<td>0.25 0.5 1 2 4 8 16 &gt;16</td>
</tr>
<tr>
<td>&gt;2</td>
<td>0.25 0.5 1 2 4 8 16 &gt;16</td>
</tr>
</tbody>
</table>

Figure 1C. Scattergram comparing the telavancin and vancomycin MIC results tested against 1,155 viridans group streptococcal clinical isolates. The horizontal darker line represents FDA-approved telavancin susceptible breakpoint (≤0.06 μg/ml) for the S. anginosus group, while vertical darker lines represent the vancomycin susceptible breakpoint (≤1 μg/ml for susceptible) for viridans group streptococci.

Figure 1D. Scattergram comparing the telavancin and vancomycin MIC results tested against 336 S. anginosus group. The horizontal darker line represents FDA-approved telavancin susceptible breakpoint (≤0.06 μg/ml) for the S. anginosus group, while vertical darker lines represent the CLSI vancomycin susceptible breakpoint (≤1 μg/ml for susceptible) for viridans group streptococci.
Telavancin MIC (μg/ml) | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | >2
---|---|---|---|---|---|---|---|---|---
Vancomycin MIC (μg/ml) | 2 | 4 | 1 | 0.5 | 0.25 | 0.12 | ≤0.015 | ≤0.015 | ≤0.015

Figure 1E. Scattergram comparing the telavancin and vancomycin MIC results tested against 2,424 β-hemolytic streptococci (includes 1,052 S. pyogenes, 963 S. agalactiae, 141 S. dysgalactiae and 268 other species). The horizontal darker line represents FDA-approved telavancin susceptible breakpoint (≤0.12 μg/ml) for S. pyogenes and S. agalactiae, while vertical darker lines represent the vancomycin susceptible breakpoint (≤1 μg/ml for susceptible) for β-hemolytic streptococci.