Measurement of vancomycin susceptibility has been shown to be highly predictive as a surrogate measure of oritavancin susceptibility among clinically indicated Gram-positive species. Results of studying over 30,000 pathogens (from 2011 to 2014) by cross-susceptibility analysis and determining the poor reproducibility of oritavancin-nonsusceptible results showed nearly perfect surrogate testing accuracy (99.86 to 99.94%). Any isolate of an indicated organism species with locally reproducible oritavancin-nonsusceptible results (extremely rare) should be referred to a reference laboratory for confirmation of the results and determination of the resistance mechanism.

TABLE 1 Accuracy of vancomycin susceptibility test results (2011 to 2013) to infer susceptibility to oritavancin at U.S. FDA-approved breakpoints (14) for indicated Gram-positive pathogens (22,606 isolates)

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of isolates tested</th>
<th>Surrogate accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>17,717</td>
<td>98.8</td>
</tr>
<tr>
<td>β-Hemolytic streptococci</td>
<td>2,357</td>
<td>98.1</td>
</tr>
<tr>
<td>S. anginosus group</td>
<td>368</td>
<td>100.0</td>
</tr>
<tr>
<td>E. faecalis, vancomycin</td>
<td>2,164</td>
<td>99.7</td>
</tr>
<tr>
<td>susceptible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>22,606</td>
<td>98.85</td>
</tr>
</tbody>
</table>

Notes:

- a Indicated species with interpretive criteria only (14).
- b Includes Streptococcus pyogenes, S. agalactiae, and S. dysgalactiae.
- c Includes Streptococcus anginosus, Streptococcus constellatus, and Streptococcus intermedius.

Oritavancin, a novel lipoglycopeptide, was recently approved for single-dose treatment of acute bacterial skin and skin structure infections (ABSSSIs) in the United States and Europe (1, 2). The compound (formerly LY333328) has a long history of in vitro evaluations and drug development, dating from the late 1990s (3–5) and documenting a broad anti-Gram-positive organism spectrum comparable to those of vancomycin and teicoplanin. Initial worldwide surveillance (5) suggested that oritavancin had activity similar to that of existing glycopeptides; reference methods were subsequently modified to recognize the greater oritavancin activity (8- to 16-fold superior) against Staphylococcus aureus and various streptococcal species (1, 2, 6, 7).

The physicochemical characteristics of lipoglycopeptides (oritavancin, dalbavancin, and telavancin) are particularly challenging for the development of standardized in vitro susceptibility testing methods. Poor drug diffusion through agar-based media limits the application of the agar disk diffusion method, as published by several international standards organizations (8), and the binding of drug to various plastics compromises dilution MIC testing (7, 9). Reference broth microdilution methods (10, 11) for oritavancin require the surfactant polysorbate-80 (P-80) (0.002%) to recognize full antimicrobial potency, and adaption of commonly used commercial devices appears to be uncertain. Such delays in the use of commercial susceptibility testing systems to direct oritavancin chemotherapy may necessitate alternative testing strategies, such as the use of vancomycin susceptibility testing results as a surrogate predictive measure (12). In this investigation, (i) we update the analysis of 2011-2013 oritavancin surveillance results (12) for validation of the use of vancomycin MIC results to infer oritavancin susceptibility, following retesting of strains with previous nonsusceptible results, and (ii) we present 2014 oritavancin surveillance data to confirm the high predictive value of surrogate vancomycin testing for oritavancin susceptibility.

European and U.S. oritavancin resistance surveillance isolates from 2011 to 2013 (26,993 isolates; 22,606 indicated species) and 2014 (10,002 isolates; 7,688 indicated species) were tested by validated reference broth microdilution methods (10). For species and antimicrobial-resistant subset details, refer to Tables 1 and 2, as well as to reference 12. The interpretive breakpoint criteria used for oritavancin were those selected by the U.S. Food and Drug Administration (FDA) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the criteria for vancomycin were those published by the Clinical and Laboratory Standards Institute (CLSI) (11, 13–15). All quality control (QC) results were within published ranges (13), using the following QC organisms: S. aureus ATCC 29213, Enterococcus faecalis ATCC 29212, and Streptococcus pneumoniae ATCC 49619.

An earlier publication (12) quantified the predictive accuracy of using vancomycin susceptibility to infer susceptibility to orita-
TABLE 2 Accuracy of vancomycin susceptibility test results (2014) to infer susceptibility to oritavancin at U.S. FDA-approved breakpoints (14) for indicated Gram-positive species groups (10,002 isolates)

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of isolates tested</th>
<th>Surrogate accuracy (% [no. of nonsusceptible isolates])</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5,609</td>
<td>&gt;99.9 (3)</td>
</tr>
<tr>
<td>CoNS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>641</td>
<td>100.0 (0)</td>
</tr>
<tr>
<td>β-Hemolytic streptococci&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,049</td>
<td>99.2 (8)</td>
</tr>
<tr>
<td>S. anginosus group&lt;sup&gt;a&lt;/sup&gt;</td>
<td>178</td>
<td>100.0 (0)</td>
</tr>
<tr>
<td>S. pneumoniae&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1,673</td>
<td>100.0 (0)</td>
</tr>
<tr>
<td>Enterococci&lt;sup&gt;a&lt;/sup&gt;</td>
<td>852</td>
<td>100.0 (0)</td>
</tr>
<tr>
<td>Overall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7,688</td>
<td>99.86 (11)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes the indicated species (Staphylococcus aureus, Streptococcus pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus, S. constellatus, S. intermedius, and vancomycin-susceptible E. faecalis among all enterococci).

<sup>b</sup> S. aureus interpretive criteria (susceptible, \(0.12 \mu g/ml\)) were applied to coagulase-negative staphylococci (CoNS) and pneumococci for the vancomycin surrogate test comparison only; no errors were observed.

Oritavancin (Table 1). Across all U.S. FDA-indicated species for oritavancin treatment (22,606 isolates) (14), the surrogate accuracy was 98.85%, ranging from 98.7% (β-hemolytic streptococci) to 100.0% (S. anginosus group and vancomycin-susceptible E. faecalis); the overall accuracy was 99.86%. It should be noted that, among all enterococci tested (1,086 isolates), seven vancomycin-intermediate isolates had oritavancin MIC values of 0.004 to 0.015 \(\mu g/ml\). Although oritavancin is not approved for the treatment of infections caused by vancomycin-resistant enterococci (VRE) (E. faecalis or Enterococcus faecium), 200 VRE isolates tested in this study had oritavancin MIC values ranging from 0.002 to 1 \(\mu g/ml\) and an MIC<sub>90</sub> of only 0.12 \(\mu g/ml\) (data not shown). Figure 2 illustrates the high cross-susceptibility rate (>99.9%) among the 5,609 S. aureus isolates in 2014.

Also found in Table 2 for the 2014 surveillance isolates are the cross-susceptibility statistics for coagulase-negative staphylococci (CoNS) (641 isolates) and S. pneumoniae (1,673 isolates); oritavancin is not indicated for either species (14). All of the isolates for these two pathogen groups were vancomycin susceptible (MICs of ≤1 or =2 \(\mu g/ml\), respectively), except for one isolate of vancomycin-intermediate CoNS. Oritavancin was also very active, with all MIC results being ≤0.06 and ≤0.12 \(\mu g/ml\) for the pneumococci and CoNS, respectively.

Oritavancin has a remarkable combination of high antimicrobial activity against prevalent Gram-positive pathogens (1, 2) and a pharmacokinetic (PK)/pharmacodynamic (PD) profile that justifies single-dose intravenous therapy for ABSSSIs (14, 16, 17). Favorable results from the phase III SOLO I and SOLO II trials demonstrated comparable (noninferior) outcomes, compared to vancomycin-containing regimens (18, 19). Additional in vitro investigations support potential future studies regarding use against VRE infections (20), methicillin-resistant S. aureus (MRSA) infections with the novel mecC gene mechanism or infections emerging in the community setting (21, 22), some S. aureus strains with elevated vancomycin MIC values or heteroresistant variations (23, 24), and uncommonly isolated Gram-positive species (25). Furthermore, favorable in vitro drug combination (synergy) results have been reported for oritavancin testing against staphylococci (26).

FIG 1 Chart comparing vancomycin and oritavancin MIC results for 17,717 S. aureus isolates obtained between 2011 and 2013. Data for 60 vancomycin-intermediate S. aureus isolates (vancomycin MICs of 4 or 8 \(\mu g/ml\)) and 10 vancomycin-resistant S. aureus isolates (MICs of 64 to 1,024 \(\mu g/ml\)) are also shown (originally reported in reference 24). CLSI breakpoints (solid vertical line) and U.S. FDA breakpoints (dashed horizontal line) for vancomycin and oritavancin, respectively (13, 14), as modified from the report by Jones et al. (12), are shown.

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With this favorable microbiological, PK/PD, and clinical trial background, oritavancin provides a valuable addition to our antimicrobial armamentarium to treat infections caused by resistant Gram-positive cocci. Unfortunately, direct measurements of oritavancin susceptibility in hospital clinical microbiology laboratories will be compromised by the technical difficulties of in vitro testing for this antimicrobial class (lipoglycopeptides) (7, 9). A highly accurate and simple solution would be to utilize the test results for another drug in the same class (vancomycin, a glycopeptide of lesser potency) to predict oritavancin susceptibility. The results of a 4-year cross-susceptibility analysis of surveillance isolates from the United States and Europe reported here (Tables 1 and 2) confirm the nearly perfect accuracy (99.86 to 99.94%) of this testing option across all species listed by regulators for oritavancin therapy (11, 14). The occurrences of nonsusceptibility to oritavancin among contemporary Gram-positive clinical isolates is exceedingly rare. When oritavancin in vitro tests become available and such oritavancin-nonsusceptible values are observed (a very low probability), the test should be repeated to ensure reproducibility.

Finally, the background data presented here in part have led to the following statements in the oritavancin U.S. FDA product labeling: “The current absence of resistant isolates precludes defining any results other than ‘Susceptible.’ Isolates yielding test results other than ‘Susceptible’ should be retested, and if the result is confirmed, the isolate should be submitted to a reference laboratory for further testing” (14). The recommendation that susceptibility to dalbavancin, oritavancin, and telavancin can be inferred from the vancomycin susceptibility results is also found in the USCAST breakpoint tables (27). Furthermore, the EUCAST has published the following three relevant guidelines regarding oritavancin tests and breakpoints (15).

### REFERENCES

7. Arhin FF, Sarmiento I, Kelley A, McKay GA, Draghi DC, Grover P,
Vancomycin Results Imply Oritavancin Susceptibilities


