

Evaluation of Vancomycin Susceptibility Testing for Methicillin-Resistant *Staphylococcus aureus*: Comparison of Etest and Three Automated Testing Methods

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We evaluated the ability of four commercial MIC testing systems (MicroScan, Vitek 2, Phoenix, and Etest) to detect vancomycin MIC values of ≤ 1 to ≥ 2 in 200 methicillin-resistant *Staphylococcus aureus* (MRSA) strains compared to the Clinical and Laboratory Standards Institute broth microdilution (BMD) reference methods. Compared to the BMD method, absolute agreement ($0 \pm$ dilution) was highest for the Phoenix system (66.2%) and the MicroScan turbidity method (61.8%), followed by the Vitek 2 system (54.3%). The Etest produced MIC values 1 to 2 dilutions higher than those produced by the BMD method (36.7% agreement). Of interest, the MicroScan system (prompt method) was more likely to overcall an MIC value of 1 mg/liter (74.1%), whereas the Phoenix (76%) and Vitek 2 (20%) systems had a tendency to undercall an MIC of 2 mg/liter. The ability to correctly identify vancomycin MIC values of 1 and 2 has clinical implications and requires further evaluation.

The overall prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) continues to increase, with vancomycin (VAN) remaining the mainstay of therapy for serious infections (1–3). Over the last several years, there have been a number of studies that have demonstrated an association between vancomycin MICs of 1.5 or 2 mg/liter and failure of vancomycin therapy, even though these values lie within the Clinical and Laboratory Standards Institute's (CLSI's) and the FDA's acceptable vancomycin susceptibility range (≤ 2 mg/liter). The majority of these reports were derived from patients with MRSA-complicated bacteremia in whom a vancomycin MIC of 1.5 or 2 mg/liter was associated with persistent signs and symptoms of infection, including prolonged days of bacteremia, increased complications, increased lengths of hospital stay, and mortality (4–9). A recent observational study of 532 patients with MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia noted a significantly higher 30-day mortality rate associated with patients who had an isolate for which the MIC exceeded 1.5 mg/liter (by Etest methods). Of interest, this association did not seem to be related to vancomycin treatment, since patients who had MSSA bacteremia with an elevated vancomycin MIC and were treated with flucloxacillin had worse clinical outcomes than flucloxacillin-treated patients with MSSA bacteremia that had a lower vancomycin MIC value ($P = 0.012$) (10). In addition, a recent systematic review and meta-analysis of the literature regarding the relationship of vancomycin susceptibility and patient outcome concluded that vancomycin MIC values of 1.5 or 2 mg/liter were associated with greater treatment failure and mortality rates in patients with MRSA infections (11). Patients who have serious high-inoculum infections (i.e., infective endocarditis, medical device infections, etc.) with MRSA and for which the strain has been identified as heteroresistant vancomycin-intermediate *S. aureus* (hVISA) are also more likely to experience prolonged days of bacteremia, increased complications, multiple drug resistance, and relapse or recurrence of infection than those patients with suscep-

tible strains (12–18). It has been demonstrated that some percentage of hVISA infections exist within the vancomycin susceptibility range and that the prevalence of these strains increases as the MIC reaches up to the breakpoint of 2 mg/liter (19–21). Taken together, these results suggest that in patients with serious, complicated, high-inoculum infections treated with vancomycin, the likelihood of treatment failure is greater when the *S. aureus* isolates demonstrate an MIC that exceeds 1 mg/liter.

The patient's exposure to vancomycin relative to the susceptibility of the organism to vancomycin is also a predictor of patient outcome. Based on *in vitro*, animal, and clinical data, it has been suggested that a specific vancomycin pharmacokinetic and pharmacodynamics (PK/PD) 24-hour area under the curve (AUC_{24})/MIC ratio target of ≥ 400 should be obtained in order to improve the outcomes of patients with severe staphylococcal infections, such as complicated bacteremia (3, 8). However, when the MIC is 2 mg/liter, obtaining this ratio is highly unlikely without exceeding vancomycin doses that would cause serious adverse events (22–24). Of interest, the inability to achieve this vancomycin PK/PD target when the MIC is 2 mg/liter is specifically mentioned in the recent vancomycin consensus guidelines and the Infectious Disease Society of America (IDSA) MRSA guidelines (25). Although the patient's clinical response to vancomycin therapy should be the primary consideration irrespective of the van-

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TABLE 1 Comparison of BMD with the automated systems and Etest MIC results

| Consensus log ₂ MICs per BMD method | Susceptibility testing system (no. tested) | No. (%) of isolates with a log ₂ dilution variation ^a (compared to the reference BMD) of: | | | | |
|--|--|---|-----------|------------|------------|----------|
| | | -2 | -1 | 0 | +1 | +2 |
| 0.25 < MIC < 8 | MicroScan prompt (210) | — | — | 72 (34.3) | 131 (62.4) | 7 (3.3) |
| | MicroScan turbidity (207) | — | 4 (1.9) | 128 (61.8) | 75 (36.2) | — |
| | Phoenix (210) | — | 56 (26.7) | 139 (66.2) | 15 (7.1) | — |
| | Vitek 2 (210) | 2 (1.0) | 68 (32.3) | 114 (54.3) | 26 (12.4) | — |
| | Etest (210) | — | — | 77 (36.7) | 126 (60.0) | 7 (3.3) |
| MIC = 0.5 | MicroScan prompt (52) | — | — | 8 (15.4) | 37 (71.1) | 7 (13.5) |
| | MicroScan turbidity (51) | — | — | 15 (29.4) | 36 (70.6) | — |
| | Phoenix (52) | — | — | 44 (84.6) | 8 (15.4) | — |
| | Vitek 2 (52) | — | — | 38 (73.1) | 14 (26.9) | — |
| | Etest (210) | — | 9 (17.3) | 37 (71.1) | 6 (11.6) | — |
| MIC = 1 | MicroScan prompt (120) | — | — | 31 (25.8) | 89 (74.1) | — |
| | MicroScan turbidity (118) | — | 1 (0.8) | 82 (69.5) | 35 (29.7) | — |
| | Phoenix (120) | — | 37 (30.8) | 81 (67.5) | 2 (1.7) | — |
| | Vitek 2 (120) | — | 63 (52.5) | 50 (41.7) | 7 (5.8) | — |
| | Etest (210) | — | 40 (33.3) | 79 (65.9) | 1 (0.8) | — |
| MIC = 2 | MicroScan prompt (25) | — | — | 23 (92.0) | 2 (8.0) | — |
| | MicroScan turbidity (25) | — | 3 (12.0) | 21 (84.0) | 1 (4.0) | — |
| | Phoenix (25) | — | 19 (76.0) | 5 (20.0) | 1 (4.0) | — |
| | Vitek 2 (25) | 2 (8.0) | 3 (12.0) | 17 (68.0) | 3 (12.0) | — |
| | Etest (25) | — | — | 20 (80.0) | 5 (20.0) | — |

^a —, no value found at this dilution.

comycin MIC value, there has been increasing importance placed on vancomycin susceptibility for clinical decision making, especially when the patient's condition is worsening or not responding to therapy (3, 25–27).

Most investigations that evaluated the precision of automated susceptibility testing for vancomycin versus verified referenced MIC values used the essential agreement method (the MIC \pm 1 log₂ dilution). Based on the results of these studies, investigators have concluded that there are no major differences between automated systems for determining the vancomycin MIC value (28, 29).

However, several recent reports pointed out discrepancies in the ability of automated susceptibility testing methods to determine the vancomycin MIC for MRSA compared to the ability of the Etest or standard broth microdilution (BMD) methods (30, 31, 32). Based on the MRSA and vancomycin dosing and monitoring guidelines' emphasis on the importance of vancomycin susceptibility for clinical decision making, it is important to know the precision of automated MIC testing (3, 25). Therefore, our objective was to compare the ability of the currently available commercial automated BMD susceptibility testing methods (Vitek 2, MicroScan, and BD Phoenix) to identify vancomycin MIC values compared to standard reference BMD and Etest methods for MRSA.

MATERIALS AND METHODS

A collection of 200 clinical MRSA blood isolates was selected from an 1,800-isolate collection from nine U.S. medical centers (one from each consensus region) collected between 2002 and 2006, and 10 control strains with an MIC range of 0.25 to 8 mg/liter were utilized (33). Vancomycin MIC values were determined in two separate laboratories, in duplicate, using reference broth microdilution (frozen-form panels) and

Etest methods. Frozen panels were prepared with 36 precise incremental dilutions ranging from 64 to 0.06 mg/liter, thus mimicking the Etest strip scale for comparison purposes. The CLSI standards for microdilution methods were followed throughout with quality control strains within published guidelines (34). Vancomycin susceptibility was determined with the Etest according to the manufacturer's instructions (bioMérieux, Durham, NC). A consensus MIC value was established for vancomycin using MIC values provided by the two reference laboratories. For example, for a 0.5-doubling-dilution difference, the higher MIC value was selected. If an MIC differed by a 1-dilution difference, the median value was selected as the consensus MIC. Meanwhile, the 10 control strains and 200 challenge strains were sent to the three outside clinical laboratories to determine the vancomycin MIC values by the three different automated testing systems. These included the BD Phoenix automated microbiology system (Franklin Lakes, NJ), the panel type PMIC/ID-107, the MicroScan WalkAway (Dade Behring, Deerfield, IL), the PC33 and the Vitek 2 (bioMérieux, Hazelwood, MO), and the AST-GP70. In order to evaluate the performance of the various automated BMD methods, the incremental reference scale MIC values were converted to the CLSI-referenced log₂-based microdilutions. The Etest method results were compared to those of the incremental reference microdilution using the exact-dilution scale and with the MIC rounded up to the next dilution. The differences between the automated systems and the reference BMD method were calculated by the essential agreement method (MIC = 0 \pm dilution and \pm 1 log₂ dilution), as previously described (35).

RESULTS

The reference laboratory consensus vancomycin MICs for the BMD and Etest methods ranged from 0.25 to 6 and 0.5 to 8 mg/liter, respectively. Comparing the MIC results between the two reference laboratories, out of the 210 strains evaluated, there were 9 (4.2%) strains that differed by \pm 1 log₂ dilution, there was 1 strain (0.4%) that differed by 2 log₂ dilutions, and there were no

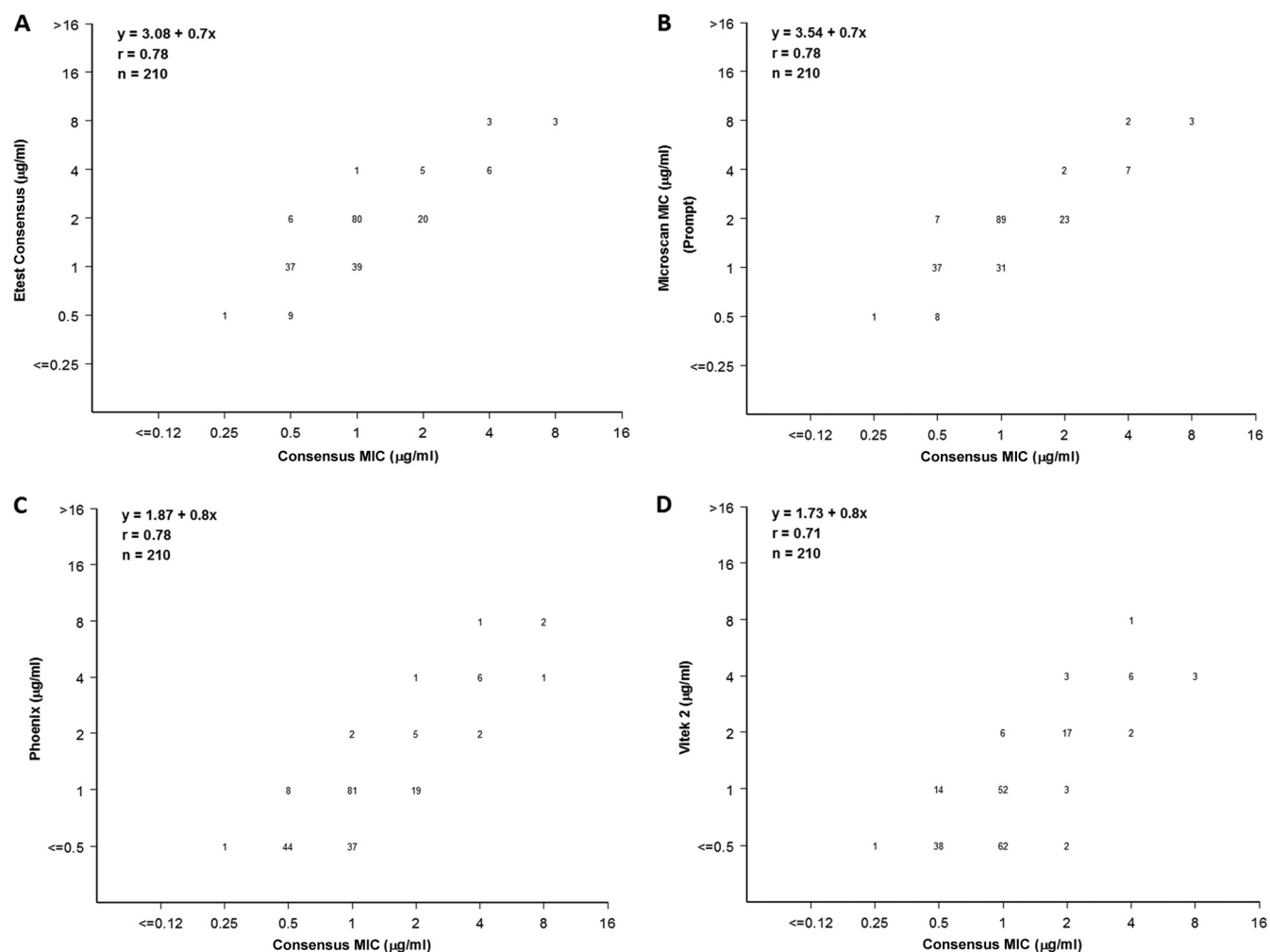


FIG 1 Scattergrams of the correlation between vancomycin MICs obtained by the broth microdilution method performed with frozen panels and the Etest (A), the MicroScan (B), the Phoenix (C), and the Vitek 2 (D) systems.

strains that differed by $>2 \log_2$ dilutions, resulting in very few instances where the consensus rule had to be applied. Overall, the Etest results tended to be higher than those of the broth microdilution values by 1 to 2 \log_2 dilutions for the two reference laboratories. The overall results for the BMD reference method, the Etest, and the commercial automated susceptibility testing methods are listed in Table 1. The results are presented as the \log_2 dilution variation from the reference BMD. Figure 1 shows scattergram plots of each method compared to the reference consensus vancomycin MIC. The MicroScan system has two methods for organism plate inoculation. Both the prompt and turbidity method results are listed in Table 1. All the methods displayed some variation compared to the reference BMD method. Agreement ($\pm 0 \log_2$ dilution) was the highest for the Phoenix (66.2%) and the MicroScan turbidity method (61.8%), followed by the Vitek 2 system at 54.3%. The lowest agreement noted was for the MicroScan prompt method at 34.3%, followed by the Etest at 36.7%. A one-dilution overcall was highest for the MicroScan prompt method (62.4%), followed by the Etest at 60% and the MicroScan turbidity method at 36.2%. The Vitek 2 and the Phoenix systems were more likely to undercall the vancomycin MIC by

1 dilution at 32.3 and 26.7%, respectively. Of note, using a $\pm 1 \log_2$ dilution agreement scale, all of the automated systems provided 100% agreement, except for the Vitek 2 (99%), the MicroScan (prompt method, 96.7%), and the Etest (96.7%).

When examining the specific MIC values of 0.5, 1, and 2 mg/liter (Table 1), the MicroScan prompt and turbidity methods tended to overcall the MIC of 0.5 mg/liter by 1 dilution at 71.1 and 70.6%, respectively. The Phoenix and Vitek 2 systems overcalled by 1 dilution at 15.4 and 26.9%, respectively. At the vancomycin MIC of 1 mg/liter, the MicroScan prompt and turbidity methods overcalled by 74.1 and 29.7%, respectively. However, the Phoenix and Vitek 2 systems had a tendency to undercall by 30.8 and 52.5%, respectively. The Etest was 1 dilution higher (11.6%) and 1 dilution lower (17.3%) at an MIC of 0.5 mg/liter and 1 dilution higher (0.8%) and 1 dilution lower (33.3%) at an MIC of 1 mg/liter.

There was a total of 25 isolates that the reference laboratories identified with a vancomycin MIC value of 2 mg/liter (Table 1). All 25 strains were further evaluated by a modified population analysis as described elsewhere for hVISA (19). There were 19 (76%) that were found to be hVISA among these stains.

For these 25 strains, the $\pm 0 \log_2$ dilution agreement was the highest with the MicroScan prompt and turbidity methods (92 and 84%, respectively) followed by the Etest (80%). The MicroScan turbidity method, however, undercalled 3 strains (12%), and all of them were hVISA with the propensity to fail vancomycin therapy (18). In contrast, neither the Etest nor the MicroScan prompt method undercalled any of the strains with vancomycin MICs of 2 mg/liter (Fig. 1). The most alarming result regarding the identification of an organism with a vancomycin MIC value of 2 mg/liter, especially in hVISA, was observed with the Phoenix system, with a $\pm 0 \log_2$ agreement of 20% (5 strains), and 19 isolates were undercalled (76%), including 18 hVISA strains. Finally, the Vitek 2 system had a $\pm 0 \log_2$ agreement of 68% (17 strains), but 5 strains (20%) were undercalled by 1 or 2 \log_2 dilutions, all of them being hVISA.

DISCUSSION

In patients with serious *S. aureus* infections, such as pneumonia and complicated bacteremia, including infective endocarditis, a vancomycin MIC of >1 mg/liter has been associated with poor patient outcomes (11). Although a vancomycin MIC value of 2 mg/liter should not be the only deciding factor for whether to change the therapy to alternative agents, it is an important consideration when assessing a patient's response to vancomycin therapy. In the recent IDSA MRSA guidelines, the management of persistent vancomycin treatment failures in adult patients is thoroughly discussed. Although declaring a treatment failure is a complex issue, it is recommended that an alternative therapy to vancomycin be considered when patients are persistently bacteremic or have a worsening clinical condition despite adequate debridement and removal of infection foci or if the vancomycin MIC is 2 mg/liter, especially in critically ill patients (25). Therefore, the ability to determine the vancomycin MIC with some degree of precision is important to clinical decision making. In addition, it has been reported that the proportion of hVISA is higher for isolates demonstrating an MIC value of 2 mg/liter (19–21). Since hVISA is associated with poor patient outcomes, including persistent infections, the ability to distinguish between MICs of 1 and 2 mg/liter is exceedingly important (18, 36). Our results only highlight the risk of automated systems missing vancomycin MICs of 2 mg/liter, especially when hVISA is involved. The therapeutic outcome of such results might be serious considering that clinicians might not change therapies for isolates with a vancomycin MIC of 1 mg/liter, as reported by the automated system (even though the actual MIC value may be 2 mg/liter), thus putting the patient at risk for failure especially if hVISA is present (18).

As with previous evaluations of automated susceptibility testing, we found that the current Phoenix, MicroScan, and Vitek 2 systems are relatively close in precision for vancomycin susceptibility testing when derived MIC values are within ± 1 dilution (28, 29). Swenson et al. determined the vancomycin susceptibility of 129 *S. aureus* isolates using 6 commercial methods (including the Phoenix, Vitek 2, MicroScan, and Etest systems) and BMD. Using an essential agreement method with an accuracy of $\pm 1 \log_2$ dilution, the results were reported as 98.4% for the Phoenix system and 100% for the three other methods (28). Similarly, Krusel et al. determined the vancomycin susceptibility of 161 blood isolates (with MIC values of ≤ 1 mg/liter) by broth microdilution methods, using both in-house-prepared and commercially prepared microtiter panels, and via automated systems such as the BD

Phoenix, the Vitek 2, and the MicroScan. Using the same essential agreement method, the Vitek 2 and MicroScan systems demonstrated 96.3% agreement, whereas the Phoenix system had only 88.8% agreement. Only the Etest method varied significantly at 76.4% agreement (29).

Given the importance of identifying MRSA isolates with vancomycin MIC values that exceed 1 mg/liter, it would seem that accepting MIC values of $\pm 1 \log_2$ dilution would not be in the clinician's best interest for treating patients with serious MRSA infections. It is of interest that in the literature (18), vancomycin Etest values of ≥ 1.5 mg/liter have consistently been reported to predict poor outcomes in patients with MRSA bacteremia. Although the Etest has been demonstrated to read slightly higher than BMD methods, it may be the best conservative alternative for evaluating MRSA vancomycin MICs in patients with serious and life-threatening infections.

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