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Vancomycin MICs for Methicillin-Resistant *Staphylococcus aureus* Isolates Differ Based upon the Susceptibility Test Method Used[▽]

Recent studies have questioned treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections with vancomycin because of treatment failures, despite vancomycin MICs in the susceptible category (MIC ≤ 2 μg/ml) (2, 3, 5, 6, 7). Some of these studies have used broth microdilution for determining vancomycin MICs (5), while others have used the Etest commercial product (AB Biodisk, Solna, Sweden) (2, 7). We sought to determine if substantive differences might result from using different susceptibility test methods for determining vancomycin MICs.

A group of 101 previously characterized strains of MRSA recovered between 2002 and 2006 from bacteremic patients in our institution were selected. Fifteen to 25 isolates per year were chosen, with MICs in the range of 0.5 to 2 μg/ml, based upon initial tests. Isolates were stored frozen at −70°C in skim milk and subcultured twice prior to being tested. Each isolate was tested by the CLSI broth microdilution and the CLSI agar dilution methods (1) and by the Etest method using two different brands of Mueller-Hinton agar plates (BBL agar [BD Microbiology Systems, Cockeysville, MD] and Remel agar [Remel, Lenexa, KS]). All tests were performed at the same time from the same inoculum suspension.

Results are depicted in Table 1. Vancomycin MICs generated by Etest were consistently one twofold dilution higher than MICs determined by CLSI broth or agar dilution; i.e., the modal vancomycin MIC determined by both the CLSI broth and agar dilution methods was 1 μg/ml, while the modal vancomycin MIC by Etest was 2 μg/ml with both Mueller-Hinton agar brands. In fact, 89 to 98% of MICs were 1.5 or 2 μg/ml by Etest, but only 3 to 12% of vancomycin MICs were 2 μg/ml when determined by the CLSI broth or agar dilution method.

Our findings raise several issues. Pharmacodynamic studies have shown that the area under the vancomycin concentration curve-to-MIC ratio (AUC/MIC) is the optimal method for predicting vancomycin efficacy against *S. aureus* infections (7). Furthermore, the probability of achieving an optimal AUC/MIC ratio has been shown to be much lower when the vancomycin MIC is 2 μg/ml than when it is 1 μg/ml (4). Therefore, even a one dilution difference in the MIC can substantially affect the MIC/AUC ratio and the ability to optimize treatment (7). If differences of only one dilution are relevant to predicting clinical outcomes of MRSA infections, the MIC method used is a critical part of the equation.

The differences between MICs generated by the Etest and those generated by the CLSI reference broth microdilution and agar dilution methods reflect a one dilution-higher vancomycin MIC when determined by the Etest. It is widely held that the precision of a dilution susceptibility test method is plus or minus one twofold dilution. Thus, it is unprecedented that a single dilution difference in the vancomycin MIC in the range of 0.5 to 2 μg/ml would have significant clinical implications. Until further evidence is generated to determine if such small differences in the vancomycin MIC are indeed significant, therapeutic recommendations should specify the MIC method on which the recommendations are based.

TABLE 1. Comparison of vancomycin MICs determined by broth microdilution, agar dilution, and Etest[a]

Vancomycin MIC (μg/ml)	No. of isolates (%) with MIC (μg/ml) determined by:			
	Broth microdilution	Agar dilution	Etest (Remel agar)	Etest (BBL agar)
0.5	21 (20.8)	1 (1)	0 (0)	0 (0)
0.75			1 (1)	1 (1)
1	77 (76.2)	88 (87)	11 (10.9)	1 (1)
1.5			69 (68.3)	62 (61.4)
2	3 (2.97)	12 (11.9)	20 (19.8)	37 (36.6)
Modal MIC (μg/ml)	1	1	2	2

[a] MICs were determined for 101 MRSA blood isolates obtained between 2002 and 2006.

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