Vancomycin Minimum Inhibitory Concentration in Methicillin-Susceptible Staphylococcus aureus and Mortality: More Than Handwaving?

To the Editor—We read with great interest the study by Cervera and colleagues on the effect of vancomycin minimum inhibitory concentration (van-MIC) on clinical outcome in 93 patients with left-sided infective endocarditis due to methicillin-susceptible Staphylococcus aureus (MSSA) [1]. However, various questions remain unanswered.

The 3-fold higher mortality in the group of patients with a van-MIC value ≥1.5 mg/L leads the authors to suggest that van-MICs as determined by Etest can be used to stratify the risk of mortality in patients with MSSA endocarditis. From a biological perspective, it is not straightforward to explain how an increased van-MIC could be linked to mortality, especially if vancomycin is not used for treatment. The authors hypothesize that an elevated van-MIC may indicate a more virulent phenotype, potentially associated with the bacterial genotype or mutations in the accessory gene regulator. Unfortunately, no evidence for this is provided, making their assumption purely speculative.

Few studies have reported mortality in bloodstream infection caused by MSSA with increased van-MICs. In a recent meta-analysis, van-MIC was not associated with increased mortality (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.65–10.49; P = .76) [2]. Cervera et al found the odds ratio of a higher van-MIC to predict outcome to remain significant using a multivariable logistic regression model (OR, 3.1; 95% CI, 1.2–8.2). However, limited by the number of subjects, only 5 dichotomous variables were incorporated into the statistical model (age <60 years, diagnosis before 2004, septic and nonseptic complicated endocarditis, and van-MIC). Main drivers of mortality, such as severity of disease at onset, duration of illness before admission, duration of bacteremia, vegetation size, and delay of institution of appropriate therapy with a β-lactam antibiotic were neither reported nor incorporated in the model. Furthermore, the higher median Charlson score in the high van-MIC group (2 vs 1) suggests differences between groups.

Unfortunately, there is critical information missing from the manuscript. The actual van-MIC values and their distribution are not disclosed; reproducibility of Etest results and interobserver variance were not addressed. Also, data on previous healthcare contact and exposure to vancomycin are missing. Strikingly, the survival curves of the 2 patient groups appear to deviate after day 12 of antimicrobial therapy, a time when management issues may be more important than pathogen factors. Finally, it remains unclear why S. aureus isolates with increased van-MIC values virtually disappeared during the last observation period (2008–2011). This suggests that local epidemiology and clonal distribution may determine the frequency of S. aureus isolates with elevated van-MICs.

Theoretically, 3 scenarios could explain higher mortality in this setting: (1) enhanced pathogenicity of MSSA strains with increased van-MICs; (2) decreased efficacy of standard treatment; or (3) the presence of patient-related risk factors associated with increased van-MIC values. None of these factors has been shown convincingly to play a role in the current study.

In conclusion, the inherent technical problems with determining van-MIC values with different methodologies [3], the lack of biological plausibility, and the high risk for bias in this retrospective analysis do not allow a firm conclusion on the relationship between increased van-MIC and mortality. Rather, increased van-MIC may be a surrogate marker for unfavorable host factors, management issues, or an as yet unidentified pathogen factor. We concur with the authors that their findings require confirmation in further studies to clarify the clinical significance of a high van-MIC. Therefore, we advise caution when using van-MIC values determined by a single Etest to predict mortality or even guide therapy in patients with MSSA endocarditis as there is an inherent danger of misinterpreting P values in studies with questionable starting hypotheses, as highlighted in a recent publication [4].

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