Is High Vancomycin Minimum Inhibitory Concentration a Good Marker to Predict the Outcome of Methicillin-Resistant Staphylococcus aureus Bacteremia?\(^1\)

To the Editor—A recent article by Peleg et al [1] demonstrated that methicillin-resistant Staphylococcus aureus (MRSA) strains with elevated vancomycin minimum inhibitory concentrations (MICs) were significantly less virulent than strains with lower MICs. From a clinician’s perspective, 2 recent articles by Soriano et al [2] and Price et al [3] provided conflicting data regarding mortality risk associated with MRSA bacteremia caused by strains with a high vancomycin MIC (>1 μg/mL).


We performed a retrospective observational cohort study of patients with MRSA bacteremia from January 2002 through December 2004 in a tertiary-care hospital. Patients were prospectively followed for 3 years. Sixty-three patients with MRSA bacteremia were treated exclusively with vancomycin. Vancomycin MIC was determined by E-test with use of a 0.5 McFarland inoculum in brain-heart infusion agar. The cut off point of vancomycin MIC was 1.5 μg/mL. Thirteen (20.6%) of 63 patients had an MRSA strain with vancomycin MIC ≥1.5 μg/mL.

The main clinical characteristics of the MRSA bacteremia episodes according to the vancomycin MIC (vancomycin MIC ≥1.5 μg/mL or <1.5 μg/mL) are shown in Table 1. There were no significant differences between both groups in the time to vancomycin therapy initiation or in the duration of treatment. Patients with MRSA strains with MIC ≥1.5 μg/mL had a lower degree of systemic inflammatory response (7.7% vs 56%; \(P < .005\)) and a nonsignificant trend to a lower risk of septic shock (7.7% vs 24%; \(P = .36\)) than those harboring strains with MIC <1.5 μg/mL. There were no differences in the number of patients with breakthrough bacteremia after ≥72 h of treatment with vancomycin (23% vs 34%; \(P = .68\)). Attributable mortality was 15.4% in the MIC ≥1.5 μg/mL group and 20% in the MIC <1.5 μg/mL group (\(P = .098\)).

### Table 1. Clinical Characteristics of Patients with Methicillin-Resistant Staphylococcus aureus Bacteremia, by Vancomycin Minimum Inhibitory Concentration (MIC)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MIC ≥1.5 μg/mL ((n = 13))</th>
<th>MIC &lt;1.5 μg/mL ((n = 50))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter-related bacteremia</td>
<td>6/13 (46.15)</td>
<td>22/50 (44)</td>
<td>.87</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>1/13 (7.69)</td>
<td>8/50 (16)</td>
<td>.75</td>
</tr>
<tr>
<td>Infective endocarditis(^b)</td>
<td>2/13 (15.38)</td>
<td>2/50 (4)</td>
<td>.39</td>
</tr>
<tr>
<td>Time to initiate vancomycin, mean days ± SD</td>
<td>1.36 ± 2.24</td>
<td>1.64 ± 1.829</td>
<td>.64</td>
</tr>
<tr>
<td>Duration of vancomycin treatment, mean days ± SD</td>
<td>24.76 ± 16.59</td>
<td>20.4 ± 18.34</td>
<td>.439</td>
</tr>
<tr>
<td>Appropriate duration of vancomycin therapy(^b)</td>
<td>8/12 (66.7)</td>
<td>26/47 (55.3)</td>
<td>.699</td>
</tr>
<tr>
<td>Any degree of systemic inflammatory response</td>
<td>1/13 (7.7)</td>
<td>28/50 (56)</td>
<td>.005</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>1/13 (7.7)</td>
<td>12/50 (24)</td>
<td>.367</td>
</tr>
<tr>
<td>Complicated bacteremia(^b)</td>
<td>3/13 (23)</td>
<td>8/50 (16)</td>
<td>.864</td>
</tr>
<tr>
<td>Breakthrough bacteremia (≥72 h)</td>
<td>3/13 (23)</td>
<td>17/50 (34)</td>
<td>.674</td>
</tr>
<tr>
<td>Global mortality</td>
<td>2/13 (15.4)</td>
<td>14/50 (28)</td>
<td>.57</td>
</tr>
<tr>
<td>Attributable mortality</td>
<td>2/13 (15.4)</td>
<td>10/50 (20)</td>
<td>.986</td>
</tr>
<tr>
<td>Long-term complications</td>
<td>5/8 (62.5)</td>
<td>3/16 (18.75)</td>
<td>.094</td>
</tr>
</tbody>
</table>

**NOTE.** Data are proportion (%) of patients, unless otherwise indicated. SD, standard deviation.

\(^a\) In each group (MIC ≥1.5 μg/mL or MIC <1.5 μg/mL) there was a patient with native valve infective endocarditis and prosthetic valve infective endocarditis.

\(^b\) Fourteen days of vancomycin treatment was considered to be appropriate for patients with uncomplicated bacteremia and 28 days in patients with complicated bacteremia (defined as the presence of metastatic complications resulting either from hematogenous seeding of a distant site or from local extension of infection).

Univariate analysis showed that bacteremia caused by an MRSA strain with vancomycin MIC ≥1.5 μg/mL was a risk factor for late complications (relative risk, 8 [95% confidence interval, 1.13–56.79]).

Our results suggest that MRSA strains with vancomycin MICs ≥1.5 μg/mL are less aggressive and produce less sepsis and less systemic inflammatory response than MRSA strains with vancomycin MICs <1.5 μg/mL. This could be the reason why attributable mortality was not higher in patients infected with these strains, as was noted in the study by Price et al [3], despite lower antimicrobial susceptibility. Some authors have hypothesized that the low pathogenic activity of vancomycin-resistant strains could be related to impaired growth during the first hours of incubation, which may contribute to attenu-
ated virulence [1]. Other authors relate this lower virulence to an increased thickness of their cell walls [4]. This would elicit a milder proinflammatory cytokine response, blunting immune activation, and consequently, the development of shock [2]. The higher incidence of late complications in our patients (especially those carrying prosthetic materials) experiencing bacteremia by MRSA strains with vancomycin MIC $\geq 1.5 \mu g/mL$ could be related to a slower growth rate of these strains. It would allow them to remain in a stationary phase, avoiding eradication, most notably so if embedded into the biofilm of a prosthetic material. In summary, we suggest that the different response to antibiotics and virulence of MRSA strains stems from the bacterial structure itself and not from vancomycin susceptibility. If this proves to be true, vancomycin resistance would only be a surrogate marker of low virulence in MRSA strains.

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References


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Reply to Lalueza et al

To the Editor—We thank Lalueza et al [1] for their communication regarding our work on the pathogenic consequences of reduced susceptibility to vancomycin in Staphylococcus aureus. These clinical data provide support of our laboratory findings and, interestingly, align with several other recent clinical reports [2–5].

Initial observational series of patients infected with vancomycin-intermediate S. aureus (VISA) or heteroresistant VISA (hVISA) isolates demonstrated that such patients often had complicated staphylococcal bacteremia with deep-seated infection. These patients had prolonged periods of bacteremia, despite treatment with vancomycin, and eventual poor clinical outcomes. The issue with interpretation of such data relates to the “chicken or egg” conundrum; are patients that present with complicated staphylococcal bacteremia more likely to have developed the complication as a consequence of being infected with an hVISA/VISA isolate, or is an hVISA/VISA isolate more likely to develop in someone who presents with bacteremia complicated by deep-seated infection? We favor the latter theory. As such, and given the association of complicated disease with poor outcome, the severity and extent of the staphylococcal infection must be adjusted for in any analysis trying to interpret the clinical impact of hVISA/VISA versus methillin-resistant S. aureus. As an aside, if one believed that it was the hVISA/VISA strain causing the initial complications, then you would avoid adjusting for this disease severity covariate, as it would be in the causal pathway between hVISA/VISA and poor outcome.

Recent interesting clinical data begin to define the pathogenic potential of hVISA/VISA strains. By prospectively assessing all clinical methillin-resistant S. aureus cultures during a 10-month period, Horne et al [2] showed that hVISA/VISA strains were less likely to be associated with infection (more likely to be a colonizer) and were associated with a lower rate of bacteremia. No differences in treatment outcomes were observed. Other investigators have also shown, after appropriately adjusting for important confounding variables, that mortality from hVISA/VISA bacteremia is similar to that from vancomycin-susceptible methillin-resistant S. aureus bacteremia [3, 4]. Interestingly, Soriano et al [6] showed that as the minimum inhibitory concentration to vancomycin increased from 1 μg/mL to 1.5 μg/mL and from 1.5 μg/mL to 2.0 μg/mL, the adjusted odds ratio for the development of shock from staphylococcal bacteremia decreased in a minimum inhibitory concentration–dependent fashion. These results are in accordance with what is being shown by Lalueza et al [1] in their correspondence; however, an unadjusted analysis is being shown.

Despite the results from these studies and our laboratory data showing attenuated killing by hVISA/VISA strains in a non-mammalian model system [7], it is important to emphasize that infection with these organisms can still be very serious and complicated and can lead to patient mortality if not treated appropriately. Furthermore, these strains may be more persistent than vancomycin-susceptible strains, and this may be mediated through dysfunction of the agr system, which may increase the organism’s ability to form biofilm [8] and fibronectin-binding protein [9], the latter being important for adhesion to mammalian cells. Further work in understanding the evolution of reduced susceptibility to vancomycin will provide...