Predictors of persistent methicillin-resistant Staphylococcus aureus bacteraemia in patients treated with vancomycin

Young Kyung Yoon, Jeong Yeon Kim, Dae Won Park, Jang Wook Sohn and Min Ja Kim*

1Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea; 2Institute of Emerging Infectious Diseases, Korea University College of Medicine, Seoul, Korea

*Corresponding author. Division of Infectious Diseases, Korea University College of Medicine, Seoul, Korea. Tel: +82-2-920-5658; Fax: +82-2-920-5616; E-mail: macropha@korea.ac.kr

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Objectives: The high prevalence of methicillin-resistant Staphylococcus aureus (MRSA) coupled with an increase in vancomycin use have induced vancomycin tolerance in MRSA, adversely affecting the outcome of MRSA bacteraemia. This study aimed to identify predictors of persistent MRSA bacteraemia (PMRSAB) in patients treated with vancomycin.

Methods: A retrospective, case-control study was performed at a university hospital in Korea from January 2006 to February 2009. Subjects included 96 patients who had MRSA bacteraemia and received vancomycin under therapeutic drug monitoring. We compared the clinical characteristics, management and outcomes of cases with PMRSAB (≥7 days, n = 31) with controls with non-PMRSAB (≤3 days, n = 32). Vancomycin MICs were determined by the Vitek 2 system.

Results: Of 96 patients with MRSA bacteraemia, MRSA isolates from 21 patients (21.9%) showed a vancomycin MIC of 2 mg/L. Independent predictors of PMRSAB were: retention of implicated medical devices (odds ratio [OR], 10.35; 95% confidence interval [CI], 1.03–104.55); MRSA infection of at least two sites (OR, 10.24; 95% CI, 1.72–61.01); and vancomycin MIC of 2 mg/L (OR, 6.34; 95% CI, 1.21–33.09). The frequency of side effects and mean trough serum vancomycin concentrations were not significantly different between the two groups. Sixteen patients with PMRSAB subsequently received teicoplanin ± arbekacin, linezolid or quinupristin/dalfopristin, due to vancomycin failure or intolerance.

Conclusions: To minimize the risk of PMRSAB, early removal of implicated devices and evaluation for metastatic infections should be encouraged. Alternative antibiotic therapy is warranted for infections due to isolates with elevated vancomycin MICs, as well as for the high rates of side effects.

Keywords: risk factors, minimum inhibitory concentration, case-control study

Introduction

Staphylococcus aureus bacteraemia (SAB) is a serious infection in which one-third of patients develop local complications or distant septic metastases.1 Patients with persistent SAB have significantly worse outcomes than patients with non-persistent SAB.2 Recent reports identified methicillin resistance, medical devices, chronic renal failure, more than two sites of infection, diabetes, metastatic infection and vancomycin treatment as risk factors.2,3

Vancomycin has been used as the primary therapeutic agent against methicillin-resistant S. aureus (MRSA) infections for the past 40 years. However, the previous reports show numerically small increases in the MICs of vancomycin over time, known as the phenomenon ‘MIC creep’.4 Vancomycin may provide suboptimal therapy for patients with MRSA bloodstream infections when vancomycin MICs are within the CLSI susceptible range.5

Recently, persistent MRSA bacteraemia (PMRSAB) has been increasingly recognized among hospitalized patients. Unfortunately, though, there are limited clinical data on the microbial properties and host factors related to PMRSAB.

The purpose of this study was to assess the clinical characteristics and risk factors associated with PMRSAB in the hospital setting of MRSA endemicity. In addition, we addressed the clinical efficacy of vancomycin therapy against MRSA bacteraemia, with a vancomycin MIC of ≥2 mg/L.
Methods

Study population and setting

The retrospective, case-control study was conducted at an 850 bed academic medical centre in the Republic of Korea during the period January 2006 through February 2009.

MRSA bacteraemia was defined according to the criteria of the Centers for Disease Control and Prevention. Case patients were selected for this study if they had an episode of PMRSAB lasting >7 days after the initiation of vancomycin treatment. Control patients were included if they had non-PMRSAB, defined as no further positive blood cultures 3 days after vancomycin treatment. Echocardiography was performed in all patients included in this study, except for four control patients. Patients with more than one organism were excluded in this study. Only the first episode of MRSA bacteraemia for each patient was included for the analysis. Clinical data were collected by review of the patients’ medical records.

Vancomycin use is controlled under the hospital’s antibiotic restriction programme and requires approval by an infectious disease specialist. Therapeutic drug monitoring of vancomycin is routinely performed on all patients receiving vancomycin, at day 3 and then at 3–4 day intervals, at the pharmacy department (Abbottbase Pharmacokinetic Vancomycin System, version 1.10). Clinicians adjust the dosage in order to achieve or maintain the concentration of 15–20 mg/L.

Microbiological tests

This hospital runs the BacT/ALERT® 3D Microbial Detection System (bioMérieux, Inc., Durham, NC, USA) for all blood cultures. MRSA identification and antimicrobial susceptibility tests were performed using the Vitek identification and susceptibility cards (bioMérieux, Hazelwood, MO, USA), according to the CLSI criteria.

Statistical analysis

Comparisons between patients with PMRSAB and those with non-PMRSAB were performed using the χ² test for categorical variables and Student’s t-test for continuous variables. P ≤0.05 was considered to be significant. Variables with P ≤0.05 in univariate analysis were included in multivariate logistic regression analysis to estimate the predicted probability of the PMRSAB. The odds ratio (OR) was calculated for each variable using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Predictors associated with PMRSAB

During the study period, a total of 96 patients had significant MRSA bacteraemia. Patients who had MRSA bacteraemia for an intermediate-length duration (4–6 days) (n=13), who did not have follow-up blood cultures taken (n=11) or who received vancomycin therapy for <7 days (n=9) were excluded from the analysis. Of 63 patients analysed, 31 (49.2%) had PMRSAB and 32 (50.8%) had non-PMRSAB. The median age in the case and control groups was 68 years (range, 25–84) and 70 years (range, 27–86), respectively.

The univariate analysis showed no significant differences between patients with PMRSAB and those with non-PMRSAB in demographics and baseline clinical history of corticosteroid therapy, haemodialysis, surgery, stay in intensive care units or hospitalization days within 30 days before the onset of MRSA bacteraemia. Frequency of co-morbid illness or Charlson score, distribution of infection site and their exposure to invasive procedures or antibiotic therapy before MRSA bacteraemia were not different between the two groups, except for the frequency of pulmonary diseases (6.5% in the case group versus 28.1% in the control group; P=0.043) or catheter-related bloodstream infection (61.3% versus 32.4%; P=0.045), the presence of at least two sites of infection or of metastatic infections (48.4% versus 12.5%; P=0.005), and the retention of implicated medical devices (32.3% versus 3.1%; P=0.003). The retention of implicated medical devices included prosthetic heart valves, an implantable cardioverter defibrillator, prosthetic grafts of great vessels, a permanent dialysis access and a bone prosthesis. Most of them were ineradicable sources for PMRSAB.

All initial MRSA isolates from 96 patients with MRSA bacteraemia were susceptible to vancomycin (MIC ≤2 mg/L) and 21 strains (21.9%) had a vancomycin MIC of 2 mg/L. A higher vancomycin MIC of 2 mg/L was significantly associated with PMRSAB (Table 1).

In the multivariate analysis, independent risk factors associated with PMRSAB included a higher vancomycin MIC of 2 mg/L, MRSA infection of at least two sites (metastatic MRSA infections) and the retention of implicated medical devices (Table 2).

Clinical management and outcomes of patients with PMRSAB

In the univariate analysis, the mean time of initiation of vancomycin and the time to the therapeutic level were not significantly different between the two groups. Most of the patients achieved therapeutic trough levels of ≥15 mg/L (74.2% versus 73.1%). Vancomycin combined with rifampicin or alternative antibiotics to vancomycin were more frequently given to patients with PMRSAB, compared with patients with non-PMRSAB. Rifampicin was mostly combined with vancomycin in patients who had medical devices, regardless of the eradication of MRSA bacteraemia. Teicoplanin, linezolid, quinupristin/dalfopristin or arbekacin, uniquely or in combination, were used to treat 16 case patients (51.6%) after initial vancomycin therapy, due to either suboptimal clinical response or drug toxicity. Adverse events of vancomycin, including nephrotoxicity, drug rash, drug fever and leucopenia, were not uncommon in both groups.

MRSA bacteraemia-related mortality was significantly higher in the PMRSAB group than in the non-PMRSAB group (Table 1), whereas in-hospital mortality with all causes was not different between the two groups. Interestingly, MRSA bacteraemia-related mortality was significantly higher in patients with a vancomycin MIC of 2 mg/L, compared with a vancomycin MIC of ≤1 mg/L (50.0% versus 19.0%; OR, 4.25; 95% confidence interval, 1.28–14.15; P=0.027).

Discussion

In this case-control study, the independent risk factors that interfered with the eradication of MRSA bacteraemia among patients who received vancomycin treatment were the retention of implicated medical devices, metastatic MRSA infections and a higher vancomycin MIC of 2 mg/L. In addition, our study showed that adverse events of vancomycin requiring alternative drugs.
were not uncommon. We also identified the poor clinical outcome of PMRSAB, which had a high mortality rate (45.2%). These findings highlight the importance of the identification of high-risk factors for PMRSAB, and the application of appropriate and aggressive management.

In particular, we found that a higher vancomycin MIC of 2 mg/L was an independent predictor of PMRSAB. A number of studies have recently established that vancomycin treatment failures were not uncommon and that a higher vancomycin MIC was associated with a higher mortality, despite meeting the CLSI standard criteria for susceptibility. Therefore, hospital microbiology laboratories should provide vancomycin MIC values for individual patients with serious MRSA infections for whom vancomycin therapy is being considered.

Appropriate antimicrobial therapy has proven to be an important prognostic factor in patients with sepsis. Suboptimal clinical response and the high rate of side effects with vancomycin therapy should raise the role of alternative antimicrobial agents in the treatment of MRSA bacteraemia, including teicoplanin, linezolid, quinupristin/dalfopristin and daptomycin. However, these agents have not demonstrated established data to support them being the standard of treatment for MRSA bacteraemia.

For the treatment of patients with MRSA bacteraemia who have limited treatment options, consultation with an infectious disease specialist is recommended to optimize the choice of the alternative agent or the combination of agents, or dosing regimen.

Our study has some limitations. First, this is a retrospective, single-centre study. Follow-up blood cultures were not taken on a regular basis (every 2–4 days) until clearance. The number of cases is small and data on vancomycin MICs might not be representative of other hospitals. Second, vancomycin MICs of the MRSA strains were determined by the automated Vitek 2 system, which is unable to detect the hetero vancomycin-intermediate S. aureus. The Vitek 2 system provides vancomycin MIC results that are consistently lower than those provided by the Etest.

**Table 1.** Univariate analysis of antibiotic therapy and clinical outcomes between persistent MRSA bacteraemia and non-persistent MRSA bacteraemia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Case (n=31)</th>
<th>Control (n=32)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to initiation of vancomycin, days, mean±SD</td>
<td>1.3±2.1</td>
<td>1.4±1.3</td>
<td>0.848</td>
<td></td>
</tr>
<tr>
<td>Time to the therapeutic vancomycin level, days, mean±SD</td>
<td>3.2±1.4</td>
<td>3.1±1.5</td>
<td>0.757</td>
<td></td>
</tr>
<tr>
<td>Intravascular catheter removal, n (%)</td>
<td>19 (61.3)</td>
<td>16 (50.0)</td>
<td>0.450</td>
<td></td>
</tr>
<tr>
<td>Retention of implicated medical devices, n (%)</td>
<td>10 (32.3)</td>
<td>1 (3.1)</td>
<td>0.003</td>
<td>14.76 (1.76–124.10)</td>
</tr>
<tr>
<td>Vancomycin therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vancomycin MIC of 2 mg/L, n (%)</td>
<td>14 (45.2)</td>
<td>4 (12.5)</td>
<td>0.010</td>
<td>5.69 (1.59–20.33)</td>
</tr>
<tr>
<td>trough levels (mg/L), n (%)</td>
<td></td>
<td></td>
<td>0.358</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>8 (25.8)</td>
<td>7 (21.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–25</td>
<td>15 (48.4)</td>
<td>10 (31.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>8 (25.8)</td>
<td>9 (28.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>side effects, n (%)</td>
<td>14 (45.2)</td>
<td>11 (34.4)</td>
<td>0.446</td>
<td></td>
</tr>
<tr>
<td>Alternative therapy, n (%)</td>
<td>16 (51.6)</td>
<td>7 (21.9)</td>
<td>0.019</td>
<td>3.81 (1.28–11.39)</td>
</tr>
<tr>
<td>teicoplanin</td>
<td>11 (35.5)</td>
<td>3 (9.4)</td>
<td>0.041</td>
<td>3.85 (1.07–13.85)</td>
</tr>
<tr>
<td>linezolid</td>
<td>9 (29.0)</td>
<td>3 (9.4)</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>arbekacin</td>
<td>4 (12.9)</td>
<td>0 (0)</td>
<td>0.053</td>
<td>1.15 (1.00–1.32)</td>
</tr>
<tr>
<td>quinupristin/dalfopristin</td>
<td>3 (9.7)</td>
<td>1 (3.1)</td>
<td>0.355</td>
<td></td>
</tr>
<tr>
<td>combination therapy with rifampicin</td>
<td>21 (67.7)</td>
<td>12 (37.5)</td>
<td>0.041</td>
<td>3.85 (1.07–13.85)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection-cause mortalitya, n (%)</td>
<td>14 (45.2)</td>
<td>3 (9.4)</td>
<td>0.002</td>
<td>7.96 (2.00–31.75)</td>
</tr>
<tr>
<td>in-hospital mortality, n (%)</td>
<td>16 (51.6)</td>
<td>15 (46.9)</td>
<td>0.803</td>
<td></td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus; SD, standard deviation; OR, odds ratio; CI, confidence interval.

**Table 2.** Results of multivariate analysis for predictors of persistent MRSA bacteraemia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin MIC of 2 mg/L</td>
<td>6.34</td>
<td>1.21–33.09</td>
<td>0.029</td>
</tr>
<tr>
<td>Retention of implicated medical devices</td>
<td>10.35</td>
<td>1.03–104.55</td>
<td>0.048</td>
</tr>
<tr>
<td>MRSA infection of at least two sites</td>
<td>10.24</td>
<td>1.72–61.01</td>
<td>0.011</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus; OR, odds ratio; CI, confidence interval.

Following pulmonary diseases, catheter-related bloodstream infection, infection of at least two sites, vancomycin MICs and retention of implicated medical devices were included in the multivariate model as independent variables.
In summary, our study indicates that the removal of implicated medical devices, and earlier detection and control of metastatic infections should be encouraged to minimize the risk of PMRSAB. Furthermore, the identification of higher vancomycin MIC values of 2 mg/L in patients with MRSA bacteraemia could be predictive of vancomycin failure, requiring appropriate alternative antibiotic therapy. Finally, it might be necessary to establish the most appropriate breakpoint of the vancomycin MIC, in terms of vancomycin efficacy.

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Transparency declarations
None to declare.

Author contributions
Y. K. Y. collected and analysed the data, and wrote the manuscript. J. Y. K., D. W. P. and J. W. S. participated in the epidemiologic surveillance. M. J. K. coordinated the study and revised the manuscript. All authors read and approved the final manuscript.

References