Health Care-Associated Endocarditis Caused by *Staphylococcus aureus* with Reduced Susceptibility to Vancomycin

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Infective endocarditis (IE) caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility (SARV) has been reported worldwide. We report the successful treatment of a pediatric patient with SARV IE and characterization of the infecting strain. The MIC of vancomycin rose from 1.5 to 2 μg/ml, and the SARV was confirmed by population analysis.

CASE REPORT

A 5-year-old girl with complicated congenital heart disease was admitted to our hospital for redo coarctation of aorta repair. She attended our outpatient department every 3 months for more than 1 year before her admission this time. Two weeks after the operation, she developed sternal wound methicillin-resistant *Staphylococcus aureus* infection (isolate A1160). Transthoracic echocardiography (TTE) revealed no vegetation initially. She received 6 weeks of vancomycin therapy (10 mg/kg of body weight/dose, every 6 h), and the wound culture was sterile after that treatment. One week after completing vancomycin therapy, the patient suffered from frequent bacteremia and endocarditis. Blood cultures performed on days 11 to 13 after starting the vancomycin and rifampin combination therapy still yielded MRSA (isolate A1230), and intermittent high fever was still noted. The vancomycin dose was changed to 15 mg/kg/dose on day 15 due to inadequate levels (trough level, 9.23 μg/ml). Surveillance blood cultures performed on days 16 and 21 were negative. However, fever and MRSA bacteremia recurred on day 24 (isolate A1234). MRSA isolates A1230 and A1234 demonstrated antimicrobial susceptibility profiles similar to the profile of the patient’s first isolate, A1160 (Table 1), except that the MIC of vancomycin was 1.5 μg/ml in isolate A1160 and 2 μg/ml in isolates A1230 and A1234 and the rifampin MIC increased from <0.016 μg/ml in isolates A1160 and A1230 to >256 μg/ml in isolate A1234, as determined by the Etest method (AB Biodisk). The organisms were also resistant to clindamycin, clarithromycin, gentamicin, and ciprofloxacin, but were susceptible to fusidic acid, teicoplanin, and linezolid (MIC, 1 to 1.5 μg/ml). TTE was performed again and still revealed vegetation at the same site.

We then switched the therapeutic regimen to linezolid (10 mg/kg, intravenous, every 8 h) plus fusidic acid for 42 days, followed by an oral formulation for an additional 14 days. The patient became afebrile, and blood culture was sterile within 48 h after starting linezolid and fusidic acid combination therapy. Subsequent surveillance blood cultures performed during this combination therapy all yielded no growth. The patient tolerated the intravenous infusion of linezolid without adverse effect. Liver, renal, and hematological parameters, monitored weekly, were normal during the treatment course. TTE obtained 2 weeks after the end of therapy revealed complete resolution of the vegetation.

Isolates A1160, A1230, and A1234 were subjected to further genotypic testing. Virulence and toxin genes, the macrolide-lincosamide-streptogramin resistance genes (*ermA, ermB*, and *ermC*), and the staphylococcal cassette chromosome *mec* type III and had indistinguishable pulsed-field gel electrophoresis patterns. These results indicated that the same strain of MRSA was responsible for the initial sternal infection and the subsequent bacteremia and endocarditis. Because of the poor clinical response to vancomycin treatment, we performed a population analysis profile study on the three MRSA isolates to test for reduced susceptibility to vancomycin (Fig. 1) (9, 10). The population analysis profile area under the concentration-time curve (AUC) of the test strains was compared to the AUC of Mu3, a heterogenous vancomycin-intermediate *S. aureus* (hVISA) strain (ATCC 700698). All three MRSA strains fit the criterion of hVISA, which was defined as a vancomycin MIC of ≤2 μg/ml, and the ratio of the AUC of the test strain to that of Mu3 was >0.9 (10, 21). The first two isolates, A1160 and A1230, and Mu3 had AUC ratios of >0.9, while the last isolate, A1234, and Mu3 had an AUC ratio of >1. The increased AUC ratio of the last strain indicated the further emergence of a subpopulation of isolates with reduced susceptibility to vancomycin.

MRSA endocarditis is a serious, potentially life-threaten-
ing clinical event. Currently, vancomycin is the leading treatment of choice. The emergence of S. aureus isolates with reduced susceptibility to vancomycin (SARV), including hVISA and VISA, among patients with endocarditis has become problematic around the world (2, 6, 11). The possible reason for the emergence of SARV and ideal therapy for patients with endocarditis due to SARV are still unknown. We report the successful treatment with a combination of linezolid and fucidic acid of a patient with health care-associated SARV endocarditis. Our characterization of the causative strain in clinical sequence also provides an association between failure of vancomycin therapy and the emergence of SARV.

Similar to other patients with hVISA, VISA, or SARV infections (3, 12, 20), our patient was treated with an extended course of vancomycin in the context of nosocomial MRSA infection. Although a thickened cell wall and the loss of accessory gene regulator function are notable common features (7, 8, 15, 16, 19), the precise mechanisms of hVISA resistance to vancomycin have not been elucidated. Previous studies have shown that low vancomycin trough levels (<10 µg/ml), particularly in the early stages of therapy, could result in the induction of preexisting low-level vancomycin resistance or could select for new vancomycin-resistant strains (8, 11). A subinhibitory concentration of vancomycin could be an important factor leading to the selection of SARV strains. Besides, even the isolates were fully susceptible to vancomycin (MIC, <2 µg/ml); MRSA strains with a vancomycin MIC of <0.5 µg/ml responded much more readily than did MRSA strains with MICs of 1 to 2 µg/ml (17). Subtle changes in increasing vancomycin MICs well within the susceptible range and differences in susceptibility

<table>
<thead>
<tr>
<th>Isolate; source, when obtained</th>
<th>Oxacillin</th>
<th>Vancomycin</th>
<th>Teicoplanin</th>
<th>Linezolid</th>
<th>TMP-SMX</th>
<th>Clindamycin</th>
<th>Clarithromycin</th>
<th>Rifampin</th>
<th>Gentamicin</th>
<th>Ciprofloxacin</th>
<th>Fucidic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1160; sternal wound, prior to a 6-wk vancomycin therapy course</td>
<td>&gt;256</td>
<td>1.5</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>&gt;256</td>
<td>&gt;256</td>
<td>&lt;0.016</td>
<td>&gt;256</td>
<td>&gt;32</td>
<td>0.094</td>
</tr>
<tr>
<td>A1230; blood, 13 days after vancomycin and rifampin therapy</td>
<td>&gt;256</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
<td>4</td>
<td>&gt;256</td>
<td>&gt;256</td>
<td>&lt;0.016</td>
<td>&gt;256</td>
<td>&gt;32</td>
<td>0.094</td>
</tr>
<tr>
<td>A1234; blood, 24 days after vancomycin and rifampin therapy</td>
<td>&gt;256</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>&gt;256</td>
<td>&gt;256</td>
<td>&gt;256</td>
<td>&gt;256</td>
<td>&gt;32</td>
<td>0.125</td>
</tr>
</tbody>
</table>

*The MICs were determined by the Etest method. TMP-SMX, trimethoprim-sulfamethoxazole.
to killing may contribute to clinical failure (16). In the present case, we provide a clear clinical sequence. We suggest that a healthcare-associated vancomycin-susceptible \textit{S. aureus} strain with a higher vancomycin MIC and a reduced-susceptibility subpopulation was primarily responsible for the infection initially but ineffective vancomycin therapy selected for the SARVs and resulted in glycopeptidase treatment failure.

It is noteworthy that resistance to rifampin also developed during vancomycin and rifampin combination therapy in our case. In a previous study, in vitro antagonism had been shown when rifampin was added to vancomycin (18). In a prospective, randomized trial, Levine et al. demonstrated that the addition of rifampin to vancomycin was counterproductive in patients with MRSA endocarditis. Fever was sustained and bacteremia was prolonged (13). Howden et al. also reported resistance to rifampin developing during vancomycin and rifampin combination therapy in three cases with bacteremia (11). The emergence of resistance and prolonged bacteremia appeared to be risk factors contributing to our patient’s failure to respond to vancomycin and rifampin combination therapy. Thus, in attempts to improve the bactericidal capacity in patients with endocarditis, the regimens of combination therapy require further evaluation.

Our patient was treated for 8 weeks with linezolid and fucidic acid combination therapy, with apparent resolution of the vegetation as demonstrated by echocardiography. In a previous report, the addition of either rifampin or trimethoprim-sulfamethoxazole to the linezolid regimen was considered as an alternative to treat patients with endocarditis (20). For this patient, we used linezolid and fucidic acid because the isolates were resistant to many antibiotics. Moreover, the availability of switching to an oral formulation allowed an early discharge.

The role of linezolid in the treatment of endocarditis caused by multidrug-resistant gram-positive pathogens is unresolved. Although animal and clinical studies showed therapeutic efficacy of linezolid in endocarditis (1, 14), clinical treatment failure have also been reported recently (4). Therefore, linezolid should be used prudently in selected patients, and testing for the bactericidal capacity of linezolid with other antistaphylococcal-agent combinations is suggested.

Daptomycin has been approved for use in patients with MRSA bacteremia, including that associated with right-sided endocarditis (5). However, the usual dose for pediatric patients is unknown and the efficacy for SARV should be further evaluated.

The emergence of SARV is becoming a challenge to clinicians. Monitoring therapeutic levels and adjusting the dosage of vancomycin in treating complicated cases are warranted. An alternative regimen for SARV is needed for inoperable patients, and linezolid could be considered as a therapeutic option. With the increasing recognition of SARV, further characterizations will help predict which isolates are most likely to respond.

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REFERENCES


