Endocarditis Caused by *Staphylococcus aureus* with Reduced Susceptibility to Vancomycin

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Clinical management of infective endocarditis (IE) is expected to become more difficult with the emergence of *Staphylococcus aureus* with reduced susceptibility to vancomycin (SARV) in the United States and worldwide. We report the strain characterization and treatment of a patient with SARV IE.

Vancomycin is the treatment of choice for infective endocarditis (IE) and other infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The first clinical *S. aureus* isolate with intermediate susceptibility to vancomycin (VISA; MIC, 8 µg/mL) was reported from Japan in 1997 [1, 2]. Since that initial report, 8 clinical VISA isolates and an additional 23 *S. aureus* isolates with reduced susceptibility to vancomycin (SARV; MIC, 4 µg/mL) have been identified in the United States [3, 4]. Three of the 23 patients with SARV had IE; 2 patients with left-side IE died soon after diagnosis, and 1 patient with right-side IE survived after receiving treatment with vancomycin and rifampin. The ideal therapy for patients with IE due to SARV is unknown, but we report the apparent successful use of linezolid therapy for left-side IE due to SARV and further characterize the causative strain.

**Case report.** In April 2000, a 63-year-old man with an automated implantable cardiac defibrillator (AICD) and transfusion-dependent myelosuppression due to non-Hodgkin lymphoma was admitted to the intensive care unit (Durham Veterans Administration Medical Center; Durham, NC) for management of an acute pulmonary hemorrhage due to bronchoscopic biopsy. One month after admission, he developed nosocomial MRSA bacteremia. He received 3 weeks of vancomycin therapy. Follow-up cultures of blood samples obtained 1 week into therapy yielded no growth. One day after completing vancomycin therapy, the patient developed fever and recurrent MRSA bacteremia. Transesophageal echocardiography (TEE) performed 2 weeks later revealed vegetations on both the aortic and mitral valves. He received vancomycin (1.25 g daily). Surveillance blood cultures performed on day 11 and day 14 yielded no growth. Despite adequate vancomycin levels (trough level, 15 µg/mL), fever and *S. aureus* bacteremia recurred on day 21 of therapy. The *S. aureus* demonstrated an antimicrobial susceptibility profile similar to the patient’s previous isolates (table 1), except that the MIC of vancomycin had increased to 8 µg/mL when tested with the NCCLS broth microdilution method using Mueller-Hinton broth analyzed after 24 h of incubation. TEE performed 2 days later showed resolution of the aortic valve vegetation but apparent enlargement of the mitral valve vegetation. Broth microdilution testing was repeated and confirmed an MIC of vancomycin of 8 µg/mL. By the Etest method (AB Biodisk), the MIC of vancomycin was determined to be 6 µg/mL. The organism was also resistant to clindamycin, erythromycin, and levofloxacin, but it was susceptible to linezolid (MIC determined by Etest, 2 µg/mL), tetracycline, rifampin, and trimethoprim-sulfamethoxazole (TMP-SMX).

Vancomycin therapy was discontinued, and the patient was treated with linezolid (600 mg iv q12h) for 67 days. The patient became afibrile ≤48 h after starting linezolid therapy. Multiple surveillance blood cultures performed during linezolid therapy all yielded no growth. The patient’s AICD was removed 5 weeks into therapy without complication. TEE was performed 6 weeks after completion of therapy and revealed complete resolution of the vegetations.

The patient tolerated the intravenous infusion of linezolid without difficulty. His monthly blood transfusion requirement did not change, and his platelet count remained stable (91,000–
Table 1. Antibiograms of *Staphylococcus aureus* isolates obtained from a patient with endocarditis caused by *S. aureus* with reduced susceptibility to vancomycin and diagnosed in June 2000.

<table>
<thead>
<tr>
<th>Time</th>
<th>Sample</th>
<th>Oxacillin</th>
<th>Vancomycin</th>
<th>TMP-SMX</th>
<th>Clindamycin</th>
<th>Levofloxacin</th>
<th>Rifampin</th>
<th>Tetracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 of vancomycin therapy</td>
<td>Blood</td>
<td>&gt;32</td>
<td>&lt;0.5</td>
<td>1/19</td>
<td>&gt;64</td>
<td>8</td>
<td>&lt;0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>Day 20 of vancomycin therapy</td>
<td>Blood</td>
<td>&gt;32</td>
<td>1.0</td>
<td>2/38</td>
<td>&gt;64</td>
<td>16</td>
<td>&lt;0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>Day 40 of vancomycin therapya</td>
<td>Blood</td>
<td>&gt;32</td>
<td>&gt;64</td>
<td>&gt;16</td>
<td>16</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Day 4 of linezolid therapy</td>
<td>Nares</td>
<td>&gt;32</td>
<td>&lt;0.5</td>
<td>2/38</td>
<td>&gt;64</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Week 6 after completion of linezolid therapy</td>
<td>Blood</td>
<td>&gt;32</td>
<td>1.0</td>
<td>2/38</td>
<td>&gt;64</td>
<td>&gt;16</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

**NOTE.** TMP-SMX, trimethoprim-sulfamethoxazole.

*One day before commencement of linezolid therapy.*

222,000 platelets/mL) throughout the duration of his linezolid therapy.

The Epidemiology and Laboratory Branch of the Centers for Disease Control and Prevention (CDC; Atlanta, GA) received the isolate on a chocolate agar slant. The isolate had undergone 2 passages onto sheep blood agar before shipment. The CDC laboratory confirmed an MIC of vancomycin of 4 µg/mL by broth microdilution and of 6 µg/mL by Etest. In addition, the organism did not grow on brain-heart infusion agar containing 6 µg/mL vancomycin. Thus, the organism was classified as *S. aureus* with reduced vancomycin susceptibility [5].

The patient was placed on strict isolation with dedicated nursing, staff and family compliance with contact precautions was monitored, and an epidemiologic investigation was performed in accordance with the CDC’s guidelines for investigation and control of VISA [6]. In addition to surveillance samples obtained from the patient for culture, nare cultures were performed on 44 staff members, 30 patients, and 1 family member who had either worked or been cared for in the medical intensive care unit during the month preceding the isolation of SARV. No screened persons were colonized with either a VISA or SARV. An MRSA isolate was recovered from the patient’s nares 6 days after he initiated therapy with linezolid. However, 3 subsequent nare cultures did not grow MRSA.

Between his completion of linezolid therapy and his death 18 weeks later, the patient had multiple nosocomial infections, including candidemia and ventilator-associated pneumonia. Six weeks after completion of linezolid therapy, the patient developed another case of MRSA bacteremia (MIC of vancomycin, 1 µg/mL). PFGE of *Sma*I-macrorestricted genomic DNA showed the MRSA bacteremia isolated and the SARV strain to be indistinguishable.

The patient died of respiratory failure 4 weeks after resolution of recurrent *S. aureus* bacteremia. An autopsy demonstrated complete resolution of the vegetation on both his aortic and mitral valves and shared no evidence of other residual sites of infection.

**Discussion.** We describe a patient with definite IE [7] in whom clinical failure of vancomycin therapy for MRSA infection was associated with the development of SARV. Similar to other patients with VISA or SARV infection, our patient was chronically ill and was treated with an extended course of vancomycin in the context of a prosthetic device [8]. The device was removed, and the patient was treated for 2 months with linezolid monotherapy, with apparent resolution of the vegetations, as demonstrated by echocardiography and postmortem evaluation of the valve.

Although initially believed to be VISA, the CDC confirmed that the isolate recovered from our patient was SARV. The isolate did not have subpopulations with variable resistance, as demonstrated by population analyses (figure 1). On subsequent evaluation, neither the SARV nor the MRSA isolate produced

![Vancomycin population analysis](image)

**Figure 1.** Vancomycin population analysis of *Staphylococcus aureus* isolate with reduced susceptibility to vancomycin (SARV) that was obtained from a patient before initiation of linezolid therapy and of an isolate from a case of recurrent methicillin-resistant *S. aureus* (MRSA) bacteremia that was recovered from the same patient 6 weeks after completion of linezolid therapy. Bacteria were grown overnight, and a 1.0 McFarland suspension (25 µL) and serial 10-fold dilutions were plated on brain-heart infusion agar with varying concentrations of vancomycin (range, 0–16 µg/mL). Colonies were counted after 48 h of growth at 35°C. CFU, colony-forming units.
δ hemolysin [9], suggesting down-regulation of the accessory gene regulation (agr) locus. A down-regulated agr locus has been associated with an intrinsic survival advantage under glycopeptide selective pressure [10]. However, these isolates were agr group III, unlike most VISA and SARV isolates identified in the United States (agr group II) [10, 11]. Furthermore, it is noteworthy that, according to a previously published dendo-gram based on PFGE of Smal-macrorestricted chromosomal DNA, this isolate is not closely related to the other VISA and SARV isolates from the United States [4].

As with most isolates of VISA or SARV, the isolate obtained from this patient was resistant to multiple antibiotics but susceptible to rifampin, TMP-SMX, and tetracycline [5]. Monotherapy with TMP-SMX or minocycline, continuation of vancomycin therapy, or the addition of either rifampin or TMP-SMX to the linezolid regimen were considered as possible alternatives to linezolid monotherapy. However, there is little published literature regarding synergy or antagonism between linezolid and additional antibiotics, and the patient had a history of intolerance of sulfa medications. Limited experimental data [12] and published clinical experience [13] exist for tetracycline derivatives as treatment for endocarditis. Newer agents, such as tigecycline and daptomycin, were not available at the time for clinical use.

The role of linezolid for the treatment of endocarditis caused by drug-resistant gram-positive pathogens is unresolved. Although initial animal models [14] and clinical data [15, 16] supported the use of linezolid for the treatment of complicated infections with gram-positive pathogens, including endocarditis, recent reports have described poor response rates in animal MRSA IE models treated with linezolid [17], clinical failures for complicated MRSA and enterococcal infections treated with linezolid [18–21], and linezolid resistance in clinical S. aureus strains [22, 23]. Taken together, these observations suggest that, although linezolid is not an optimal antibiotic choice for the treatment of endocarditis, it may represent a therapeutic alternative in selected patients.

Our patient developed recurrent S. aureus bacteremia 2 months after completing therapy with linezolid. This isolate was no longer resistant to vancomycin, although the remainder of the antibiogram was similar. PFGE revealed indistinguishable patterns for the SARV and the later MRSA isolate. In addition, the pattern of an MRSA isolate obtained from the patient’s nares at the time of his SARV bacteremia was also identical to that of the SARV. This PFGE pattern is frequently observed from other clinical isolates at our institution and is not related to patterns reported for previous isolates of SARV. Because the postmortem examination failed to reveal any evidence of residual infection, we believe that the patient probably had a new catheter-associated infection with the same S. aureus strain. Alternatively, it is possible that the recurrent MRSA bacteremia was due to reversion to vancomycin susceptibility in an un-

identified site of persistent S. aureus infection, a phenomenon that has been previously described in vitro [24]. However, the lack of growth on surveillance cultures, the long period between the cessation of linezolid therapy and the onset of subsequent MRSA bacteremia, and the absence of vegetations noted during postmortem evaluation make this possibility less likely.

Even with ideal antibiotic therapy and a susceptible organism, therapeutic failures occur frequently in cases of staphyloccal IE. SARV is an emerging problem in the United States and worldwide, and IE is a likely clinical scenario for development of these organisms. SARV may prove to be difficult to eradicate because of limited bactericidal options. Perhaps even more concerning is the recent confirmation of 2 clinical isolates of vancomycin-resistant S. aureus (MIC, ≥32 μg/mL) [25, 26]. Despite the lack of bactericidal action against S. aureus, linezolid may be useful in the treatment of IE caused by these organisms, and additional characterization may help predict which isolates are most likely to respond.

References