Daptomycin-Nonsusceptible Vancomycin-Intermediate *Staphylococcus aureus* Vertebral Osteomyelitis Cases Complicated by Bacteremia Treated with High-Dose Daptomycin and Trimethoprim-Sulfamethoxazole

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We report two cases of daptomycin (DAP)-nonsusceptible (DNS) vancomycin-intermediate *Staphylococcus aureus* (VISA) vertebral osteomyelitis cases complicated by bacteremia treated with high-dose daptomycin and trimethoprim-sulfamethoxazole. Both patients responded rapidly and favorably to this combination. The clinical isolates from the two patients were tested *post hoc* in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model to confirm the bactericidal activity and enhancement of daptomycin and trimethoprim-sulfamethoxazole. The combination of high-dose daptomycin and trimethoprim-sulfamethoxazole should be explored further for the treatment of DNS VISA strains.

Treatment of *Staphylococcus aureus* infections displaying decreased susceptibility to both vancomycin and daptomycin (DAP) is challenging. Agents that retain activity are generally bacteriostatic, making the clearance of bacteria in deep-seated infections like osteomyelitis difficult, or they have concerning adverse effect profiles. This is especially true if appropriate surgical intervention and debridement cannot be performed. The following two cases illustrate the use of a novel bactericidal combination of high-dose daptomycin and trimethoprim-sulfamethoxazole (SXT) for the treatment of daptomycin-nonsusceptible (DNS) vancomycin-intermediate *Staphylococcus aureus* (VISA) vertebral osteomyelitis.

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In February 2010, an 80-year-old male with a history of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presented as an outpatient to his primary care physician with nausea, vomiting, and hypotension. Blood cultures were obtained, and 48 h later, the Gram stain was positive for Gram-positive cocci. The patient was admitted to the hospital and treated with vancomycin intravenously (i.v.) after 3 days of oral linezolid therapy as an outpatient. Results from both a three-phase nuclear bone scan and magnetic resonance imaging (MRI) of the spine were consistent with T9 and T10 vertebra osteomyelitis, discitis, and paravertebral phlegmon. Surgical debridement was not considered due to the location of the infection. A transesophageal echocardiogram was negative for endocarditis.

On hospital day 3 (day 3 in the hospital), vancomycin was discontinued, and 650 mg of quinupristin-dalfopristin (7.5 mg/kg of body weight) i.v. every 8 h was initiated based on culture results. The outpatient blood cultures had two distinct *S. aureus* isolates: *S. aureus* H9749-1 (vancomycin MIC of 16 μg/ml and daptomycin MIC of 2 μg/ml) and isolate two (vancomycin MIC of 2 μg/ml and daptomycin MIC of 0.5 μg/ml). Both isolates were susceptible to SXT (*Table 1*). On hospital day 5, the patient was switched to daptomycin (10 mg/kg/day) plus SXT i.v. (8 mg/kg/day of the trimethoprim [TMP] component) given every 8 h based on *in vitro* evidence of bactericidal activity against a DNS heterogeneous VISA (hVISA) strain (23). Repeat blood cultures taken on hospital admission were negative. On hospital day 11, the patient was transitioned to oral therapy, two double-strength (DS) SXT tablets twice daily while continuing daptomycin 10 mg/kg/day. On day 16 of hospitalization, his serum creatinine (SCR) rose to 2.0 mg/dl, and he complained of intolerable nausea and vomiting. Daptomycin (10 mg/kg/day) was continued, but the SXT dose was decreased to one DS SXT tablet twice daily. Twenty-four days later, his serum creatinine returned to baseline and he was put back on two DS SXT tablets twice daily with daptomycin (10 mg/kg/day). The patient tolerated the daptomycin-SXT combination therapy for 2 months when his creatinine phosphokinase (CPK) increased to 1,280 IU/liter without symptoms of myopathy. Daptomycin was discontinued, and the CPK level returned to baseline (17 IU/liter). He completed 6 months of SXT suppression therapy and was deemed a clinical cure.

In June 2010, a 65-year-old female with a history of recurrent MRSA leg wounds with bacteremia was admitted to the hospital with intractable back pain. A MRI of the spine showed T6 to T7 vertebral enhancement, suspicious for vertebral osteomyelitis, with no evidence of an abscess. Surgical debridement was not performed due to the location of the infection. On hospital day three, the patient was switched from empirical vancomycin i.v. to daptomycin at 6 mg/kg per day when the Gram stain method was positive for Gram-positive cocci. Two separate peripheral blood cultures grew *S. aureus* isolate F31774 with a vancomycin MIC of...
2 μg/ml by automated susceptibility testing (Vitek 2), 3 μg/ml when repeated by Etest, and confirmed VISA with a MIC of 4 μg/ml by the New York State reference laboratory. The daptomycin MIC was 4 μg/ml (Table 1). On day six, the daptomycin dose was increased to 10 mg/kg/day, and SXT i.v. (8 mg/kg/day of the TMP component) given every 8 h was added after repeat blood cultures remained positive. The blood cultures were negative 48 h later. The patient tolerated the high-dose SXT given i.v. in combination with daptomycin therapy for 7 days (hospital day 12), while repeat blood cultures remained negative (day 10), until her SCr increased to 2.6 mg/dl (from a baseline of 1.2 mg/dl) with potassium of 6.0 mmol/liter, prompting the discontinuation of SXT and replacement with oral rifampin (300 mg) without myopathy. On day 15 of hospitalization, the patient experienced an increase in dyspnea, and chest computed tomography (CT) revealed numerous pulmonary nodules thought to be septic emboli from a presumed tricuspid valve endocarditis; however, a transesophageal echocardiogram and chest CT remained negative. The blood cultures were negative 48 h later. A 48-h combination of daptomycin plus SXT was rapidly bactericidal (8 h), reached the limit of detection (1 log10 CFU/ml) at 24 h, and was significantly better than either agent alone (24 to 48 h) (P ≤ 0.004).

The activity of daptomycin, vancomycin, SXT, rifampin, daptomycin plus SXT, and daptomycin plus rifampin against S. aureus strain F31774 in the in vitro PK/PD model can be seen in Table 1. The activity of daptomycin, vancomycin, SXT, and daptomycin plus SXT against S. aureus strain H9749-1 in the in vitro PK/PD model are displayed in Fig. 1A. Vancomycin and SXT were bacteriostatic, while daptomycin displayed sustained bactericidal activity from 8 to 48 h. The combination of daptomycin plus SXT was rapidly bactericidal (8 h), reached the limit of detection (1 log10 CFU/ml) at 24 h, and was significantly better than either agent alone (24 to 48 h) (P ≤ 0.004).

There are limited case reports of VISA bone and joint infections. Successful outcomes have been reported with linezolid monotherapy, linezolid with fusidic acid, linezolid with rifampin, quinupristin-dalfopristin, and a combination of vancomycin, nafcillin, and gentamicin (11–13, 17, 18). SXT and daptomycin have concentration-dependent bactericidal activity against VISA/hVISA strains and also have clinical data to support their use in the treatment of osteomyelitis (5, 7, 9, 18, 23, 26). Multiple studies have evaluated the safety of high-dose daptomycin and found the incidence of symptomatic myopathy and CPK elevation to be comparable to that of standard doses (4, 8, 10, 14, 15, 20). Dapto-

### Table 1: Vitek 2 MICs for VISA isolates

<table>
<thead>
<tr>
<th>Antimicrobial agent(s)</th>
<th>Isolate 1 (S. aureus H9749-1)</th>
<th>Isolate 2 (S. aureus F31774)</th>
<th>Case 2, isolate 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinupristin-dalfopristin</td>
<td>0.5</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2 [2–4]</td>
<td>0.5 [0.25]</td>
<td>4 [4]</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤0.5</td>
<td>≤0.5</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Linezolid</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Telavancin (0.38) (%)</td>
<td>4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>SXT 0.5/9.5 [0.03/0.6]</td>
<td>4</td>
<td>0.5/9.5 [0.03/0.6]</td>
<td>N/A</td>
</tr>
<tr>
<td>Rifampin</td>
<td>≥32</td>
<td>≥32</td>
<td>N/A</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.25</td>
<td>0.5</td>
<td>≤0.12</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>≥8</td>
<td>≥8</td>
<td>≥8</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>≥4</td>
<td>≥4</td>
<td>≥4</td>
</tr>
</tbody>
</table>

a. MIC confirmed by broth microdilution at the Anti-Infective Research Laboratory shown in brackets. N/A, not available (no quinupristin-dalfopristin disks were available due to back order). For trimethoprim-sulfamethoxazole (SXT), the value for trimethoprim is shown before the slash and the value for sulfamethoxazole is shown after the slash.

b. MIC by Etest.
mycin regimens up to 12 mg/kg/day have been studied in healthy patients and in patients with deep-seated VISA infections (2, 16). In each of our patient cases, CPK levels were elevated from normal baseline levels, but neither patient developed symptoms of myopathy despite these elevations. Adverse reactions of SXT include gastrointestinal symptoms, increased serum creatinine, and hyperkalemia (1, 3, 19). A rise in serum creatinine in both patients and hyperkalemia in the second patient led to reduction of the SXT dose in the first patient and cessation of SXT therapy in the second patient. Following cessation of SXT therapy, the second patient experienced a rapid clinical decline. It is important to note the in vitro data from the isolates from the two patients demonstrate bactericidal and enhancement of activity of daptomycin and SXT against DNS VISA at a lower dose of TMP (360 mg/day) than what was used initially in these cases. At this lower dose, an increase in creatinine is more likely due to competitive tubular secretion and not a change in the actual glomerular filtration rate, allowing patients to continue therapy and avoid switching to a less-effective regimen (3).

Although tested post hoc, the results from our in vitro PK/PD model correlated with the clinical outcomes. The first patient achieved osteomyelitis resolution, and the second patient cleared persistent bacteremia on daptomycin plus SXT. Concern has been raised regarding the efficacy of SXT in treating infections where high exogenous thymidine released from damaged host tissues may be present and antagonizing SXT activity (21). The clinical outcomes in our patients while on combination therapy with SXT were good, despite no surgical management to remove dead tissue, and correlated with the results of the in vitro model. Daptomycin appeared bactericidal when combined with rifampin in our model; however, this did not correlate with the second patient’s clinical course and may represent an area for further research. High-dose daptomycin combined with SXT may be a viable option for patients with DNS VISA infections.

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REFERENCES


FIG 1 Activity of tested antimicrobial agents in a one-compartment in vitro pharmacokinetic/pharmacodynamic model. The antimicrobials were tested against S. aureus (SA) H9749-1 and S. aureus F31774. Symbols: ○, no drug (growth control); ●, daptomycin (10 mg/kg) every 24 h (maximum concentration of the free, unbound fraction of drug in serum [Cmax] of 13.17 mg/liter and half-life [1/2]o of 6 h); ▼, vancomycin (1 g) every 12 h (q12h) (Cmax of 15 mg/liter and 1/2o of 8 h); △, rifampin (300 mg) every 24 h (Cmax of 0.8 mg/liter and 1/2o of 3 h); ○, trimethoprim-sulfamethoxazole (160/800 mg) every 12 h (Cmax of 1.3 and 30 mg/liter, respectively, and 1/2o of 10 h for each drug); ■, daptomycin plus trimethoprim-sulfamethoxazole; ▲, daptomycin plus rifampin.


