Daptomycin-Resistant, Methicillin-Resistant \textit{Staphylococcus aureus} Bacteremia

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We describe a patient who developed daptomycin-resistant, methicillin-resistant \textit{Staphylococcus aureus} (MRSA) during an episode of presumed septic thrombophlebitis of the portal vein. Although daptomycin is an alternative agent for treatment of drug-resistant gram-positive bacterial infections, development of resistance during prolonged use may occur with MRSA bacteremia from a persistent focus.

Daptomycin, a semisynthetic lipopeptide antibiotic derived from the fermentation of \textit{Streptomyces roseosporus}, is a promising new alternative for the treatment of drug-resistant gram-positive bacterial infections [1]. Daptomycin has concentration-dependent bactericidal activity against enterococci and staphylococci, and its spectrum of activity includes treatment of infection caused by methicillin-resistant \textit{Staphylococcus aureus} (MRSA), methicillin-resistant \textit{Staphylococcus} species (MRSS), glycopeptide-intermediate \textit{S. aureus} (GISA), penicillin-resistant \textit{Streptococcus pneumoniae}, and vancomycin-resistant \textit{Enterococcus} (VRE) species. To date, daptomycin resistance has not been well documented. We describe a patient who developed daptomycin resistance while experiencing failure of therapy for high-grade MRSA bacteremia.

\textbf{Case report.} A 54-year-old man with end-stage liver disease secondary to alcohol-related cirrhosis, complicated by a history of spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding, was admitted to a hospital in the Boston, Massachusetts, area (hereafter referred to as the “outside hospital”) on 5 January 2004 with hyponatremia, hyperkalemia, confusion, and worsening edema of the lower extremities. On the day of admission, he reported chronic back pain, suprapubic tenderness, occasional chills, and frequent bowel movements but no fever or sweating. At examination, he was disoriented with regard to date and time and appeared to have jaundice, but, otherwise, he was not in acute distress. His temperature was 35.7°C, blood pressure was 109/58 mm Hg, pulse was 96 beats/min, and respiration rate was 20 breaths/min. The findings of a physical examination included anicteric sclerae, multiple spider angiomata on the anterior chest wall, abdominal distension without tenderness, and pitting edema of the lower extremities. There was no peripheral lymphadenopathy, abnormal breath sounds, heart murmurs, or hepatosplenomegaly. Initial laboratory results revealed a WBC count of 11,800 cells/μL, with 74% polymorphonuclear leukocytes and 8% bands; hematocrit of 24.8%; platelet count of 69,000 cells/μL; and levels of sodium of 119 mmol/L, potassium of 5.6 mmol/L, blood urea nitrogen of 20 mg/dL, and creatinine of 0.6 mg/dL. His total bilirubin level was 19.2 mg/dL, and he had levels of aspartate aminotransferase of 68 U/L, alanine aminotransferase of 66 U/L, and alkaline phosphatase of 241 U/L and an international normalized ratio of 1.86.

Treatment with ceftriaxone (1 g iv q24h) was started empirically, on the day of admission. On 6 January, when culture of blood samples obtained at admission yielded MRSA, treatment with ceftriaxone was discontinued, and treatment with vancomycin (1 g iv q12h) was initiated. Urine cultures also grew $10^4$ cfu MRSA/mL. In an attempt to identify the source of the bacteremia, diagnostic tests were done, including a chest radiography, paracentesis, indium-tagged WBC scanning, transthoracic echocardiography, and an ultrasound of the lower extremities; all test results were unremarkable. A bone scan showed an L11 compression fracture and increased activity at L2 that was of indeterminate etiology. A follow-up spine MRI revealed an L4 compression fracture but no other abnormalities.

After 10 days of therapy with vancomycin, the bacteremia persisted. On 16 January, the antibiotic regimen was changed to daptomycin (4 mg/kg iv q24h). Linezolid was avoided because of a concern that it might exacerbate the patient’s underlying pancytopenia. After 4 days, the initial daptomycin dosage was increased (to 6 mg/kg iv q24h), when the patient continued to be bacteremic. Blood samples drawn during this treatment, on 19 January and 28 January, revealed daptomycin-resistant, methicillin-resistant MRSA on culture. Twenty-one blood samples col-
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Table 1. Results of susceptibility testing of methicillin-resistant Staphylococcus aureus isolates from blood.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptibility, by location and date of testing</th>
<th>MIC in µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outside hospital</td>
<td>Tufts-NEMC, 11 Feb 2004</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Linezolid</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Vancomycin</td>
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<td>S</td>
</tr>
</tbody>
</table>

**NOTE.** NEMC, New England Medical Center; NT, not tested; R, resistant; S, susceptible.

a “Outside hospital” indicates the Boston-area hospital where the case patient initially received treatment.

b As determined by means of Kirby-Bauer disk diffusion.

c As determined by means of broth microdilution.

lected between 5 January and 28 January grew MRSA on culture that also was susceptible to vancomycin and linezolid.

On 11 February, 27 days after the start of daptomycin therapy, the patient was transferred to Tufts–New England Medical Center (Boston) for further evaluation and treatment. Blood culture samples obtained from the patient at admission continued to yield MRSA, but susceptibility testing now revealed resistance to daptomycin, by both Kirby-Bauer and MIC testing. The zone size for daptomycin was 14 mm, and the MIC was 2 µg/mL (tested in 2 different laboratories). Treatment with daptomycin was discontinued, and treatment with linezolid (600 mg iv q12h) was initiated. A CT scan of the abdomen revealed a nonocclusive thrombus in the extrahepatic portal vein, which was thought to be the origin of the bacteremia. The first negative surveillance blood culture results were obtained on day 5 of linezolid therapy. Because of worsening thrombocytopenia and gastrointestinal bleeding, anticoagulation was not initiated; linezolid therapy was stopped on 18 February, and treatment with vancomycin (1 g iv q.d.) and gentamicin (70 mg iv q24h, for synergy) was started. Thereafter, surveillance blood samples obtained from the patient had no growth on culture.

After renal failure developed, which likely was secondary to hepatorenal syndrome, the patient’s family decided to stop all antibiotic therapy, on 4 March, and to continue comfort care only. A follow-up blood culture performed on 8 March, 4 days after completion of the 15-day course of vancomycin and gentamicin, yielded no growth. The patient was ultimately discharged to hospice care.

**Methods.** The susceptibility of isolates to antibiotics was determined by Kirby-Bauer disk diffusion and broth microdilution methods, in accordance with guidelines of the NCCLS [2, 3]. NCCLS interpretive criteria were used to determine a qualitative report of susceptible, intermediate, or resistant. The MIC was read as the lowest concentration of daptomycin that completely inhibited growth of the organism in the wells, as detected by visual inspection. The MIC of daptomycin that defined susceptibility for MRSA was ≤1 µg/mL. Criteria for intermediate susceptibility and resistance have not yet been determined, because of a lack of daptomycin-resistant strains [4].

The bactericidal or bacteriostatic effect of the antibiotics used for therapy (daptomycin, vancomycin, linezolid, and gentamicin) against the pathogen (MRSA) causing infection in the patient was determined by time-kill curves, in accordance with NCCLS recommendations [5]. For the testing of daptomycin, the broth was supplemented with calcium at physiological concentrations (MHCa++). A bactericidal effect was defined as a reduction of ≥3 log₁₀ of the initial bacterial inoculum. A lesser reduction in bacterial count (<3 log₁₀) was defined as a bacteriostatic effect [5, 6].

**Results.** From 5 January to 16 February, a total of 23 positive blood culture results were obtained. All cultures grew MRSA susceptible to tetracycline, trimethoprim-sulfamethoxazole, and vancomycin but resistant to ampicillin/sulbactam, ceftriaxone, cefazolin, ciprofloxacin, clindamycin, erythromycin, oxacillin, and nafcillin. Testing for daptomycin susceptibility, on 19 January and 28 January, at the outside hospital found susceptible isolates (Kirby-Bauer zone size of >16 mm, the cutoff for susceptibility). However, by 11 February, the MRSA isolates had become daptomycin resistant, as determined by a Kirby-Bauer zone size of ≤14 mm. Susceptibility patterns remained the same for all other antibiotics tested previously. Isolates were further tested by broth microdilution and were found to be susceptible to quinupristin/dalfopristin, linezolid, gentamicin, and rifampin (table 1).

Time-kill experiments using daptomycin-resistant isolates of MRSA demonstrated a bactericidal effect with daptomycin at 8 µg/mL. However, daptomycin at 1, 2, and 4 µg/mL showed only bacteriostatic activity. Linezolid and vancomycin showed bacteriostatic activity at all concentrations tested.

**Discussion.** We describe a patient with high-grade MRSA bacteremia, which most likely was secondary to an infected
portal vein thrombus, in whom daptomycin resistance developed during a prolonged course of daptomycin therapy. Initially, isolates had been found to be daptomycin susceptible, by Kirby-Bauer disk diffusion done at the referring hospital. After a protracted course of daptomycin therapy, the patient experienced treatment failure with the emergence of resistance after 28 days of therapy. To our knowledge, this is the first well-documented report of the development of daptomycin resistance in a clinical isolate of MRSA that was associated with bacteriologic treatment failure. The implications of this finding are significant, because daptomycin has been welcomed as a novel and alternative agent for the treatment of infection with drug-resistant gram-positive bacteria.

The in vitro activity of daptomycin against MRSA, MRSS, GISA, penicillin-resistant S. pneumoniae, and VRE species is 2–4-fold superior to that of vancomycin [7]. More recently, in vitro studies have documented daptomycin activity against MRSA and VRE comparable to that of linezolid [8]. Daptomycin is an ideal alternative to vancomycin and linezolid because of its once-daily dosage and low side effect profile. In September 2003, the US Food and Drug Administration approved use of daptomycin for the treatment of complicated skin and soft-tissue infections caused by these organisms; ongoing clinical trials are in progress to determine whether it can be used for more-serious infections, such as bacteremia. A recent animal study suggested that daptomycin is effective for serious MRSA infections, including infective endocarditis [9].

The mechanism of resistance to daptomycin is unknown [10]. To date, there have been no reports of clinical isolates initially resistant to daptomycin, and the incidence of the development of spontaneous resistance appears to be very low [11]. One patient with MRSA infection reportedly had an increase in the MIC for daptomycin during clinical trials, but no information on clinical outcome was provided [4].

The limitations of this case report are that the original, daptomycin-susceptible isolates were not saved and could not be compared directly with the daptomycin-resistant isolates by molecular fingerprinting. However, standard methodology for susceptibility testing was used in both instances. In addition, the reason for the failure of initial vancomycin therapy is not understood. The isolates may have exhibited vancomycin heteroresistance; by means of time-kill curves, we demonstrated that vancomycin was not bactericidal at 24 h. These findings are consistent with the report by Sakoulas et al. [12].

Clinicians using daptomycin for treatment of MRSA bacteremia should be aware of the potential for the development of daptomycin resistance, especially during prolonged therapy for high-grade bacteremia.

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