

# Treatment Failure Resulting from Resistance of *Staphylococcus aureus* to Daptomycin

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**Daptomycin, a new cyclic lipopeptide, was recently approved for the treatment of infections by gram-positive organisms, including infections with methicillin-resistant *Staphylococcus aureus* (MRSA). A patient infected with infected with MRSA developed resistance to daptomycin after prolonged exposure, which resulted in clinical failure. Clinicians should be aware of the possibility of daptomycin resistance and should consider routine testing for daptomycin susceptibility.**

## CASE REPORT

A 64-year-old woman with diabetes mellitus, treated breast cancer in remission, severe osteoarthritis, bilateral knee prostheses, hypertension, hyperlipidemia, and morbid obesity was well until October 2003, when she developed septic arthritis and bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA) following a bimalleolar left ankle fracture. A transesophageal echocardiogram did not show evidence of endocarditis. She underwent ankle debridement and then received treatment with intravenous vancomycin for 6 weeks. This was followed by open reduction and internal fixation of the left ankle. Two weeks after surgery the ankle became erythematous with a small draining wound. Vancomycin was restarted, and the patient received treatment for 6 weeks. Rifampin was added for a brief period, but she could not tolerate it. Linezolid was administered for 2 days, but the patient had severe nausea, and thus it was not continued. Removal of the hardware was suggested, but the patient refused surgery. Thus, daptomycin was administered for 6 weeks. The initial dose was 8 mg/kg/day, and the subsequent dose was 6 mg/kg/day. The patient noted decreased drainage from the ankle but had continued ankle pain. She finally agreed to removal of hardware in April 2004. After removal of the ankle hardware she showed mild improvement but continued to have purulent drainage from the ankle. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remained high, and daptomycin was increased to 8 mg/kg/day. A technetium-99 three-phase bone scan showed significantly increased uptake on blood flow, blood pool, and delayed images in the left distal tibia and fibula.

The patient underwent left below-the-knee amputation in May 2004. After the amputation, she developed a stump infection due to methicillin-susceptible *S. aureus* (MSSA) and was treated with daptomycin 6 mg/kg per day for 3 weeks, with resolution of the infection. Because the ESR and CRP remained high she underwent a technetium-99-labeled white-blood-cell scan, which did not reveal any signs of an inflam-

matory process and specifically did not reveal any increased uptake in the right knee prosthesis. Magnetic resonance imaging (MRI) of the shoulders was also done because of complaints of bilateral shoulder pain and revealed avascular necrosis of the left shoulder but no evidence of infection.

In November 2004 the patient presented with a right lower leg abscess 5 weeks after minor local trauma to her anterior tibia. Physical examination was significant for temperature (99.7°F) and a 20-by-10-cm raised area of warmth and erythema, with a central area draining purulent material. The white-blood-cell count was  $7.6 \times 10^3$  cells/ $\mu$ l with 72% neutrophils. Incision and drainage was performed, with removal of 40 ml of pus, which grew MRSA. The organism was susceptible to vancomycin (MIC  $\leq 2$   $\mu$ g/ml), rifampin (MIC  $\leq 1$   $\mu$ g/ml), trimethoprim-sulfamethoxazole (MIC  $\leq 2$  and  $\leq 38$   $\mu$ g/ml, respectively), gentamicin (MIC  $\leq 1$   $\mu$ g/ml), and tetracycline (MIC  $\leq 4$   $\mu$ g/ml) and resistant to clindamycin (MIC  $> 2$   $\mu$ g/ml). The patient received treatment with vancomycin for 10 days, followed by doxycycline at 100 mg twice daily for 14 days. Improvement was noted; however, drainage increased again 2 weeks after cessation of antibiotic therapy, and thus it was administered for an additional 14 days. Culture of the drainage again grew MRSA, with the same susceptibility profile.

In January 2005, the patient underwent drainage of the right anserine bursa and of the anteromedial tibia. The right knee prosthesis was noted to be free of infection. MRI examination on 24 February 2005 revealed inflammation and/or edema within the subcutaneous tissues anterior to the right tibia. There was no evidence of osteomyelitis, no fluid collection, and no evidence of infection of the prosthesis. Daptomycin at 6 mg/kg/day was restarted on 13 January 2005. The wound drainage decreased minimally, but then in April 2005 the patient noted significantly increased wound drainage. A culture of the drainage revealed MRSA with the same susceptibility profile as previous isolates. Additional susceptibility testing by E-test revealed resistance to daptomycin with an MIC of 4  $\mu$ g/ml. This result was confirmed by broth microdilution. Another culture of the drainage obtained 1 week later revealed MRSA with identical susceptibilities. The daptomycin MIC on the repeat isolate was again 4  $\mu$ g/ml by E-test.

Daptomycin was discontinued, and oral linezolid at 600 mg twice daily was administered for 6 weeks but eventually had to

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be discontinued due to severe nausea and anorexia. While the patient was receiving linezolid, the wound drainage decreased significantly and the CRP and ESR decreased from 79 mg/liter and 114 mm/h to 4.9 mg/liter and 50 mm/h, respectively. Another technetium-99 three-phase bone scan was performed and was normal. A technetium-99-labeled white-blood-cell scan was also normal. After the patient did not receive antibiotics for 2 weeks, drainage increased and CRP and ESR rose to 10.3 mg/liter and 79 mm/h. Thus, in June 2005 she received oral minocycline at 100 mg twice daily and trimethoprim-sulfamethoxazole DS at two tablets twice per day. Minocycline was changed to doxycycline at 100 mg twice per day due to nausea. The wound gradually closed, and the drainage decreased over the next 2 months. The CRP and ESR decreased to 3.6 mg/liter and 47 mm/h, respectively. The patient continues to receive doxycycline and trimethoprim-sulfamethoxazole without signs of active infection.

**Discussion.** We report here a case of MRSA infection resistant to daptomycin that resulted in clinical failure.

The MIC of 4.0  $\mu\text{g/ml}$  was confirmed from two separate isolates on separate occasions. This is two dilutions above the proposed breakpoint for nonsusceptible of 1.0  $\mu\text{g/ml}$  (daptomycin package insert) and clearly above the MIC at which 90% of the isolates tested are inhibited of 0.5  $\mu\text{g/ml}$  for MRSA found in prior studies (2, 5). It is likely that resistance developed while on therapy, given the fact that the patient initially improved while receiving daptomycin only to subsequently worsen after receiving prolonged daptomycin. However, because we were not able to retrieve and test the original bacterial isolates prior to daptomycin administration, we cannot rule out preexisting daptomycin resistance. This patient received prolonged daptomycin (a total of 28 weeks) over 2 years. It is likely that this prolonged course of daptomycin was a risk factor for acquisition of resistance.

We are aware of only one well-documented clinical report of daptomycin-resistant *S. aureus*. In the prior report, a patient with bacteremia due to MRSA that was initially susceptible to daptomycin developed resistance to daptomycin while on therapy for 27 days (1). In that case the likely source for bacteremia was a septic thrombophlebitis, thus resulting in a high-grade prolonged bacteremia, an ideal milieu for the development of bacterial resistance. Another patient with daptomycin-resistant *S. aureus* is mentioned in the daptomycin package insert (dap-

tomycin package insert). However, further details of this case have not been reported.

Daptomycin, a cyclic lipopeptide, was recently approved for treatment of complicated skin and skin structure infections due to susceptible gram-positive organisms. It has a unique mechanism of action, namely, depolarization of the bacterial cell membrane, allowing potassium efflux with resultant imbalance in the cell membrane potential and cell death. The antibiotic has broad in vitro activity versus gram-positive bacteria, including MSSA and MRSA, as well as *Streptococcus agalactiae*, *Streptococcus pyogenes*, and *Enterococcus faecalis* (3). It has a prolonged elimination half-life and is rapidly bactericidal, making it an appealing alternative to vancomycin, the current gold standard for treatment of MRSA infections. In vitro studies have demonstrated a low rate of spontaneous resistance to daptomycin, and only one case of significant resistance has been reported (1, 4).

Daptomycin testing is not currently part of routine *S. aureus* susceptibility testing panels. Acceptable testing procedures for daptomycin include E-test and broth dilution. Kirby-Bauer disk diffusion testing is currently not available due to an unacceptably high frequency of major errors (resistant organisms appear to be susceptible) (Cubist Pharmaceuticals, Inc.). As the use of daptomycin increases in the future, inclusion of daptomycin in commercial susceptibility testing panels should assist clinicians in the appropriate use of the drug. For patients infected with *S. aureus*, in whom the infection is slow to clear while receiving daptomycin, clinicians should consider susceptibility testing of repeat bacterial samples in order to detect the possibility of daptomycin resistance developing on treatment.

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