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# Development of High-Grade Daptomycin Resistance in a Patient Being Treated for *Corynebacterium striatum* Infection

**Saira Ajmal, Omar Abu Saleh, Elena Beam**

Division of Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA

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We report a case of a 62-year-old male with ischemic cardiomyopathy complicated by cardiogenic shock who underwent placement of a left-ventricular assist device (LVAD; HeartMate II) in July 2013 as destination therapy. This was complicated by a sternal infection with *Candida albicans* and *Staphylococcus epidermidis* in October 2013, which was managed conservatively with chronic suppression with fluconazole and minocycline. In December 2016, he presented with a febrile illness without localizing signs and was diagnosed with a *Corynebacterium striatum* bloodstream infection, which cleared within 24 h of vancomycin initiation. Computed tomography (CT) of the chest, abdomen, and pelvis noted a tiny amount of retrosternal fluid adjacent to the LVAD cannula. Transesophageal echocardiography (TEE) was not suggestive of endocarditis. Susceptibility testing revealed resistance to ciprofloxacin (MIC of >2 $\mu$g/ml), clindamycin (MIC of >2 $\mu$g/ml), ceftriaxone (MIC of >2 $\mu$g/ml), and trimethoprim-sulfamethoxazole (MICs of >2/38 $\mu$g/ml). The isolate was susceptible to meropenem (MIC of ≤0.25 $\mu$g/ml), vancomycin (MIC of ≤1 $\mu$g/ml), linezolid (MIC of ≤2 $\mu$g/ml), and doxycycline (MIC of ≤4 $\mu$g/ml) and intermediately susceptible to penicillin (MIC of 1 $\mu$g/ml). Daptomycin susceptibility testing was performed by the concentration gradient diffusion method Etest on Mueller-Hinton agar containing 5% sheep blood and revealed a MIC of 0.12 $\mu$g/ml. He was switched to intravenous daptomycin (6 mg/kg/day) for outpatient therapy for 7 weeks with plans for chronic suppression. About 6 weeks into therapy, the patient was readmitted with recurrence of fevers and chills. Blood cultures grew a *C. striatum* strain that had developed high-grade daptomycin resistance (MIC of >256 $\mu$g/ml) but retained susceptibility to vancomycin (MIC of ≤1 $\mu$g/ml). His intravenous line was removed, a tip culture was negative, and TEE and CT results were unchanged. He was switched to intravenous vancomycin, and his blood cultures cleared within 24 h. He is currently undergoing 6 weeks of vancomycin therapy without a relapse of bacteremia.

An increase in the number of clinically significant infections due to *Corynebacterium* sp. is reported as more complex patients are managed with immunosuppression and long-term prosthetic devices. Daptomycin inhibits bacterial replication by multiple mechanisms, including membrane targeting and interruption of cell wall synthesis, resulting in disruption of the bacterial cell wall and leakage of cellular components and cell death. Data are limited regarding the development of high-grade daptomycin resistance during therapy. We performed a literature search and identified three similar cases of patients with LVAD-associated infections with *C. striatum* that developed high-grade daptomycin resistance during therapy, resulting in relapsed infection (1, 2).

The genetic basis of daptomycin resistance in *Corynebacterium* sp. is not fully understood. It is proposed that a large bacterial burden with large prosthetic devices and/or prolonged exposure to daptomycin may be causative factors. In other Gram-positive pathogens, such as *Staphylococcus aureus* and *Enterococcus* sp., mutations

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Address correspondence to Saira Ajmal, ajmal.saira@mayo.edu.

affecting the genes involved in cell wall biosynthesis and cell wall stress response are thought to lead to phenotypic daptomycin resistance, primarily by repulsion, decreased cell membrane depolarization, and change in the cell wall charge and/or thickness. *Enterococcus faecalis* appears to act differently, with alteration in the cell wall causing diversion of daptomycin from the primary site of action in the cell wall (3). *In vitro* experiments have found that incubation of susceptible *C. striatum* isolates with daptomycin can result in high-level resistance, which is rapid in onset and, in some isolates, durable on passage in antibiotic-free media. An initial delay in growth was observed in the daptomycin-exposed strains compared to that of the controls, which was no longer present at 24 h, suggesting inducible resistance or selection of a resistant strain from a mixed population (1). This finding correlates with the clinical picture in our patient, i.e., initial improvement with subsequent relapsed infection due to the emergence of high-level resistance with prolonged exposure.

Given the increasing use of daptomycin and increasing resistance to traditional agents, we feel that it is important to be cognizant of this phenomenon and be cautious with prolonged daptomycin therapy of *C. striatum*. Further research regarding the mechanism and extent of this phenomenon is warranted.

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