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Luis A. Marcos
Washington University School of Medicine in St. Louis
Bernard C. Camins
Washington University School of Medicine in St. Louis

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Successful Treatment of Vancomycin-Intermediate *Staphylococcus aureus* Pacemaker Lead Infective Endocarditis with Telavancin▽

Luis A. Marcos* and Bernard C. Camins

Division of Infectious Diseases, Washington University School of Medicine, Saint Louis, Missouri

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Emerging infections caused by vancomycin-intermediate *Staphylococcus aureus* (VISA) isolates are more likely to be associated with treatment failures than infections caused by other types of *S. aureus*. We present a case of pacemaker lead infective endocarditis caused by a non-daptomycin-susceptible strain of VISA. After 8 weeks of parenteral telavancin therapy, the patient achieved microbiological and clinical cure.

This case involves a 57-year-old woman with rheumatoid arthritis, paroxysmal atrial fibrillation, asthma, and congenital complete atrioventricular heart block which had required a pacemaker for the previous 20 years. She presented to an outside hospital with a 2-week history of fevers, chills, and tachycardia. On physical exam, she was found to have small red macular lesions in her toes and fingers. She was transferred to our hospital because blood cultures were persistently positive for methicillin-resistant *Staphylococcus aureus* (MRSA) with an elevated MIC of vancomycin of 2 μg/ml by the broth microdilution method. Intravenous vancomycin was replaced with daptomycin at 8 mg/kg intravenously (i.v.) daily. She remained bacteremic for the next 5 days. A transesophageal echocardiogram (TEE) revealed multiple small, highly mobile, linear echogenic densities attached to the pacemaker leads in the right atrium, consistent with small vegetations. The first *S. aureus* isolate cultured from the blood at our hospital was resistant to cefazolin, clindamycin, erythromycin, oxacillin, and penicillin by the disk diffusion method and susceptible to doxycycline, linezolid, trimethoprim-sulfamethoxazole, and vancomycin. By broth microdilution, MICs for this *S. aureus* isolate were 2 μg/ml of vancomycin, 0.5 μg/ml of daptomycin, and 4 μg/ml of linezolid. On day 6 of hospitalization, the pacemaker was explanted and replaced with a temporary transvenous pacemaker because of her complete heart block. MRSA was also isolated from the pacemaker pocket. On day 10, blood cultures became sterile for the first time since the patient had been on intravenous daptomycin at 8 mg/kg i.v. daily. On day 15, however, the patient developed ventricular tachycardia, and blood cultures were again positive for MRSA. At this point, daptomycin was increased to 10 mg/kg i.v. daily. On day 17, because of back pain and the recurrence of bacteremia, a computed tomography of the chest, abdomen, and pelvis was performed to search for other potential sources of bacteremia. The exam revealed a large epidural abscess at the level of the L4-L5 spine and two retained foreign bodies (part of the pacemaker wire, approximately 1 cm and 2 cm in length) lodged in her pulmonary arteries. On day 18, the MICs for the MRSA isolate from the blood sample drawn on hospital day 15 were available, and they were 4 μg/ml of vancomycin (VISA) and 2.0 μg/ml of daptomycin (non-daptomycin-susceptible *S. aureus* [DNSSA]); the linezolid MIC remained at 4 μg/ml by the broth microdilution method and the telavancin MIC was 0.25 μg/ml by Etest. Daptomycin was discontinued and telavancin was initiated at 10 mg/kg i.v. daily. On day 19, blood cultures were negative, and the patient underwent incision and drainage and laminectomy of the L4-L5 vertebrae. Gram stain of the operating room cultures was positive for Gram-positive cocci in clusters, but cultures were sterile. The blood samples drawn on the same day were sterile again, and all blood samples drawn afterwards remained sterile. A repeat TEE on day 24 (day 6 of telavancin) showed new multiple smaller echogenic densities consistent with vegetations along the superior cava vein and on the temporary wire. On day 33, at 15 days after initiation of telavancin, since all blood samples drawn after day 19 remained sterile, new epicardial ventricular leads were implanted and the temporary, presumably infected, pacemaker wire was removed. The patient continued to improve clinically and completed an 8-week course of telavancin at a skilled nursing care/rehabilitation facility. Her renal function (creatinine level) was monitored at least twice a week, and it remained normal throughout the course of therapy. Because of the potentially infected piece of pacemaker wire lodged in the pulmonary artery, she was treated with doxycycline at 100 mg orally twice a day as chronic suppressive therapy. At follow-up 2 months after completion of therapy, she complained only of chronic back pain and was able to walk short distances again. Surveillance blood samples drawn after discontinuation of telavancin and 2 weeks prior to the follow-up were sterile. A summary of the clinical course and MICs is presented in Table 1.

The emergence of vancomycin-intermediate *S. aureus* (VISA) and heterogeneous vancomycin-intermediate *S. aureus* (hVISA) subpopulations of MRSA and VISA has been associated with a high rate of glycopeptide treatment failures (5). Infections caused by these isolates, which are tolerant of vancomycin, are particularly difficult to treat because of limited data on the alternatives to vancomycin. This is also complicated by reports that VISA strains which initially test susceptible to daptomycin have been found to develop higher MICs of daptomycin during therapy and become nonsusceptible, as in this case. This phenomenon is thought to be

* Corresponding author. Mailing address: Division of Infection Diseases, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8051, Saint Louis, MO 63110-1093. Phone: (314) 454-8214. Fax: (314) 454-5392. E-mail: lmarcos@dom.wustl.edu.

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TABLE 1. Summary of days of bacteremia, blood culture results, antibiotics MICs, and therapy

Day	Result for bacteremia	MIC[a] (μg/ml) of:				Therapy
		Vancomycin	Daptomycin	Televancin	Linezolid	
−1[b]	First blood culture positive at hospital 1	2	NA	NA	NA	Vancomycin, 1 g i.v. q12h
1	First blood culture positive at hospital 2	2	0.5	NA	4	Daptomycin, 6 mg/kg i.v. q24h
10	Last blood culture positive before initial sterilization	2	0.5	NA	4	Daptomycin, 8 mg/kg i.v. q24h
15	First new blood culture positive					Daptomycin, 10 mg/kg i.v. q24h
18		4	2.0	0.25	4	Telavancin, 10 mg/kg i.v. q24h
19	Negative blood culture					Epidural abscess drainage

[a] MICs were determined by broth microdilution for vancomycin, daptomycin, and linezolid and by Etest for telavancin. NA, not available.
[b] One day prior to transfer to hospital 2.

secondary to changes in the cell wall caused by a single point mutation at position 1259 in the *mprF* gene that impacts cell membrane biosynthesis (6).

Currently, vancomycin is the therapy for MRSA endocarditis recommended by the American Heart Association guidelines for treatment of infective endocarditis (IE) (1). Very limited data are available on IE caused by VISA. Linezolid has been reported to be successful at treating cases of MRSA endocarditis, but therapy with linezolid can be limited because of its nonbactericidal effect on MRSA and its potential long-term adverse effects and drug-drug interactions. Daptomycin has been shown to be effective for MSSA and MRSA bacteremia, including right-sided endocarditis, and well tolerated (3), but nonsusceptible isolates of MRSA and VISA are being reported. IE is difficult to treat because it involves a large amount of organisms and valvular vegetations are not easily penetrated by antibiotics, especially glycopeptides, to exert their effect. The hVISA phenotype is also more likely to be expressed in the presence of subtherapeutic drug levels, which makes infection of the heart valves an ideal site for expression of heterogeneous resistance (4). In a recent study that evaluated hVISA and MRSA phenotypes in IE, the hVISA phenotype was present in five isolates (83%; $n = 6$) reported to have a vancomycin MIC of 2 μg/ml as determined by the Etest method and in eight isolates (62%; $n = 13$) as determined by broth microdilution (2). Although we do not have the capability to test heterogeneous resistance to vancomycin, the MRSA and VISA isolates/colonies in our case are consistent with the hVISA phenotype, since all initial blood cultures showed MRSA with a vancomycin MIC of 2 μg/ml. But later on, after being exposed to both vancomycin and daptomycin, colonies with higher MICs of vancomycin and daptomycin were isolated. An uncontrolled source of infection such as endocarditis may increase the emergence of subpopulations with variable resistance to glycopeptides. Without the use of glycopeptides like vancomycin, therapeutic options for MRSA endocarditis are limited, and clinicians may have to use antimicrobials for which there is very limited clinical experience to date.

Telavancin, a semisynthetic derivative of vancomycin, is a novel lipoglycopeptide with rapid bactericidal activity and two mechanisms of action against Gram-positive bacteria, including methicillin-resistant, glycopeptide-intermediate, and vancomycin-resistant strains of *S. aureus.* Its dual mechanism of action is characterized by inhibition of the transglycosylation process of peptidoglycan cell wall synthesis by the formation of a complex with the D-alanyl-D-alanine precursors and depolarization of the bacterial membrane. In addition, its activity against a contemporary (2007-2008) global collection of 10,000 *S. aureus* isolates showed that it was very active against MSSA and MRSA, with MICs for 50% and 90% of isolates of both types of 0.12 and 0.25 μg/ml. It was also two-, four-, and eightfold more potent against MRSA than daptomycin, vancomycin, and quinupristin-dalfopristin and linezolid, respectively (8).

The clinical experience with telavancin for treatment of MRSA IE is limited to just one case report. To our knowledge, this is the first case report of VISA endocarditis treated with telavancin. There are two experimental rabbit models of aortic valve endocarditis caused by VISA and MRSA, and those studies showed that telavancin rapidly sterilizes the vegetations but at serum levels that are 5 to 10 times higher than serum levels achieved in human studies (7, 9). There is only one published case report of MRSA IE (vancomycin MIC ≤ 0.5 μg/dl) that was treated successfully with telavancin (10). The authors reported that the patient was treated with telavancin after he continued to have persistent bacteremia, but persistent bacteremia from MRSA endocarditis is not an uncommon occurrence. In our case, the isolate was both a VISA and a DNSSA and also had a high MIC of linezolid (4 μg/ml). Telavancin was chosen over linezolid because of its bactericidal activity, as opposed to the bacteriostatic activity of linezolid, and to avoid serotonin syndrome, since our patient was on a selective serotonin reuptake inhibitor (SSRI). In this case, the bacteremia resolved within 48 h of the initiation of telavancin. Although clearance of bacteremia could have been attributed to the administration of high-dose daptomycin, telavancin was used to complete the patient's treatment for endocarditis, osteomyelitis, and epidural abscess in the presence of a non-daptomycin-susceptible VISA isolate. This case indicates that the presence of VISA isolates can be induced by treatment with glycopeptides and lead to therapeutic failure. We recommend repeat resistance testing of isolates that are cultured from deep-seated infections during glycopeptide therapy, since these isolates may be susceptible to vancomycin and daptomycin at initiation of therapy but then become intermediately susceptible or even nonsusceptible after prolonged exposure to the antimicrobials. Nonetheless, the most important therapeutic intervention in this case was likely the controlling of the source of the infection (epidural abscess). Only through vigilance were we able to provide adequate therapy for these deep-seated infections. In conclusion, we report the successful treatment of a patient with complicated VISA endocarditis

who had multiple subpopulations of *S. aureus*, including MRSA, VISA, and DNSSA. To our knowledge, this is the first case of VISA endocarditis successfully treated with telavancin.

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