Successful treatment of vancomycin-intermediate Staphylococcus aureus pacemaker lead infective Endocarditis with Telavancin

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Abstract

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

Case presentation

This case involves a 57-year-old woman with rheumatoid arthritis, paroxysmal atrial fibrillation, asthma, and congenital complete atrioventricular heart block requiring a pacemaker for the last 20 years. She presented to an outside hospital with a two 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 of persistently positive blood cultures with methicillin-resistant S. aureus (MRSA) with an elevated minimum inhibitory concentration (MIC) to vancomycin of 2 µg/mL by broth micro dilution method. Intravenous vancomycin was replaced with daptomycin at 8 mg/kg i.v. daily. She remained bacteremic for the next 5 days. A transesophageal echocardiogram (TEE) was performed which revealed multiple small, highly mobile, linear echogenic densities attached to the pacer 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 through the disk diffusion method and susceptible to doxycycline, linezolid, trimetoprin-sulfamethaxole and vancomycin. By micro broth dilution method, MICs for this S. aureus isolate against the following antimicrobials were: 2 µg/ml to vancomycin, 0.5 µg/ml to daptomycin, and 4 µg/ml to linezolid. On day 6 of hospitalization, the pacemaker was explanted and it had to be 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 while 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 chest, abdomen and pelvis was performed in search for other potential sources of bacteremia. The exam revealed a large epidural abscess at the level of L4-L5 spine and two retained foreign bodies (part of the pacemaker wire– approximately 1 cm and 2 cm in length, respectively) was lodged in her pulmonary arteries. On day 18, the MICs for the MRSA isolate from the blood culture drawn on hospital day 15 were available and they revealed a
vancomycin MIC of 4 µg/mL (VISA) and a daptomycin MIC of 2.0 µg/mL (daptomycin non-
susceptible S. aureus -DNSSA), linezolid MIC remained at 4 µg/ml and telavancin was 0.25 mcg/ml
through microbroth dilution method. Daptomycin was discontinued and telavancin was initiated at 10
mg/kg i.v. daily. On day 19, blood cultures were negative, the patient underwent incision and drainage
and laminectomy of L4-L5 vertebral spine. Gram stain of the operating room cultures was positive for
gram positive cocci in clusters but cultures were sterile. The blood cultures drawn on the same day
were sterile again and all other blood cultures drawn afterwards remained sterile. A repeat TEE on day
24 (day 6 of telavancin) showed new multiple smaller echogenic densities consisted with vegetations
along the superior cava vein and on the temporary wire. On day 33, at 15 days after initiation of
telavancin and since all blood cultures drawn after day 19 remained sterile, new epicardial ventricular
leads were implanted and the temporary, presumably infected, pacer wire was removed. She continued
to improve clinically and completed an eight-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 for chronic suppressive therapy. At follow-up two months after completion of therapy, she
only complained of chronic back pain and she was finally able to walk short distances again.
 Surveillance blood cultures drawn after discontinuation of telavancin and two weeks prior to the
follow-up were sterile.

**Discussion**

The emergence of vancomycin-intermediate S. aureus (VISA) and heterogeneous vancomycin-
intermediate S. aureus (hVISA) subpopulations of MRSA and VISA have been associated with a high
rate of glycopeptide treatment failures [Howden et al., 2010]. Infections caused by these isolates that
are tolerant of vancomycin are particularly difficult to treat because of limited data on the alternative
treatment modalities to vancomycin. This is also complicated by reports that VISA strains which
initially test susceptible to daptomycin have been found to develop higher MIC to daptomycin while
on therapy and become non-susceptible, as in this case. This phenomenon is thought to be 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 [Julian et al., 2007].

Currently, vancomycin is the recommended therapy for MRSA endocarditis by the American
Heart Association guidelines for treatment of infective endocarditis (IE) [Baddour et al., 2005]. Very
limited data is available on IE caused by VISA. Linezolid has been reported to be successful at treating cases of MRSA endocarditis, but therapy can be limited with linezolid because of its non-bacteridical effect on MRSA and potential long-term adverse effects and drug-drug interactions. Daptomycin has been shown to be effective and well tolerated for MSSA and MRSA bacteremia, including right-sided endocarditis [Dress & Boucher 2006] but non-susceptible isolates of MRSA and VISA are being reported. IE is difficult to treat because it involves a high inoculum 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 under an environment of sub therapeutic drug levels which makes infection of the heart valves an ideal site for expression of heterogeneous resistance [Hiramatsu 2001]. In a recent study that evaluated hVISA and MRSA phenotypes in IE, the hVISA phenotype was present in 5 isolates (83%; n=6) reported to have a vancomycin MIC of 2 µg/ml defined by the method Etest; and 8 isolates (62%; n=13) defined by broth micro dilution [Bae et al., 2009]. 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 MIC to vancomycin and daptomycin were isolated. An uncontrolled source of infection such as endocarditis may increase the emergence of subpopulations of 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 are very limited clinical experience to date.

Telavancin, a semi-synthetic 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 showed that it was very active against MSSA and MRSA with MIC50/90, for both at 0.12/0.25 µg/ml. It was also two, four and eight fold more potent against MRSA than daptomycin, vancomycin or quinupristin/dalfopristin, and linezolid, respectively [Mendes et al., 2010].

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 these studies have shown that telavancin rapidly sterilizes the vegetations but at serum levels that are 5 to 10 times higher than serum levels achieved in human studies [Madrigal et al., 2005; Miro et al., 2007]. There is only one published case report of MRSA IE (vancomycin MIC ≤ 0.5 mcg/dl) that was treated successfully with telavancin [Nace & Lorber 2010]. 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 DNSSA and also had a high MIC to linezolid (4µg/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 an SSRI. In this case, the bacteremia resolved within 48 hours 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 daptomycin non-susceptible VISA isolate. This case illustrates 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 while on glycopeptide therapy since these isolates may be susceptible to vancomycin and daptomycin at initiation of therapy but then become intermediately susceptible or even non-susceptible after prolonged exposure to these antimicrobials. Nonetheless, the most important therapeutic intervention in this case was likely to control 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.

References

international cohort of patients with infective endocarditis: prevalence, genotype, and clinical significance. J. Infect. Dis.; 200: 1355-1366


Table 1. Summary of days of bacteremia, blood cultures results, antibiotics MICs and therapy.

<table>
<thead>
<tr>
<th>Day</th>
<th>Blood cultures</th>
<th>Vancomycin µg/ml</th>
<th>Daptomycin µg/mL</th>
<th>Televancin mcg/mL</th>
<th>Linezolid µg/mL</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>#-1</td>
<td>1st BC+ at Hosp 1</td>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Vancomycin 1gr IV Q12h</td>
</tr>
<tr>
<td>#1</td>
<td>1st BC+ at Hosp 2</td>
<td>2</td>
<td>0.5</td>
<td>N/A</td>
<td>4</td>
<td>Daptomycin 6mg/kg</td>
</tr>
<tr>
<td>#10</td>
<td>Last BC+ before initial sterilization</td>
<td>2</td>
<td>0.5</td>
<td>N/A</td>
<td>4</td>
<td>Daptomycin 8mg/kg</td>
</tr>
<tr>
<td>#15</td>
<td>1st new BC+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daptomycin 10mg/kg</td>
</tr>
<tr>
<td>#19</td>
<td>Negative BC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Epidural abscess drainage</td>
</tr>
<tr>
<td>Available MICs in Day#18</td>
<td>4</td>
<td>2.0</td>
<td>0.25</td>
<td>4</td>
<td>Telavancin 10mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

BC: blood culture; +: positive; N/A: no available. OSH: Outside hospital. -1: 1 day prior transfer to BJH. BJH: Barnes-Jewish Hospital. MICs by Broth Microdilution for vancomycin, daptomycin and linezolid. E-test for Telavancin.