

Use of Daptomycin in the Treatment of Prosthetic Pulmonary Valve Endocarditis.

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Citation

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Abstract

Infective endocarditis is relatively uncommon, affecting approximately 10,000 to 20,000 people in the United States, and accounting for one of every 1000 hospital admissions.¹ These infections can involve the right or left side of the heart and both native and prosthetic valves. Of the left-sided native valve infections, the aortic valve accounts for 5% to 36% of cases, mitral valve 28% to 45% of cases and zero to 35% of cases involve both valves. In right-sided native valve infections, the tricuspid valve is involved in zero to 6% of cases and the pulmonary valve is involved in less than 1% of cases.¹ The incidence of prosthetic valve endocarditis (PVE), while not as common as native valve infections, is reported to be 3.1%, with the probability of infection being highest within the first year of valve placement.² The coagulase-negative staphylococcus, *Staphylococcus epidermidis*, is the most common pathogen of prosthetic valve endocarditis, especially within the first year after surgery. Methicillin-resistant strains, which are most common in the first year, can account for up to 79% of infections.³ The treatment of methicillin-susceptible organisms include nafcillin plus rifampin in combination with gentamicin. The recommendation for methicillin-resistant organisms or those with a penicillin allergy is vancomycin plus rifampin and gentamicin. Other agents used include linezolid and quinupristin-dalfopristin.⁴ Daptomycin, a novel antibiotic, is emerging as a new treatment option for right-sided endocarditis resulting from methicillin-resistant *Staphylococcus* species. Originally approved in 2003 for skin and skin structure infections, it was approved in 2006 for the treatment of *S. aureus* (methicillin-susceptible (MSSA) and resistant isolates (MRSA)) bacteremia and right-sided endocarditis.⁵ To our knowledge, we present the first case of a patient with pulmonary valve endocarditis due to methicillin-sensitive *Staphylococcus epidermidis* treated with valve replacement and daptomycin.

CASE REPORT

A 31-year-old female with a history of pulmonary valve replacement presented with fevers and chills of unknown etiology. On initial evaluation the patient was worked up by her primary care physician but no final diagnosis was made. She then presented to the emergency room five months later with recurrent fever and chills associated with an occasional cough. She was initially diagnosed with bronchitis and given a macrolide, but continued to have symptoms. She was then admitted to the hospital after an echocardiogram revealed a vegetation suggestive of endocarditis of the pulmonary prosthetic valve.

On admission, abnormal laboratory values include a white blood cell count of 15,000/cu mm, a hemoglobin level of 8g/dL, a hematocrit level of 27% and a erythrocyte sedimentation rate of 48mm/h. Vital signs on examination were temperature of 101.1 °F, blood pressure of 110/70 and a pulse of 78. Physical examination revealed no murmurs or

rubs. A transesophageal echocardiogram revealed the presence of a medium size vegetation suggestive of endocarditis. Based on the echocardiogram, empiric therapy with vancomycin and gentamicin was started. Blood cultures later grew methicillin-sensitive *Staphylococcus epidermidis* (MSSE).

The minimal inhibitory concentration (MIC) demonstrated that the organism was susceptible to vancomycin (MIC \leq 1 μ g/ml) and gentamicin (MIC \leq 0.5 μ g/ml). Because the patient had a questionable history of penicillin allergy she was continued on vancomycin 1 gm IV q12 hours with a trough between 15-20mcg/ml.

Upon evaluation four weeks later, the patient had failed vancomycin therapy and a daptomycin susceptibility test was ordered. The MIC for daptomycin was found to be 0.19 μ g/ml, and the patient was switched to daptomycin at a dose of 6mg/kg every 24 hours. The MIC for vancomycin remained at $<$ 1 μ g/ml. The patient subsequently underwent

surgical removal and exchange of the infected valve while on daptomycin and completed a 4 week course of this antibiotic. Follow up 6 weeks and 6 months later revealed no evidence of recurrent bacteremia and the echocardiogram showed no evidence of recurrence of the vegetation.

DISCUSSION

Daptomycin is currently the only agent in the lipopeptide class of antibiotics. Its mechanism of action is binding to bacterial membranes, causing rapid depolarization of the membrane potential. The loss of this potential leads to inhibition of protein, and DNA and RNA synthesis, resulting in cell death.^{5,6} The spectrum of daptomycin includes the following susceptible Gram positive organisms: *Staphylococcus aureas* (including methicillin-resistant), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (not including vancomycin-resistant organisms). The indications of daptomycin are complicated skin and skin structure infections (cSSI), bloodstream infections (bacteremia) and right-sided endocarditis due to both MSSA and MRSA. It demonstrates concentration-dependent killing activity for doses up to 12 mg/kg and is eliminated renally.⁵

In a non-inferiority study, daptomycin was compared to low-dose gentamicin plus either an antistaphylococcal penicillin or vancomycin for the treatment of bacteremia or endocarditis caused by MSSA and MRSA. Results showed that daptomycin was not inferior to standard treatment for either bacteremia or right-sided endocarditis.⁶ In a subset analysis of this study; investigators looked at bacteremia and endocarditis caused by MRSA. The treatment comparison was daptomycin versus vancomycin plus gentamicin. This analysis also demonstrated that daptomycin was non-inferior to vancomycin and is an effective alternative for MRSA infections.⁷ It should be mentioned that none of these studies specified valve involvement. The patient in our report was initially started on vancomycin and failed even though she had a susceptible organism. This may have been due to the fact that the drug could not achieve high enough concentrations in the prosthetic valve and in addition, it has been demonstrated that it is extremely difficult to clear endocarditis in this clinical situation without surgical intervention. In our case, daptomycin therapy cleared the bacteremia; however, we doubt that it would have been able to result in a permanent cure of the infection without removal of the valve.

The manufacturer suggests a dosing of 6 mg/kg every 24 hours in patients with a creatinine clearance (CrCl) of ≥ 30 ml/min or 6 mg/kg every 48 hours in those with a CrCl of ≤ 30 ml/min for the treatment of *S. aureus* bloodstream infections. Patients should be treated for a minimum of 2 to 6 weeks. There is limited information for treating for more than 28 days.⁴ Doses of up to 12 mg/kg once daily for 14 days have been studied in healthy volunteers and were well tolerated. The subjects in this study did not experienced adverse effects nor discontinuation of therapy due to adverse events. Since daptomycin exhibits concentration-dependent activity, higher doses may warrant further investigation for difficult to treat *S. aureus* infections.⁸

Strains of MSSA and MRSA are considered susceptible to daptomycin if the minimum inhibitory concentration (MIC) is ≤ 1 μ g/ml. Daptomycin intermediate and resistant minimum inhibitory concentrations have not been established. In multiple studies, an MIC of ≥ 2 μ g/ml was considered resistant to daptomycin treatment.^{6,9} The MIC of the organism in this case was 0.19 μ g/mL which is considered susceptible.

Daptomycin in combination with gentamicin and rifampin has also been used.⁹ In an in vitro study, combination gentamicin and daptomycin therapy provided enhanced bactericidal activity and suppressed emergence of resistance in susceptible isolates. While rifampin in combination with daptomycin did not enhance bactericidal activity, it did suppress the emergence of reduced susceptibility.⁸ Use of these agents in the treatment of MRSA endocarditis may be beneficial.

In prosthetic valve endocarditis, the frequency of infection is 1-3% within the first year after valve placement, with the risk of infection being highest within the first 3 months. After 6 months, the risk decreases to 0.4% annually.¹

Our case further adds information to the literature of the treatment of prosthetic valve endocarditis with gram positive infections. Daptomycin may be an effective alternative for the treatment of hard to treat endocarditis.

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