Successful Treatment of Vancomycin-Resistant Enterococcus Endocarditis with Oral Linezolid

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We report a case of vancomycin-resistant Enterococcus faecium endocarditis that failed to respond to sequential monotherapy with chloramphenicol and quinupristin/dalfopristin but was successfully treated with oral linezolid.

Vancomycin-resistant Enterococcus faecium (VREF) has become an important cause of nosocomial infections. Despite the increasing prevalence of VREF, the impact of antibiotic resistance on the mortality rate associated with VREF infection is unclear [1–3]. Treatment of infections caused by VREF, including endocarditis, is problematic due to the limited number of therapeutic agents available. In addition, most agents used for treatment of VREF infection, including chloramphenicol and quinupristin/dalfopristin, possess only bacteriostatic action against this organism, which makes successful treatment of VREF endocarditis difficult.

Linezolid, the first member of the oxazolidinone class of antimicrobial agents, was recently approved by the US Food and Drug Administration (FDA) for the treatment (iv and oral) of infections caused by either E. faecium or Enterococcus faecalis or by methicillin-resistant Staphylococcus aureus. Like other agents used for treatment of VREF, linezolid possesses only bacteriostatic activity against VREF, although it appears to have bactericidal activity against streptococci [4]. Although not approved by the FDA specifically for the treatment of endocarditis, it has been used in this setting, despite its lack of bactericidal activity [3]. We report a case of VREF endocarditis that failed to respond to sequential monotherapy with chloramphenicol and quinupristin/dalfopristin but was successfully treated with oral linezolid.

The patient was a 34-year-old African-American woman with Down’s syndrome, mental retardation, end-stage renal disease requiring hemodialysis, hypothyroidism, hyperlipidemia, and congenital cyanotic heart disease, including a common atrium and a large ventricular septal defect. On 15 December 1999, she presented for dialysis and had a fever. Blood cultures were positive for VREF. Additional blood cultures performed on 20 December were also positive for VREF, and the patient was admitted to the hospital for removal of her Ash dialysis catheter, which had been placed in March 1998. The patient was treated with chloramphenicol at a dosage of 1 g iv q6h. On 22 December the Ash catheter was removed and both a Quinton catheter and a Hohn catheter were inserted. A transthoracic echocardiogram showed no evidence of endocarditis. Follow-up blood cultures performed after removal of the dialysis line were negative for VREF, and she was discharged from the hospital. At home she continued to receive chloramphenicol through the Hohn catheter. She completed 14 days of therapy from the date her Ash catheter was removed, ending on 5 January 2000. Another Ash dialysis catheter was placed while she was receiving therapy (on 27 December).

The patient was well until February 2000, when she presented with lethargy and weakness but without fever, chills or sweats. Cultures of blood drawn from the Ash catheter at dialysis on 17 February were again positive for VREF. The Ash catheter was removed and another Hohn catheter and a Quinton dialysis catheter were placed. Chloramphenicol treatment was restarted. A second transthoracic echocardiogram showed new nodular thickening of her aortic valve, which was suggestive of endocarditis. Because there have been reports of successful treatment of prosthetic valve endocarditis with quinupristin/dalfopristin [5, 6], antimicrobial therapy was changed to quinupristin/dalfopristin at a dosage of 7.5 mg/kg iv q8h. No other antimicrobial agent was added because the infecting strain of VREF was resistant to ciprofloxacin, doxycycline, and rifampin [7], as well as ampicillin and gentamicin. The patient’s VREF bacteremia persisted despite treatment with quinupristin/dalfopristin. Cultures of blood drawn from her Hohn catheter on 2 March, after 12 days of treatment with quinupristin/dalfopristin, were still positive for VREF and now also positive for Pseudomonas.
Treatment with cefepime was started. Since the patient’s bacteremia had recurred after treatment with chloramphenicol and she had remained bacteremic despite 12 days of treatment with quinupristin/dalfopristin, a decision was made to initiate treatment with linezolid.

Linezolid was obtained through Pharmacia & Upjohn’s compassionate use protocol, and on 3 March treatment was started at a dosage of 600 mg iv b.i.d. Kirby-Bauer disk-diffusion testing indicated the infecting strain of VREF was susceptible to linezolid (inhibition zone, 26 mm diameter). After the patient had received 2 doses, blood cultures were negative for VREF. On the third day of treatment with linezolid and cefepime, both her Quinton dialysis catheter and her Hohn catheter were removed, and treatment was switched to oral linezolid. To clear the Pseudomonas infection, treatment was switched to oral ciprofloxacin (to which the infecting strain of VREF was resistant). The dialysis line was replaced 2 days later. The patient required general anesthesia for placement of the line, and, therefore, at the same time a transesophageal echocardiogram (TEE) was performed. The TEE revealed thickening of the aortic valve leaflets and vegetations on the tricuspid valve. The patient was discharged and for 6 weeks continued to receive linezolid (600 mg orally b.i.d.) and ciprofloxacin (500 mg orally b.i.d.). She tolerated this regimen well.

Surveillance blood cultures performed after 3 weeks of treatment with ciprofloxacin and linezolid were positive for Candida tropicalis but negative for VREF. The patient’s Quinton dialysis catheter was again removed, and she was treated with iv amphotericin B for 2 days in the hospital before another Quinton catheter was placed. Subsequent blood cultures were negative for VREF. She was discharged and continue the regimen of oral ciprofloxacin and linezolid. To treat catheter-associated fungemia, the patient received amphotericin B (a total of 500 mg) when she underwent dialysis. After completing 6 weeks of linezolid therapy, surveillance blood culture were negative. In addition, follow-up blood cultures performed 10 days after the completion of antibiotic therapy were negative for VREF.

Further blood cultures were performed 3 months after the completion of therapy (on 21 July) and these were also negative for VREF. In the interim the patient had been treated again with amphotericin B for candidemia due to Candida parapsilosis. She also had been treated with cefepime and then trimethoprim-sulfamethoxazole for a Stenotrophomonas maltophilia infection of her dialysis catheter. Follow-up cultures performed after treatment for these infections (5 May) were negative, and blood cultures performed on 19 December 2000, 9 months after completion of linezolid therapy, remained negative for VREF.

To our knowledge, this is the first reported case of vancomycin-resistant Enterococcus (VRE) endocarditis treated successfully (clinically stable and with cultures negative for VRE 3 months after completion of therapy) with an oral regimen (except for 3 days of iv treatment at the outset) and with a single active agent, linezolid. Recent reports have described successful treatment with linezolid of VRE septic thrombophlebitis and of bacteremia that persisted despite treatment with chloramphenicol and/or quinupristin/dalfopristin [8], as well as successful treatment of persistent bacteremia with iv linezolid and gentamicin [9]. However, data supporting the use of linezolid to treat VRE endocarditis are sparse. A recently published report of linezolid treatment for resistant gram-positive infections included 2 cases of VRE endocarditis [3]; although both patients had a bacteriologic response to linezolid, both died during therapy. Neither death was attributed to VRE infection.

The oral formulation of linezolid is 100% bioavailable, producing serum levels equivalent to the iv formulation. For our patient, 2 measurements of peak steady-state serum levels were 26.6 µg/mL and 26.9 µg/mL, which indicated optimal absorption. Linezolid has activity against several multidrug-resistant gram-positive bacteria, and because it apparently has no cross-resistance with other classes of antimicrobial agents, it is a viable option for treatment of these serious infections.

Our patient presumably had an initial catheter-related VREF bacteremia that subsequently seeded her heart valve(s). After completion of therapy with chloramphenicol, bacteremia reoccurred. The TEE showed definite vegetations on the tricuspid valve and nodular thickening of the aortic valve, which was also suspicious. The tricuspid involvement would be defined as right-side endocarditis, which is more amenable to medical treatment than is left-side endocarditis. However, this patient’s common atrium and large ventricular septal defect blur the pathophysiological significance of distinctions between right-side and left-side involvement. She may also have had aortic valve infection, as suggested by TEE.

The patient appeared to suffer no adverse events from the linezolid therapy, with the exception of minor diarrhea. Given her propensity for iv line infections and the difficulty of changing those lines, it was a notable advantage to manage her treatment with the dialysis catheter as the only venous access. If the case reported herein proves to be representative of the response to oral, single-agent therapy for enterococcal endocarditis, linezolid could provide a remarkable advance in the management of a very challenging disease entity.

References
3. Chien JW, Kucia ML, Salata RA. Use of linezolid, an oxazolidinone, in