Prosthetic Valve Endocarditis Due to Vancomycin-Resistant Enterococcus faecium: Treatment with Chloramphenicol plus Minocycline

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We report a case of prosthetic valve endocarditis and persistent bacteremia due to vancomycin-resistant Enterococcus faecium. The combination of parenteral chloramphenicol plus minocycline therapy was administered for 8 weeks and resulted in cure after treatment with quinupristin-dalfopristin had failed.

Since the 1980s, vancomycin-resistant Enterococcus faecium (VREF) has become a major public health concern [1, 2]. Nearly one-half of all nosocomial isolates of E. faecium in the United States, and up to 63% of isolates in the northeastern United States, are now resistant to vancomycin [2–4]. Quinupristin-dalfopristin and linezolid, both of which represent new classes of antibiotics, are now available to treat VREF infections [5, 6]. However, both of these agents are bacteriostatic rather than bactericidal against enterococci. Treatment of infections due to VREF, such as endocarditis, for which bacteriocidal therapy is generally considered to be required, remains highly problematic [5, 7, 8]. We report a case of prosthetic valve endocarditis due to VREF in which the combination of chloramphenicol and minocycline resulted in cure after treatment with quinupristin-dalfopristin had failed.

Case report. A 68-year-old white woman presented with low-grade fever, dyspnea, and fatigue 4 weeks after she had undergone elective aortic valve replacement and coronary artery bypass surgery. Her medical history was remarkable only for adult-onset diabetes mellitus, which was well controlled. Physical examination revealed that she was in mild respiratory distress, with a temperature of 38°C, blood pressure of 107/64 mm Hg, and a mid-systolic murmur with mechanical heart sounds. All surgical wounds were well healed, and there were no cutaneous or mucosal stigmata of endocarditis.

Laboratory studies revealed the following values: WBC count, 9800 cells/μL; hemoglobin, 10.3 g/dL; platelet count, 210,000 platelets/μL; aspartate aminotransferase, 29 U/L; alanine aminotransferase, 15 U/L; and erythrocyte sedimentation rate, 97 mm/h. E. faecium was isolated from all 6 sets of blood cultures. Strains of E. faecium isolated from stool cultures were identical to strains isolated from blood cultures. Genetic fingerprinting analysis (by pulsed-field gel electrophoresis) confirmed the phenotypic relatedness of these enterococcal isolates (figure 1). Penicillin-susceptible E. faecium was isolated from a voided urine specimen. A transthoracic echocardiogram showed a mobile mass measuring 7 mm at the proximal aortic root (figure 2A and 2B).

Initial therapy with vancomycin (for the first 2 days; 1 g b.i.d.) was switched to quinupristin-dalfopristin (7.5 mg/kg q8h) when the E. faecium isolate was found to be susceptible to quinupristin-dalfopristin (MIC, <1.0 μg/mL) but resistant to vancomycin (MIC, >256 μg/mL) as well as penicillin G (MIC, >16 μg/mL), ampicillin (MIC, >256 μg/mL), and gentamicin (MIC, >1024 μg/mL). Additional testing of antimicrobial combinations failed to show in vitro synergy against the infecting strain of VREF, as follows: ampicillin plus streptomycin (MICs, >256 μg/mL and >128 μg/mL, respectively), ampicillin plus gentamicin (MICs, >256 μg/mL and >1024 μg/mL, respectively), and vancomycin plus gentamicin (MICs, >256 μg/mL and >1024 μg/mL, respectively).

Blood samples obtained on days 5, 8, and 12 of quinupristin-dalfopristin therapy revealed VREF on culture. Therefore, quinupristin-dalfopristin was discontinued after 12 days, and treatment was initiated with chloramphenicol (2 g q.d. given iv in 4 divided doses; disk-diffusion zone size, >18 mm) and minocycline (200 mg q.d. given iv in 2 divided doses; MIC of tetracycline, <1.0 μg/mL). Blood samples obtained on days 4 and 6 of this regimen were sterile on culture. The patient was considered to be too high risk for a second aortic valve replacement. Therefore, the chloramphenicol-minocycline regi-
Figure 1. Genetic fingerprinting analysis using pulsed-field gel electrophoresis of vancomycin-resistant Enterococcus faecium isolates recovered from stool and blood samples. Restriction fragments were obtained by SmaI endonuclease and base-pair weight analysis was evaluated by Chef Mapper electrophoresis (BioRad Laboratories). The genetic relatedness was determined by dendrogram analysis (Molecular Analyst Fingerprinting Plus Software; BioRad Laboratories). Blood and stool samples were obtained on days 1, 5, and 8 after the initiation of quinupristin-dalfopristin therapy.

Figure 2. Transesophageal echocardiogram in 2 views (A and B) showing a 7-mm mobile mass in the aortic root (straight arrows) proximal to aortic valve replacement (curved arrow). AO, aorta; AVR, aortic valve replacement; LA, left atrium; LV, left ventricle; PA, pulmonary artery.

men was continued for 8 weeks. No occurrence of VREF has been observed during 24 months of follow-up.

Discussion. Most systemic infections due to Enterococcus species arise from the flora of the gastrointestinal or genitourinary tract. In our patient, lower intestinal tract colonization with VREF was probably acquired during the previous prolonged hospitalization after aortic valve placement, and it served as a reservoir for systemic infection [9, 10].

Isolation of antibiotic-resistant organisms ranks high among the indications for surgical intervention in endocarditis [11–14]. In our patient, surgical replacement of the prosthetic aortic valve was considered to be high risk [15, 16]. We initially chose quinupristin-dalfopristin therapy on the basis of in vitro susceptibility studies. In a recent prospective trial of quinupristin-dalfopristin for the treatment of systemic VREF infections, an overall response rate of 66% was observed; however,
only 20% of the patients with endocarditis responded to therapy [17]. Some patients with bloodstream infection due to VREF refractory to quinupristin-dalfopristin therapy have been treated successfully with linezolid [18, 19]. However, de novo resistance of VREF to both quinupristin-dalfopristin [17] and linezolid [20] has emerged during therapy. Chloramphenicol may be another option for infections due to VREF that are difficult to treat. More than 85% of VREF isolates are susceptible in vitro to chloramphenicol [17], and chloramphenicol-based regimens have been used successfully to treat persistent bacteremia in immunocompromised patients and in patients with endocarditis [21, 22]. When bacteremia persisted in our patient, despite 12 days of administration of quinupristin-dalfopristin therapy, we considered the possibility of de novo resistance and elected to institute treatment with chloramphenicol and minocycline. The favorable outcome confirms that chloramphenicol-based regimens may be useful alternatives for serious VREF infections in highly selected patients.

References