CASE REPORT

Linezolid- and Vancomycin-Resistant *Enterococcus faecium* Endocarditis: Successful Treatment with Tigecycline and Daptomycin

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Enterococci are a leading cause of endocarditis and nosocomial infections. Vancomycin-resistant enterococci (VRE) emerged in the 1980s and now represent most nosocomial isolates in the United States. The first case of VRE endocarditis was reported in 1996.[1] Although increasing enterococcal antibiotic resistance has prompted increasing reliance on newer antibiotics,[2] a recent review of VRE endocarditis noted that survival rates were similar to those for vancomycin-sensitive enterococcal endocarditis.[1] Cure was achieved in several patients with bacteriostatic agents in the absence of valve replacement, but no patients were infected with truly linezolid-resistant organisms. This case of linezolid-resistant VRE endocarditis represents the first reported cure of infective endocarditis with a tigecycline-containing regimen.

CASE REPORT

A 62-year-old man presented with hypoglycemia and delirium. His medical history included diabetes mellitus, coronary and peripheral arterial disease, and end-stage renal disease. He had had endocarditis of an unknown type 12 years prior to admission. He had recently developed septic shock because of a *Candida parapsilosis, Enterobacter cloacae,* and *Staphylococcus epidermidis* infection of a peripherally inserted central catheter (PICC) and received 14 days of vancomycin, meropenem, and fluconazole administered through a new PICC. This catheter was not removed, and 39 days after completion of the antibiotic therapy, he developed hypoglycemia, which was attributed to weight loss without adjustment of his insulin regimen. He was afebrile; examination revealed a new 3/6 holosystolic murmur radiating to the axilla. There were no other stigmata of infective endocarditis, and his PICC and arteriovenous fistula sites appeared normal. Delirium resolved after administration of intravenous glucose.

E. faecium grew from all 6 initial blood cultures. A transesophageal echocardiogram revealed a new 3-mm mitral valve vegetation with perforation and severe regurgitation. He had definite endocarditis on the basis of 2 major criteria.[3] He was given vancomycin (1 g IV, then administered by levels), then switched to linezolid (600 mg orally every 12 hours), and finally tigecycline (100 mg IV followed by 50 mg IV every 12 hours) plus daptomycin (6 mg/kg IV every 48 hours) as further sensitivity data became available.

The organism was resistant to ampicillin, chloramphenicol,

DOI 10.1002/jhm.236
Published online in Wiley InterScience (www.interscience.wiley.com).

and linezolid (MIC > 20 μg/mL), as well as vancomycin (MIC > 50 μg/mL), quinupristin/dalfopristin (MIC 2.5 μg/mL), and gentamicin (MIC > 200 μg/mL), and demonstrated high-level streptomycin resistance (>2000 μg/mL). It was intermediate to doxycycline (MIC 5 μg/mL). It was susceptible to daptomycin (MIC 4 μg/mL) and tigecycline (MIC 0.06 μg/mL).

Blood cultures done on hospital days 1, 4, 6, and 7 (day 1 of tigecycline) were positive, and multiple cultures were negative from day 10 on. Because of the lack of experience with tigecycline in infective endocarditis, unrevascularized left-main coronary artery disease, and severe mitral regurgitation, the patient was advised to undergo valve replacement and coronary artery bypass surgery after antibiotic therapy. Because he feared surgical complications, he refused and received 70 days of tigecycline plus daptomycin therapy, which was complicated only by nausea. He remained clinically well and had negative blood cultures 16 weeks after completion of therapy.

DISCUSSION

Tigecycline, the first available glycylcycline, is a minocycline-derived antibiotic that remains active in the presence of the ribosomal modifications and efflux pumps that mediate tetracycline resistance. Thus, it possesses broad-spectrum bacteriostatic activity, including activity against VRE. A PubMed search revealed no published data about the use of tigecycline for endocarditis in humans. However, tetracyclines have been used to treat endocarditis due to such organisms as Bartonella, *Coxiella burnetti,* or methicillin-resistant *Staphylococcus aureus* (MRSA), frequently for prolonged courses. Tetracyclines were combined with other antibiotics in 5 published cases of VRE endocarditis. All patients survived; 3 were cured with the tetracycline regimen and 2 with other antimicrobials.[1] In animal models of endocarditis, tigecycline stabilized vegetation counts of *E. faecalis* and reduced vegetation counts of MRSA and 1 strain of *E. faecium*.[4]

Daptomycin, the first available cyclic lipopeptide, kills by nonlytic depolarization of the bacterial cell membrane. In a recent study, daptomycin was non-inferior to vancomycin or antistaphylococcal penicillins for *S. aureus* bacteremia or endocarditis. Although a few patients had left-sided endocarditis, only 1 of them experienced a successful outcome with daptomycin therapy, and daptomycin displayed a trend toward higher rates of persistent or relapsing infection.[5] Less evidence supports the use of daptomycin for serious enterococcal infections.[2] One report noted the deaths of 6 of 10 patients treated with daptomycin for VRE bacteremia, including both patients with endocarditis.[6] Daptomycin was used successfully in a case of VRE endocarditis in combination with gentamicin and rifampin for 11 weeks[1] and at least 6 other reported cases of VRE bacteremia.[7,8]

In summary, despite tigecycline's lack of bactericidal activity or proven efficacy in endocarditis, daptomycin's prior performance in VRE bacteremia, and the isolate's borderline daptomycin susceptibility, prolonged combination therapy resulted in a cure of VRE endocarditis. This success extends the experience with using both agents in the treatment of resistant infections. As linezolid-resistant VRE and other resistant pathogens become more common, the need for research on treatment options becomes more urgent, and familiarity with novel and lesser-used antibiotics becomes more crucial for hospitalists.

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Received 28 February 2007; revision received 3 April 2007; accepted 24 April 2007.

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