Endocarditis Caused by Methicillin-Resistant *Staphylococcus aureus:* Treatment Failure with Linezolid

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We describe 2 cases of endocarditis caused by methicillin-resistant *Staphylococcus aureus* that failed to respond to intravenous linezolid therapy but were successfully treated with trimethoprim-sulfamethoxazole plus gentamicin and vancomycin plus rifampin.

Treatment of endocarditis caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is problematic because of the limited number of effective antimicrobial agents available. Currently, vancomycin is the standard treatment for serious infections caused by MRSA, including endocarditis. Because some patients are intolerant of vancomycin and experience serious adverse effects and because MRSA has developed resistance to the drug, new alternative antimicrobials are being used to treat MRSA infections, including quinupristin/dalfopristin and linezolid.

Linezolid, an oxazolidinone, is an antibiotic that inhibits formation of the initiation complex during bacterial protein synthesis. Few cases have been reported of serious infections caused by vancomycin-resistant *Enterococcus faecium* (VREF) that were successfully treated with linezolid [1–3]. There has been limited or no clinical experience with use of linezolid for the treatment of endocarditis caused by MRSA. We describe 2 patients with endocarditis caused by MRSA for whom linezolid treatment failed.

Patient 1. A 77-year-old man was admitted to the intensive care unit because of exacerbation of chronic obstructive pulmonary disease. The patient had no history of central intravenous access or injection drug use. On hospital day 5, the patient developed leukocytosis (leukocyte count, 25,000 cells/mm^3) and fever; blood cultures yielded MRSA. No source for the bacteremia was identified. Vancomycin was administered (1.0 g iv q.d., increased to 1.5 g iv b.i.d.), and it achieved a peak level in serum of 39 μg/mL. The patient subsequently developed a diffuse desquamating rash on hospital day 14. On hospital day 7, the patient developed signs consistent with a cerebrovascular accident, and transesophageal echocardiography revealed a vegetation (diameter, 2 mm) on the anterior leaflet of the mitral valve. Cardiac examination did not reveal any murmur.

On hospital day 20, MRSA was again isolated from blood cultures; the patient had developed progressive renal insufficiency, and urinalysis showed an eosinophil level consistent with interstitial nephritis secondary to vancomycin therapy. Treatment with linezolid (600 mg iv b.i.d.) was initiated on hospital day 22 and was continued for 7 days. The patient remained bacteremic despite the linezolid therapy. Throughout the hospitalization, all MRSA isolates from this patient showed susceptibility to vancomycin (MIC, 2 μg/mL), linezolid (MIC, 3 μg/mL), gentamicin (MIC, <2 μg/mL), and trimethoprim-sulfamethoxazole (MIC, <10 μg/mL). No serum levels of linezolid were determined. All MRSA isolates from the patient were tested for linezolid susceptibility with use of the E-test (AB Biodisk) and continued to be susceptible in vitro. On hospital day 29, treatment was initiated with trimethoprim-sulfamethoxazole (400 mg iv q12h) plus gentamicin (120 mg iv q36h); at this dosing interval, the peak serum level of gentamicin was 3.6 μg/mL, and the trough serum level was 0.7 μg/mL. Additional cultures of blood samples obtained 24 h after the initiation of this regimen were negative for MRSA. The patient remained afebrile, with improvement of his renal insufficiency and neurological deficits. His hospital course was complicated by recurrence of interstitial nephritis while receiving trimethoprim-sulfamethoxazole, and antibiotic therapy was discontinued on hospital day 55, after almost 7 weeks of total antibiotic therapy. The patient remained afebrile, and blood cultures remained sterile on hospital day 60. The patient stayed in the hospital for rehabilitation and had upper gastrointestinal bleeding on hospital day 69. It was noted at this time that a right intrajugular catheter was oozing. On hospital day 70, the patient developed hypotension and died. Cultures of blood obtained during this episode grew *Morganella morganii.*

Patient 2. A 75-year-old man was admitted to the hospital with shoulder pain, shortness of breath, chills, and purulent drainage from an intravenous catheter that had been placed 4 days prior to admission for chemotherapy. His past medical

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history was notable for laryngeal carcinoma that developed after he underwent laryngectomy and tracheostomy, lung carcinoma with bony metastases that had been treated with chemotherapy, and polycystic kidney disease with chronic renal insufficiency. At the time of admission to the hospital, the patient was febrile and had a leukocyte count of 11,200 cells/mm^3. Cultures of blood, sputum, and catheter exit site specimens were positive for MRSA. The intravenous catheter was removed at admission, and the patient was treated with linezolid (600 mg iv q12h). The patient was discharged on hospital day 5 to receive linezolid (600 mg iv q12h) as an outpatient.

Four days after discharge, the patient returned to the hospital with severe respiratory failure requiring intubation, which was due to multifactorial causes, including fluid overload in combination with resolving pneumonia and lung carcinoma. Cultures of sputum and wound tissue samples were sterile, and the site of a previous catheter insertion showed no evidence of infection. Cultures of a blood sample obtained at the time of the second admission to the hospital were again positive for MRSA, and blood cultures were persistently positive on day 19 after the first admission and initial diagnosis of bacteremia, despite receipt of linezolid therapy. Both the isolate recovered at the time of the first admission and the isolate recovered at the time of the second admission were susceptible to linezolid, as determined by the E-test. Hemodialysis was initiated, and antibiotic therapy was changed to vancomycin and rifampin (rifampin dosage, 300 mg po every other day). Serum vancomycin levels were determined, and the dosage was adjusted to achieve adequate therapeutic levels. Five days after initiation of intravenous vancomycin therapy, blood cultures were again negative for MRSA. Transesophageal echocardiography revealed an aortic valve vegetation, but a murmur was not detected. The patient was discharged from the hospital to receive intravenous vancomycin and rifampin and received 6 weeks of antibiotic treatment. Subsequent blood cultures were negative for MRSA, and the patient improved clinically. At a follow-up examination 3 months after discharge, the patient was clinically stable, and the episode of bacteremia had fully resolved.

Discussion. Endocarditis caused by MRSA is uncommon and has been described primarily among injection drug users with right-side valvular lesions, protracted bacteremia, and fever [4]. However, there are case reports of community-acquired MRSA endocarditis in patients who were not injection drug users or nursing home residents. For instance, a 65-year-old man who had an aortic valve replacement and no history of injection drug use or having been a nursing home resident presented almost 2 years after valve replacement surgery with endocarditis caused by MRSA [5].

The incidence of nosocomial infection due to MRSA has increased exponentially in major teaching hospitals and community hospitals in the past 2 decades, which highlights the need to use new agents, such as quinupristin-dalfopristin and linezolid, that are effective against drug-resistant gram-positive bacteria [6]. The spectrum of activity of linezolid makes it a reasonable alternative drug for the treatment of infections due to drug-resistant gram-positive organisms. In addition, the availability of an oral preparation coupled with high oral bioavailability make linezolid an attractive alternative. An open-label, multinational, phase III trial comparing the use of linezolid and vancomycin with or without gentamicin in the treatment of methicillin-resistant staphylococcal infections found equivalent cure rates in both groups [7]. The linezolid group had a cure rate of 73.2%, compared with a cure rate of 73.1% for the vancomycin group. However, patients with endocarditis, osteomyelitis, or CNS infections were excluded from this study. A patient with vertebral osteomyelitis and bacteremia due to MRSA and VREF with presumptive aortic valve endocarditis was effectively treated with linezolid [3].

In vivo experiments with a rabbit model of methicillin-susceptible *S. aureus* (MSSA) aortic valve endocarditis compared the efficacy of linezolid and vancomycin for reduction of bacterial growth in vegetations [8]. In this study, the vancomycin group (dosage, 25 mg/kg iv b.i.d.) and the high-dose linezolid group (dosage, 75 mg/kg po t.i.d.) had similar results; culture of valve specimens was negative for MSSA in 8 of 11 and 8 of 10 animals, respectively. In contrast, in the middle-dose linezolid group (dosage, 50 mg/kg po t.i.d.), 6 of 12 animals had negative valve cultures, and, in the low-dose linezolid group (dosage, 25 mg/kg po t.i.d.), 0 of 5 animals had negative valve cultures. The mean peak serum levels ($\pm$SD) of linezolid achieved on day 5 of treatment were 49.4 $\pm$ 8.5 μg/mL for the high-dose linezolid group, 29.6 $\pm$ 6.7 μg/mL for the middle-dose linezolid group, and 11.0 $\pm$ 7.6 μg/mL for the low-dose linezolid group. In humans, the approved dosage of linezolid (600 mg iv b.i.d.) will achieve a mean ($\pm$SD) peak steady-state serum level of 15.1 $\pm$ 2.52 μg/mL, which is similar to the mean peak levels achieved with a dosage of 25 mg/kg po t.i.d. in this study. The mean trough serum level ($\pm$SD) of linezolid achieved with a dosage of 75 mg/kg po t.i.d. was 11.6 $\pm$ 6.1 μg/mL, and that achieved with a dosage of 50 mg/kg po t.i.d. was 1.5 $\pm$ 1.3 μg/mL; with use of standard dosages, the mean trough level ($\pm$SD) achieved in humans is 3.68 $\pm$ 2.36 μg/mL. In this study, both the peak and trough levels achieved were higher than those achieved in humans with use of a standard dosing schedule.

A similar study in an experimental rabbit MRSA endocarditis model that compared intravenously administered vancomycin to orally administered linezolid (linezolid dosages: 25 mg/kg, 50 mg/kg, or 75 mg/kg po t.i.d.) found smaller reductions in bacterial counts in vegetations for the linezolid group, compared with the vancomycin group. Mortality was 73% in the low-dose linezolid (i.e., 25 mg/kg po t.i.d.) group and 15% in

the vancomycin group, and there was no mortality in the high-dose linezolid (i.e., 75 mg/kg po t.i.d.) group. In the vancomycin group, 11 of 11 animals had valve cultures negative for MRSA, compared with 10 of 13 animals with negative valve cultures in the high-dose linezolid group and 2 of 12 animals with negative valve cultures in the middle-dose linezolid (i.e., 50 mg/kg po t.i.d.) group. For the high-dose linezolid group, the mean peak serum level ($\pm$SD) achieved was 54.8 $\pm$ 23.2 μg/mL, and the trough level was 10.8 $\pm$ 5.0 μg/mL at steady state, which is higher than levels attained with the recommended linezolid dosage in humans [9]. In this same study, both the middle-dose and high-dose linezolid treatment arms achieved negative blood cultures. Only the low-dose linezolid group did not achieve negative blood cultures; the serum levels achieved with the standard human dosage are greater than those achieved in the low-dose linezolid group.

These studies raise the question of whether appropriate serum levels of linezolid were achieved. In both of the cases we describe, blood cultures remained positive for MRSA throughout the course of linezolid therapy. Data on serum linezolid levels were not obtained. Of clinical concern is a report of a patient with peritonitis caused by MRSA that developed linezolid resistance after a month of therapy with intravenously administered linezolid [10]. However, in both of our cases, the MRSA isolates remained susceptible to linezolid.

There are limited data on the clinical efficacy of linezolid for the treatment of endocarditis. Few cases of bacteremia and endocarditis caused by VREF that were successfully treated with linezolid have been reported. To our knowledge, the present case reports are the first to describe MRSA endocarditis treated with linezolid. Although data from animal studies of linezolid to treat MRSA endocarditis are accumulating, very little clinical evidence exists to warrant the use of linezolid to treat endocarditis caused by MRSA in humans. Use of higher doses of linezolid, if they are tolerated, with monitoring of serum levels should be considered in the future. Our cases lead us to emphasize that close monitoring of patients with endocarditis caused by MRSA is warranted when treatment with linezolid is administered.

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