Endocarditis Caused by Penicillin-Resistant Viridans Streptococci: 2 Cases and Controversies in Therapy

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Although penicillin-resistant viridans streptococci have been isolated from samples from the mouth, blood, and wounds in increasing numbers, viridans streptococci isolated from patients with endocarditis have remained sensitive to penicillin for the past 5 decades. We report the cases of 2 patients with penicillin-resistant viridans streptococcal endocarditis, review 6 other cases from the literature, and summarize 2 studies that used an animal model of penicillin-resistant viridans streptococcal endocarditis.

In 1999, we were consulted regarding 2 patients with penicillin-resistant viridans streptococcal endocarditis. The cases of these patients and 2 other cases reported in 1999 [1, 2] raise the question of whether this disease is becoming increasingly common, as has endocarditis caused by other drug-resistant, gram-positive organisms such as Staphylococcus aureus or enterococci. In addition, these 4 cases call attention to controversies in selecting optimal therapy.

Methods and case summaries. We searched the MEDLINE database for reports made from 1966 through 2000 of viridans streptococcal and nonenterococcal group D endocarditis. Bibliographies of the identified articles were searched for additional studies. Cases of viridans streptococcal endocarditis in adults that were caused by organisms resistant to penicillin (MIC, >0.5 μg of penicillin per mL) were selected. Cases caused by Streptococcus bovis and Abiotrophia species (nutritionally deficient streptococci) were excluded. MEDLINE was also searched for studies of the animal model for endocarditis caused by penicillin-resistant viridans streptococci.

We found 6 cases of penicillin-resistant viridans streptococcal endocarditis in the literature in addition to the 2 new cases (patient 1 and patient 2) reported here. We found 2 studies of the animal model of endocarditis caused by penicillin-resistant viridans streptococci.

Patient 1, a critically ill 65-year-old woman with multiple medical and surgical problems, was admitted from a subacute facility with a 1-day history of mental status changes and fever. The patient had recently completed a 3-month hospitalization in the intensive care unit. At that admission, the patient had undergone 4-vessel coronary artery graft bypass surgery. Her leg subsequently developed ischemia that required amputation of the leg above the knee; the patient also experienced bowel ischemia that required a resection of the ileum and right colon. She was also found to have clinical and radiologic evidence of several previous cerebrovascular events. The patient received several short courses of antibiotics, including ampicillin, piperacillin-tazobactam, ceftazidime, and gentamicin.

At readmission, the patient was ill and had a temperature of 38.3°C (101°F). The patient had a tracheostomy in place and was unable to speak, but she was able to follow simple commands. On cardiovascular examination, her heart demonstrated an irregular rhythm with no murmur. She had a large midline surgical wound that had a drainage bag. Two blood cultures of samples acquired on admission grew viridans streptococci. The organism was resistant to penicillin (MIC, >4 μg/mL; measured by Etest [AB Biodisk]); resistant to ceftriaxone (MIC, >2 μg/mL; measured by Etest); sensitive to clindamycin, erythromycin, and vancomycin (measured by disk diffusion test); and sensitive to ≤0.5 μg/mL of gentamicin (measured by disk diffusion test). Breakpoints are those specified for enterococci by the National Committee for Clinical Laboratory Standards. The patient underwent transesophageal echocardiography, the results of which showed a 0.8-cm irregular vegetation attached to the aortic valve. A diagnosis of viridans streptococcal endocarditis was made, and treatment with vancomycin (1 g iv every 12 h) and gentamicin (60 mg iv every 12 h) was begun. Subsequent blood cultures were sterile. The patient continued to deteriorate; she experienced multiorgan failure, including pancreatitis and short-bowel syndrome requiring parenteral alimentation and acute respiratory distress syndrome requiring ventilatory support. This support was withdrawn on the 18th day of hospitalization, and the patient died. An autopsy was not performed.

Patient 2, an 82-year-old man, was admitted with a 2-month
history of fatigue and 2 weeks of intermittent, low-grade fever. He had a bioprosthetic aortic valve placed in 1994. At admission, he was afebrile and displayed a I/VI systolic murmur. Six blood cultures drawn over the course of 3 days grew viridans streptococci. The organism was resistant to penicillin (MIC, 1.5 μg/mL; measured by Etest); resistant to ceftriaxone (MIC, 2 μg/mL; measured by Etest); sensitive to clindamycin, erythromycin, and vancomycin (measured by disk diffusion test); and sensitive to <500 μg/mL of gentamicin (measured by disk diffusion test). The patient had preexisting renal insufficiency with a creatinine level of 3.0 mg/dL. Transesophageal echocardiography showed a bioprosthetic aortic valve with mild aortic insufficiency and a 1-mm echo density at the base of the aortic valve prosthesis, but no definite vegetation was seen. A clinical diagnosis of possible prosthetic valve endocarditis caused by viridans streptococcus was made, and treatment with ampicillin (2 g iv every 4 h) and gentamicin (60 mg iv every 24 h) was started. The patient was discharged on the fourth hospital day with an outpatient treatment regimen of ceftriaxone (2 g iv every 24 h) and gentamicin (60 mg iv every 24 h). Follow-up blood cultures were sterile, and therapy was modified to a regimen of ampicillin (2 g iv every 6 h) and gentamicin (40 mg iv every 12 h) for 2 weeks and then penicillin (5 million units iv every 6 h) and gentamicin (60 mg iv every 24 h) for 4 more weeks. The patient’s creatinine and serum peak and trough gentamicin levels were monitored while he was an outpatient; the serum creatinine level was 1.9–2.5 mg/dL, with peak gentamicin levels of 5.2 μg/mL and trough levels of 1.0 and 0.7 μg/mL. The patient remained well 11 months later.

The viridans streptococcal isolates from patients 1 and 2 were sent to the US National Institutes of Health (NIH) Microbiology Service laboratory for further studies. Identification was obtained by use of biochemical characteristics obtained from the API 20S Strep panel (bioMerieux), the Rapid ID 32 Strep (bioMérieux), and additional conventional biochemical testing. The isolate from patient 1 was identified as Streptococcus mitis and that from patient 2 as Streptococcus sanguis (biotype 1). According to newly proposed nomenclatural designations, both of these species belong to the mitis group of viridans streptococci [3]. In vitro sensitivity testing performed by the NIH (MICs measured by MICroSTREP panel [Dade Behring] and Etest) confirmed our original sensitivity results. Both organisms remained resistant to penicillin after 12 transfers, indicating a relatively stable resistance pattern. For both organisms, subculture of the highest dilution that was inhibitory for each organism (MIC) showed it to be bactericidal as well (to >99.9% of the inoculum); thus, the minimal bactericidal concentration was equal to the MIC. Discussion. In recent letters, 2 cases of penicillin-resistant viridans streptococcal endocarditis were reported. Both isolates were S. mitis. The sensitivity pattern for isolates from one patient showed an MIC for penicillin of >4 μg/mL [1]. The patient had a prosthetic valve with a paravalvular leak and a third-degree block on electrocardiography and was treated with a 4-week course of vancomycin alone, without an aminoglycoside. “Eradication” of S. mitis was achieved.

The sensitivity pattern of isolates from the other patient showed MICs for penicillin of 2 and 3 μg/mL (in duplicate analysis) and an MIC for cefotaxime of 2 μg/mL [2]. The patient was treated with 2 weeks of vancomycin alone and then switched to cefotaxime and gentamicin for 4 weeks after he developed discitis and echocardiography revealed new vegetations. One month after completion of antibiotic therapy, the patient’s aortic and mitral valves were replaced. Cultures of samples from both valves were negative, but many gram-positive cocci were seen on histopathologic testing of samples from the mitral valve. The patient was given vancomycin and gentamicin for 3 weeks, followed by 3 weeks of vancomycin alone. He was clinically well 15 months later.

Very few cases of penicillin-resistant viridans streptococcal endocarditis have been reported in the literature. In 1979, Parrillo et al. [4] described a woman receiving penicillin prophylaxis for rheumatic fever who developed endocarditis caused by S. mitis with an MIC of 4 U of penicillin per mL (2.7 μg/mL). This patient relapsed after a 3-week course of moderate-dose penicillin alone, then relapsed after 3 weeks of moderate-dose penicillin and streptomycin, and was finally cured with a subsequent course of high-dose penicillin and gentamicin for 6 weeks. These authors also reported a patient with S. sanguis endocarditis. The organism had an MIC for penicillin of 1.0 U of penicillin per mL (0.7 μg/mL). She was treated initially with moderate-dose, and later with high-dose, penicillin combined with gentamicin for 7 weeks and had a successful outcome.

Karchmer et al. [5, 6] reported the case of a patient with viridans streptococcal endocarditis caused by an organism with an MIC of 1.0 U of penicillin per mL (0.7 μg/mL). The patient was treated successfully with 28 days of sequential single-drug therapy: high-dose penicillin for 6 days, followed by cephalothin for 13 days, and finally vancomycin for 9 days.

Wilson and Geraci [7] reported the case of 1 patient with viridans streptococcal endocarditis with an MIC for penicillin of 1 μg/mL in a series of 142 patients treated at the Mayo Clinic in Rochester, Minnesota. This patient was treated successfully with a 2-week course of penicillin and streptomycin.

These 6 cases are summarized in table 1.

Experimental animal models of endocarditis have been used to study the efficacy of only a few antibiotics (administered alone or in combination). Wilson et al. [8], who used a rabbit model in their study, compared penicillin to a combination of penicillin and streptomycin against penicillin-sensitive (MIC, 0.09 μg/mL) and penicillin-resistant (MIC, 1.0 μg/mL) viridans streptococci. The combination of penicillin and streptomycin was
significantly more effective than penicillin alone in decreasing concentrations of organisms in cardiac valve vegetations caused by penicillin-resistant strains of viridans streptococci.

Martinez et al. [9], who used a rabbit model and penicillin-resistant Strep- tococcus **sanguis** (MIC, 8 μg of penicillin per mL), evaluated responses to therapy by using mortality curves, time to negative blood cultures, weight of vegetations, concentrations of **S. sanguis** in vegetations, and rate of sterilization of vegetations. The combination of vancomycin and gentamicin was the therapy most successful against penicillin-resistant **S. sanguis endocarditis**. Combinations of imipenem and gentamicin and of teicoplanin and gentamicin were also effective. The use of vancomycin and imipenem as single drugs had some efficacy, but less than when either drug was used in combination with gentamicin.

**Conclusion.** Present consensus guidelines determined by Wilson et al. [10] suggest that penicillin-resistant viridans streptococcal endocarditis should be treated in the same manner as enterococcal endocarditis, including use of an aminoglycoside with the associated risk of renal or eighth nerve damage. A critical question is whether less toxic antibiotic regimens that exclude aminoglycosides would be as efficacious. There are few data to suggest that penicillin-resistant viridans streptococci are analogous to enterococci in their response to therapy, and thus inclusion of an aminoglycoside may not be required in all cases. On the other hand, use of a penicillin alone for “penicillin-resistant” viridans streptococci is counterintuitive. Vancomycin—or newer antibiotics active against drug-resistant, gram-positive bacteria—may be effective when used alone or in combination with other antibiotics. More extensive work involving animal models could help to guide clinical studies.

**References**