

Endocarditis Caused by *Actinobacillus actinomycetemcomitans*

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***Actinobacillus actinomycetemcomitans* is a gram-negative coccobacillus which is a very rare cause of bacterial endocarditis. Preexisting cardiac lesions are a main contributing factor, and antibiotic prophylaxis has long been felt necessary before dental or other manipulation to prevent endocarditis. Penicillin in combination with an aminoglycoside has been the most often used treatment regimen. We present a case of endocarditis caused by this organism which developed after antibiotic prophylaxis for dental cleaning. Streptomycin and rifampin therapy resulted in the cure of the infection. The treatment and epidemiology of *Actinobacillus* endocarditis are reviewed.**

Actinobacillus actinomycetemcomitans was first described as an etiological agent in endocarditis in 1964 by Mitchell and Gillespie (15). Subsequently, there have been 32 additional well-documented cases (1-4, 5-7, 9-13, 15, 16, 18, 19-28). Page and King (17) also presented 23 cases in 1966, but few clinical details were provided. Several therapeutic regimens have been attempted over the years, most commonly penicillin or ampicillin in combination with an aminoglycoside. We present a case of *Actinobacillus* endocarditis in which rifampin in combination with an aminoglycoside resulted in an apparent cure.

Case report. A 60-year-old female with known aortic and mitral insufficiency of rheumatic origin was admitted to the hospital on 13 January 1983, complaining of sudden onset of chills, diaphoresis, dyspnea, and fever. The patient admitted to a 9-month history of low-grade temperatures, chills, increasing shortness of breath, petechiae, muscle weakness, weight loss of 20 lb (9.08 kg), and increasing generalized malaise. Approximately 2 weeks before onset of her initial symptoms, she had her teeth cleaned. The patient had been prophylaxed with erythromycin (250 mg orally four times a day) 1 day before and on the day of the procedure.

Physical examination revealed a mildly diaphoretic female with a temperature of 103°F (39.44°C). Cardiac examination revealed a grade 3/6 systolic ejection murmur, heard best at the right sternal border, radiating into the neck. A grade 2/6 diastolic decrescendo murmur was heard along the left sternal border. Skin was without petechiae, and fundoscopic exam was negative for Roth's spots.

On admission, her leukocyte count was 17,000/mm³ (4,000 to 11,000), with a differential count of 40 segmented neutrophils, 51 bands, and seven lymphocytes. The hemoglobin was 9.4 g/dl. Rheumatoid factor was positive at 1:640. The chest X ray revealed no cardiomegaly, pulmonary congestion, or infiltration.

Hospital course. Numerous blood cultures were obtained immediately on admission. Because of the onset of signs of congestive heart failure and because of a penicillin allergy, vancomycin (500 mg intravenously every 6 h) and tobramycin (30 mg intravenously every 8 h) were started on hospital day 6. On day 7 of her hospitalization, a facultative gram-negative rod was found on her initial blood cultures drawn 6 days earlier. Chloramphenicol (1 g intravenously every 6 h) was started, and vancomycin was stopped. On hospital

day 12, the organism was determined to be *A. actinomycetemcomitans*. Ultimately 15 of 16 blood cultures were positive. The MIC and MBC of several drugs were subsequently reported, as indicated in Table 1. These tests were done by the macrobroth method. These values governed our decisions to make the following alterations in therapy. On day 17, tetracycline (500 mg orally every 4 h) was started, and chloramphenicol was discontinued; on day 21, tobramycin and tetracycline were discontinued, and rifampin (300 mg orally every 12 h) and streptomycin (500 mg intramuscularly per day) were started. On day 26, streptomycin levels were reported as >64 µg/ml, both pre- and postdose. Serum creatinine was also high at 2.2 mg/dl. Therefore, her streptomycin doses were withheld. On day 28, multiple petechiae developed on the plantar surfaces of the feet, so streptomycin (500 mg intramuscularly per day) was restarted. The petechiae gradually diminished. On day 34, serum inhibitory dilutions were <1:2 trough and 1:16 peak, whereas serum bactericidal titers were <1:2 and 1:8, respectively. Streptomycin was subsequently changed to 500 mg intramuscularly every other day. The patient remained afebrile throughout her course after spiking to 101°F (38.33°C) on day 12. The congestive heart failure was effectively treated with diuretics. She received several blood transfusions during her hospitalization for anemia, thought to be due to both microangiopathic destruction secondary to the endocarditis as well as decreased production secondary to anemia of chronic disease. She was discharged in good health on day 41 and completed the remainder of a 6-week course of streptomycin (500 mg intramuscularly every other day) and rifampin (300 mg orally every 12 h) on an outpatient basis. Two outpatient follow-up blood cultures were negative, and the patient was doing well 6 months after discontinuation of antibiotics with no apparent sequelae.

Microbiological studies. Blood cultures were obtained by inoculating blood into Columbia broth. The organism grew only at 35°C. No growth was seen at 25 or 42°C. A CO₂-enriched atmosphere was necessary.

All biochemical reactions were carried out on commercial tube media. The organism exhibited growth on blood agar and chocolate agar. No growth was seen on MacConkey or phenylethyl alcohol agar. Results with triple sugar-iron agar were acid/acid. Fermentation tests were positive for the production of acid with glucose and mannitol and negative with sucrose, lactose, and xylose. The organism produced catalase but was negative for the production of oxidase,

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TABLE 1. MICs and MBCs of various drugs to *A. actinomycetemcomitans*

Drug	MIC ($\mu\text{g/ml}$)	MBC ($\mu\text{g/ml}$)
Tetracycline	0.78	6.12
Gentamicin	3.12	3.12
Chloramphenicol	25.00	25.00
Rifampin	0.39	0.39
Streptomycin	1.56	1.56

indole, urea, and lysine. Gram stain was negative. Motility was negative. The organism was both X and V factor negative.

Discussion. *A. actinomycetemcomitans* is a very rare cause of endocarditis, and only 33 well-described cases have been reported. The organism is a small, nonmotile, gram-negative coccobacillus. Its fastidious nature and requirements for CO₂-enriched media delay the isolation of the organism. Although the average incubation period of blood cultures before turning positive is 8 days, incubation periods of up to 25 days have been reported (6).

Although the source of infection is not fully understood, a dental origin may be responsible. Page and King (17) have reported that this bacterium was present in the normal flora of the oral cavity in 5 of 30 healthy individuals. Further, oral disease or manipulation could be cited as a possible precipitating factor in 48.5% of the cases reviewed herein.

The mainstay of treatment in most reports was cephalothin, penicillin, or ampicillin in combination with an aminoglycoside. This has been a reliable combination, with a 71% survival rate. As was the case in many reports, the slow growth of the organism caused us to use different antibiotic combinations on an empiric basis before exact identification was made. Our definitive therapy as dictated by MIC and MBC values was streptomycin and rifampin. As depicted in Table 1, the MICs and MBCs of rifampin were clearly superior to those of the other drugs tested. Since rifampin is known to be associated with the emergence of resistant bacteria, we felt that using this drug in combination with an aminoglycoside would be best, even though killing levels with rifampin alone were adequate. Only one other in vivo use of rifampin has been reported (11). These investigators added rifampin to gentamicin and penicillin a little more than halfway through a 6-week course of total antibiotic therapy and successfully treated a patient with a porcine prosthetic mitral valve. They reported an MIC of 0.04 $\mu\text{g/ml}$ and an MBC of 0.08 $\mu\text{g/ml}$ for rifampin. This activity level was higher than those of the other drugs they tested.

Other in vitro studies lend considerable justification for using rifampin. Höffler et al. (8) tested the in vitro susceptibility of 14 strains of *A. actinomycetemcomitans* to 45 different antibiotics by utilizing MICs as determined by the plate dilution method. Resistance was demonstrated by some strains to all of the penicillins and cephalosporins. The highest activity was exhibited by trimethoprim, chloramphenicol, rifampin, and methacycline. These inhibited all 14 strains of the organism at an MIC of 0.8 $\mu\text{g/ml}$. Specifically, rifampin inhibited six strains at an MIC of 0.8 $\mu\text{g/ml}$, seven strains at 0.4 $\mu\text{g/ml}$, and one strain at 0.2 $\mu\text{g/ml}$. The only drug tested that showed higher activity in this study was trimethoprim, which inhibited more than one-half of the strains at an MIC of 0.1 $\mu\text{g/ml}$.

Page and King (17) reported the following susceptibilities of 25 strains to some of the more commonly used antibiotics. All strains were susceptible to tetracycline at a MIC of 3.12 $\mu\text{g/ml}$, streptomycin at 12.5 $\mu\text{g/ml}$, and chloramphenicol at

1.5 $\mu\text{g/ml}$. Only 40% of strains were susceptible to penicillin at an MIC of 6.25 $\mu\text{g/ml}$, whereas 33% of strains were susceptible to ampicillin at 3.12 $\mu\text{g/ml}$. As in our case, the clinical use of MICs and MBCs in determining therapy has been used frequently and appears to be a very valuable tool in *A. actinomycetemcomitans* infections. In one case, the organism showed resistance to penicillin by the Kirby-Bauer disk method. However, the MBC value for penicillin was 4 $\mu\text{g/ml}$, and treatment was successfully completed with penicillin (10).

The best antibiotic combination is difficult to determine because of the paucity of cases and the variety of treatment regimens used. Even though cure is possible with single-agent therapy (13, 21), double-agent therapy for 4 to 6 weeks after the last positive culture is the most widely used mode of therapy. Although rifampin has been utilized in only one other case before ours, MICs and MBCs directed us to use it in combination with an aminoglycoside to successfully treat a case of *Actinobacillus* endocarditis.

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