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Penicillin-resistant Viridans Streptococcus Endocarditis Related to the Administration of Penicillin G or Carbenicillin and Alterations in Mouth Flora

Keith Burch, MD, Edward L. Quinn, MD, Donald Romig, MD, Frank Cox, MD, Evelyn Fisher, MD, and T. Madhavan, MD*

Of 135 patients with streptococcal (non-group D) endocarditis seen at the Henry Ford Hospital (1957-1973), 133 had isolates which were penicillin-sensitive (inhibited by ≤ 0.2 µg/ml of penicillin G). The remaining two causative organisms were inhibited by 0.8 µg/ml of penicillin G and both of the infected patients received antibiotics just prior to the onset of endocarditis. The first patient received oral penicillin G for rheumatic fever prophylaxis and the second high dose parenteral carbenicillin. Using high dose parenteral therapy with ampicillin and streptomycin, the first patient was cured while the other patient relapsed. The second patient responded to retreatment with clindamycin. As reported in prior studies following oral penicillin administration, these current studies demonstrated penicillin-resistant viridans streptococci in the oropharynx of patients receiving parenteral carbenicillin (avg. MIC 0.56 µg/ml). Therefore, carbenicillin-induced changes in the oral flora are important in selecting antibiotics for prophylaxis or treatment of endocarditis in a patient with pre-existing valvular disease.

Recent studies documented the increased incidence of resistant organisms causing infective endocarditis. Finland and Barnes ascribed this to "extensive usage of antimicrobials" and other nosocomial factors. Despite this, penicillin-resistant viridans streptococcus endocarditis has been only rarely reported since the original description in 1962 by Garrod and Waterworth of two cases related to prior penicillin administration.

Subsequent investigators demonstrated that, although penicillin-resistant streptococci were present in only small numbers of control patients, they were found with great frequency in the oropharynx of patients receiving oral penicillin for rheumatic fever prophylaxis. This was ascribed to the overgrowth of resistant organisms which replaced more sensitive organisms as the normal flora. Since the organism responsible for viridans streptococcus endocarditis may have its origin in the patient's mouth flora, alteration of the susceptibility of these organisms may be important in the pathogenesis of resistant cases of endocarditis. Doyle and associates, in a carefully documented study of a large number of children receiving prophylactic antimicrobial agents for rheumatic fever over a 10-year period, reported that in 6 of 13 who developed viridans streptococcus endocarditis, the...
organism showed increased resistance to penicillin. Thus, in a given institution, the proportion of penicillin-resistant cases of viridans streptococci endocarditis should reflect prior administration of certain types of antibiotics. Seen during the years 1957-1973, the majority of our 135 patients with streptococcal (non-group D) endocarditis had not received prior antibiotics. Organisms from 133 patients had a MIC of penicillin G \( \leq 0.2 \mu g/ml \) and 90% were \( \leq 0.1 \mu g/ml \). In the other two patients, the isolates were inhibited by 0.8 \( \mu g/ml \) of penicillin G. Both had received prior penicillin antibiotics.

The first case represents the classic description of penicillin-resistant viridans streptococcus endocarditis in that the patient was receiving oral penicillin for rheumatic fever prophylaxis. The second case represents a new observation in that the infection occurred after six weeks of therapy with high dose parenteral carbenicillin.

Materials and Methods

Diagnostic criteria. From 1957-1973, 135 patients with streptococcal (non-group D) endocarditis were studied prospectively. The usual clinical criteria for the diagnosis of endocarditis and the presence of two or more positive blood cultures were required. Only two of the 135 causative organisms were resistant to penicillin G (inhibited by \( >0.2 \mu g/ml \)).

The two organisms identified as resistant viridans streptococci (MIC 0.8 \( \mu g/ml \)) were not typable with group D antiserum and did not grow in SF broth (BBL). The serial twofold-dilution technique was employed to determine the MIC and MBC (Minimal Bactericidal Concentration) of penicillin G for each isolate using a \( 10^{-3} \) dilution of an 18-hour culture as the inoculum. The MIC was defined as the lowest concentration of penicillin G that inhibited growth of bacteria after incubation for 18 hours at 37°C. The MBC of each isolate was defined as the highest dilution from which no more than 20 colonies grew after a 0.01 ml loopful was subcultured onto 10% sheep blood agar and incubated overnight. Antibacterial activity of serum was determined in a manner similar to the MIC determination.

Study of oral flora after carbenicillin. Thirteen patients receiving \( \geq 18 \) g parenteral disodium carbenicillin or 2-4 g oral indanyl carbenicillin daily were studied. When possible, throat cultures were obtained prior to therapy and after four days or more of carbenicillin therapy. We excluded patients who received antibiotics other than gentamicin or tobramycin within the month preceding the study.

Case Reports

Case one. S.P., a 25-year-old male with rheumatic heart disease and aortic insufficiency, received oral penicillin daily for 14 years for rheumatic fever prophylaxis. When admitted on 12-18-69, he complained of weakness, easy fatigability and migrating arthralgias of six weeks' duration. Dental work had been performed three months prior to admission without the recommended coverage for prevention of bacterial endocarditis.

Physical examination revealed an alert, oriented, white male with temperature 38.4°C, blood pressure 140/40 mm/Hg, and pulse 104 per minute. Positive physical findings included a high pitched blowing grade IV/V decrescendo diastolic murmur along the left sternal border. Abdominal examination disclosed an enlarged spleen. No petechiae were present.

The hemoglobin was 11.9 g/100 and leukocyte count 10,300/mm². Latex fixation was reactive. Six blood cultures grew viridans streptococcus with a MIC and MBC of penicillin G 0.8 \( \mu g/ml \) and ampicillin 0.4 \( \mu g/ml \).

Because the patient's history of receiving oral penicillin suggested the possibility of a resistant infection, treatment was begun with crystalline penicillin G, 20 million units iv daily, and streptomycin, 1 g im twice daily. On this regimen, serum bactericidal levels were only 1:8 to 1:16. Accordingly, treatment was changed to ampicillin, 12 g iv daily, and streptomycin, 1-2 g im twice daily. Serum bactericidal levels with this program were 1:64 to 1:256. The antibiotic
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Figure 1.
Case two. Graphic course of a patient with endocarditis due to a penicillin-resistant viridans streptococcus.

Treatment was continued for six weeks and the patient had an uneventful recovery from his endocarditis.

Case two. A.R. was a 36-year-old male heroin addict, first seen in February, 1973. He had a one-week history of fever and pain with swelling in his right knee (Figure 1). Physical examination revealed an alert, febrile black male with temperature of 39°C, blood pressure 130/70 mm/Hg, and pulse 110 per minute. Examination of the lungs was negative. A grade II/VI pansystolic murmur was heard along the left sternal border, radiating to the left axilla and back. An apparently different grade II/VI pansystolic murmur, that increased with deep inspiration, was heard along the left sternal border. Both mitral and tricuspid regurgitation were suspected. There was neither splenomegaly nor petechiae. The right knee was swollen, warm and painful. Cultures of the joint fluid grew Pseudomonas aeruginosa, as did multiple blood cultures.

Treatment was initiated with tobramycin, 100 mg im every eight hours. After five days, when the patient remained febrile and bacteremic, carbenicillin, 30 g iv per day, and probenecid, 2 g orally per day, were added. The tobramycin was increased to 100 mg every six hours, and the three agents continued for six weeks. During this time, he was afebrile and abacteremic.

Two weeks later, fever recurred and the patient was readmitted. On this second admission, nine blood cultures showed viridans streptococcus with a MIC and MBC of both penicillin G and ampicillin 0.8 µg/ml. The MIC of carbenicillin was 15.6 µg/ml. The patient promptly became afebrile. He began a six week course of treatment which was interrupted at day 28 by his leaving the hospital against medical advice. Forty-eight hours later, he returned with fever, and treatment was reinstituted. He was given 20 million units of crystalline penicillin G iv for 12 days and subsequently, 12 g of ampicillin iv for 30 days. Concomitant with this, he received 1 or 2 g of streptomycin im daily for six weeks. Serum bactericidal levels during penicillin G were 1:4 to 1:8, and during ampicillin 1:32 to 1:64.
Figure 2.
The penicillin G susceptibility of oral viridans streptococci related to the administration of parenteral carbenicillin.

Three days after his second discharge, fever (38.4 to 39°C) recurred, but blood cultures remained negative until six weeks later. At this time, viridans streptococcus with the same antibiotic susceptibility was found in multiple blood cultures. Because the patient had received two six-week courses of aminoglycoside antibiotics and both prior regimens had failed, alternate antibiotics were considered. The organism was susceptible to clindamycin (MIC and MBC .02 µg/ml). Because of our previous experience with this antibiotic, he was given a six-week course of clindamycin, 450 mg im every 8 hours, with clinical and bacteriologic cure. Serum bactericidal levels while receiving clindamycin were 1:64 to 1:512.

Results

In vitro data and serum bactericidal levels. Since the usual recommended treatment for enterococcal endocarditis is a combination of a penicillin with an aminoglycoside, we empirically employed this combination in our first patient. The serum bactericidal levels were higher against this patient's causative organisms with combined ampicillin and streptomycin therapy than with ampicillin alone. However, in the second patient, combined therapy failed, even though the serum bactericidal levels demonstrated synergy. This latter patient responded to clindamycin. It is noteworthy that unlike group D enterococci, which are resistant to this antibiotic, both patients' organisms were very susceptible to clindamycin. Furthermore, the causative organism in both patients was susceptible to the cephalosporins, a further indication that these bacteria were not enterococci.

The oral flora after carbenicillin. We studied 28 isolates of viridans streptococci from 13 patients prior to carbenicillin administration. Of the 61 isolates obtained during therapy, 21 were from patients re-
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Receiving oral and 40 from those receiving parenteral carbenicillin.

The average MIC of penicillin G for the pretreatment strains and isolates from patients receiving oral carbenicillin was equivalent, namely, 0.035 \( \mu \text{g/ml} \) and 0.046 \( \mu \text{g/ml} \), respectively. In contrast, the average MIC of penicillin G for the 40 strains from patients receiving parenteral carbenicillin was 0.56 \( \mu \text{g/ml} \) (figure 2). Furthermore, 82% of the pretreatment strains were inhibited by \( \leq 0.03 \mu \text{g/ml} \), while only 15% of strains isolated during parenteral carbenicillin therapy were inhibited by this concentration. Finally, all pretreatment strains had a MIC of penicillin G \( \leq 0.2 \mu \text{g/ml} \), while 48% of strains isolated during parenteral therapy had a MIC \( \leq 0.4 \mu \text{g/ml} \).

Discussion

Viridans streptococci from the oropharynx and from patients with classical viridans streptococci endocarditis are almost always penicillin-sensitive (defined as inhibited by \( \leq 0.2 \mu \text{g of penicillin G} \)) in vitro. Such organisms are difficult to classify, produce alpha hemolysis on blood agar plates, and can be further specified by biochemical tests. Furthermore, patients with endocarditis due to such organisms have a good prognosis.

On the other hand, most group D streptococci (enterococci) are relatively penicillin-resistant in vitro and in vivo. Patients with endocarditis due to these agents have a poorer prognosis.

While in recent years enterococci and other penicillin-resistant organisms have become more common as a cause of endocarditis, penicillin-resistant viridans streptococci are still rarely causative agents. Although common in the oropharynx of patients receiving oral penicillin, they almost always require pre-existing valvular disease in order to implant and multiply. Furthermore, recently modified antibiotic programs to cover surgical procedures in patients with heart disease receiving oral penicillin may prevent endocarditis due to resistant viridans streptococci.

Earlier studies showed that a greater number of penicillin-resistant organisms could be found in patients receiving oral penicillin when compared with those receiving monthly injections of benzathine penicillin. Later studies by Spencer and associates suggested that the variation in incidence was related to the magnitude of the peak serum concentration achieved with the respective penicillin preparation. Our failure to find resistant strains in patients receiving oral carbenicillin was expected since peak serum concentration achieved with the oral antibiotic is only 5% of that attained with high dose parenteral carbenicillin.

Other factors may play a role in alteration of normal flora. Penicillin-resistant viridans streptococci were acquired more rapidly in hospitalized patients receiving penicillin prophylaxis than in similar non-hospitalized controls. In the present study, all patients who received parenteral carbenicillin were hospitalized for much longer periods than those receiving oral carbenicillin. In addition, many of the patients who received parenteral carbenicillin also received an aminoglycoside antibiotic. Because of the small number of patients studied, no attempt was made to distinguish between those who received both agents or carbenicillin alone. It is possible that administration of the two agents may produce a more resistant flora than that produced with carbenicillin alone.

Regardless of the precise mechanism, the administration of oral penicillin G or V or parenteral carbenicillin may be followed by penicillin-resistant viridans streptococcus endocarditis. Therefore, in addition to the current recommendations for altered antibiotic prophylaxis of endocarditis in susceptible patients receiving oral penicillin, measures should be taken for the preven-
tion and treatment of resistant viridans streptococcus endocarditis in patients recently given high dose parenteral carbenicillin.

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