J Microbiol Immunol Infect
2002;35:129-132

Endocarditis caused by penicillin-resistant *Streptococcus mitis* in a 12-year-old boy

I-Fei Huang[1], Christine C Chiou[1,3], Yung-Ching Liu[2,3], Kai-Sheng Hsieh[1]

Section of Infectious Disease, Departments of [1]Pediatrics and [2]Medicine, Kaohsiung Veterans General Hospital, Kaohsiung and [3]National Yang-Ming University, Taipei, ROC

Received: September 6, 2001 Revised: November 22, 2001 Accepted: December 20, 2001

A case of congenital coronary arteriovenous fistula with infective endocarditis caused by penicillin-resistant *Streptococcus mitis* is reported. Lack of prophylactic antibiotics during dental procedure may cause the development of endocarditis. Bactericidal test (Schlichter test) was performed to guide the therapy for this case of bacterial endocarditis caused by penicillin-resistant viridans streptococci. This case highlights the importance of antibiotic prophylaxis in patients with underlying heart disease undergoing dental procedures.

Key words: Congenital coronary arteriovenous fistulas, penicillin-resistant viridans streptococci, bacterial endocarditis

Bacterial endocarditis remains a formidable diagnostic and therapeutic problem for clinicians. Viridans streptococcus accounts for 45% to 50% of all cases of bacterial endocarditis. Most strains of viridans streptococci are exquisitely susceptible to penicillin, with a minimum inhibitory concentration (MIC) of less than 0.2 μg/mL [1-6]. However, with widespread use of antibiotics, the rate of penicillin-resistant viridans streptococci is increasing gradually [7,8]. We report a patient with congenital coronary arteriovenous fistula who did not receive antibiotic prophylaxis for dental procedure. He received intermittent antibiotic therapy before the diagnosis of endocarditis was established. Penicillin-resistant *Streptococcus mitis* was isolated from blood after admission to the Kaohsiung Veterans General Hospital. Serum bactericidal titers were less than 1:2 after 6 days of high dose penicillin therapy (400 000 units/kg/d). This case illustrates the importance of antibiotic prophylaxis for dental procedures in patients with underlying heart disease and the use of serum bactericidal test (Schlichter test) in guiding the therapy for bacterial endocarditis.

Case Report

A 12-year-old boy was hospitalized because of a 5-month history of intermittent fever and chest pain, and a 2-month history of bodyweight reduction.

Corresponding author: Dr. Christine C Chiou, Department of Pediatrics, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung, 813, Taiwan, ROC. E-mail: chenchia@yahoo.com

The child had previously been in good health. He received a dental procedure 7 months before this admission. Fever and chest pain developed 2 months after the dental procedure. He had been admitted twice to other hospitals and was treated for pneumonia with penicillin G for 7 days on the first admission. Blood culture yielded viridans streptococcus on the second admission and penicillin and gentamicin were administered for 3 weeks. Echocardiography was performed and a right coronary arteriovenous fistula to the right ventricle was found. Both the parents and the child were not aware of an underlying congenital heart disease, thus no prophylactic antibiotics were given during the dental procedure.

On admission, physical examination revealed a well-developed and well-nourished child with a temperature of 38.5°C, heart rate 101 /min, respiratory rate 24 /min, and blood pressure 110/62 mm Hg. Breathing sounds were clear. Examination of the eye fundi was normal. Grade 3 pansystolic murmur over the left upper sternal boarder was noted. No hepatosplenomegaly was noted. No Osler's nodes, Janeway's lesion, or splinter hemorrhage were found over his extremities.

The laboratory data revealed white blood cell count of 9420 /mm^3, hemoglobin 10.6 g/dL, and C-reactive protein 0.79 mg/dL (normal, < 0.6 mg/dL). Transthoracic echocardiography showed several miliary vegetations over the orifice where the fistula joined the right ventricle. The diagnosis of infective endocarditis was established based on the finding of vegetation and the results of blood culture. Five of 6 sets of blood cultures

yielded *Streptococcus mitis* (Papi 20 Strep, bioMerieux, France). The isolate was resistant to penicillin (MIC, 1.5 μg/mL). As penicillin G has been recommended for the treatment of endocarditis caused by drug resistant viridans streptococci [9,10], penicillin (400 000 units/kg/d), and gentamicin (3 mg/kg/d) were administered intravenously. Fever subsided 2 days after the administration of antibiotics. Serum bactericidal test (Schlichter test) was performed 6 days after the antibiotics were started to explore the *in vivo* efficacy. The bactericidal titer was less than 1:2 on both occasions (peak and trough) (Table 1), thus the dosage of penicillin G was increased to 450 000 units/kg/d. However, the bactericidal titer was still low despite the increased dosage (Table 1). Therefore, penicillin G was shifted to teicoplanin (12.5 mg/kg/d). The third Schlichter test was performed when teicoplanin had been administered for 6 days. The inhibitory titer was 128 fold of the bactericidal titer, suggesting poor bactericidal activity (Table 1). As a result, vancomycin (15 mg/kg/d) was administered in place of teicoplanin. The patient received vancomycin for 42 days and no more fever occurred during the course of vancomycin treatment. He received corrective cardiac surgery 2 months after the completion of the treatment for endocarditis. No vegetation was found during the operation.

Discussion

The patient's parents had been informed of the symptom of heart murmur since birth, but the family did not pay any attention to it. Thus, no diagnostic or therapeutic measures had been performed. Being unaware of the existence of the heart condition, no prophylaxis was given when the patient received a dental procedure. He presented with prolonged fever without other manifestations (except for chest pain and bodyweight loss). This non-specific presentation and lack of awareness about underlying heart anomaly delayed the diagnosis of endocarditis.

Bacterial endocarditis in children with underlying heart disease or indwelling intravascular catheters is commonly caused by infection with viridans streptococci and enterococci. Most strains of viridans streptococci are exquisitely susceptible to penicillin, with an MIC of less than 0.2 μg/mL [1-6]. However, 15% to 20% of viridans streptococci have an MIC equal to or greater than 0.2 μg/mL and are defined arbitrarily as relatively resistant [11]. The mechanism of resistance is altered affinity of penicillin binding protein instead of production of beta-lactamase [12]. The rate of penicillin-resistant viridans streptococci in neutropenic patients has been reported to have increased gradually in recent years due to the use of penicillin for prophylaxis [7,8]. In one study, penicillin-resistant isolates were cultured from the oral cavity in 19 (61.3%) of 31 children at risk for endocarditis, suggesting a high prevalence of penicillin-resistant viridans streptococci in the oral flora [13]. In a comparison between penicillin-resistant and penicillin-susceptible viridans streptococci bacteremia, the administration of β-lactam antibiotics during the previous 2 weeks was the only factor significantly associated with penicillin-resistant cases [7]. The patient in this study received penicillin G treatment for 1 and 3 weeks before the diagnosis of endocarditis was established; whether the patient was colonized with a resistant organism in his oral cavity, or this infecting organism acquired its resistance during the course of intermittent treatment remains unclear.

In vitro measurement of the antibacterial activity of serum has been used for many years to assess the efficacy of antimicrobial therapy. The bactericidal test is also known as the serum-killing power assay or the Schlichter test [14]. There is a logical rationale for use of the serum bactericidal test. Determination of the activity of drugs under conditions that more closely approximate the *in vivo* environment than do most other *in vitro* tests is an appealing concept. For example, some antibiotics are highly protein-bound, so that only a fraction of the concentration that is measured in an antimicrobial assay is free in the serum. The serum

Table 1. Serum bactericidal test (Schlicter test) results for various drugs and dosages used in a 12-year-old patient with *Streptococcus mitis* endocarditis

Antimicrobial agent	Serum concentration			
	SIT		SBT	
	Peak	Trough	Peak	Trough
Penicillin G (400 000 units/kg/d)	1:16	1:16	<1:2	<1:2
Penicillin G (450 000 units/kg/d)	1:8	<1:2	1:8	<1:2
Teicoplanin (12.5 mg/kg/d)	>1:1024	1:512	1:8	1:4
Vancomycin (15 mg/kg/d)	1:128	1:64	1:16	1:4

Abbreviations: SIT = serum inhibition titer; SBT = serum bactericidal titer

bactericidal assay, in contrast, measures only that fraction of antibiotic that is free for biologic activity. Serum bactericidal test can help guide the therapy for bacterial endocarditis [14]. High serum bactericidal levels must be maintained long enough to eradicate organisms that are growing in relatively inaccessible avascular vegetations. Using a standardized microdilution method, a peak titer of 1:64 and trough titer of 1:32 were 100% predictive of bacteriologic cure; however, failure to achieve these titers did not predict bacteriologic failure because many patients with streptococcal endocarditis were cured despite low serum bactericidal titers [14,15]. Although the role of monitoring the inhibitory and bactericidal activity of the patient's serum is controversial, it may be of help when the infecting organism is not susceptible to penicillin. In this patient, the bactericidal titer to penicillin was less than 1:2, indicating no bactericidal activity at all. Although most studies have indicated that endocarditis caused by relatively resistant streptococci should be treated with high doses of penicillin combined with 2 to 4 weeks of an aminoglycoside or even penicillin alone [9,10], we still switched the antibiotic to glycopeptide based on the results of serum bactericidal test.

Congenital coronary arteriovenous fistulas are rare, accounting for 0.2% to 0.4% of congenital cardiac defects [16-19]. Even though many patients with this condition are asymptomatic, late complications occur, which include congestive heart failure, myocardial ischemia, infective endocarditis, atrial fibrillation, pulmonary hypertension, venous rupture, and thrombus and venous obstruction [16,20-22]. Consequently, surgical ligation of the arteriovenous communication has been recommended to prevent these complications [20,23]. The patient in this study was asymptomatic as in most cases of congenital coronary arteriovenous fistulas and the cardiac defect was not detected until after the development of endocarditis. Total surgical correction was performed after completion of the treatment of endocarditis. He remained in good health at a 3-year follow-up.

This case highlights the importance of antibiotic prophylaxis in patients with underlying heart disease. The serum bactericidal test can guide therapy in endocarditis especially when the infecting organism is not susceptible to conventional therapy.

References

1. Lerner PI, Weinstein L. Infective endocarditis in the antibiotic era. N Engl J Med 1966; 274:199-206.
2. Tompsett R. Bacterial endocarditis: changes in the clinical spectrum. Arch Intern Med 1967;119:329-32.
3. Shinebourne EA, Cripps CM, Hayward GW, Shooter RA. Bacterial endocarditis 1956-1965: analysis of clinical features and treatment in relation to prognosis and mortality. Br Heart J 1969;31:536-42.
4. Weinstein L, Rubin RH. Infective endocarditis - 1973. Prog Cardiovasc Dis 1973;16:239-74.
5. Garvey GJ, Neu HC. Infective endocarditis—an evolving disease: a review of endocarditis at the Columbia—Presbyterian Medical Center 1968-1973. Medicine 1978;57:105-27.
6. McCarthy VP, Cho CT, Diehl AM, Ramsey BW. Bacterial endocarditis due to penicillin-resistant *Streptococcus viridans*. Clin Pediatr 1979;18:263-6.
7. Carratala J, Alcaide F, Fernandez-Sevilla A, Corbella X, Linares J, Gudiol F. Bacteremia due to viridans streptococci that are highly resistant to penicillin: increase among neutropenic patients with cancer. Clin Infect Dis 1995;20:1169-73.
8. Spanik S, Trupl J, Kunova A, Botek R, Sorkovska D, Grey E, Studena M, Lacka J, Oravcova E, Krchnakova A, Rusnakova V, Svec J, Krupova I, Grausova S, Stopkova K, Koren P, Krcmery V. Viridans streptococcal bacteremia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer center before and after penicillin is used for prophylaxis. Scand J Infect Dis 1997;29:245-9.
9. Bisno AL, Dismukes WE, Durack DT, Kaplan EL, Karchmer AW, Kaye D, Rahimtoola SH, Sande MA, Sanford JP, Watanakunakorn C. Antimicrobial treatment of infective endocarditis due to viridans streptococci, enterococci and staphylococci. JAMA 1989;261:1471-7.
10. DiNubile MJ. Treatment of endocarditis caused by relatively resistant nonenterococcal streptococci: is penicillin enough? Rev Infect Dis 1990;12:112-7.
11. Starke JR. Infective endocarditis. In: Feigin RD, Cherry JD, eds. Textbook of Pediatric Infectious Diseases. Vol 1. 4th ed. Philadelphia: Academic Press; 1998:315-31.
12. Quinn JP, DiVincenzo CA, Lucks DA, Luskin RL, Shatzer KL, Lerner SA. Serious infections due to penicillin-resistant strains of viridans streptococci with altered penicillin-binding proteins. J Infect Dis 1988;157:764-9
13. Nishi J, Yoshinaga M, Nomura Y, Dajani AS, Taubert KA, Ferrieri PL. Prevalence of penicillin-resistant viridans streptococci in the oral flora of Japanese children at risk for infective endocarditis. Circulation 1999;99:1274-5.
14. Weinstein MP, Stratton CW, Ackley A, Hawley HB, Robinson PA, Fisher BD, Alcid DV, Stephens DS, Reller LB. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am J Med 1985;78:262-9.
15. Koneman EW, Allen SD, Janda WM, Schreckenberger PC, Winn WC, eds. Color Atlas and Textbook of Diagnostic Microbiology. 4th ed. Philadelphia: Academic Press; 1992:609-68.
16. McNamara JJ, Gross RE. Congenital coronary artery fistula. Surgery 1969; 65:59-69.
17. Perry SB, Rome J, Keane JF, Baim DS, Lock JE. Transcatheter closure of coronary artery fistulas. J Am Coll Cardiol 1992;20:205-9.
18. Reidy JF, Anjos RT, Qureshi SA, Baker EJ, Tynan MJ. Transcatheter embolization in the treatment of coronary artery fistulas. J Am Coll Cardiol 1991;18:187-92.
19. De Wolf D, Terriere M, De Wilde P, Reidy JF. Embolization of a coronary fistula with a controlled delivery platinum coil in a

2-year-old. Pediatr Cardiol 1994;15:308-10.
20. Wilde P, Watt I. Congenital coronary artery fistulae: six new cases with a collective review. Clin Radiol 1980;31:301-11.
21. Edwards JE. Anomalous coronary arteries with special reference to arteriovenous-like communications. Circulation 1958; 17:1001-6.
22. St John Sutton MG, Miller GA, Kerr IH, Traill TA. Coronary artery steal via large coronary artery to bronchial artery anastomosis successfully treated by operation. Br Heart J 1980;44:460-3.
23. Kirklin JW, Barratt-Boyes BG, eds. Cardiac Surgery. Vol 2. 2nd ed. New York: Academic Press; 1986:1171-93.