

Bacterial endocarditis due to a penicillin-tolerant group C streptococcus

D. PORTNOY, MD; I. WINK, RT; G.K. RICHARDS, MD, FRCP[C]; M.Z. BLANC, MD

The group C streptococcus has frequently been associated with infections in animals. The organism has been recovered from the skin, nose, throat and vagina of healthy people,^{1,2} but it has also caused puerperal, skin and wound infections,^{3,4} tonsillitis,⁵ glomerulonephritis,⁶ cellulitis,⁷ pulmonary infection, urinary tract infection and bacteremia.⁸

Endocarditis due to group C streptococcus is rare in humans: only nine such cases have been reported in the literature.^{2,8-12} We report here the first case in Canada of endocarditis due to the group C streptococcus.

Case report

A 71-year-old man was well until 4 weeks prior to his admission to hospital, when he experienced progressive weakness. His physician prescribed tetracycline for "pneumonia", but he took the antibiotic irregularly. No further details of his illness were obtainable.

At the time of admission the patient was disoriented. His temperature was 40°C, blood pressure 150/50 mm Hg, pulse rate 98 beats/min and respiratory rate 28/min. Petechiae were noted on the trunk, extremities and buccal mucosa. The heart sounds were normal and there were no murmurs. The liver was tender and was palpable 4 cm below the right costal margin. The spleen was not palpable. There was nuchal rigidity, but Kernig and Brudzinski signs could not be elicited.

The cerebrospinal fluid had an erythrocyte count of $40 \times 10^6/l$,

a leukocyte count of $25 \times 10^6/l$, a lymphocyte count of $5 \times 10^6/l$, a glucose level of 1.8 mmol/l (33 mg/dl) (the blood glucose level was 6.7 mmol/l [121 mg/dl]) and a protein level of 76 mg/dl. No organisms were seen in a Gram-stained smear, and culture yielded no bacteria. The blood hemoglobin level was 8.7 g/dl, the hematocrit 25.1% and the leukocyte count $6.1 \times 10^9/l$, with 84% neutrophils, 9% lymphocytes and 7% monocytes. Urinalysis showed a trace of albumin and occasional erythrocytes, leukocytes and granular casts; culture yielded no bacteria.

A tentative diagnosis of partially treated bacterial meningitis was made, and treatment with chloramphenicol, 1.5 g intravenously every 6 hours, and penicillin G, 3 million U intravenously every 4 hours, was begun. Group C β -hemolytic streptococci were cultured in five sets of blood drawn at the time of admission. The organism was confirmed as *Streptococcus equisimilis* by the national streptococcus reference centre of the Laboratory Centre for Disease Control in Ottawa. The organism was found to be sensitive to penicillin, tetracycline and chloramphenicol by disc sensitivity testing, and the chloramphenicol was discontinued.

Chest roentgenograms and an electrocardiogram were normal. Echocardiography 2 days after admission showed aortic insufficiency and minimal left ventricular dilatation. The mitral valve was normal. No vegetations were seen.

The patient's condition deteriorated, and on the seventh hospital day acute pulmonary edema and renal failure requiring peritoneal dialysis developed. On the ninth day a grade 3/6 systolic murmur was heard for the first time at the apex, and a grade 2/6 early diastolic murmur was noted as well. Minimum bactericidal concentra-

tion and synergism studies were requested the next day, but the patient became hypotensive and died that morning. Permission for autopsy was denied.

Antibiotic susceptibility studies

Methods

The minimum inhibitory concentration of the antibiotics to which the organism was sensitive was estimated by the doubling dilution tube technique, with the use of tryptone soya broth (Oxoid) and an inoculum of streptococci in the log phase of growth such that the final concentration of colony-forming units would be approximately $10^5/ml$. The tubes were incubated at 37°C for 18 hours before the results were read.

The minimum bactericidal concentration was determined by subculture of the contents of the tubes that showed no visible growth. Aliquots of 0.03 ml were inoculated onto three plates of 5% horse blood-Columbia agar (Oxoid CM 331), and the plates were incubated aerobically at 37°C for 24 hours. The minimum bactericidal concentration was defined as the least amount of antibiotic with which subculture yielded no growth.

Synergism of penicillin and gentamicin was assessed by a checkerboard titration incubated at 37°C for 18 hours, after which the bacteriostatic end-points were determined. The contents of tubes that showed no visible growth were subcultured in triplicate by the procedure just described. Combinations of antibiotics with which subculture yielded no growth were considered bactericidally synergistic.

Results

The results are presented in

From the department of microbiology, Montreal General Hospital

Reprint requests to: Dr. D. Portnoy, Department of microbiology, Montreal General Hospital, 1650 Cedar Ave., Montreal, PQ H3G 1A4

Table I. The difference between the minimum inhibitory and bactericidal concentrations, which were confirmed by the national streptococcus reference centre, was more than 128-fold. When 0.25 U/ml of penicillin was combined with 1.25 $\mu\text{g/ml}$ of gentamicin, there was a fourfold or greater reduction in the minimum bactericidal concentration of each drug than with either antibiotic used alone, which indicated synergism of the two drugs.

Discussion

Group C streptococcal endocarditis was first reported in 1940 in a 26-year-old woman following septic abortion.⁹ Since then eight other cases have been reported.^{2,8,10-12} In seven of the cases there were three deaths, and in most of these accounts, as in our case, the diagnosis of endocarditis was made on the basis of multiple positive blood cultures and a new or changing murmur.^{2,8,11,12} The antibiotic susceptibility of the organism was usually determined by disc sensitivity testing alone. *S. equisimilis* is the group C streptococcus most likely to be involved in infections in humans.¹³

Patients with bacterial endocarditis may present with meningitis.¹⁴ In a series of 218 patients with endocarditis Pruitt and colleagues¹² noted that 84 patients (39%) suffered neurologic complications, and in 36 (17%) a neurologic complaint was the presenting symptom. Meningoencephalitis is the most common central nervous system complication of bacterial endocarditis. The cerebrospinal fluid of patients with this complication may be normal or may contain a greater than normal number of cells, a reduced amount of sugar and an elevated amount of protein; organisms cannot usually be cultured

from the fluid.¹⁵ Similar cerebrospinal fluid abnormalities may be seen with other central nervous system complications of endocarditis, such as brain abscess, ruptured mycotic aneurysm or septic embolism.^{12,15}

The diagnosis at the time of admission of our patient was meningitis, and the sterile culture of cerebrospinal fluid was attributed to the previous antibiotic therapy. When a cardiac murmur and congestive heart failure developed, a diagnosis of endocarditis was made. It has been shown that in patients with endocarditis and severe heart failure valve replacement is superior to medical management.^{16,17} Echocardiography in such patients with aortic insufficiency may demonstrate early mitral valve closure, which indicates volume overload of the ventricles and the need for early valve replacement.^{18,19} However, in this patient surgery was not contemplated until shortly before his death.

Recently Sabath and colleagues²⁰ described a new type of penicillin resistance of *Staphylococcus aureus*. These penicillin-"tolerant" organisms were defined as having a low minimum inhibitory concentration but a high minimum bactericidal concentration, often more than 100 times the former. For the group C streptococcus isolated from our patient there was a difference of more than 128-fold between the minimum inhibitory and bactericidal concentrations of penicillin (Table I), which indicated that the isolate was penicillin-tolerant. "Tolerant" organisms differ from "persisters"²⁰ in that when "persisters" are re-exposed to penicillin more than 99.9% are killed after 24 hours' incubation. In two of the nine previous cases of group C streptococcal endocarditis minimum inhibitory and bactericidal concentrations

were determined and tolerance to penicillin was not noted.^{2,10}

Schauf and colleagues²¹ considered synergism to be present when bacterial inhibition or killing was produced by a concentration of each drug in the combination that was fourfold less than the concentration of either antibiotic when used alone. The penicillin-tolerant strain isolated from our patient demonstrated synergy of gentamicin and penicillin according to this criterion.

The addition of an aminoglycoside to penicillin in the therapy of enterococcal endocarditis is well established. The use of this combination in treating *S. viridans* endocarditis has been proposed as well,²² but is still controversial.

Casey and Miller²³ have suggested the following guidelines for the treatment of *S. viridans* endocarditis: Organisms for which the minimum bactericidal concentration of penicillin is less than 0.1 U/ml are considered sensitive, and the treatment is 2 million U of the drug every 4 hours, given intravenously. Organisms for which that concentration of penicillin is between 0.1 and 1.0 U/ml are considered moderately sensitive, and the treatment is 3 million U of the drug every 4 hours, given intravenously. Organisms for which that concentration is greater than 1.0 U/ml are considered relatively resistant; therapy with an aminoglycoside may also be required.

In contrast, penicillin alone has been recommended for the treatment of β -hemolytic streptococcal endocarditis.²⁴⁻²⁷ The results of disc sensitivity testing or the minimum inhibitory concentration alone can be misleading. The minimum bactericidal concentration should be established, as should serum killing levels. The marked difference in the two concentrations for our isolate has important therapeutic implications. We recommend that the guidelines suggested by Casey and Miller apply to β -hemolytic streptococcal endocarditis. For initial therapy an aminoglycoside in addition to penicillin should be used until the results of appropriate in vitro sensitivity testing are available.

Table I—Antibiotic susceptibility of the group C streptococcus isolated from the patient

Drug	Minimum concentrations	
	Inhibitory	Bactericidal
Penicillin	0.007 U/ml	1.0 U/ml
Gentamicin	2.5 $\mu\text{g/ml}$	10 $\mu\text{g/ml}$
Penicillin (in the presence of 1.25 $\mu\text{g/ml}$ of gentamicin)	0.0017 U/ml	0.25 U/ml
Penicillin (in the presence of 5 $\mu\text{g/ml}$ of gentamicin)	Not applicable	0.03 U/ml

Addendum

Since this report was written two additional cases of group C streptococcal endocarditis have been reported in the literature.^{28,29}

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continued from page 32

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