Enterococcal endocarditis — a case treated with teicoplanin and amoxycillin

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The study aimed to determine the antibacterial therapy effective in the cure of endocarditis caused by *Enterococcus faecalis* resistant to clinically achievable levels of vancomycin. Isolation of the causative enterococcus had been achieved by direct inoculation of the resected valve into the culture medium in theatre. The patient was known to have had an aortic valve defect since childhood and had recently undergone splenectomy following trauma. Blood cultures were negative prior to valve replacement. A perivalvular abscess was noted at operation. *In vitro* minimal bactericidal results and serum activity were the basis of the postoperative choice of drugs. The minimal bactericidal level of teicoplanin was 250 µg/ml and that of amoxycillin 64 µg/ml. Neither is achievable with the advocated dosage. A combination of these two cell-wall-active agents successfully eliminated the infection. Acting at two different sites in the synthesis of the bacterial cell wall, teicoplanin and amoxycillin were found to be bactericidal *in vitro* at the trough levels of the antibiotics in the serum. The patient recovered fully.

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While all around there are reports[1-3] of clinical isolates of heteroresistant enterococci, there is a dearth[4] of publications on antibiotic susceptibility profiles of enterococci in South Africa.

Clinical findings

A 39-year-old farmer with known aortic incompetence of rheumatic origin was admitted with low-grade fever and complaints of tiring easily. Six months previously he had been treated for infective endocarditis elsewhere and more recently he had had a splenectomy after trauma. On current admission, the typical murmur of aortic incompetence was present as well as an Austin Flint murmur over the mitral area. The left ventricle was enlarged both clinically and on sonar examination, and there was a vegetation on the aortic valve. ECG confirmed left ventricular enlargement. Chest radiography also confirmed cardiomegaly and grade I pulmonary venous hypertension. On sonar the left ventricular diameter was 5.3 cm with an increased diastolic and systolic muscle thickness of 14 mm and 16 mm, respectively. Left ventricular function was normal with an ejection fraction of 67%. The patient was classified as NYHA class III. Blood cultures did not yield any isolates and empirical treatment was commenced with penicillin G (6 million units 6-hourly) and amikacin (500 mg 12-hourly intravenously) for 6 weeks. Because of the symptoms, the state of the left ventricle and the vegetation it was decided to proceed with an aortic valve replacement under ampicillin cover.

On 16 July 1996 a median sternotomy was undertaken. The patient underwent cardiopulmonary bypass, and the aorta was cross-clamped and opened longitudinally. Blood cardioplegia was induced directly in the coronary arteries. The aortic valve was grossly abnormal with thickened edges, and a large vegetation was present. The valve was excised and placed aseptically directly into a wide-mouthed container holding Robertson's meat medium. A Carbomedics mechanical replacement valve (size 25) was placed in the supra-annular position with single non-absorbable sutures, It was noted that a perivalvular abscess was present in relation to the left right commissure. The aorta was closed, the heart de-aired and the patient was weaned from cardiopulmonary bypass without any problems and on minimal inotropic support. He was transferred to the ICU where he was ventilated for 16 hours and then extubated. On day 2 he was transferred to the ward. He continued to experience a low-grade fever and, when mobilised, experienced dyspnoea on the slightest exertion. On the basis of microbiological results of the valve culture he was given amoxycillin 1 g, 8-hourly and 3 doses of teicoplanin 400 mg 12-hourly, after which the dosage was reduced to 400 mg daily.

Within days the patient's condition improved and after 2 weeks of combination therapy he was discharged on oral amoxycillin for a further 4 weeks. Follow-up 6 months later found him to be in excellent health.

Microbiology

Three sets of Bactec blood cultures failed to culture the causative organism. From the resected valve in the Robertson's meat medium, which had been incubated at 37°C immediately and left undisturbed until turbidity appeared, *Enterococcus faecalis* was isolated on the 4th day and identified according to standard procedures[5] as well as by polymerase chain reaction (PCR).[1] Primers were used to amplify the species-specific gene $ddl_{E\ faecalis}$.

In addition the enterococcus was found to be resistant to a number of antibiotics usually prescribed for endocarditis. Minimal inhibitory concentrations (MICs) were determined on Mueller-Hinton agar[6] according to the National Committee of Clinical Laboratory Standards (NCCLS) agar dilution method (Table I).

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Table I. *E. faecalis* isolate v. nine antimicrobial agents

	MIC	MBC
Gentamicin	16 µg/ml	
Tobramycin	16 µg/ml	
Amikacin	256 µg/ml	
Kanamycin	> 1 024 µg/ml	
Streptomycin	> 1 024 µg/ml	
Ampicillin	1 µg/ml	64 µg/ml
Ciprofloxacin	0.25 µg/ml	
Vancomycin	0.25 µg/ml	> 256 µg/ml
Teicoplanin	≤ 0.01 µg/ml	128 µg/ml

MBC = minimum bactericidal concentration.

Forty-eight hours after commencement of amoxycillin and teicoplanin therapy, the bactericidal activity of the patient's serum (drawn after stabilisation) was estimated. Bacteriostatic activity was demonstrated at a dilution of 1:32 and bactericidal activity at 1:4.

Further examination of the enterococcus by PCR:[7] 40 cycles of 94°C for 25 seconds, 49°C for 30 seconds, 70°C for 60 seconds in a Perkin Elmer 9600 GeneAmp thermal cycler using primers for the $ddl_{E\ faecalis}$ gene: E_1 5¢ATCAAGTACAGTTAGTCT and E_2 5¢ACGATTCAAAGCTAACTG the *van*A gene: UP5¢ATGAATAGAATAAAAGTTGCAATAC and DOWN5¢CCCCTTTAACGCTAATACGAT as well as the *van*B gene: B_1 5¢ATGGGAAGCCGATAGTC and $B_2$5¢GATTTCGTTCCTCGACC.

Results: *van*A and *van*B PCR were both negative.

Discussion

Separately, neither the teicoplanin nor the amoxycillin levels achievable clinically would have been bactericidal, according to the *in vitro* results. In combination these two cell-wall-active agents, acting at different points in bacterial cell wall synthesis, proved bactericidal. The choice was made on the basis of the laboratory results and the fact that teicoplanin has outstanding penetration into cardiac muscle,[8] especially important in view of the abscess noted at operation. The pharmacokinetics of teicoplanin, which has a long half-life, is another clinically important property. The basis of the postoperative choice of drugs rested on the *in vitro* minimal bactericidal results and the serum activity. Carbon[9] has recently stressed the importance of initial high concentrations above the MIC of the infecting organism in experimental endocarditis. This has been corroborated by Martin *et al.*[10] in the clinical situation.

The favourable outcome enabled the patient to resume the strenuous occupation of farming. The purpose of this case report is to make South African clinicians aware that resistant enterococci are emerging here and that classic therapy with a penicillin and an aminoglycoside is not necessarily curative anymore.

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