Archives of Disease in Childhood, 1986, **61**, 394–399

Improving survival in bacterial endocarditis

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SUMMARY Twenty six cases of bacterial endocarditis in infancy and childhood were treated with a mortality of less than 8%. Twenty two had recognised congenital heart disease and four had previously normal hearts. Thirteen out of the 24 cases with positive blood cultures had staphylococcal infection. Appropriate antibiotics were identified by measurement of the minimum bactericidal concentration as an indicator of antibiotic sensitivity. The bactericidal activity of the patient's serum during treatment was monitored by back titration against the causative organism to assess the optimal antibiotic combination and dosage. Treatment was continued for six weeks in most cases, comprising intravenous treatment for at least the first three weeks, but then being substituted with oral treatment in some. Twenty one cases were successfully treated medically. Five developed complications requiring surgery, two of whom died.

Bacterial endocarditis is an uncommon disease in childhood. Most series from major cardiac centres report three or four cases each year. Despite the current rarity of bacterial endocarditis complicating rheumatic heart disease in children in the Western world, the overall number of cases of infective endocarditis is increasing. It now affects patients with previously normal hearts as a complication of prolonged intravenous feeding through central lines or after intravenous drug abuse. The disease remains an important cause of morbidity and mortality, though survival has now considerably improved since the advent of antibiotic treatment. In the era before treatment with antibiotics mortality was virtually 100%. Subsequently, mortalities of between 17% and 40% have been reported in paediatric series.[1–4] The most recent accounts of the management of bacterial endocarditis in children over the last 10 years quote mortalities of 14%[5] and 19%.[6] Advances in the early diagnosis of bacterial endocarditis using cross sectional echocardiography and earlier medical and surgical management have contributed to the improved survival rates.

This paper reports our experience in the management of endocarditis in infancy and childhood over the last 10 years and gives details of our management technique.

Material and methods

Cases of bacterial endocarditis diagnosed and treated at the Birmingham Children's Hospital over the last 10 years (1975–84) were identified by the hospital activity analysis computer records, ward admission registers, and postmortem reports. Excluded from the series were cases treated predominantly at other hospitals and three babies in whom the diagnosis of bacterial endocarditis complicating intravenous feeding was not considered during life and was only established at necropsy.

The criteria for the diagnosis of bacterial endocarditis were:

(1) A classical picture of positive blood cultures and new or changing cardiac murmurs (nine cases).

(2) Positive blood cultures, known pre-existing heart lesion with persistent fever, embolic phenomena, splenomegaly, and cardiac failure (nine).

(3) Positive blood cultures, a known heart lesion, and persistent fever with no other explanation (six).

(4) Negative blood cultures, pre-existing heart lesion, and persistent fever with a valvular vegetation on cross sectional echocardiography (one).

(5) Negative blood culture, pre-existing heart lesion, and Roth's spots (one).

Up to six blood cultures were taken from all patients in the first 24 hours after admission. Treatment was begun using appropriate intravenous bactericidal antibiotic combinations as soon as cultures proved positive. Subsequent treatment was modified by the clinical course, the organism's sensitivity to antibiotics, and estimation of the bactericidal activity of the patient's serum during treatment.

The sensitivity of the organism was assessed by

determining the 'minimum bactericidal concentration' of the antibiotics being used. Iso-sensitest broth (Oxoid) with 50% added horse serum was inoculated with 10^5 organisms. Synergistic activity of combinations of drugs was assessed by chequerboard titration. The end point in both of these tests was the lowest dilution that killed 99·9% of the original inoculum after overnight incubation. Serum bactericidal activity (back titration) was determined by making serial twofold dilutions of the patient's serum in 50% serum broth with an inoculum of 10^5 organisms. Samples were obtained before and one hour after administration of antibiotics during intravenous treatment and before and two hours after dosage during oral treatment. Serum bactericidal titre was the highest dilution of the patient's serum that killed the patient's own organism.

We aimed to achieve a bactericidal titre at a minimum of a fourfold dilution and to maintain this effect for at least two thirds of the dose interval. Dosage was increased or the antibiotic changed if this was not achieved. When gentamicin was given concentrations were also routinely assessed to determine dosage and dose interval and prevent toxicity.

Oral treatment was considered for patients in whom adequate bactericidal activity had been shown in the light of clinical progress and the data obtained from 'back titration' while receiving intravenous antibiotics, this usually being after three to four weeks of intravenous treatment.

Results

Twenty six cases of bacterial endocarditis were identified during the 10 year period, with an age range of 2 months to 16 years. Twenty two patients had an underlying congenital heart lesion (mean age 10 years, range 1·7 to 16·5 years), all of whom were already known to the Cardiac Department (Table 1). The remaining four with previously normal hearts were as follows:

(1) A 10 year old with an oesophageal stricture who required prolonged intravenous feeding postoperatively and developed staphylococcal mitral valve vegetations.

(2) A 6 year old with congenital hydrocephalus who had staphylococcal tricuspid valve vegetations as a complication of an infected ventriculoatrial shunt.

(3) A 2 month old who developed staphylococcal tricuspid valve vegetations after prolonged intravenous feeding with a central line after neonatal gut surgery.

(4) A 3 month old who developed staphylococcal aortic valve vegetations after a septicaemic episode associated with septic arthritis and osteomyelitis.

Identifiable invasive events preceded endocarditis in nine patients with congenital heart disease. Cardiac surgery had been undertaken within the previous two months in three cases. Six had had a dental procedure within the preceding three months conducted in general dental practice. Of these six patients, one had received antibiotic prophylaxis with intramuscular cephaloridine before tooth extraction followed by two days of oral erythromycin; three had had dental fillings, one with oral penicillin V prophylaxis; and two had had scale and polishing, with oral erythromycin prophylaxis in one case.

Bacteriological data. Single species of bacteria were isolated from blood cultures in 24 of the 26 cases (Table 2). Antibiotic sensitivities as indicated by minimum bactericidal concentrations were determined in 22 cases (Table 3). The range of bactericidal titres obtained by back titration during intravenous and oral treatment is listed in Table 4.

The patients in the current series were all treated with two bactericidal antibiotics for most of the duration of treatment. Children with streptococcal infections were treated for four to six weeks with intravenous penicillin G (300 mg/kg/day) and gentamicin (6 mg/kg/day). Oral treatment was not considered in most of these cases because of the variable absorption of oral penicillin and the need

Table 1 *Underlying congenital heart lesions in 26 cases of bacterial endocarditis*

Lesion	*Unoperated*	*Operated*
Aortic valve	4	4
Ventricular septal defect	6	1
Patent ductus arteriosus	1	
Coarctation	1	
Mitral valve		2
Complex with shunts		2
Fallot's tetralogy		1
No cardiac lesion	4	
Total	16	10

Table 2 *Organisms isolated in 26 cases of bacterial endocarditis*

Organism	*No of patients*
Congenital heart disease:	
Staphylococcus aureus	9
Streptococcus viridans	8
Streptococcus type unknown	1
Escherichia coli	1
Unidentified gram positive coccus	1
No organism	2
No cardiac lesion:	
Staphylococcus aureus	3
Staphylococcus albus	1

Table 3 *Range (median) of minimum bactericidal concentrations (mg/l) of antibiotics used in treatment of bacterial endocarditis*

Organism	*n=*	*Penicillin*	*Gentamicin*	*Fusidic acid*	*Flucloxacillin*	*Clindamycin*	*Cefuroxime*
Streptococcus viridans	8	0·01–2·5 (1·0)	2·0–4·0 (2·5)				
Staphylococcus aureus	12		1·0–8·0 (4·0)	2·0–32·0 (8·0)	0·25–6·5 (1·0)		
Staphylococcus albus	1		1·25			1·25	
Escherichia coli	1		4·0				8·0

Table 4 *Range of bactericidal titres obtained by back titration during intravenous and oral treatment in 28 patients*

Organism	*n=*	*Intravenous treatment*		*Oral treatment*	
		Pre-dose	*Post-dose*	*Pre-dose*	*Post-dose*
Streptococcus viridans	8	½–1/256	⅛–1/512		
Staphylococcus aureus	12	½–1/32	⅛–1/256	½–1/32	½–1/128
Staphylococcus albus	1	⅛	1/32	⅛	1/32
Escherichia coli	1	¼	⅛		

for parenteral administration of gentamicin. In two early cases, however, oral penicillin V with probenecid was given for the final two of the six weeks' treatment.

Eight of nine cases of streptococcal endocarditis were successfully treated medically. The remaining case, complicating coarctation of the aorta, required surgical intervention because of recurrent emboli to the legs. Culture of the resected coarctation was sterile. Adequate bactericidal titres during intravenous treatment with antibiotics were obtained in all except two of the nine cases on the original doses of antibiotics. In the first of these the bactericidal titre one hour pre-dose was only 1/2 and one hour post-dose 1/8. An increase of antibiotic dosages from 300 to 360 mg/kg/day of penicillin and from 6 to 7·5 mg/kg/day of gentamicin provided satisfactory titres of 1/8 pre-dose and 1/64 post-dose. In the second case it was impossible to perform back titrations due to a metabolic defect of the organism. In one case intravenous antibiotics were only administered for two weeks because of the development of drug allergy. The organism had been highly sensitive to antibiotics (minimum bactericidal concentrations of penicillin of 0·01 mg/l and of gentamicin of 2 mg/l) with synergistic activity. Bactericidal titres of 1/32 pre-dose and 1/512 post-dose had been shown. It was therefore estimated that two weeks of treatment would probably have been sufficient to cure the infection. Another patient developed an urticarial macular rash while receiving penicillin. This was managed symptomatically with antihistamines and the treatment with penicillin continued successfully.

Staphylococcus aureus endocarditis was usually treated with four weeks of intravenous flucloxacillin (100 mg/kg/day) and fusidic acid (20 mg/kg/day) and was followed by two weeks of oral administration in most cases. In one case with particularly difficult veins, however, intravenous treatment lasted for only one week, oral treatment being maintained for five weeks.

Bactericidal titres were satisfactory during intravenous treatment in all but one of 12 cases of *Staph. aureus* endocarditis. In this early case treatment continued for seven week using intravenous antibiotics. Of those cases in which oral treatment was used bactericidal titres were found to be inadequate in three. Higher than normal minimum bactericidal concentrations to fusidic acid (16 mg/l and 32 mg/l) necessitated an increase in dosage of oral antibiotics in one case (initial bactericidal titre less than 1/2 pre-dose) and a return to intravenous treatment in another (bactericidal titre 1/2 post-oral dose). In the third case resistance to fusidic acid developed during oral treatment. Blood cultures again became positive and the minimum bactericidal concentration of fusidic acid for the new isolate was 32 mg/l compared with 2 mg/l for the original isolate. Treatment with clindamycin in combination with flucloxacillin was therefore begun, and adequate bactericidal titres were obtained.

Staphylococcus albus resistant to flucloxacillin and fusidic acid but sensitive to clindamycin and gentamicin was isolated in one case with a previously normal heart after intravenous feeding through a central line. Two weeks' treatment with intravenous clindamycin and gentamicin followed by

four weeks of oral clindamycin was successful. One case of *Escherichia coli* endocarditis was associated with a urinary tract infection and septicaemia. The organism was moderately resistant to gentamicin (minimum bactericidal concentration 4 mg/l) and to cefuroxime (minimum bactericidal concentration 8 mg/l). Because bactericidal titres were low (1/4 pre-dose, 1/8 post-dose) and a suitable oral agent could not be identified, intravenous treatment was continued throughout. A penicillin resistant, gram positive coccus was found in another case. It proved impossible to determine the minimum bactericidal concentration or measure bactericidal titres in this case because of difficulties in growing the organism in our routine culture media. Empirical treatment with ampicillin, gentamicin, and co-trimoxazole was successful.

In two cases no organisms were isolated. The first of these occurred after a dental scaling without antibiotic prophylaxis and was treated with penicillin and gentamicin as if due to *Streptococcus viridans*. The second case occurred two months after aortic valve repair for aortic incompetence and was treated assuming *Staph. aureus* infection. Intravenous treatment was begun with flucloxacillin and gentamicin. Uncontrolled cardiac failure secondary to aortic incompetence, however, necessitated aortic valve replacement. Cultures of the aortic vegetations were sterile.

Twenty one of the 26 patients were successfully treated medically with no relapses. The other five developed haemodynamic complications during the course of treatment with antibiotics that required surgical intervention. Of these five, three developed uncontrollable cardiac failure secondary to aortic incompetence necessitating aortic valve replacement in two cases and aortic cusp replacement using calf pericardium in the third. The fourth patient developed aneurysmal dilatation of a patch on the right ventricular outflow tract after correction of Fallot's tetralogy. The fifth patient had persistent emboli to the legs arising from an infected coarctation of the aorta.

Only two deaths occurred in the study group (mortality less than 8%), both associated with perioperative complications—namely, dehiscence of an aortic valve replacement and failure to come off cardiopulmonary bypass after aneurysm repair in the case of corrected Fallot's tetralogy.

Discussion

This report concentrates on the role of the laboratory in the management of bacterial endocarditis in infancy and childhood. Appropriate bactericidal antibiotic combinations were identified and antibiotic activity monitored in the patient to ensure adequate 'killing power' against the organism. All patients initially received intravenous antibiotics, and in some cases oral treatment was substituted.

In our series six of the 22 patients with congenital heart disease had a preceding dental procedure within three months of the diagnosis of endocarditis. Three of these patients had received antibiotic prophylaxis but not in accordance with the subsequently published recommendations of the Working Party of the British Society for Antimicrobial Chemotherapy.[7] We support the use of prophylactic oral amoxycillin one hour before dental extraction or scaling, though three of our cases had dental fillings, a procedure for which routine antibiotic prophylaxis is not recommended.

Blood cultures were positive in 24 out of the 26 patients. It is notable that prior treatment with ampicillin or erythromycin for fever or non-specific symptoms did not prevent isolation of the causative microbe in any of our cases, despite administration for between one week and two months. Several of our patients had been seen initially in other hospitals where organisms had been grown in blood cultures. We obtained these isolates for estimation of minimal bactericidal concentration of the antibiotics used for back titration determination of bactericidal activity of the patient's serum against the organism while on treatment with antibiotics.[8 9] The synergistic effect of combinations of bactericidal antibiotics was tested in chequerboard titrations where the bactericidal effect of varying antibiotic concentrations in combination was superior to treatment with the same concentration of a single drug.

The amount by which the blood concentration of antibiotic should exceed the concentration needed to kill the organism in vitro is not known, nor is it known for how long concentrations should be bactericidal. We aim to exceed the bactericidal titre in our 'back titrations' by a considerable margin and often achieve titres of 64- to 512-fold. We suggest that the minimum acceptable bactericidal titre for fairly resistant organisms should be a fourfold dilution, and on pragmatic grounds we try to exceed this for at least two thirds of the interval between doses.[10] Failure to achieve this margin of overkill indicates a need for higher dosage or a change of route of administration providing that the minimum bactericidal concentration determinations suggest susceptibility of the pathogen. Where the minimum bactericidal concentration shows total resistance to a drug or partial resistance to a fairly toxic drug a change of antibiotics is indicated.

The minimum bactericidal concentration of our isolates of staphylococci to fusidic acid were much higher than usually reported. This agent, however,

is 97% bound to protein in vivo. Protein bound drug is microbiologically inactive, although drug does displace from albumin as blood concentrations fall. We have shown the minimum bactericidal concentrations of fusidic acid to be roughly 100-fold higher in the presence of 50% serum than when tests are performed in broth. Flucloxacillin is roughly 94% protein bound. While this effect is not detectable with low protein binding antibiotics, we recommend that the test for the minimum bactericidal concentration should routinely be performed in the presence of serum when assessing activity of agents for the management of endocarditis.

It is common practice to treat bacterial endocarditis for six weeks with intravenous antibiotics to maintain adequate drug concentrations. During this period infusion sites have to be changed regularly unless an indwelling central line is inserted. In paediatric practice there may be difficulty in siting intravenous lines, and the subsequent changes result in large numbers of painful injections. It has been suggested that oral administration of antibiotics for bacterial endocarditis is possible after an initial period of intravenous treatment.[11] A series of 14 episodes of endocarditis where oral treatment has been given with satisfactory results has been reported.[12] It was suggested that oral treatment should be considered for children who were not seriously ill and who had sensitive organisms. *Strep. viridans* affected most of those cases. Bactericidal titres, however, were only determined in a few cases, and treatment was with one antibiotic alone.

We were successful in treating 10 of 13 cases of staphylococcal endocarditis with a combination of bactericidal antibiotics (usually flucloxacillin and fusidic acid) for a total of six weeks initially by intravenous and then by oral administration. In a number of cases determination of the minimum bactericidal concentration has been important in finding the correct choice and dosage of antibiotic. Monitoring of back titration titre during oral treatment has reassured us that bactericidal activity has been adequate to combat a form of endocarditis that has previously been considered to be particularly lethal. Back titrations showed that adequate blood concentrations of antibiotic could be achieved in most of the patients by both the intravenous and oral route of administration. We therefore favour the use of this antibiotic combination for sensitive staphylococcal infections rather than gentamicin or vancomycin, which require parenteral administration. Three cases of staphylococcal endocarditis required surgical intervention after intravenous then oral treatment. Bactericidal titres, however, had been adequate in these cases, and culture of the infected sites at operation were sterile. Failure of medical treatment was due to mechanical factors rather than bacteriological deterioration.

The increasing incidence of staphylococcal over streptococcal endocarditis has been noted in recent series.[4 6] In our patients staphylococcal infection accounted for 13 of the 26 cases. Staphylococcal infections are associated with a higher complication rate and mortality compared with infections due to other organisms. Mortality as high as 47% has been reported in a recent series.[4] The mortality from staphylococcal endocarditis in our series was 15% (two cases). Both deaths occurred as a complication of surgery. The overall mortality in our entire series of 26 cases was less than 8%.

Penicillin hypersensitivity occurred in two cases, requiring symptomatic treatment with antihistamines in one and stopping the drug in another after two weeks of treatment without subsequent relapse. Alternative strategies would be desensitisation of the patient or substitution of a different antibiotic to which the organism is sensitive.

Our policy for the management of bacterial endocarditis is to begin treatment with two intravenous bactericidal antibiotics as determined by bacterial sensitivities of blood culture isolates. For streptococci we use penicillin G and gentamicin and for staphylococci flucloxacillin and fusidic acid. Once the minimum bactericidal concentration of the antibiotics has shown the offending pathogen to be sensitive and back titrations of serum have shown adequate concentrations, it can usually be predicted whether therapeutic concentrations of antibiotics can be achieved by the oral route. We favour intravenous treatment for two to four weeks followed by oral treatment to complete six weeks of anti-staphylococcal treatment. While streptococcal infections were usually treated with a full six week course of intravenous penicillin G and gentamicin, we suggest that oral amoxycillin may be substituted for intravenous treatment during the last three weeks. We favour amoxycillin rather than penicillin V because of the unpredictable absorption of the latter. We maintain that part oral treatment for endocarditis is possible and indeed desirable in paediatric practice as long as bactericidal titres are monitored. Clinical deterioration due to mechanical factors rather than bacteriological deterioration must be recognised early as an indication for surgical intervention.

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Received 13 January 1986