Infective endocarditis in neonates

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SUMMARY Five patients with neonatal infective endocarditis were reviewed, two of whom survived. Infection was caused by *Staphylococcus aureus* in four and by *Candida albicans* in one. All cases of bacterial endocarditis had clinical signs of septicaemia, positive blood cultures, thrombocytopenia, microscopic haematuria, and heart murmurs. Three developed skin abscesses early in their illnesses. Three patients had two dimensional echocardiographic studies that showed bacterial vegetations. One of these studies was done before the heart murmur could be heard. We suggest that echocardiography in conjunction with the clinical picture described may help in making an early diagnosis of endocarditis in neonates.

Bacterial endocarditis in neonates is a rare and usually fatal disease; the first survivor was reported in 1983.^{1,2} We became interested in the disease after two patients in our neonatal unit survived. We therefore reviewed all five cases of neonatal infective endocarditis seen at this hospital over the past 10 years to see if we could find similarities that could lead to earlier diagnosis and treatment; this is the largest published series that we know of.

Case reports

CASE 1

A boy weighing 1000 g was born by spontaneous vaginal delivery at 28 weeks' gestation. He required resuscitation after birth with endotracheal ventilation. Sodium bicarbonate and dextrose were given through a catheter in the umbilical vein. His Apgar scores were 1 at one minute and 3 at five minutes. He was transferred to this hospital.

Initial management included mechanical ventilation, intravenous fluid replacement, and treatment with penicillin and gentamicin. Vascular access catheters were inserted in the radial artery and a central vein. At 7 days of age a patent ductus arteriosus was confirmed by two dimensional echocardiography. The heart was structurally normal and the baby was successfully treated with indomethacin.

At 15 days of age he had an abscess over the left posterior iliac spine; a full blood count showed thrombocytopenia and analysis of the urine showed microscopic haematuria. Methicillin resistant *Staphylococcus aureus* was cultured from pus from the abscess, and from the cerebrospinal fluid, blood,

and tracheal aspirates; he was treated with intravenous vancomycin.

At 26 days of age the baby had not improved and a systolic murmur could be heard. Echocardiography showed vegetation round the mitral valve. Despite the addition of fusidic acid to his treatment he continued to deteriorate and died at 28 days.

The diagnosis of vegetative bacterial endocarditis due to methicillin resistant *S aureus* was confirmed at necropsy, together with lung changes consistent with bronchopulmonary dysplasia. There were also periventricular cystic changes and a cerebral haemorrhage.

CASE 2

A girl weighing 2800 g was delivered by elective caesarean section at term. She required resuscitation with endotracheal ventilation. Sodium bicarbonate and dextrose were administered through a catheter in the umbilical vein. Her Apgar scores were 1 at one minute and 9 at five minutes.

She was slow to begin breast feeding and despite the early passage of normal meconium she developed progressive abdominal distension. At 4 days of age she underwent a laparotomy for severe necrotising enterocolitis of the entire colon. Treatment included penicillin, gentamicin, and metronidazole. Vascular access catheters were inserted in the radial artery and a central vein. No organisms were grown from cultures.

A systolic murmur accompanied by congestive cardiac failure was heard postoperatively. An atrio-ventricular canal was diagnosed by two dimensional echocardiography and she was treated with digoxin and diuretics. At 23 days of age, having received no

54 Infective endocarditis in neonates

antibiotics for seven days, she showed clinical signs of septicaemia. *S aureus* was cultured from her blood and she was treated with flucloxacillin and gentamicin. At 25 days of age she developed nodal rhythm and multiple supraventricular and ventricular arrhythmias. She died three days later despite full intensive care.

Necropsy showed vegetations on the pulmonary valve with extension into the main pulmonary artery, which had ruptured. There was an atrio-ventricular canal and patent ductus arteriosus. The bowel showed necrotising enterocolitis and there was an abscess in the loops of small bowel.

CASE 3

A boy weighing 3100 g was born at term by spontaneous vaginal delivery following an uncomplicated pregnancy. His condition at delivery was good. He started breast feeding and was discharged when 5 days old.

At 21 days he developed a fever, a generalised rash, and malaise. Cultures of blood, swabs of the skin lesions, and a specimen of urine aspirated suprapubically grew *S aureus* that was sensitive to gentamicin. A full blood examination showed a platelet count of $10\,000 \times 10^9/l$. Despite initial treatment with penicillin and gentamicin he failed to

respond. At 27 days of age a swab from a skin pustule grew methicillin resistant *S aureus*; treatment with vancomycin and rifampicin was started.

At 28 days a pansystolic murmur was heard and two dimensional echocardiography showed a mobile vegetation attached to the papillary muscle of the mitral valve (fig 1). Fundoscopy showed four chorioretinal atrophic areas and computed tomography of the brain showed several embolic areas.

Antibiotic treatment was continued for six weeks, and echocardiography at 7 weeks of age showed no evidence of vegetations. At discharge he had completely recovered with no obvious sequelae.

CASE 4

A boy weighing 800 g was born at 26 weeks' gestation and transferred to this hospital shortly after delivery. The mother's membranes had been ruptured for four days before delivery and there had been a small antepartum haemorrhage. Apgar scores at birth were 6 at one minute and 9 at five minutes. He was intubated, ventilated at low ventilator settings, and treatment was started with penicillin and gentamicin. Initial cultures showed no evidence of sepsis and his clinical condition was consistent with hyaline membrane disease.

At 2 days of age an echocardiogram was done

Fig 1 Two dimensional echocardiogram (apical four chamber view) showing pedunculated vegetation in left ventricle attached to papillary muscle. RA=right atrium; RV=right ventricle; TV=tricuspid valve; MV=mitral valve; LV=left ventricle; PV=pulmonary valve, and V=vegetation.

which showed normal cardiac anatomy and no evidence of a patent ductus arteriosus. Methicillin resistant *S aureus* was cultured from surface swabs. At 8 days he developed persistent metabolic acidosis and methicillin resistant *S aureus* was isolated from blood cultures; he was treated with vancomycin, but on day 10 methicillin resistant *S aureus* was isolated from a pustule on his chest. At 25 days, nine days after the vancomycin had been stopped, he again developed metabolic acidosis, his white cell count was high, platelets were normal and methicillin resistant *S aureus* was again isolated from blood cultures. Clotting studies were normal and a chest x-ray picture showed bronchopulmonary dysplasia. Treatment with vancomycin and rifampicin was started. A abscess developed on the left wrist and another on the upper arm, and methicillin resistant *S aureus* was isolated from the pus. The cranial ultrasound scan was normal. Two dimensional echocardiography, however, showed a pedunculated vegetation in the left atrial appendage (fig 2). The methicillin resistant *S aureus* isolated from the blood cultures was sensitive to vancomycin, rifampicin, and fusidic acid, but because of possible antagonism between vancomycin and rifampicin, rifampicin was replaced by fusidic acid.

He was extubated at 7 weeks of age at which time he became grossly oedematous with a serum albumin concentration of 19 g/l. This resolved after infusion of albumin and restriction of fluids. Anti-

biotics were continued for seven weeks, at which time cardiac ultrasound scan showed a slight decrease in the size of the vegetation. He was discharged when 12 weeks of age. When reviewed at 12 months of age neurological and developmental examinations yielded normal results. A further echocardiogram showed that the vegetation had disappeared.

CASE 5

A girl weighing 1500 g was delivered at 37 weeks' gestation by caesarean section because of falling oestriol concentrations in the mother's urine; she had had an antepartum haemorrhage at 32 weeks. The infant's Apgar scores were 2 at one minute and 5 at five minutes and she responded to three minutes of endotracheal ventilation. At 24 hours of age she developed tachypnoea and became unwell. Cultures of blood and cerebrospinal fluid grew *S aureus* and she was treated with flucloxacillin and gentamicin. Her condition deteriorated and she developed disseminated intravascular coagulation. An exchange transfusion was carried out but her condition continued to deteriorate and she required mechanical ventilation. She developed severe cholestatic jaundice, and acute hepatic necrosis was suspected. Three further exchange transfusions were carried out; despite full intensive care she died at 19 days of age.

Necropsy showed peritonitis, pleurisy, peri-

Fig 2 Echocardiogram of a vegetation in left atrial appendage (long axis view). PV=pulmonary valve; LA=left atrium; RV=right ventricle; MV=mitral valve, and V=vegetation.

56 Infective endocarditis in neonates

carditis, focal necrotic lesions in the spleen, and hepatic necrosis. There was systemic candidiasis with lesions in many organs including the brain. *Candida* pericarditis and myocarditis were present with a vegetation on the mitral valve that was thought to be the origin of the septic foci in the other organs.

Discussion

The number of reports of infective endocarditis in children have increased during the past 10 years. Symchych *et al*³ reported an incidence of about 3% among 100 neonatal necropsies carried out in one year, but other studies reported lower figures.^{4 5} The true incidence is difficult to determine.

There seems to be an increased incidence of bacterial endocarditis in children who require resuscitation at birth and subsequent intensive care, especially if central venous lines are inserted.^{1 6-8} Three of our five cases had had central venous lines in place before the endocarditis developed. All five were clinically unwell and had blood, cerebrospinal fluid, and urine taken for culture before antibiotic treatment was started.

Previous studies have reported that the dermatological lesions of endocarditis such as Janeway's spots, Osler's nodes, and Roth's spots are seen in less than 5% of paediatric patients.¹² In our patients skin abscesses or pustules that were thought to be seedlings of infection from the cardiac vegetations appeared in three of the four patients with bacterial endocarditis. Two of the five developed petechia during their illnesses.

The first echocardiographic diagnosis of bacterial endocarditis was in 1977 by an M mode scan.⁷ In 1983 Kavey *et al* found that 82% of the children with infective endocarditis that they examined had echocardiographic findings compatible with the diagnosis.⁹ Vegetations as small as 1-3 mm could be seen.¹⁰

Murmurs or changing murmurs were present in all four patients later in their illnesses. Thrombocytopenia and microscopic haematuria were present in all babies at an early stage. In two cases the development of a murmur led to two dimensional echocardiographic examination that showed a vegetation. In one case, with the clinical signs of septicaemia, skin pustules, haematuria, and thrombocytopenia, two dimensional echocardiography showed a vegetation in the left atrial appendage before a murmur could be detected. Fourteen days earlier a patient with similar signs was treated with vancomycin for 10 days after methicillin resistant *S aureus* had been isolated from cultures. Echocardiography

at that stage might have shown a vegetation and resulted in a prolonged course of antibiotics with the hope of preventing further damage. Interestingly in older children the mean duration of symptoms before the diagnosis of bacterial endocarditis is 35 days.

With the increasing availability of two dimensional echocardiography neonates with septicaemia, especially if it is prolonged or recurrent, and skin pustules, haematuria, and thrombocytopenia, may warrant a cardiac scan to search for vegetations before a heart murmur has developed.

Non-bacterial endocarditis is an important predisposing factor to the development of bacterial endocarditis because it may form a nidus for bacterial superinfection and increase the possibility of embolisation. In one study of neonates who died 10% had evidence of thrombotic endocarditis at necropsy.³ Eighty per cent of them had had an intracardial central venous catheter inserted. The initial event in the development in thrombi is thought to be endocardial damage, presumably traumatic in these cases.^{3 8 11} Congenital heart disease is also an important predisposing factor, and it was present in one of our patients. In addition, one report suggested an association between persistent fetal circulation and non-bacterial endocardial thrombosis in neonates.¹²

In bacterial endocarditis the bacteraemia is usually low grade and constant, and detectable in 77-96% of the first blood cultures. This is increased to nearly 100% if three blood cultures are taken.¹³ *S aureus* has become an increasingly common cause of endocarditis since antibiotics have been used, and it is more virulent than other bacterial causes of endocarditis. The complication rate is higher, congestive cardiac failure occurs more often, and mortality increases.¹³ The treatment of infection by methicillin resistant *S aureus* with vancomycin alone is usually satisfactory. There is some evidence, however, that the addition of rifampicin or fusidic acid may improve the response, particularly for endocarditis or when skin infection occurs during treatment. Minimum inhibitory concentrations and minimum bactericidal concentrations of any antibiotic used in the treatment of endocarditis should be routinely tested.^{14 15} The serum bactericidal titre should be at least 1/8-1/16, and preferably higher.

Fungal endocarditis in neonates is rare, and we found no other case reports. The diagnosis in our case was made at necropsy, and there was concurrent endocarditis and pericarditis. The occurrence of pericarditis has not been described in neonatal fungal infections, and in neonates with bacterial endocarditis it has only been reported once previously.

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Received 30 July 1987