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# Early and late neonatal septicaemia

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SUMMARY Between 1979 and 1982 we reviewed 1000 consecutive admissions to the neonatal intensive care unit of this hospital. Sixty five infants had positive blood cultures. Mortality was 70% among 17 infants who had septicaemia in the first 48 hours of life and for whom appropriate treatment may have been too late because of difficulties of early diagnosis. In the remaining 48 infants mortality was 12%, septicaemia occurred later, and was associated with *Staphylococcus epidermidis* (56%) and with the presence of an intravascular catheter (50%).

Despite careful hygiene and powerful broad spectrum antibiotic treatment, neonatal septicaemia remains an unsolved problem associated with a high mortality rate. New techniques of inhibition of maternal labour and neonatal intensive care may make conditions more favourable to the development of septicaemia. A survey of all admissions to this intensive care unit between 1976 and 1979 reported a mortality rate of 64% for septicaemia occurring within the first 48 hours of life and 29% for later septicaemias.[1] In both these groups of infants *Staphylococcus epidermidis* was the predominant organism. At Queen Charlotte's hospital an overall mortality rate of 40·7% was reported,[2] with mortality in inverse proportion to birthweight. Here Gram negative rods predominated. We have recently completed a second study of admissions to this regional neonatal intensive care unit and review the aetiology, clinical features, and management of both early and late infections.

## Patients and methods

Clinical records and bacterial isolates were obtained from 1000 consecutive admissions to the neonatal intensive care unit of this hospital between August 1979 and September 1982. Six hundred and thirty of these infants had been born in this hospital and 370 had been referred. In all infants with suspected infection blood samples were drawn from a peripheral vein before beginning antibiotic treatment. The blood was innoculated into a set of 3 culture bottles and a diagnosis of septicaemia was made when organisms were grown in at least 2 of the 3 bottles and haematological and clinical features were also suggestive of infection. All positive cultures were divided into 2 groups—those occurring in the first 48 hours of life and those occurring later.

## Management

**Early infection.** In all infants with a history of prolonged rupture of the membranes (>24 hours) or with symptoms suggesting infection, antibiotic treatment was given immediately after blood samples, surface swabs, and lumbar punctures had been taken. Penicillin and gentamicin were given initially but where resistant organisms were found a more appropriate antibiotic was prescribed. Other important supportive measures included maintenance of circulation, ventilatory support, correction of acidosis, and management of coagulation disorders, renal failure, and convulsions.

Profound circulatory collapse frequently accompanied septicaemia and required urgent treatment. Plasma expander, sometimes in volumes of up to 50 ml/kg, was given to correct blood pressure and capillary perfusion. The choice of expander depended on the presence of other haematological abnormalities—purified protein fraction was used in the management of hypotension alone, fresh blood if there was anaemia, and fresh frozen plasma for abnormal coagulation. Exchange transfusion was not performed routinely. The volume of maintenance fluids was usually minimal because of accompanying renal impairment and was calculated separately from plasma expander.

**Later infection.** When septicaemia was suspected in older infants cultures were taken and any possible source of infection (for example, intravascular catheter) was removed and cultured before beginning

antibiotic treatment. Penicillin and gentamicin were usually given but if routine swabs taken within the previous 7–10 days had revealed a resistant organism, a more appropriate antibiotic was chosen. Antibiotic treatment usually lasted for 10 days. In older infants supportive measures were required less frequently and these included correction of hyperglycaemia, anaemia, and acidosis, temporary cessation of oral feeds, and occasional ventilatory support.

## Results

Of 1000 infants admitted 65 had proved septicaemia, 17 within the first 48 hours of life and 48 later. Clinical details including possible aetiological factors are shown separately for each group in Tables 1 and 2 and bacterial isolates in Table 3. In 150 of 1000 infants, birth followed prolonged rupture of maternal membranes (>24 hours). Five of these infants (3·3%) developed early onset sepsis.

**Early infection.** The early clinical features in babies less than 34 weeks' gestation were indistinguishable from those of birth asphyxia or respiratory distress syndrome. The more mature babies were sometimes well at birth but then presented with apnoeic attacks or respiratory distress during the subsequent 24 hours. More specific signs of septicaemia, present in most infants, included profound hypotension associated with metabolic acidosis and disseminated intravascular coagulation. Neutropenia (0–500 neutrophils $\times 10^6$/l (0–500/mm$^3$)) was seen in 10 of the 17 infants, all of whom died.

Antibiotic treatment began between 1 hour and 56 hours (mean 12 hours) after birth and with the exception of 1 infant who died from group B streptococcal septicaemia, the regimen was penicillin 50 000 units/kg 12 hourly and gentamicin 2·5 mg/kg 12 hourly. The mean age of beginning antibiotic treatment in the survivors was 10·9 hours and treatment was continued for 10 days.

The 5 infants with group B streptococcal septicaemia (mean gestational age 32·6 weeks) were all

Table 1 *Clinical details of infants with septicaemia occurring in the first 48 hours of life*

| | | |
|---|---|---|
| Total No | | 17 |
| Inborn (includes in utero transfers) | | 4 |
| Outborn | | 13 |
| Birthweight (g) | mean | 1410 |
| | range | 620–2880 |
| Gestation (weeks) | mean | 29·7 |
| | range | 26–38 |
| Boys : Girls | | 11 : 6 |
| Prolonged rupture of membranes (>24 hours) | | 5 |
| Maternal antibiotics | | 5 |
| Spontaneous vaginal delivery | | 11 |
| Forceps delivery | | 5 |
| Caesarean section | | 1 |
| Mortality | | 12 (70%) |

Table 2 *Clinical details of infants with septicaemia occurring after first 48 hours of life*

| | | |
|---|---|---|
| Total No | | 48 |
| Inborn : outborn | | 20 : 28 |
| Birthweight (g) | mean | 1530 |
| | range | 730–3250 |
| Gestation (weeks) | mean | 31·1 |
| | range | 26–40 |
| Boys : Girls | | 30 : 18 |
| Age at diagnosis of septicaemia (days) | mean | 16·5* |
| | range | 3–70 |
| Intravascular catheter: | | |
| Umbilical arterial catheter | | 10 |
| Central venous catheter | | 13 |
| Spitz-Holter valve | | 1 |
| Previous surgery | | 8 |
| Necrotising enterocolitis | | 2 |
| Duration of intravascular catheter (days) | mean | 9·6 |
| | range | 3–40 |
| Current antibiotic treatment | | 26 |
| Previous antibiotic treatment | | 43 |
| Mortality | | 6 (12·8%) |

* Excludes three children over 3 months of age; after gut surgery.

Table 3 *Bacterial isolates in early and late infection*

| | *Early* | *Late* |
|---|---|---|
| Gram positive | | |
| *Staphylococcus epidermidis* | | 27 |
| *Staphylococcus aureus* | | 7 |
| Group B *streptococcus* | 5 | 2 |
| *Streptococcus faecalis* | | 2 |
| *Streptococcus viridans* | 1 | |
| *Streptococcus pneumococcus* | 2 | |
| *Micrococcus* | | 1 |
| Total | 8 | 39 |
| Gram negative: | | |
| *Escherichia coli* | 6 | 4 |
| *Haemophilus* | 2 | |
| *Pseudomonas* | | 3 |
| *Enterobacter* | | 1 |
| *Klebsiella* | | 1 |
| *Alcaligenes* | 1 | |
| Total | 9 | 9 |

referred from other hospitals, and were delivered vaginally with no history of prolonged ruptured membranes. In spite of a classic history of respiratory distress and apnoeic attacks antibiotic treatment had been either delayed (mean time of onset 31 hours) or given in a low dosage (benzyl penicillin 25 000 units/kg) and 4 of these 5 infants died.

All the organisms responsible for early septicaemia, with the exception of haemophilus, were fully sensitive to penicillin and gentamicin. The haemophilus was only moderately sensitive and treatment was changed to ampicillin with good effect.

Three of the 4 infants born at Hammersmith Hospital had been transferred in utero because of prolonged ruptured membranes at less than 30 weeks' gestation. In spite of receiving maximal supportive measures from birth and antibiotics before two hours of age, they died.

Outcome was fatal in 70% of infants. Survival related to organisms isolated is shown in Table 4. Gestational ages of infants who died ranged from 26 to 35 weeks (mean 28·8 weeks) compared with 26 to 38 weeks in the 5 survivors.

**Late infection.** Clinical presentation was less acute in these infants and common features included lethargy, acidosis, milk intolerance, hyperglycaemia, fall in haemoglobin values, and episodes of apnoea. Each of these infants became septicaemic while receiving intensive care and none was admitted from a 'lying-in' ward.

Twenty six of the 48 infants were already receiving antibiotic treatment when they became septicaemic. In 15 infants, including 8 with an intravascular catheter in situ, the organism isolated was resistant to the antibiotics. In the remaining 11 infants the organism was sensitive but other factors predisposing to infection were present; central venous or arterial catheter (5), virulent organism—*Pseudomonas*, *Klebsiella*, *Escherichia coli* (4), and extremely sick premature infants (2).

Of the 39 infants with Gram positive septicaemia the organism was fully sensitive to flucloxacillin and gentamicin in 35. Three of the remaining 4 infants had septicaemia associated with an infected central venous catheter or shunt and all recovered after removal of the catheter or shunt and the appropriate antibiotic.

The organisms responsible for the 9 cases of Gram negative septicaemia were all gentamicin sensitive. Because of the virulent nature of the organisms, however, an additional appropriate antibiotic was also prescribed.

Three cases of septicaemia (*Streptococcus faecalis*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*) were associated with classic features of necrotising enterocolitis, including bloody stools and intramural gas. Two of the infants recovered but 1 infant of 27 weeks' gestation died.

There were 6 deaths directly attributable to septicaemia (Table 5). Excluding 1 infant of 37 weeks' gestation with an infected exomphalos, gestational ages ranged from 26 to 28 weeks and problems of extreme prematurity were considered to contribute to the mortality.

Table 4 *Survival in early septicaemia related to organisms*

| *Organism* | *Number* | *Survival* | *Prolonged ruptured membranes (>24 hours)* |
|---|---|---|---|
| Group B streptococcus | 3 | 1 | 0 |
| *Streptococcus viridans* | 1 | 0 | 0 |
| *Streptococcus pneumococcus* | 2 | 2 | 0 |
| *Escherichia coli* | 6 | 0 | 3 |
| *Haemophilus* | 2 | 1 | 2 |
| *Alcaligenes* | 1 | 1 | 0 |

## Discussion

**Early onset of septicaemia.** Results of treatment of early septicaemia show that in spite of antibiotics and intensive supportive measures most infants do not survive. Prolonged rupture of the membranes in the preterm fetus is known to be associated with neonatal infection.[3 4] Modern obstetric management of preterm labour includes administration of tocolytic agents and glucocorticoids, which gain maturity and protection from respiratory distress syndrome, but at the risk of exposing the fetus to infection.

Table 5 *Deaths from late septicaemia*

| *Case No* | *Gestational age (wks)* | *Birthweight (g)* | *Other clinical details* | *Age at onset (days)* | *Age at death (days)* | *Organism* |
|---|---|---|---|---|---|---|
| 1 | 27 | 900 | *RDS | 3 | 4 | *Staphylococcus aureus* |
| 2 | 27 | 910 | Necrotising enterocolitis | 3 | 4 | *Staphylococcus epidermidis* |
| 3 | 28 | 1180 | Day 4: apnoeas | 5 | 6 | *Staphylococcus aureus* |
| 4 | 26 | 1100 | Day 20: apnoea and collapse | 20 | 22 | *Staphylococcus epidermidis* |
| 5 | 27 | 1100 | *RDS, day 4: collapse | 4 | 7 | *Escherichia coli* |
| 6 | 37 | 2820 | Infected exomphalos sac | 16 | 29 | *Pseudomonas* |

*RDS: Respiratory distress syndrome.

Group B streptococcal infection in our study was not associated with prolonged rupture of membranes or extreme prematurity. The poor outcome may have been related to delayed diagnosis and sebsequent delay in antibiotic treatment. Cowan *et al.*[5] found a raised respiratory rate to be an early and consistent sign of group B streptococcal infection and suggested that all infants developing tachypnoea in the neonatal period should receive antibiotics.

The absence of *Staphylococcus epidermidis* as a cause of early septicaemia was in marked contrast to the earlier review,[1] when this organism was associated with 24% of cases of early septicaemia. This change may reflect recent emphasis on more meticulous attention to handwashing[6] and preparation of the skin with iodine and alcohol[7] before drawing the blood culture.

The usual choice of antibiotics for early infection has been penicillin and gentamicin.[8] Gentamicin is excreted by the kidneys and serum values may vary widely depending on age, gestation, and renal status.[9] Because of possible risks of toxicity, particularly in the sick premature infant, a suboptimal dose may be prescribed. In spite of good broad spectrum activity, penicillin and gentamicin provide inadequate cover for haemophilus infection which has become an increasingly common pathogen in early septicaemia.[10] For these reasons, the efficacy of alternative non-toxic broad spectrum antibiotics is now being studied.

The outlook for early septicaemia may be improved by more accurate detection of fetal infection—a difficult condition to diagnose. After delivery, transfusion of fresh blood, buffy coat, or white cell concentrate may be beneficial, particularly if there is profound neutropenia—associated with 100% mortality in this study.

**Late infection.** From our experience, we recommend that initial treatment of late septicaemia should consist of flucloxacillin and a broad spectrum antibiotic with wide Gram negative cover. *Staphylococcus epidermidis* has frequently been dismissed as a contaminant when isolated from neonatal blood cultures[11] but more recent studies have produced strong evidence for its pathogenicity.[1 12] This was confirmed in our study where it was associated particularly with apnoeic episodes, lethargy, glucose intolerance, and in 50% of infants with a centrally placed catheter.

Snydman *et al.*[13] in a study on adults and children receiving total parenteral nutrition found a 61% incidence of contaminated cannula tip or septicaemia after positive skin cultures taken during the previous week from the insertion site of the cannula. The cultures were concordant for skin and cannula. Only 2% of negative skin cultures were associated with infection. Assuming the same is true of neonates, routine swabs taken from the site of catheter insertion at dressing changes could provide useful information about organisms and choice of antibiotics in the event of future sepsis.

The association of septicaemia with the use of broad spectrum antimicrobial treatment and centrally placed catheters should alert one to the diagnosis in any 'at risk' infant. Current antibiotic treatment to which the organism is not fully sensitive may mask overt symptoms of infection and also isolation of the organism from blood cultures. If septicaemia is suspected, centrally placed catheters must be removed and cultured. The use of antibiotics may suppress the septicaemia but a colonised catheter will provide a continuing source of infection.

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