Changing blood culture isolates in a referral neonatal intensive care unit

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SUMMARY   An analysis was made of all cases of bacteraemia that had occurred in the referral neonatal intensive care unit at Hammersmith Hospital during the years 1976–79. One hundred and thirteen infants had positive blood cultures; 27 were born in the hospital, and 86 admitted from elsewhere. This gave a rate of 5·7/1000 live hospital births, and 165/1000 outborn admissions to the unit. The latter infants were predominantly of very low birthweight or were ill. Thirty-three of the isolates were cultured in the first 48 hours of life (early) and the remaining 80 after that time (later). *Staphylococcus epidermidis* was the organism most often isolated both early and later. These results were different from those recorded in the previous 9 years (1967–75) from the same unit. Then, group B β-haemolytic streptococcus was the organism most often isolated early, while Gram-negative bacteria predominated among later isolates. The changing nature of care may contribute to these findings.

Bacteraemia continues to be an important cause of morbidity and mortality in neonatal intensive care units, and periodic review of cases may help to stress any changing trends in the infecting organisms, and in the newborn host. It also serves to monitor to some extent the safety of various forms of care. In a previous survey from Hammersmith Hospital for the years 1967–75 inclusive,[1] the group B β-haemolytic streptococcus was found to be the organism most often isolated in the first 48 hours of life. After that time however, Gram-negative isolates were more than twice as common as Gram-positive ones (H Jeffery *et al.*, 1977, unpublished data). We have now analysed results from the succeeding 4 years, and report a changing pattern of infection.

Patients and methods

The infants studied were (1) the 4737 live births of mothers delivered in the maternity unit of Hammersmith Hospital between the years 1976 and 1979 inclusive, and (2) the 521 newborn infants admitted from other hospitals and elsewhere to the referral neonatal intensive care unit during the same period. The latter infants were almost entirely of low birthweights or were ill; most were both. During the study period 598 of the 4737 inborn infants were also

admitted to the intensive care unit. The proportion of low birthweight infants born in the hospital is much higher than for the country as a whole, for many mothers in premature labour are referred from other hospitals, and the socioeconomic status of the population served by the hospital is generally low.

Blood was drawn for culture from a peripheral vein whenever possible as part of the routine investigations for suspected infection before anti-microbial therapy was started. Infection was suspected if infants were ill at birth and had come from an infected intrauterine environment; if they were febrile, or presented with signs such as lethargy, poor feeding, vomiting, diarrhoea, unusual jaundice, and recurrent apnoea; or if there were suspicious findings on clinical examination. Blood was also drawn for culture, usually by direct cardiac puncture, immediately after death in infants dying, whether or not the death was suspected of being infective. The skin at the site of venous or cardiac puncture was prepared by careful swabbing with 70% isopropyl alcohol. The blood specimens were inoculated into a set of two or three bottles, one containing tryptone soya broth and including an agar slope (Castaneda), and the other one or two containing thioglycollate broth.

The records of all infants with positive blood cultures were reviewed, and details of their clinical

course abstracted. The isolates were divided into those occurring in the first 48 hours of life (early infection) and those occurring after that time (later infection). Comparisons were made with the previous study (H Jeffery *et al.*, 1977, unpublished data),[1] in which the indications for blood culture had been identical.

An antibiotic spray containing polymyxin, bacitracin, and neomycin was applied to the infant's umbilical cord at birth (or on admission from elsewhere) and once daily thereafter until the cord separated. No antibacterial substance was applied to the skin until the infant was well enough to be bathed or had been transferred from an incubator to a cot. Chlorhexidine was then used, but in every case this was some time after blood had been drawn for culture. This routine for cord and skin has been unchanged for many years except that chlorhexidine was substituted for hexachlorophane in 1971, the fifth year of the previous 9-year survey.[1]

Results

One hundred and thirteen of the 5258 infants cared for had positive blood cultures: in 27 inborn infants (giving a rate of 5·7/1000 for live hospital births) and in 86 outborn infants (giving a rate of 165/1000 for outborn admissions to the neonatal unit). These figures must be taken as a minimum rather than as an exact estimate for we cannot be certain that our routine for taking blood cultures was followed in every case. Some infants admitted from elsewhere, for instance, were already receiving antimicrobial therapy on entering the unit.

Clinical details. Details of the 113 infants are given in Table 1. The mean time of isolation in the early and later cases was 34 ± 6 hours, and 24·4 ± 2·7 days respectively. Many of the later infections occurred beyond the strict confines of the neonatal period (first 28 days) and were among infants of very low birthweights and immature gestations who stayed in the nursery for many weeks after birth.

Infecting organisms. Details of the nature of the isolates are given in Table 2. It can be seen that *Staphylococcus epidermidis* predominated in early and later infections. It was isolated from 34 (38%) of 90 infants who had drips inserted into peripheral or central veins, or had umbilical artery catheters passed. It was however recovered only from outborn infants in the first 48 hours of life. Early group B β-haemolytic streptococcus and *Staphylococcus aureus* isolates were similarly confined to outborn infants.

Mortality. Death was more common among early infected infants, and among those from whom Gram-negative rather than Gram-positive organisms were isolated, whether early or later (Table 3.)

Comparison with 1967–75 analysis. Expressing results as isolates per year for the two unequal time periods 1967–75 (H Jeffery *et al.*, 1977, unpublished data)[1] and 1976–79 (Table 4) the prevalence of Gram-negative organisms has not changed appreciably—6·0 compared with 8·2 isolates a year respectively. This is true both for early (2·6 v 2·7) and later isolates (3·4 v 5·5). Gram-positive isolates however have increased from 3·2 a year in 1967–75 to 20 a year in 1976–79 (P <0·01). The increase is not significant among early isolates (2·6 v 5·5), but it is

Table 1   *Clinical details of 113 infants*

	Early infection (n = 33)	Later infection (n = 80)
Boys	19	50
Girls	14	30
Birthweight (kg)		
Mean (± SD)	1·52 (±0·65)	1·46 (±0·47)
Range	0·77–3·57	0·62–2·3
Gestation (weeks)		
Mean (± SD)	31·3 (±6·5)	30·9 (±1·03)
Range	26–40	26–40

Table 2   *Nature of isolates*

Isolates	Number of isolates	
	Early	Later
Gram-positive (n = 80)		
Staphylococcus epidermidis	8	47
Staphylococcus aureus	1	4
Group B β-haemolytic streptococcus	6	1
Other*	7	6
Gram-negative (n = 33)		
Escherichia coli	1	5
Pseudomonas aeruginosa	3	5
Klebsiella-Enterobacter-Serratia		
group	0	5
Other†	7	7

*Micrococci, diphtheroids, non-haemolytic streptococci.
†Aerobic spore bearers, *Acinetobacter* sp, *Bacteroides* sp.

Table 3   *Mortality. (Numbers of deaths and isolates)*

	Early	Later	Total
Gram-positive	13/22	14/58	27/80 (34%)
Gram-negative	8/11	9/22	17/33 (51%)
Total	21/33 (64%)	23/80* (29%)	44/113 (39%)

*Death occurred significantly more often among all early infections than among all later infections (P <0·05).

Table 4   *Comparison of isolates 1967–75 and 1976–79.*
(*Figures expressed as isolates/year*)

Isolates	1967–75	1976–79
Gram-positive	3·2	20·0*
Early	2·6	5·5
Later	0·6	14·5*
Gram-negative	6·0	8·2
Early	2·6	2·7
Later	3·4	5·5

*Differences significant (P<0·01–with Yates's correction for small numbers).

Table 5   *Results for 1967–75 compared with those for 1976–79*

	1967–75	1976–79
Rate/1000 live hospital births	1·6	5·7
Rate/1000 outside admissions (ill or infants of low birthweight)	76	165
Median birthweight (kg)	1·6	1·3
Predominant isolate		
Early	Group B β-haemolytic streptococcus	*Staphylococcus epidermidis*
Later	*Escherichia coli*	*Staphylococcus epidermidis*

so among later isolates (0·6 v 14·5) (P<0·01). A summary of the main differences between the periods 1967–75 and 1976–79 is given in Table 5.

Discussion

A change in the pattern of bacterial isolates cultured from the blood stream of infants nursed in the referral neonatal intensive care unit at Hammersmith Hospital has taken place during the last few years. Gram-positive organisms are now foremost among both early and later infections, whereas in the preceding 9 years Gram-negative isolates were equally prevalent among early infections and completely dominated the later infections. A striking recent increase in isolation of *S. epidermidis* is largely responsible for this change.

This organism, a skin commensal, is recognised as an important coloniser of cerebrospinal fluid shunt systems and indwelling catheters.[2] Its ability to produce virulence factors and to develop antibiotic resistance is now more widely appreciated,[3] and it is becoming acknowledged as a cause of major infection among otherwise normal children.[4] It has generally been dismissed as a contaminant when isolated from newborn blood cultures in the past,[5][6] although its occasional significance for preterm infants, albeit

with a low morbidity and mortality, has been noted by some.[7] We are in no doubt about its pathogenicity for many of our infants. Ten of the 55 babies with positive cultures for *S. epidermidis* also had clinical and radiological evidence of pneumonia, but other associated illness—such as meningitis or urinary tract infections—was not seen. The picture more commonly presented was that of a very immature infant having total parenteral nutrition suddenly becoming less well with recurrent apnoea and significant neutropenia. The majority of these recovered with prompt use of antimicrobial therapy and the removal of centrally placed intravenous catheters. Others with positive cultures for this organism who appeared only mildly ill frequently had a pronounced neutrophil leucocytosis.

In a study of colonisation patterns from a neonatal intensive care unit, it, together with *S. aureus* and Gram-negative enteric bacilli, was considered an abnormal pharyngeal inhabitant.[8] A high colonisation rate by methicillin-resistant *S. epidermidis* has also been associated with an outbreak of bacteraemia in another newborn intensive care unit where the use of antibiotics was widespread, according to a preliminary report.[9] A survey from Yale[10] where careful records of neonatal bacteraemia have been kept for 50 years, also suggests a recent increase of *S. epidermidis* isolates, together with other unusual bacteria. It has been recovered from the blood stream of 12% of infants 'failing to thrive' and from 12% of jaundiced infants in a maternity nursery where normal infants had sterile cultures;[11] attempts at identification of the isolates suggested there was more similarity between those from blood stream and nasopharynx, than between blood stream and skin.[12]

Possible reasons for the finding in our survey have to be sought in the treatment of the newborn host, and in the host himself. During 1976–79, there were more very low birthweight infants (≤1500 g) admitted to the unit from elsewhere, most of whom were ill. An unusual number of very immature infants was also born in the hospital, and the median birthweight of the 113 infants studied was 1·3 kg. The inability of the most immature to mount a satisfactory immune-inflammatory response is well known.[13] In addition to umbilical artery catheterisation for blood gas monitoring which has been thought necessary for many of them, there has been a steadily increasing use of total parenteral nutrition, and of intravenous drips in general. Ninety per cent of the study infants had had a catheter passed into an umbilical or central blood vessel or had an infusion needle into a peripheral vein, and either of these was retained there for varying periods. Further detailed analysis of the association between infection,

drug therapy, umbilical vessel catherisation, and intravenous infusions is being conducted prospectively. Although every effort is made to conduct the insertion of drip needles and catheters in a sterile field, the inevitable technical difficulties with a few of the tiniest babies may mitigate against this. However it is clear that the most meticulous practical technique, together with stringent and frequent review of all aspects of drip and catheter care are nowhere more necessary than in a neonatal intensive care unit if the chance of infections due to S. epidermidis and other skin contaminants is to be lessened. Random checks of the infusion fluids used have not suggested contamination. Others have reported it as a common environmental contaminant of milk drip feeds.[14]

Overuse of antimicrobial therapy in neonatal units is recognised[15] and is to some extent inevitable. At present about 52% of infants in our referral nursery are treated with such drugs, and in the first 6 months of 1980 several strains of S. epidermidis resistant to all the commonly used antibiotics have been found. Care of the umbilicus practised by us—the use of a polymyxin, bacitracin, and neomycin spray—has been unchanged in the hospital for well over 15 years. This too could possibly be furthering the hold of the organism in the unit. The skin has been found to become profusely colonised by coagulase-negative staphylococci when powders containing chlorhexidine or hexachlorophane are used to control colonisation by S. aureus.[16]

One final aspect of this survey which is more encouraging, although possibly fortuitous, is the fact that among inborn infants during 1976–79, there has been no case of early group B β-haemolytic streptococcus bacteraemia. This organism was the most frequent cause of early bacteraemia during 1967–75, and had a high mortality. It still occurs among outborn infants. Since 1975 at Hammersmith Hospital, when surgical induction of labour proves necessary, it is first ascertained whenever possible whether or not the mother is a carrier for β-haemolytic streptococcus. If this proves to be the case the induction and subsequent labour are covered with penicillin. In addition to these measures, our obstetricians are now carrying out surgical induction less frequently. Treatment of selected mothers[17] seems to be a more hopeful solution to this devastating fetal and neonatal illness than treatment of the infants, often started too late to be effective.

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