Eur J Pediatr (1992) 151:451–454

European Journal of
Pediatrics

Nosocomial bacterial infections in very low birth weight infants

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Received January 11, 1991 / Accepted after revision October 24, 1991

Abstract. The occurrence of congenital and nosocomial bacterial septicaemia has been documented by identifying the number of positive blood cultures by reviewing the laboratory and clinical records of 394 very low birth weight infants who were consecutively admitted to a neonatal intensive care unit over a 40-month period. The incidence of congenital septicaemia was 6% and of nosocomial septicaemia 17%. The commonest causes of congenital infection were *Streptococcus agalactiae Staphylococcus epidermidis* and *Enterococcus faecalis* (each in 18% of cases). The commonest cause of nosocomial infection was *S. epidermidis* (51% of cases), except in infants of birth weight less than 750 g. Risk factors for nosocomial infection were extremely low birth weight, very preterm birth and prolonged ventilation. Nosocomial infection was associated with significantly lengthened hospital admission.

Key words: Nosocomial infection – Low birth weight – Prematurity

Introduction

Survival rate of preterm infants has improved over the last 20 years, even amongst those born with an extremely low birth weight (< 1000 g) [10]. Such infants, however, may require prolonged ventilation and remain on neonatal intensive care units (NICU) for many months [21]. These infants have impaired defence mechanisms against infection and are at risk of nosocomial infection, caused either by viruses or bacteria. Organisms previously considered to be contaminants, are pathogenic in the preterm neonate resulting in morbidity [7] and even mortality [17]. Our aim was to determine the cause, frequency and influencing factors of bacterial septicaemia in very low birth weight infants (VLBW) receiving neonatal intensive care in order to improve the specificity of future prevention and treatment strategies.

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Abbreviations: NICU = neonatal intensive care unit; PDA = patent ductus arteriosus; VLBW = very low birth weight

Methods

The results of blood cultures taken from infants with a birth weight ≤ 1500 g (VLBW) who were consecutively admitted to the NICU at King's College Hospital between 1 January 1987 and 30 April 1990 were retrospectively reviewed. The infants were initially identified from the laboratory records, but then the medical notes of all admissions to the neonatal unit were reviewed to ensure complete collection of all infants on whom blood cultures had been performed. Blood culture was routinely performed on all babies on admission to the NICU and repeated prior to commencing antibiotic therapy when the infants' condition deteriorated and sepsis was suspected by the clinical team: increasing frequency of apnoea, temperature instability, vomiting, rapidly deepening jaundice, increased ventilatory requirements, sudden collapse. Examination of the medical records confirmed that blood cultures had been taken from all infants who had such clinical signs.

On each occasion blood was obtained by a sterile technique after careful preparation of the skin. It was then aseptically introduced into a set of two blood culture bottles using a new needle for each bottle. All samples were cultured using a radiometric method (Bactec, Becton-Dickinson Diagnostic Instrument Systems, Towson MD, USA). The result of the blood culture was defined as positive if a known pathogen was isolated from at least one of the two bottles. If coagulase-negative staphylococci such as *Staphylococcus epidermidis* were isolated this was considered to be a significant infection, only if the organism was isolated from both culture bottles and the antibiotic sensitivites were identical. Stoke's comparative method [19], a disk diffusion test, was used for sensitivity testing and all coagulase-negative staphylococci were routinely screened for methicillin resistance. All coagulase-negative staphylococci are reported by our laboratory as *Staph. epidermidis.*

Congenital septicaemia was defined as a positive blood culture taken within 24 h of birth. Nosocomial (acquired) septicaemia was defined as a positive blood culture taken 4 or more days after birth. If the same organism was isolated from an infant on more than one occasion within a 7-day period this was counted as one episode of septicaemia only.

All infants who had respiratory distress and/or clinical signs suggestive of sepsis on admission and those who subsequently became unwell would be commenced on penicillin and gentacmicin. These antibiotics would then be modified as soon as antibiotic sensitivities became available. If no organisms were isolated and the infant's clinical condition had improved, antibiotics would be stopped after 48 h.

Infants who experienced one or more episodes of nosocomial septicaemia were retrospectively matched for birth weight and gestational age and, where possible, gender, with controls who had neither nosocomial nor congenital infection. These two groups were then compared regarding their duration of ventilation, occurrence of patent ductus arteriosus (PDA), requirement for neonatal intensive care and mortality. Our routine policy is to discharge in-

fants once their weight is greater than 1500 g, they are feeding totally by breast and/or bottle and are gaining weight. Umbilical catheter usage and the timing of onset of feeding were also determined in the two groups.

Differences between infants with and without congenital or nosocomial infection were assessed for statistical significance using either Fisher's exact test or the Wilcoxon rank sum test.

Results

We admitted 394 VLBW infants to the NICU during the 40-month period. They had a median gestational age of 28 weeks (range 27–37 weeks) and a median birth weight of 1080 g (range 398–1500 g).

Of the 394 blood cultures taken in the first 24 hours of life 22 were positive (Table 1) giving a 6% incidence of congenital bacterial septicaemia. The most common causes of congenital infection were *Staph. epidermidis, Streptococcus agalactiae* and *Enterococcus faecalis* (Table 1). Infants with congenital infection tended to be born at an earlier gestation, and were of lower birth weight (median gestational age 27 weeks, range 23–33; median birth weight 870 g, range 510–1460) than the remainder of the cohort (median gestational age 28 weeks, range 22–37; median birth weight 1078 g, range 398–1500), though these differences were not significant. The mortality of the neonates who had congenital septicaemia was found to be 6/22 (27%) which was similar to that of non-infected infants (21%), non-significant.

The incidence of nosocomial infection was 17%. Sixty-five infants had 92 episodes of acquired bacterial septicaemia at a median age of 19 days (range 4–146 days). In addition candida was isolated from blood cultures from two of these infants, both of whom had a birth weight of less than 750 g.

The 65 infants were born at an earlier gestation and were of lower birth weight (median gestational ages 27, range 23–30; median birth weight 896 g, range 452–1430)

Table 1. Infective episodes

	Number of episodes of:	
	Congenital infection	Nosocomial infection
Staphylococcus epidermidis	4	48
Streptococcus agalactiae	4	1
Enterococcus faecalis	4	21
Escherichia coli	2	0
Pseudomonas	2	5
Bacillus	1	1
Bacteroides	1	0
Enterobacter	1	3
Haemophilus influenzae	1	0
Listeria monocytogenes	1	0
Viridans streptococci	1	1
Klebsiella	0	8
Candida albicans	0	2
Streptococcus pneumoniae	0	1
Morganella	0	1

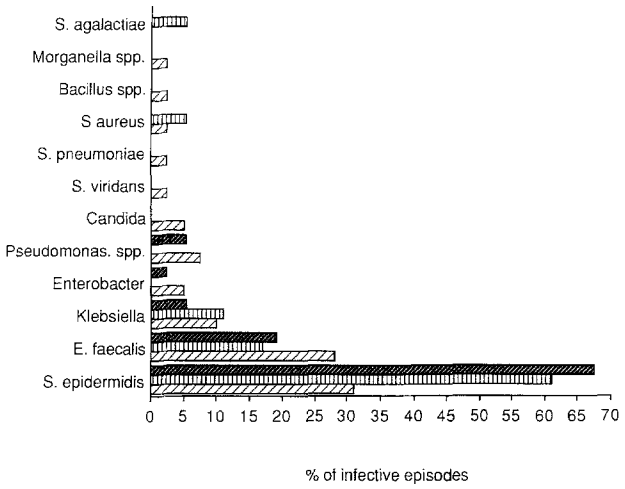

Fig. 1. Frequency distribution of acquired sepsis in birthweight categories: ▨ <750 g; ▥ 750–1000 g; ▩ 1000–1500 g; *S. epidermidis, Staphylococcus epidermidis; E. faecalis, Enterococcus faecalis; Pseudomonas, Pseudomonas species, S. viridans, Streptococcus viridans; S. pneumoniae, Streptococcus pneumoniae; S. aureus, Staphylococcus aureus; S. agalactiae, Streptococcus agalactiae*

than the non-infected infants (median gestational age 29 weeks, range 22–37; median birth weight 1100 g, range 398–1500) $P<0.001$, $P<0.001$, respectively. Thirteen infants had recurrent septicaemias and were of a significantly lower birth weight (median 642 g, range 510–1108) than those with only one septicaemic episode (median birthweight 938 g, range 452–1430) $P<0.05$. There was no statistically significant difference in the gestational ages of the infants with recurrent septicaemia (median 25 weeks, range 23–29) and those with only a single episode (median 27 weeks, range 23–32). Infants with a birth weight less than 750 g were more likely to have had at least one nosocomial septicaemic episode (39 episodes in 81 infants) than infants with a birth weight of between 750–1000 g (18 of 80), $P<0.01$ or those with a birth weight between 1000–1500 g (37 of 231), $P<0.001$.

Staph. epidermidis caused approximately 50% of nosocomial infections. The second most common isolate was *E. faecalis* resulting in 23% of nosocomial infections (Fig. 1). The proportion of infections due to *Staph. epdermidis* was lower in infants of birth weight less than 750 g (12 of 37) compared to those of birth weight between 750 and 1000 g (11 of 18) and to those of 100–1500 g (25 of 37) (trend with birth weight $P<0.01$). *E. faecalis* was isolated from blood culture in 11 of 37 infected infants in the birth weight <750 g group; 3 of 18 in those of birth weight between 750–1000 g; and 7 of 37 in those of birth weight between 1000 and 1500 g, (non-significant). No surgical operation had been performed on these patients at a time close to the isolation of the *E. faecalis*.

The 65 infants who developed nosocomial infection were compared with 65 gestational age-matched controls who had a median gestational age of 27 weeks (range 23–30) and birth weight 907 g (range 476–1476 g). There was no significant difference in the gender distribution between the two groups being 40 males and 25 females in

the infected group and 36 males and 29 females in the control group.

Infants with nosocomial infection required a longer duration of ventilation (median 15 days, range 0–125) than their matched controls (median 3 days, range 0–126), $P<0.002$. The number of infants ventilated in each group, however, was similar being 58 of the infants with nosocomial infections and 52 of the controls. Twelve infants (19%) with nosocomial infection had a PDA at sometime during their admission compared to seven controls (11%), non-significant. The duration of stay in the NICU was significantly longer for infants with nosocomial infection (median 60 days, range 7–190) than for the controls (median 21 days, range 1–183) $P<0.0001$. The mortality though did not differ significantly between the two groups, being 25% in the nosocomial group and 37% in the control group. There was no significant difference in the number of infants who had indwelling umbilical catheters being 49 in infants with nosocomial infection and 39 in the controls. Five of the infants with nosocomial infection and 15 of the controls were never fed (non-significant) and there was no significant difference in the timing of introduction of feeds being 8 days (median, range 1–41) in the infants who developed infection and 7 days (median, range 1–14 days) in the controls.

Discussion

Congenital sepsis was most frequently due to *Staph. epidermidis, Strep. agalactiae* and *E. faecalis*. This finding of congenital infection due to *Staph. epidermidis* is surprising as such infections have been thought to be hospital-acquired and are usually diagnosed after the 1st week of life [6]. This organism has, however, been previously isolated in the first 48 h of life in outborn infants [1].

The major cause of nosocomial infection was *Staph. epidermidis,* as has been noted by others [13], but the proportion of infections this organism caused in our nursery (50%) is higher than others have reported. It is unlikely that our results were due to contamination of the blood by organisms from the infant's skin, as our standard method of sampling and criteria for the diagnosis of septicaemia due to *Staph. epidermidis* were very strict, although we did not attempt 'phage-typing. Sepsis was only diagnosed as being due to *Staph. epidermidis* if the organism with the same antibiotic sensitivity was isolated from both blood culture bottles. All these infants had clinical signs of septicaemia and all made a clinical response to either intravenous flucloxacillin or vancomycin. This is contrary to previous experience, as strains of *Staph. epidermidis* involved in neonatal infection have previously been reported to be resistant to a wide range of antibiotics [11]. Such strains frequently colonise intravascular catheters [18], but in the present study we found no significant association with usage of intravascular catheters and occurrence of nosocomial septicaemia. This may explain the difference in the present and previous results [11] regarding antibiotic sensitivity.

The second most common organism causing nosocomial septicaemia was *E. faecalis* (23%), confirming the findings of Lenoir et al. [14]. Epidemics of *E. faecalis* infection have been previously reported [2, 15], but in our NICU, cases of *E. faecalis* septicaemia were sporadic.

The only group of infants in whom gram negative organisms caused more septicaemic episodes than gram positive organisms were those with a birth weight of less than 750 g, which is surprising. Previous reports suggest that the major risk factor associated with *Staph. epidermidis* septicaemia is the presence of indwelling intravascular lines [3–5], which are likely to be used most commonly in infants less than 750 g at birth. Our data, therefore, suggest other factors must determine the causative organisms in different birth weight groups. This hypothesis is supported by there being no significant difference in umbilical arterial catheter usage between the septic and control groups. As a similar onset of feeding was also noted in the two groups.

The birth weight and gestational age of infants who developed nosocomial infection were significantly lower than noninfected infants. Hemming et al. [12] demonstrated an increased rate of nosocomial infection in infants who weighed less than 1500 g at birth and we show that within this high risk group, the lower the birth weight the more likely nosocomial infection is to occur. A significantly increased duration of mechanical ventilation was found in the infected infants when compared to their gestation- and birth weight-matched controls. The majority of nosocomial infections were acquired beyond the age at which the controls had been extubated, which suggests that mechanical ventilation is a risk factor for nosocomial infection. Certainly in adults intubation has been significantly related to the occurrence of nosocomial infection [4]. The risk of nosocomial infection has been suggested to be increased in infants with PDA [8]. In the present study, a greater proportion of infected infants than their matchend controls had had a PDA, but this trend did not reach statistical significance.

The incidence of nosocomial bacterial septicaemia in our nursery of 17% is very similar to that found by others, with reports varying between 11% and 26% [14, 20]. It has been suggested that nosocomial infection increases mortality [20], but this has been disputed [9]. One study of post-operative wound infection reported no mortaility in either group they investigated [9]. We also failed to demonstrate an increase in mortality associated with nosocomial infection. In support of our findings, adult patients with nosocomial infection, when compared with two matched controls, did not have a significant increase in mortality [5]. An explanation for the differences in mortality between the present and previous study [20] may be differences in the virulence of the organisms. The major cause of infection in the present study was *Staph. epidermidis,* which has not previously been associated with an increased mortality [7]. The clinical signs of infection with coagulase negative staphylococci are often minor with insidious onset of frequency of apnoea and poor perfusion. Such signs, in the present study however, were immediately investigated and treated, this policy may have reduced mortality as delayed treatment has previously been associated with disseminated disease [16].

Infants with nosocomial septicaemia compared to the matched control group remained in hospital significantly longer, this has also been demonstrated in adult patients [5]. Nosocomial infection itself may increase hospital stay, but an alternative explanation of this association is that prolonged admission increases the infant's risk of infection. The median onset of nosocomial infection was 19 days, at which age the controls were still resident within the NICU and thus equally at risk of acquiring infection. Thus the more likely explanation is that nosocomial infection is prolonging the duration of admission, which has important implications for the cost of care [20]. In adults nosocomial infection and its effects resulted in an excess cost for medical services of approximately $ 3,600, per patient [20].

This study demonstrates acquired septicaemia is an important cause of prolonged stay on the NICU. Further preventative measures are therefore urgently required.

Acknowledgements. Research Fellows Dr. P. J. Thompson and Dr. M. F. Hird are supported by Children Nationwide Medical Research Fund. We thank Ms. Sue Williams for secretarial assistance.

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