Serious infection in a neonatal intensive care unit: A two-year survey

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SUMMARY

Over a two-year period 160 episodes of serious infection occurred in 139 infants admitted to a regional neonatal intensive-care unit. Eighty-seven (26%) of very low birth weight (VLBW) neonates and 52 (8%) of infants of birth weight > 1500 g were infected. The majority (84%) had bacteraemia alone. Though the clinical features of infection were not distinctive, in 94% of episodes the peripheral white blood cell or band counts were abnormal. Thirty-three (21%) of the infections occurred in infants under 48 h old and 15 of these followed prolonged rupture of membranes (>48 h). All of the infections due to group B streptococci (5), *Streptococcus viridans* (2) and *Haemophilus influenzae* (3) occurred in this group. Coagulase-negative staphylococci (CONS) accounted for 49% of the infections and there was a marked increase in incidence of such infections during the survey. Infections with CONS were not necessarily associated with parenteral nutrition, the presence of intra-arterial catheters or mechanical ventilation but the rise in incidence was coincident with change in skin disinfectant usage and the general use of a third-generation cephalosporin to which the CONS were resistant.

Although VLBW infants with meningitis were more likely to die than those of higher birthweight, the risk for those with bacteriaemia was the same in both groups. Infants with CONS sepsis were less likely to die than those with infections due to Gram-negative bacteria and the time from onset of infection to death was significantly longer for the former.

INTRODUCTION

The care of the newborn infant has altered considerably in recent years. In 1946 it was rare for infants of low birth weight to survive (Douglas & Gear, 1977), but with the introduction of neonatal intensive care up to 85% of infants of very low birth weight (<1500 g) survive (Starte *et al.* 1980). Such infants are at a greater risk of developing life-threatening infections.

Recent surveys have indicated that the prevalence of bacterial septicaemia and meningitis are respectively 1·1 cases and 0·04 cases per 1000 live births for infants of birth weight greater than 2500 g (Klein & Marcy, 1976). The prevalence in infants born weighing less than 2500 g is 13·3 cases of septicaemia and 2·6 cases

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of meningitis per 1000 live births. Among neonates admitted to intensive care units the incidence of septicaemia can be even higher, with estimates varying from 10% (Battisti, Mitchison & Davies, 1981) to 22% (Hoogkamp-Korstanje *et al*. 1982).

The results of a retrospective analysis of serious infections occurring in neonates admitted to a large regional intensive care unit are described.

MATERIALS AND METHODS

In the two-year period 1981–2, 989 infants were admitted to the Mersey Regional neonatal intensive-care unit. There were 339 infants (34%) of very low birth weight (VLBW, <1500 g), and 233 infants (24%) were transferred from other hospitals after delivery for intensive management. All out-born infants had a full septic screen (consisting of skin, umbilical, throat and rectal swabs, blood culture and CSF culture) performed on arrival and were given intravenous ampicillin and gentamicin. In-born infants had a septic screen performed if there was a clinical indication and antibiotic therapy was started. Antibiotic treatment was discontinued after 48 h if culture results were negative. Blood (0·5–1 ml) for culture was taken from peripheral sites using full aseptic precautions and placed in a single blood culture bottle containing medium suitable for supporting the growth of aerobes and anaerobes (Bloodgrow, Medical Wire and Equipment Co. Ltd). The bottles were incubated at 37 °C and routinely subcultured on to blood agar and MacConkey agar aerobically and blood agar anaerobically at 6–12 h, 24 h, 48 h, 72 h and 2 weeks. Bacteria were identified using conventional techniques and the API 20E system (API Products, Basingstoke). Their susceptibility to a variety of antimicrobials was determined using a controlled disk diffusion method.

Patients with serious infections were identified from records kept in the Unit and in the Laboratory and their case notes analysed. Infants with neonatal necrotizing enterocolitis have been excluded from the survey unless they became secondarily infected because the evidence for an infective aetiology is incomplete. Similarly, infants with superficial sepsis have been excluded unless they also had bacteraemia, meningitis or peritonitis.

Statistical analyses were performed using Student's *t* test and chi-squared analysis with Yates's correction where applicable.

RESULTS

Incidence of infection

A total of 160 episodes of serious infection occurred in 139 neonates (14% of those admitted) in the 2-year study (Table 1). Eighty-seven (26%) of VLBW neonates and 52 (8%) of infants of birth weight greater than 1500 g developed serious infections. Fifty-four of the infected neonates had been transferred to the unit (23% of out-born infants) and 11% of in-born infants became infected.

Site of infection

During the study period 1202 blood cultures were performed in 1060 episodes of suspected septicaemia. A total of 174 blood cultures were positive from 153 neonates. Of these, 23 episodes (16 coagulase-negative staphylococci, 1 *Staphylococcus aureus*, 1 *Enterobacter cloacae* and 5 mixed) were considered on clinical,

Table 1. *Episodes of serious infections in neonates* (1981–1982)

	Bacteraemia alone	Bacteraemia and meningitis	Meningitis alone	Bacteraemia and peritonitis	Peritonitis alone
Staph. aureus	11	0	0	0	0
Coagulase-negative staphylococci	74	3	0	1	0
Group B streptococci	5	0	0	0	0
Str. viridans	2	0	0	0	0
Str. faecalis	2	0	0	0	0
E. coli	6	4	0	0	0
Klebsiellae spp.	17	3	0	0	3
Ent. cloacae	3	1	0	0	0
Pr. mirabilis	2	1	0	0	0
Acinetobacter spp.	1	0	4	0	0
Pseudomonas spp.	7	1	0	0	0
H. influenzae	3	0	0	0	0
Mixed*	2	0	0	0	0
Candida spp.	0	1	0	1	2
Total	135	14	4	2	5

* *Pseudomonas maltophila* and coagulase-negative staphylococcus and *Streptococcus viridans* and coagulase-negative staphylococcus.

laboratory and therapeutic grounds not to be significant, leaving 151 episodes of bacteraemia occurring in 130 neonates.

In the majority of cases (84 %) the infective episodes were not focal and presented solely as bacteraemia (Table 1). In 14 cases micro-organisms were recovered both from the blood and from CSF. In the majority of these episodes bacteraemia preceded meningitis; the case of candida septicaemia and meningitis is described elsewhere (Hensey, Hart & Cooke, 1984).

The episodes of actinetobacter meningitis represent a cluster of four cases in which there was no concomitant bacteraemia (Morgan & Hart, 1982). There were seven episodes of peritonitis, two of which were accompanied by bacteraemia. In six cases peritonitis followed intestinal perforation complicating neonatal necrotizing enterocolitis and one of the cases of candida peritonitis followed peritoneal dialysis. VLBW neonates were significantly more prone to develop episodes of bacteraemia (χ^2 43·6, $P < 0·001$) and meningitis (χ^2 with Yates's correction 8·5, $P < 0·01$). The risks were respectively three- and fourfold greater than for neonates born weighing over 1500 g (Table 2).

Clinical and laboratory features

Except for cases of peritonitis or meningitis, the signs of serious infection were non-specific in the majority of neonates (Table 3). Only 5 % of neonates with bacteraemia were noted to be febrile, whereas 28 % had episodes of bradycardia and 27 % looked 'unwell'. By contrast, haematological tests proved a useful adjunct in diagnosing episodes of serious infection. There was a normal peripheral white-cell count in only 6 % of episodes (Table 4). In addition 37 of 48 infants tested (77 %) had thrombocytopenia ($< 150000/mm^3$).

Table 2. *Bacteraemia and meningitis in neonates of very low birth weight*

Birth weight (no. neonates at risk)	Bacteraemia		Meningitis	
	No.	(%)	No.	(%)
<1500 g (339)	71	(21)	12	(3·5)
>1500 g (650)	44	(6·8)	5	(0·8)

Table 3. *Clinical and laboratory indications for blood culture in 151 episodes of bacteraemia*

Sign	No.	(%)
Cardio-respiratory		
Bradycardia	43	(28)
Apnoea	31	(21)
Collapse	9	(6)
Tachypnoea	7	(5)
Cyanosis	5	(3)
Laboratory		
Acidosis	21	(14)
Abnormal white cell count	16	(11)
Other		
Looked 'unwell'	41	(27)
Premature rupture of membranes	12	(8)
Pyrexia	7	(5)
Convulsions	4	(3)

Infecting micro-organisms

Coagulase-negative staphylococci accounted for almost half of the episodes of serious infection (49%) (Table 1). However, their incidence was not evenly distributed throughout the 2-year period (Fig. 1). There was a marked increase in incidence of coagulase-negative staphylococcal infections from October 1981 which continues to the time of this communication. The next-commonest pathogens were klebsiellae (6 *K. aerogenes*, 17 *K. oxytoca*). Twelve of the isolates of *K. oxytoca* were of the same serotype, and possessed the same antibiotic-resistance pattern and same series of plasmids (Morgan, Hart & Cooke, 1984).

Escherichia coli accounted for ten episodes (6%) and group B streptococci for only five (3%).

Source of infection

Thirty-three (21%) of the infective episodes occurred when the infants were less than 48 h old. It is commonly assumed that these infections are due to micro-organisms acquired from the birth canal and it is noteworthy that in 15 (45%) of these cases prolonged rupture of membranes for up to 5 days had occurred prior to delivery. Only 9 of 78 (12%) of the coagulase-negative staphyloccal infections occurred in the first 48 h of life whereas all the infections due to group B streptococci, *Streptococcus viridans* and *Haemophilus influenzae* occurred in this group.

Seventy-nine (52%) of the neonates with bacteraemia had an umbilical artery
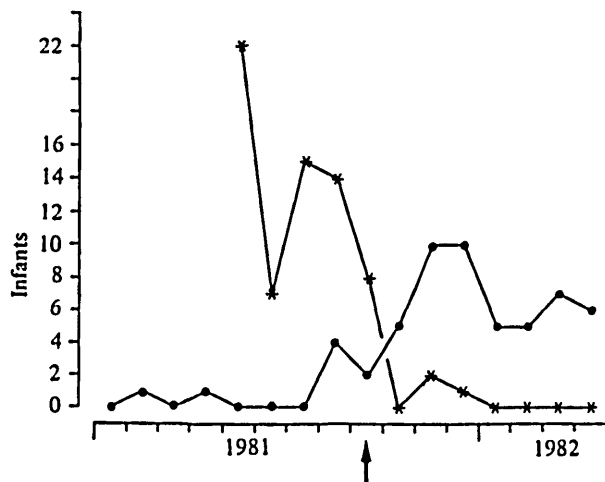
Fig. 1. The emergence of coagulase-negative staphylococci as a cause of serious infection in neonates. * Infants carrying gentamicin-resistant *Klebsiella oxytoca.* ●, Infants with serious infection due to coagulase-negative staphylococci. The arrow indicates the time of change in skin disinfectant policy.

Table 4. *Peripheral white blood cell count in* 159* *neonates with serious infection*

	No.	(%)
Neutrophilia†	90	(57)
Neutropenia	42	(26)
Bands (>5%)	97	(61)
Normal	10	(6)

* In one episode blood was not taken for haematology.

† Normal values corrected for age and maternal factors were taken from Manroe *et al.* (1979).

catheter *in situ* at the time of their infection. There was no association between the use of an umbilical artery catheter (UAC) and a particular pathogen; for example, 53 % of those infected by coagulase-negative staphylococci had a UAC *in situ* and 51 % of the rest had UAC's. One hundred and nine of the neonates (68 %) were apparently colonized by their infecting micro-organism at the time of, or prior to, their episode of infection and 71 (44 %) showed umbilical colonization. Although it is possible to state that the colonizing and infecting micro-organisms were similar in many cases, it is more difficult to prove this for the coagulase-negative staphylococci and for these we could only rely on similarities in antimicrobial susceptibility patterns.

Coagulase-negative staphylococci were cultured from 7 of 42 (17 %) umbilical artery catheter tips of infants infected with these bacteria but not from 36 artery catheter tips from neonates infected with other bacteria. Three of these 36 (8·3 %) artery catheter tips were colonized by the same bacteria (*S. aureus*, group B streptococcus and *E. coli*) that were found in the neonates blood. However, the difference in umbilical artery catheter colonization rates for coagulase-negative

staphylococci (17%) and other bacteria (8·3%) is not statistically significant ($P > 0.5$).

Finally, 37 (47%) of the neonates with bacteraemia due to coagulase-negative staphylococci and 42 (58%) of those infected with other bacteria were being ventilated mechanically at the time of their infection (a difference which is not statistically significant).

Results of infection

In the 2-year study period 143 (14·5%) of the neonates admitted to the unit died. One hundred and two (30%) of VLBW neonates died and 41 (6·3%) of those born weighing over 1500 g died. It was considered that infection played a major role in the deaths of 36 infants; 27 of the deaths occurred in VLBW neonates (26% of deaths in the VLBW groups) and 9 of the deaths in the >1500 g babies (22% of deaths in this group). Twenty-five (22%) of the neonates with bacteraemia died; a significantly lower case fatality rate ($P < 0.05$) than for those with meningitis (8/17: 47%). All of the deaths from meningitis occurred in VLBW infants whereas 16 (22·5%) of the VLBW neonates with bacteraemia died compared with 9 (20·4%) of those of birth weight greater than 1500 g. Three of the neonates with peritonitis died. Nine of the infants infected with coagulase-negative staphylococci died (11·5%) whereas 22 of those infected by Gram-negative bacteria (41%) died ($P < 0.001$). In addition, the time from onset of infection to death in those infected by coagulase-negative staphylococci (82·5±25 h) was significantly longer ($P < 0.05$) than those infected by Gram-negative bacteria (42·3±20 h).

Localized sepsis followed episodes of bacteraemia (up to 6 weeks later) in 5 (4 skin abscesses, 1 septic arthritis) of 11 infants infected by *S. aureus*. Those infections occurred only in infants treated with gentamicin and ampicillin and in each case the strain of *S. aureus* was resistant to ampicillin but sensitive to gentamicin. Skin abscesses followed episodes of bacteraemia due to coagulase-negative staphylococci in four (5%) neonates, all of whom were VLBW.

DISCUSSION

The term 'sepsis neonatorum' has been used to describe serious infections that occur in the first month of life (Siegel & McCracken, 1981). However, this definition excludes those VLBW neonates who may remain at risk of serious infection in intensive-care units for more than 1 month and it is noteworthy that 23 of the infective episodes described in our survey occurred in infants over 1 month old. Fourteen per cent of the neonates admitted to our unit developed one or more episodes of serious infection. This figure is similar to the estimate of 16·8% obtained in a national prevalence survey of nosocomial infection (Meers *et al.* 1981) and that of 13·8% described in a 6-month survey of major bacterial infection at the Hammersmith Hospital (Oto, 1982). The risk of acquiring serious infection was significantly ($P < 0.001$) greater for VLBW infants (26%) than for those of higher birth weight (8%). Surprisingly, apart from neonates with meningitis, the risk of sepsis contributing to the neonate's death was the same for both groups.

In the majority of cases the infection did not localize, presenting solely as bacteraemia, and this is paralleled by the lack of specific signs associated with

infection. However, we did find the peripheral white blood and band cell count of value as an adjunct to diagnosis; only ten neonates did not have abnormal counts.

The bacterial pathogens isolated in neonatal infections have been changing gradually. In the second quarter of this century *S. aureus* and group A β-haemolytic streptococci were the major pathogens. In the third quarter, Gram-negative bacteria, principally *E. coli* were increasingly recognized (Freedman *et al.* 1981) and more recently group B streptococci have assumed some importance (Editorial, 1981). Coagulase-negative staphylococci (CONS) have recently emerged as significant pathogens in leukaemics with in-dwelling intra-atrial catheters (Wade *et al.* 1982), in patients with ventriculo-atrial or peritoneal shunts (Callaghan, Cohen & Stewart, 1961), in patients undergoing ambulatory peritoneal dialysis (Chan *et al.* 1981), and those on long-term total parenteral nutrition (Goldman & Maki, 1973). Each of these groups of patients have in common the insertion of synthetic polymers into normally sterile body compartments most often traversing the skin. Recent reports in neonates have also noted a rise in the incidence of CONS bacteraemia (Battisti, Mitchison & Davies, 1981; Oto, 1982) although their significance was unclear.

Coagulase-negative staphylococci accounted for almost half the episodes of serious infection in our neonatal unit, and those episodes appeared to be more than just episodes of bacteraemia or contaminated blood cultures on clinical, haematological or therapeutic grounds. There was a large increase in the incidence of CONS sepsis in the second half of our survey (from 1 case/month to 4·6 cases/month) and a corresponding fall in that due to Gram-negative bacteria (from 3·7 cases/month to 1·5 cases/month). The large increase in incidence of CONS sepsis coincided with attempts to eradicate a multi-drug resistant strain of *K. oxytoca* from our unit and there was a striking temporal association between the diminishing numbers of klebsiella carriers and the rise in CONS sepsis (Fig. 1). At this time we changed the disinfectant used for skin preparation and cleaning from hexachlorophane to aqueous chlorhexidine (4 %) and were conducting a trial of the use of a 'third-generation' cephalosporin to treat serious infections. Aqueous hexachlorophane has better activity against Gram-positive bacteria than chlorhexidine, and all of our isolates of CONS were resistant to ceftazidime. It has been suggested that contaminated fluids used for parenteral nutrition act as sources of CONS infection (Fleer *et al.* 1983). Our experience does not coincide with this; firstly, the methods of preparation and administration of parenteral fluids did not alter over this period and secondly, 47 % of our neonates with CONS sepsis were not receiving parenteral nutrition prior to their episode of infection. An association between mechanical ventilation and CONS has recently been described (Davies *et al.* 1984). Although 47 % of our neonates with CONS sepsis were being ventilated mechanically, 58 % of those infected with other bacteria were also being managed in this way, indicating that mechanical ventilation is not associated solely with CONS infection.

The replacement of Gram-negative bacteria by CONS as causes of severe neonatal infection is not necessarily to the detriment of the neonate. Significantly fewer of those infected by CONS died than those infected by Gram-negative bacteria, and the time from onset of infection to death was also significantly longer

for CONS sepsis. This allows more time to select the most appropriate antimicrobial chemotherapy.

Although the majority of infections were not localized it is noteworthy that 5 of 11 neonates with *S. aureus* sepsis subsequently developed localized infection with *S. aureus* of the same phage type as their original strains. In each of these five cases, however, the neonates were treated only with a single effective antimicrobial agent. We would suggest that, at least for *S. aureus* sepsis, a combination of two active antimicrobials be used. The choice of treatment for CONS sepsis was more difficult. Only 33 % of the isolates were sensitive to the combination of ampicillin and gentamicin. We have not yet used vancomycin, to which all but one of the isolates were sensitive, but have used the combination of cefuroxime and gentamicin (95 % of the isolates were sensitive to cefuroxime) with favourable results.

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