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Bacteraemic Infections in a Neonatal Intensive Care Unit – A Nine-Month Survey

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Summary

A survey was conducted to determine the rate, outcome, and culture and sensitivity patterns of bacteraemic infections in a large Neonatal Intensive Care Unit (NICU).

Over a nine-month period, 136 episodes of infection occurred in 132 (6.9%) out of 1926 admissions. Early onset infection accounted for 35 episodes (25.7%) and was associated with a higher mortality rate compared to late onset infection (45.7% vs 23.8%, $p<0.02$). Very low birthweight (VLBW) infants had significantly higher rates of infection (19.4% vs 5.3%, $p<0.001$) and mortality (45.2% vs 23.3%, $p<0.02$) compared to bigger babies.

Gram negative bacilli accounted for 25 early and 90 late isolates while gram positive organisms accounted for 10 early and 16 late isolates. The two main organisms (*Acinetobacter* and *Klebsiella*) showed a 69.0 to 85.3% resistance to aminoglycosides and 3rd generation cephalosporins. Ten of 13 isolates of *Staphylococcus epidermidis* and 3 of 4 *Staphylococcus aureus* were methicillin resistant. Multiply resistant infections were a major problem in this NICU and efforts to eradicate them needed to be intensified.

Key Words: Bacteraemic infections, NICU, Antibiotic resistance

Introduction

Bacterial infections are a source of considerable morbidity and mortality in neonatal intensive care units throughout Malaysia. The perinatal data of the NICU of Maternity Hospital, Kuala Lumpur (MHKL) showed that of the 347 deaths in 1990, 75 (21.6%) were due to infections. Infection rates and multiresistance rate were known to be high but exact data was not available. An Infection Control Committee was set up in early 1991 and a surveillance system was instituted in the ward. This study was undertaken to determine the rate of bacteraemic infections, their relationship with birthweights, the bacteraemic mortality rates, the nature of infecting organisms and their antibiotic resistance patterns. It was hoped that the information obtained would enable the implementation of essential measures at infection control and the formulation of effective guidelines on empiric antibiotic therapy.

Patients and Methods

The Maternity Hospital Kuala Lumpur (MHKL) is a large regional referral maternity hospital with about 27,000 to 29,000 deliveries a year. The NICU caters for only inborn infants and in 1991 had an official bed number of 65 with 18 intensive care beds. The occupancy rate often reached 110%. The patients were managed by either the Ministry of Health or the Universiti Kebangsaan Malaysia neonatal units. In the 9-month period from January 1991 to September 1991 there was a total of 19,069 livebirths in MHKL. Of these 1,926 infants were admitted to NICU and 216 (11.2%) were of very low birthweight (birthweight < 1500 grams).

These infants had a septic screen performed if there was a clinical indication, and before antibiotic therapy was started. Antibiotic treatment was discontinued after 48 to 72 hours if culture results were negative and there was an alternative explanation for the initial clinical suspicion. Antibiotic therapy might be continued if the clinical diagnosis of infection remained despite negative blood cultures.

Blood (0.5 to 1.0ml) for culture was taken from peripheral sites or from cardiac puncture immediately after death, and placed in paired culture bottles containing thioglycollate broth for growth of anaerobes and tryptic soya broth with sodium polyarethol sulphonate for growth of aerobes. Sodium polyarethol sulphonate prevents clotting and neutralises the natural bactericidal substances in fresh blood. The bottles were incubated at 37°C and routinely subcultured on to blood agar and MacConkey agar aerobically and blood agar anaerobically at 24 hours and 72 hours, and 1 week for selected cases. The bacteria were identified using conventional techniques which included cultures on solid media and various biochemical tests. Their susceptibility to a variety of antimicrobials was determined using a comparative disk diffusion method.

Patients were included in the analysis if they were clinically septic and had a positive blood culture. Those with clinical sepsis or infection at other sites, but a negative blood culture were excluded. Organisms cultured from blood obtained within 48 hours of birth were considered as causing early onset infections while those after 48 hours as late onset infections. The latter were assumed to be nosocomial infections.

Results

Incidence of infection

A total of 136 episodes of bacteraemia occurred in 132 neonates (6.9% of those admitted) in the 9 month study (Table I). Forty two (19.4%) of VLBW neonates and 90 (5.3%) of infants of higher birth weight developed culture proven bacteraemic infections. This difference was statistically significant ($p<0.001$).

Of the 136 episodes of infection, 35 occurred within 48 hours. The total bacteraemic (early plus late onset) infection rate was therefore 7.1% of admissions, and the nosocomial (late onset) bacteraemic infection rate was 5.2%. An incidence of 7.1 bacteraemic infections per 1000 livebirths was recorded for this period.

There were 4 patients with two repeated episodes of infection and 5 who had mixed infections (2 isolates in 1 blood culture). There was therefore a total of 132 patients with 136 episodes of bacteraemia and 141 isolates.

Bacterial isolates and their sensitivity pattern

Details of the nature of the isolates were given in Table II. It can be seen that *Acinetobacter* and *Klebsiella* predominated in both early and late infections.

Table I
Infection vs Birthweight

Birth Wt groups	No. Admitted	No. Infected	Infection Rate
<1500g	216	42	19.4
1500 to 2499g	677	49	7.2
≥2500g	1033	41	4.0
Total	1926	132	6.9*

**In contrast to 7.1 episodes of bacteraemia per 100 admissions*

Among the 10 cases of early gram positive bacteraemias, 5 were due to group B *Streptococcus.* The sensitivity pattern of all the isolates were analysed. There was no penicillin resistance among the streptococcal isolates. However, 10 out of 13 *Staphylococcus epidermidis* and 3 out of 4 *Staphylococcus aureus* were methicillin resistant.

Practically all the gram negative organisms on the unit show a very high resistance pattern with the late onset isolates showing a slightly higher resistance than the early onset ones (Table III). *Acinetobacter* had an overall 69.0% resistance to amikacin, 84.2% resistance to cefotaxime and 64.9% resistance to ceftazidime while *Klebsiella* had 71.1%, 85.3% and 84.6% resistance respectively. *Acinetobacter* and *Klebsiella* gave a rate of less than 10 percent resistance to only imipenem and ciprofloxacin.

Mortality

Of the 132 infants studied, 40 (30.3%) died. Death was more common among the VLBW infants. The mortality rate in this group was 45.2%. For infants weighing 1500 to 2499g the rate was 22.4% and for infants weighing 2500g or more the rate was 24.4%. There was a significant difference in the mortality rate for the VLBW compared to the bigger infants ($p<0.02$).

Of the 40 infants who died, 16 were from early onset infections while 24 were associated with late onset infections. There was a significantly higher mortality rate associated with early compared to late onset infections (45.7% vs 23.8% $p<0.02$) in this study.

Table II
Nature of isolates

Isolates	No. of isolates		
	<48h	>48h	Total
Gram-negative	25	90	115
Acinetobacter	7	38	45
Klebsiella	5	37	42
Enterobacter	4	7	11
Pseudomonas	3	5	8
Escherichia coli	6	3	9
Gram-positive	10	16	26
Group B *streptococcus*	5	Nil	5
Streptococcus viridans group	3	Nil	3
Enterococcus	1	Nil	1
Staphylococcus aureus	1	3	4
Staphylococcus epidermidis	0	13	13
Total	35	106	141

Discussion

The total bacteraemic rate in NICU, MHKL of 7.1 episodes per 100 admissions were comparable to 6.5% and 11.8% recorded by two surveys in Utah[1] and Liverpool[2] respectively. Most of the infections (74.3%) were of late onset and were likely to be nosocomial in origin. A study done in Hammersmith[3] showed 70.8% of the bacteraemias were of late onset while that in Yale[4] was 51.3%.

For inborn patients the positive blood culture rate was 5.7/1000 live hospital births in the same study in Hammersmith[3]. We recorded a rate of 7.1 per 1000 live births in the present survey.

As expected the VLBW babies had a significantly higher infection rate than the bigger babies (19.4% vs 5.3%). Their mortality rate was also higher (45.2% vs 23.3%). Factors other than infection were likely to be contributory to the mortality of these infants. Many were in intensive care because of birth asphyxia, meconium aspiration, immaturity, respiratory distress syndrome and congenital anomalies. The VLBW and premature infants were often complicated by intraventricular haemorrhage, chronic lung disease and renal impairment. However this study did not look at these confounding variables on mortality.Hensey *et al*[2] found a 26.0% incidence rate in the VLBW and 8.0% in infants of more than 1500g but their case fatality rate for bacteraemia was similar in both weight groups (22.5% vs 20.4%).

The high resistance pattern of isolates in the unit was a cause for great concern. Serious therapeutic problems arise as the choice of antibiotics was limited. The unit

Table III
Per cent resistance of gram-negative isolates to antibiotics

Isolates	*Acineto-bacter*	*Kleb-siella*	*Entero-bacter*	*Pseudo-monas*	*E. coli*
Antibiotics	E=7	E=5	E=4	E=3	E=6
	L=38	L=37	L=7	L=5	L=3
	T=45	T=42	T=11	T=8	T=9
Ampicillin	80.0	80.0	50.0	**N.T	83.3
	88.5	100.0	57.1	100.0	66.6
	88.2	97.3	55.5	100.0	77.7
Cotrimozaxole	0	83.3	0	100.0	60.0
	34.5	100.0	60.0	0	66.6
	30.5	96.9	42.9	33.3	62.5
Gentamicin	50.0	66.6	0	0	40.0
	75.9	85.7	42.9	66.6	66.6
	72.8	85.3	33.3	40.0	50.0
Netilmicin	33.3	50.0	N.T	33.3	50.0
	75.9	90.0	50.0	0	100.0
	71.9	85.3	50.0	25.0	60.0
Amikacin	50.0	40.0	0	33.3	50.0
	72.0	75.8	50.0	0	50.0
	69.0	71.1	33.3	25.0	50.0
Piperacillin	50.0	100.0	N.T	N.T	100.0
	70.0	74.2	60.0	0	50.0
	68.0	75.0	60.0	0	57.1
Cefuroxime	58.3	50.0	0	N.T	33.3
	61.1	88.9	28.6	100	100.0
	60.0	83.3	18.2	100	50.0
Cefotaxime	75.0	50.0	50.0	N.T	0
	86.7	89.2	50.0	100	0
	84.2	85.3	50.0	100	0
Ceftazidime	57.1	60.0	50.0	0	0
	72.4	88.2	50.0	66.7	100.0
	69.4	84.6	50.0	40.0	50.0
Imipenem	0	0	N.T	N.T	0
	10.0	0	0	0	0
	8.5	0	0	0	0
Ciprofloxacin	33.3	0	N.T	N.T	50.0
	4.0	6.9	16.6	0	25.0
	7.1	6.3	16.6	0	40.0
Ampicillin-sulbactam	0	20.0	N.T	N.T	25.0
	12.5	55.5	50.0	N.T	25.0
	10.6	42.9	50.0	N.T	25.0

* *Top figures are for early isolates, middle figures for late isolates and bottom figures are for both isolates combined*

** *N.T. - Sensitivity not tested to respective antibiotic*

*** *E - No. of early isolates*
L - No. of late isolates
T - Total no. of isolates

has been dealing with multiresistant *Klebsiella* infection since the early '80s and epidemic outbreaks have occurred. The widespread use of cephalosporins within the last decade is believed to have selected resistant strains that hyperproduce chromosomal cephalosporinase[5]. These resistant strains have likely contaminated the hospital environment and cause infections by being transmitted in the hands of staff handling patients. In 1983 Koh et al reported the conjugal transfer of multiple antibiotic resistance from hospital isolates of *Klebsiella* to *Escherichia coli*[6] in the Kuala Lumpur Hospital. This spread of plasmids involved in the production of these enzymes to other enterobacteriaceae in the digestive tract of patients carrying the resistant *Klebsiella* has also been observed in Bichat/Claude Bernard Hospital in France[5].

An intensified infection control programme including

an effective antibiotic policy has to be implemented in the NICU to reduce the morbidity and mortality associated with infections. Overcrowding and understaffing were ongoing problems that needed to be addressed. Strict attention to handwashing, and asepsis during invasive procedures must be strictly enforced.

At the time of writing a move has in fact been made to decongest the NICU. The bed number of 65 has been reduced to 45. This has been facilitated by opening up a special care nursery for infants requiring less intensive care[7]. Guidelines on choice of empiric antibiotic therapy to be used before culture and sensitivity results are known has also been drawn up.

Crystalline penicillin and gentamicin are recommended for early onset infections (bearing in mind that about half the gram negative infections may not be correctly treated before culture and sensitivity results are known).

For late onset infections, imipenem is recommended if the infant is of very low birthweight or is very ill (eg. hypotensive and acidotic). It is felt that time is a crucial factor for these infants and it would be too risky to try, for example a 3rd generation cephalosporin like ceftazidime which is expected to fail in more than 69% of cases of *Acinetobacter* and 84% of cases of *Klebsiella* infections, the two predominant nosocomial infections. If the infant is not a VLBW infant and is less ill, cefuroxime and amikacin and in selected cases cotrimozaxole are recommended. These are felt to provide reasonable coverage till definite culture and sensitivity results are available. The cost involved and the threat of emerging rise in imipenem resistant organisms[8,9] are some of the factors taken into consideration in making this recommendation. Usually vancomycin is given only when methicillin resistant staphylococcal infection has been documented. Oral nystatin is given as prophylaxis to all VLBW infants on antibiotics, other infants on antibiotics for more than 1 week and any infants on imipenem. There is a concern that fungal infections may supercede in these situations.

Another major step taken was the closure of the ward for 2 months recently for some renovation works. It is crucial that all action is taken to prevent the recurrence of high rates of nosocomial infections and antibiotic resistance.

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