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ORIGINAL ARTICLE

COMPARISON OF THE PATTERN OF NOSOCOMIAL INFECTION BETWEEN THE NEONATAL INTENSIVE CARE UNITS OF HOSPITALS KUALA TERENGGANU AND UNIVERSITI SAINS MALAYSIA, KELANTAN

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Nosocomial infection is a common problem in the Neonatal Intensive Care Unit (NICU) and a knowledge of the pattern of nosocomial infection will contribute greatly to the intensification of infection control measures and the development of antibiotic policies in the NICU. This study aims to compare the incidence and clinical characteristics of neonates with nosocomial infection in NICU of both Kuala Terengganu Hospital (HKT) and Universiti Sains Malaysia Hospital (HUSM). Neonates who had both clinical signs of sepsis and positive blood cultures, 48 hours after admission to NICU, from 1st January to 31st December 1998, in both hospitals were retrospectively studied. Among neonates admitted to NICU, 30 (5.4%) in HKT and 65 (3.6%) in HUSM had nosocomial infection (p = 0.07). The mean duration of hospitalisation was shorter (HUSM 37 days, HKT 49 days; p = 0.02), and the number of neonates with predisposing factors for infection is higher (HUSM 100%, HKT 73.3%; p < 0.001) in HUSM compared with HKT. There were no differences in gestation, mean age of onset of infection and mortality between both hospitals. The most common organism isolated from the blood in HKT was *Klebsiella pneumoniae* (33.3%), and in HUSM *Klebsiella aerogenes* (24.6%). Half of *Klebsiella pneumoniae* isolates were resistant to cephalosporins and aminoglycosides in HKT and a similar number of *Klebsiella aerogenes* isolates were resistant to piperacillin and aminoglycosides in HUSM. In conclusion nosocomial infection is a common problem in both hospitals. Except for more frequent predisposing factors for infection in HUSM, and a longer duration of hospital stay among neonates in HKT, the clinical characteristics of neonates with nosocomial infection in both hospitals were similar.

Key Words: *nosocomial infection, neonates, Neonatal Intensive Care Unit*

Introduction

Nosocomial infections are defined as infections that manifest 48 hours after admission to the neonatal intensive care unit (1). However, the incubation period of neonatal infections differs and some perinatally acquired infections are known to manifest after 48 hours of life, especially those with maternal predisposing factors for sepsis such as chorioamnionitis, premature rupture of membranes or maternal infections (1). In this situation, it may be difficult to determine whether the infection was

hospital or perinatally acquired.

The incidence of nosocomial infection in the Neonatal Intensive Care Units (NICU) varies among countries and medical centres. It was reported to be 15.3% in infants hospitalised for more than 48 hours in NICU at the University of Utah Medical Centre, Salt Lake City (1) and 5.2% in Kuala Lumpur Hospital (2). The incidence of nosocomial infection was also noted to be higher (32.6%) in low birth weight (1000-1499 gm) babies (3). Low birth weight and prematurity are predominant risk factors for nosocomial infection because of the immaturity of the immune system in these babies (4). Other risk factors include overcrowding, understaffing, usage of invasive devices and procedures, administration of parenteral nutrition and endotracheal intubation. Common organisms causing nosocomial infection in NICU were gram negative bacilli, coagulase negative staphylococci and fungi. Nosocomial infection has been shown to cause significant mortality especially in premature and low birth weight babies.

The antibiotic policies of the two NICU's in Kuala Terengganu Hospital and Universiti Sains Malaysia Hospital could influence the antibiotic sensitivity patterns of the bacteria isolated. For HKT, intravenous penicillin and netilmicin were used for newborn infections before 48 hours of life. For nosocomial infections, intravenous cefotaxime and amikacin were used while awaiting culture results. Intravenous vancomycin would replace cefotaxime in the presence of a Methicillin Resistant *Staphylococcus Aureus* outbreak in the NICU, especially for skin, joint and bone infections. As for HUSM, penicillin and gentamicin were used for infection in the first 4 days of life and amikacin and piperacillin for infections after 4 days of life. Vancomycin would replace piperacillin if the baby also had umbilical infection.

The objective of this study was to compare the incidence and clinical characteristics of nosocomial infection in the Neonatal Intensive Care Unit (NICU) Kuala Terengganu Hospital (HKT) and Universiti Sains Malaysia Hospital (HUSM) in Kelantan.

Materials and methods

A retrospective study was done in the NICU of two tertiary hospitals, Kuala Terengganu Hospital Terengganu and Universiti Sains Malaysia Hospital, Kelantan. All neonates who developed nosocomial infection from 1st January 1998 to 31st. December 1998 in both hospitals were included in the study. Cases of nosocomial infections were identified from a register in the NICU which recorded all neonates who had positive blood cultures. Clinical information on these babies were then obtained from hospital records.

Nosocomial infection was defined as any infection that manifested clinically 48 hours after admission to the NICU and had a positive blood

Table 1: Clinical characteristic of neonates with nosocomial infection

Clinical characteristics	**HKT**		**HUSM**		**p value**
	n	**%**	**n**	**%**	
Sex					
Male	18	60	37	56.9	0.3
Female	11	36.7	28	43.1	
Underermined	1	3.3	0	0	
Birth weight (kg)					
< 1.00	1	3.3	7	10.7	0.25
1.00 - 1.49	9	30	25	38.5	
1.50-1.99	8	26.7	12	18.5	
2.00 - 2.49	3	10	1	1.5	
≥ 2.50	9	30	20	30.8	
Gestational age (weeks)					
< 28	4	13.3	5	7.7	0.31
28 - 32	6	20	25	38.5	
33 - 36	8	26.1	16	24.6	
≥ 37	12	40	19	29.2	

culture. Only the first episode of infection was studied so that the incidence of nosocomial infection for the year could be calculated. Babies were excluded from the study if maternal predisposing factors for sepsis such as premature rupture of membranes, maternal fever, and maternal infections (urinary tract infection, and chorioamnionitis) were present. Mothers who had positive VDRL during antenatal visits were also not included in the study.

The incidence of nosocomial infection was calculated as the number of patients who developed nosocomial infection divided by the total number of admissions to the NICU during the year 1998. The age of onset of infection was defined as the age when clinical features suggestive of infection were first detected. Death was attributed to that particular episode of infection if it occurred within seven days after the diagnosis of infection.

Data collected were analysed using the SPSS programme, for personal computers. The Chi square test was used to compare categorical variables and the Mann-Whitney test used to compare continuous variables. A p value of less than 0.05 was considered significant.

Results

The total neonatal admissions to NICU during 1998 was 561 in HKT and 1,806 in HUSM. This difference was probably due to different admission policies of the two hospitals. The total number of neonates with nosocomial infection was 30 in HKT and 65 in HUSM giving an incidence of 5.4% and 3.6% respectively (p = 0.06). The clinical characteristics of neonates with nosocomial infection were as shown in Table 1.

The proportion of male neonates in HKT (60%) was similar to that in HUSM (56.9%). One neonate in HKT had undetermined sex at the time of infection. In HKT, the percentage of neonates with birth weight of 1.00-1.49 kg and ≥ 2.50 kg were similar, whereas, in HUSM most neonates had birth weight of 1.00-1.49 kg (38.5%). The proportion of term babies with nosocomial infection was 40% in HKT and 29.2% in HUSM (p = 0.3).

Neonates with nosocomial infection in HUSM had significantly more risk factors than those in HKT (Table 2).

A large number of neonates were ventilated before developing nosocomial infection in both HKT (63.3%) and HUSM (70.8%). All neonates in HUSM received parenteral nutrition prior to the onset of infection compared to only 40% in HKT. Forty seven (72.3%) neonates in HUSM had a central line compared to only 10 (33.3%) in HKT. Overall all neonates in HUSM had one or more of these risk factors compared to 73.3% of neonates with nosocomial infection in HKT (p = <0.001)

The mean age at onset of infection was 11.1 days in HKT and 9.9 days in HUSM (p=0.92) (Table 3).

The mean duration of hospitalisation of neonates in HKT (48.7 days) was significantly longer (p=0.015) than that in HUSM (36.5 days) (Table 4).

The mortality rate in neonates with nosocomial infection in HKT (n = 5, 16.7%) was similar to that in HUSM (n = 14, 21.5%) (p = 0.58).

In HKT, more gram positive (62%) than gram negative (39.9%) micro organisms were isolated (Table 5). In HUSM however, the proportion of gram positive (44.6%) and gram negative (47.7%)

Table 2: Risk factors in neonates with nosocomial infection

Risk Factor	HKT		HUSM		p value
	n	%	n	%	
Ventilation	19	63.3	46	70.8	0.47
Parenteral nutrition	12	40	65	100	< 0.001
Central line[1]	10	33.3	47	72.3	< 0.001
Invasive procedure[2]	2	6.7	18	27.7	0.02

[1] Central line: neonates who have umbilical arterial or venous, femoral or internal jugular lines

[2] Invasive procedures: neonates who have undergone any form of surgical procedures or exchange transfusion

organisms isolated was similar. *Klebsiella pneumoniae* (33.3%) and *Klebsiella aerogenes* (24.6%) were the most common organisms isolated in neonates with nosocomial infection in HKT and HUSM, respectively. Candida sepsis however was detected only in HUSM (7.7%).

In HKT the organisms isolated were tested for sensitivity to cefotaxime, ceftazidime, amikacin, gentamicin, netilmicin and imipenem. Out of 10 *Klebsiella pneumoniae* isolates, 90% were resistant to cefotaxime, 90% to ceftazidime, 60% to amikacin, 50% to gentamicin, and 90% to netilmicin. All *Klebsiella pneumoniae* isolates were sensitive to imipenem. The only isolate of *Pseudomonas aeruginosa* was sensitive to all antibiotics tested and the only isolate of *Escherichia coli* was resistant to cefotaxime, ceftazidime and netilmicin.

In HUSM the bacterial isolates were tested for sensitivity to piperacillin, amikacin, gentamicin and imipenem. Out of 16 *Klebsiella aerogenes* isolates 56% was resistant to piperacillin, 19% to amikacin, 25% to gentamicin and 6.3% to imipenem. There were 2 *Pseudomonas aeruginosa* and 2 *Escherichia coli* isolates. Except for one *Escherichia coli* isolate all were sensitive to the antibiotics tested. Except for one isolate of *Klebsiella aerogenes* all gram negative bacteria were sensitive to imipenem.

Discussion

In this study, the incidence of nosocomial infection in NICU HKT (5.4%) was not significantly higher than in HUSM (3.6%). Reports in the literature have used different denominators for calculating infection rates, including the number of live births, length of stay in nurseries or number of infants discharged. Other hospitals in Malaysia have recorded higher nosocomial infection rates, 23.8% (5) and 47.6% (6). Omission of neonates with repeated infections could have accounted for the lower incidence of nosocomial infection in this study. Comparisons of incidence rates will be more accurate if all calculations were made using the total number of live births as the denominator.

In this group of neonates with nosocomial infection, the proportion of males was more than females in both hospitals, concurring with other studies (7-10). Very low birth weight infants (1.00 – 1.49 kg) were also noted to have more nosocomial infections in this and other studies (1,9-11).

Most neonates in HKT (63.3%) and HUSM (70.8%) with nosocomial infection were ventilated before the onset of infection. This is not surprising as the endotracheal tube provides a portal of entry for micro-organisms into the respiratory tract subsequently causing systemic infection. Neonates who were >12 hours of age at the time of intubation, had a duration of intubation >72 hours or were re-intubated ≥2 times, were shown to have a high risk of respiratory tract colonisation(12). Neonates on positive pressure ventilation were also exposed to regular endotracheal suctioning which may cause mechanical trauma to the tracheal mucosa. This leads to defects in anatomical barriers leading to infection. Storm demonstrated that transient bacteraemia, without clinical signs of septicaemia, occurred five minutes after endotracheal suctioning (13). Therefore, endotracheal suctioning must be considered a potential risk for the development of systemic infection. Gentle endotracheal suctioning must be performed whenever necessary and at 4 to 6 hours intervals if necessary. Other studies in Malaysia also showed a high percentage of

Table 3: Age at onset of nosocomial infection

Age at onset of infection (days)	HKT		HUSM	
	n	%	n	%
3 - 7	13	43.3	26	40
8 - 14	11	36.7	27	41.5
15 - 21	2	6.7	7	10.8
22 - 28	3	10	5	7.7
> 28	1	3.3	0	0
Total	**30**	**100**	**65**	**100**

nosocomial infection in ventilated neonates; 72% in Queen Elizabeth Hospital in Sabah (9) and 57.9% in Hospital USM in Kelantan (3).

All neonates with nosocomial infection in HUSM and 40% in HKT had received parenteral nutrition before the onset of infection. The higher proportion of neonates receiving parenteral nutrition in HUSM was probably due to different unit policies. As a routine, parenteral nutrition was administered to all patients admitted to NICU in HUSM before starting enteral feeding. In HKT however, parenteral nutrition was not a routine and the total number of patients who received parenteral nutrition was limited to five neonates at any time. The relationship between parenteral nutrition and infection is well established, especially if a central line was used because it is in direct contact with the central circulation. Sepsis associated with parenteral nutrition has been reported to be as high as 45% in neonates and children (14). In a recent study, an incidence of 3.6 infections per hundred days of total parenteral nutrition use was reported (15).

The percentage of neonates with nosocomial sepsis who also had a central line was higher in HUSM (72.3%) compared to HKT (33.3%). In previous studies the prevalence of umbilical catheter related sepsis varied from 3% to 16% (16-19). All the central lines used in HKT were umbilical vein or umbilical artery catheters. Besides the umbilical route, central venous lines were also inserted via the femoral vein or internal jugular vein in HUSM. The association between infection and the number of lines per patient could not be determined as the number of lines per patient was not counted in this study. Umbilical arterial or venous catheters provide a convenient intravenous access in sick neonates. However, these catheters carry a high risk of bacteraemia in vulnerable neonates. The risk for catheter related sepsis from umbilical arterial catheter has been shown to be related to both very low birth weight and longer duration of antibiotic therapy (16-19). Prolonged antibiotic therapy has been shown to be associated with catheter related sepsis, possibly because neonates on prolonged antibiotics have a higher prevalence of resistant organisms, or it may be just a marker for overall severity of illness and susceptibility to infection in these neonates. Low birth weight and infusion of hyperalimentation fluid were two factors which influence the risk for catheter related sepsis in infants with umbilical vein catheters. Blood stream infection rate has been shown to be significantly more in those who had central catheters in situ (15%) compared to those without catheters (2%) (20). Wong et al demonstrated that all patients with nosocomial infection had an intravascular catheter but only 42% had an umbilical catheter (9). In very low birth weight babies however, there was no significant difference in the rate of late onset sepsis in those who had or did not have an umbilical arterial catheter [3].

Almost one third of patients with nosocomial infection in HUSM had undergone invasive procedures whereas, in HKT, only two neonates had surgery. This difference was probably because HUSM has a Paediatric Surgical Unit and all surgical cases from the state were referred to HUSM.

The majority of first positive blood culture occurred during the first two weeks of life in both hospitals and the mean age at onset of infection was similar in both hospitals. The onset of nosocomial infection has been shown to occur at a later age in other studies, 16.5 days (11) and 13.6 days (6). The widespread use of antibiotic might have delayed or masked the features of infection. The duration of hospitalisation in neonates with nosocomial infection may be affected by various factors. Besides multiple episodes of infection, premature neonates are also prone to develop complications such as persistent ductus arteriosus, intraventricular haemorrhage and chronic lung disease. Infants with nosocomial infection have a longer duration of

Table 4: Duration of hospital stay of neonates with nosocomial infection

Duration of hospital stay (days)	**HKT**		**HUSM**	
	n	**%**	**n**	**%**
≤ 14	1	3.3	10	15.4
15 - 30	9	30	21	32.3
> 30	20	66.7	34	52.3
Total	**30**	**100**	**65**	**100**

hospitalisation (50.5 days) than non-infected babies (14.5 days) (1). The mean length of hospital stay was even longer in very low birth weight babies with nosocomial infection (86 days) compared to that of infants without infection (61 days) (21). The mean duration of hospitalisation among very low birth weight babies with nosocomial infection in a previous study 3 was shorter (31.1 days) than that in the present study. Due to limited data the reasons for the difference in the duration of hospitalisation among neonates in HKT and HUSM could not be explained.

The types of gram negative organisms isolated were similar to those in other studies. *Klebsiella peumoniae* (7), *Escherichia coli*, *Pseudomonas aeruginosa* and Acinetobacter species (3,5) were noted to be common gram negative organisms in previous studies. The pharynx and gastrointestinal tract of neonates in NICU were frequently colonised by these organisms and the number of neonates colonised is proportional to the duration of hospital stay. These organisms are usually transmitted from medical personnel or contaminated patient care items to neonates.

Compared to other studies gram positive organisms were still important causative organisms as they were the causative organisms seen in about half of the neonates in this study. Improved survival of premature neonates and the increasing use of invasive procedures nowadays, has resulted in the increasing prevalence of commensal organisms such as *Staphylococcus epidermidis* and Candida. Wider use of parenteral nutrition in HUSM could have accounted for the high number of neonates with candida sepsis. Among the gram positive organisms, coagulase negative staphylococci has been reported to be the commonest organism isolated (20-23). Neonates with coagulase negative staphylococci

Table 5: Types of micro organisms isolated from blood cultures in neonates with nosocomial

Types of micro organisms	**HKT**		**HUSM**		**p value**
	n	**%**	**n**	**%**	
Gram Negative Organisms					
Klebsiella pneumoniae	10	33.3	0	0	< 0.001
Klebsiella aerogenes	0	0	16	24.6	0.003
Acinetobacter specias	0	0	6	9.2	0.09
Enterobacter species	0	0	5	7.7	0.12
Escherichia coli	1	3.3	2	3.1	0.95
Pseudomonas aeruginosa	1	3.3	2	3.1	0.95
Gram Positive Organisms					
Staphylococcus aureus	3	10	4	6.2	0.51
Staphylococcus epidermidis & other coagulase-negative staphycocci	12	40	3	4.6	<0.001
Methicillin resistant *Staphylococcus aureus*	2	6.8	6	9.2	0.68
Methicillin resistant *Staphylococcus epidermidis*	1	3.3	15	23.1	0.02
Streptococcus viridans	0	0	1	1.5	0.50
Fungus					
Candida species	0	0	5	7.7	0.12
Total	**30**	**100**	**65**	**100**	

infection were more likely to be premature and had central lines (24). Coagulase negative staphylococci usually adhere to catheter surfaces and produce extracellular substances, including slime, thus making them inaccessible to phagocytes and antibiotics. Exposure to intravenous lipid emulsions, and the duration in which the non-umbilical central venous catheters were left in-situ had a clear linear relationship with coagulase negative staphylococci infection (25). Fleer et al showed that contaminated total parenteral nutrition fluid was the causative factor of many *Staphylococcus epidermidis* infections in their NICU (26). Even though more babies had invasive procedures, central lines and parenteral nutrition in HUSM, coagulase negative staphylococci was more commonly isolated in HKT. Contamination of blood culture specimens could have affected the results as the skin of neonates is commonly colonised with coagulase negative staphylococci.

In conclusion nosocomial infection is a common problem in both hospitals and the incidence and mortality rate of nosocomial infection in HKT and HUSM were similar. Except for more frequent predisposing factors for infection in HUSM, and a longer duration of hospital stay among neonates in HKT, the clinical characteristics of neonates with nosocomial infection in both hospitals were similar. Both gram positive and gram negative organisms continued to be the major causative organisms in nosocomial sepsis. The common causative organisms *Klebsiella pneumoniae* and *Klebsiella aerogenes* were resistant to most commonly used antibiotics but still sensitive to imipenem. A surveillance programme should be set up in each hospital to allow early identification of infection in at risk neonates. This will hopefully lead to better infection control and to earlier treatment of nosocomial infection in order to reduce the morbidity and mortality.

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