Neonatal Sepsis in very Low Birthweight Infants at the University Hospital of the West Indies

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ABSTRACT

*A retrospective review was conducted on the charts of all very low birthweight (VLBW) infants with culture proven sepsis admitted to the neonatal unit of the University Hospital of the West Indies (UHWI) during the period January 1, 1995 to December 31, 2000. During the study period, 22 VLBW infants were admitted to the neonatal unit with culture proven sepsis, 16 (73%) survived and 6 (27%) died. As birthweight and gestational age increased, outcome improved. There was no difference in survival based on age at presentation. Neonates with early onset disease had a significantly longer mean duration of rupture of membranes than those with late onset disease (*p = *0.009) and babies with late onset disease had a significantly lower mean Hb level than those with early onset disease (*p = *0.000). Predominant isolates were* Klebsiella sp *(10, 37%),* Streptococcus Group D *(4, 15%),* Escherichia coli *(3, 11%) and* Group B Streptococcus *(3, 11%).* Klebsiella sp *accounted for 8/13 (62%) of late onset infections. Complications included anaemia, thrombocytopenia, bleeding and multi-organ failure. Strategies aimed at prevention, such as limiting the excessive use of broad-spectrum empiric antibiotics and the periodic review and continuous reinforcement of infection control policies will help decrease the mortality and morbidity associated with nosocomial infection in the VLBW infant.*

Sepsis Neonatal en Recién Nacidos de Peso Extremadamente Bajo al Nacer en el Hospital Universitario de West Indies

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RESUMEN

*Se llevó a cabo un estudio retrospectivo de las estadísticas de todos los infantes de peso extremadamente bajo al nacer (PEBN) con sepsis probada con cultivo, ingresados en la Unidad Neonatal del Hospital Universitario de West Indies en el período comprendido de enero 1 de 1995, a diciembre 31 de 2000. Durante el periodo en estudio, 22 infantes de PEBN fueron ingresados a la unidad neonatal con sepsis probada por cultivo. De estos, 16 (73%) sobrevivieron y 6 (27%) murieron. En la medida en que aumentaron el peso al nacer y la edad gestacional, mejoraron también los resultados. No hubo diferencias en cuanto a supervivencia sobre la base de la edad al momento de la presentación. Los infantes con infección neonatal temprana tuvieron una duración media significativamente mayor de la ruptura de membranas en relación con aquellos que presentaron infección neonatal tardía (*p = *0.009), en tanto que los bebés con infección neonatal tardía presentaron un nivel de Hb significativamente más bajo en comparación con los que tuvieron infección temprana (*p = *0.000). Los aislados predominantes fueron* Klebsiella sp *10 (37%),* Streptococcus del grupo D *4 (15%),* Escherichia coli *3 (11%) y* Streptococcus del grupo B *3 (11%).* Klebsiella sp *fue la causa de 8/13 (62%) de las infecciones neonatales tardías. Las complicaciones incluyeron anemia, trombocitopenia, sangramiento y fallo multiorgánico. Estrategias que apunten a la prevención – tal como limitar el uso excesivo de los antibióticos empíricos de amplio espectro, así como la revisión periódica y el refuerzo continuo de las políticas de control de infección – ayudarán a disminuir la mortalidad y la morbilidad asociadas con la infección de los recién nacidos de PEBN.*

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INTRODUCTION

Sepsis is the most common cause of neonatal mortality in developing countries accounting for 30–50% of total neonatal deaths each year (1, 2). Neonates are deficient in humoral and cellular immunity; they produce immunoglobulins at a lower rate than adults (3). Transplacental maternal antibodies mediate humoral immunity primarily, hence very low birthweight (VLBW) premature infants are less likely to receive as many immunoglobulins as term infants. T–cell function is also less efficient in neonates (4). Complement function and phagocytic function inclusive of phagocytosis, phagocyte migration and toxin production are also deficient (5, 6).

The incidence of sepsis and its complications are therefore greater in VLBW infants and extremely premature babies. Although most premature babies survive today as a result of the availability of neonatal intensive care, they are frequently subjected to invasive procedures that increase the probability of infection.

Onset of infection within the first six days of life is thought to be primarily due to vertical transmission from mother-to-infant, while onset of infection at seven days of life or greater is more likely to be acquired through horizontal transmission. By virtue of the length of time VLBW infants may spend in the hospital setting, they are at prolonged risk for acquiring infection, particularly nosocomial infections. The identification of strategies to reduce infection in these infants will result in decreased mortality and morbidity.

The objective of this study was to describe the clinical presentation, causative organisms and outcome of bacterial sepsis in VLBW infants. The authors hypothesize that by virtue of the length of time VLBW infants spend on the neonatal unit the organisms causing infection will be predominantly nosocomial in origin.

SUBJECTS AND METHODS

The University Hospital of the West Indies (UHWI), a university affiliated institution, is located in Kingston, the capital of Jamaica. The neonatal unit at the UHWI is a thirty-bed unit; neonates admitted to the unit are mainly inborn.

This study was a retrospective analysis of culture proven cases of sepsis in VLBW infants aged 0–30 days, admitted to the neonatal unit of the UHWI during the six-year period January 1, 1995 to December 31, 2000. Infants were identified from the neonatal unit admission logbook by the discharge diagnosis recorded, this diagnosis was then cross-checked with microbiology laboratory reports. The two investigators reviewed the charts of all VLBW infants with culture proven sepsis and data on demographics, clinical presentation, causative organisms, sensitivity patterns and outcome were extracted using a data extraction sheet. During the study period, 395 VLBW infants were admitted to the neonatal unit.

All VLBW infants admitted to the unit with a presumptive diagnosis of sepsis had a full sepsis screen, which included blood culture, cerebrospinal fluid (CSF) culture, urine culture, a complete blood count and a chest radiograph (CXR). Blood for culture was taken from a peripheral vein after cleansing of the skin with an iodine solution. Samples of blood, CSF and urine were plated and analyzed according to standard bacteriological procedures. A full description of the methods of blood culture has been described from the Microbiology Department, UHWI (7). Infants were empirically commenced on a combination of a penicillin and an aminoglycoside, usually crystalline penicillin or amoxicillin and gentamicin. If the infant had previously been on these antibiotics within 72 hours of the sepsis screen, augmentin and amikacin were used.

Definitions

Neonatal sepsis was defined as the presence of positive cultures, whether in the blood, CSF, or urine, associated with systemic clinical signs of infection such as fever, temperature instability, irritability, poor feeding and respiratory distress. Very low birthweight infants were those whose birthweight was less than 1500g. Early onset infection (EOD) were infections occurring less than 7 days of life while late onset infections (LOD) – occurred at 7–30 days of life. Death as a sequel of sepsis was defined as death occurring within 10 days of a positive culture. Complications of sepsis were complications occurring within seven days of a positive culture.

The UHWI/UWI Faculty of Medical Sciences Ethics Committee granted approval for this study to be conducted.

Statistics

Descriptive analyses were performed. Continuous variables were expressed as means and compared by independent student t-test. Categorical variables were analyzed using the chi-square test with statistical significance taken at 5%.

RESULTS

During the study period 22 VLBW infants were admitted to the neonatal unit with culture proven sepsis, 20 (91%) were inborn. Sixteen (73%) infants survived and six (27%) died. There were 10 (45%) males of whom two (20%) died and 12 (55%) females of whom four (33%) died. There was no difference in outcome by gender. Table 1 shows the characteristics of neonates with culture positive sepsis by age of presentation.

A total of eight (38 %) neonates presented with early onset infection. Of these, seven (88%) presented within the first 24 hours of life, six (75%) babies with early onset infection survived. Thirteen (62%) neonates presented with late onset infection and of these nine (69%) survived. There was no difference in survival based on the age at presentation. The neonates with EOD had a significantly longer mean duration of rupture of membranes than those with LOD (p =

Table 1: Characteristics of VLBW neonates with proven infection by onset of disease

	EOD (n = 8)	LOD (n = 13)
Median age at presentation/range (days)	0 (0–6)	23 (13–75)
Mean gestational age ± SD (weeks)	30.4 ± 3	30.3 ± 2.3
Mean birthweight ± SD (g)	1137 ± 184	1066 ± 266
Mean duration of rupture of membranes ± SD (hours)	18 ± 15	4 ± 5 *
Mean duration of therapy ± SD (days)	9.5 ± 4	12.3 ± 5
Mean haemoglobin ± SD (g/dl)	15 ± 2	8 ± 2 **
M: F	5:3	5:8
Death (% within category)	2 (25)	3 (23)

* $p < 0.05$ ** $p < 0.001$

0.009). Babies with LOD had a significantly lower mean Hb level than those with EOD ($p = 0.000$).

As birthweight increased, outcome improved. Fifteen (68%) neonates with positive cultures had birthweights between 1000 – 1499g, 13 (87%) survived; seven (32%) had birthweights less than 1000g, three (43%) survived ($p = 0.05$). There were 11 (50%) babies whose gestational ages were between 31–34 weeks, seven (32%) between 27–30 weeks and four (18%) less than 27 weeks gestation. Survival improved with increasing gestational age, all four (100%) babies less than 27 weeks gestation died while one (14%) baby 27–30 weeks gestation died and one (9%) baby 31–34 weeks gestation died ($p = 0.001$).

The most common presenting clinical features were respiratory distress – 7 (32%), poor feeding – 5 (23%), vomiting – 3 (14%), abdominal distension – 3 (14%), lethargy – 2 (9%) and irritability – 2 (9%).

A total of 27 isolates were obtained, 19 (70%) were from blood cultures and eight (30%) from urine cultures. Table 2 shows the organisms isolated during the study period. Predominant isolates were *Klebsiella sp*, *Streptococcus Group D*, *Escherichia coli* and *Group B Streptococcus*. Of the organisms isolated 18 (67%) were gram-negative organisms and 9(33%) were gram-positive organisms. Of the organisms isolated from blood, 12 (63%) were gram-negative organisms and 7 (37%) were gram-positive organisms. While from the urine, 6 (75%) isolates were gram-negative organisms and two (25%) were gram-positive organisms. *Klebsiella sp* accounted for 8/13 (62%) of the late onset infections.

Table 2: Microbiology of neonatal infections in VLBW infants at UHWI

Gram negative Bacteria	Isolates in blood	Isolates in urine	Percentage
Klebsiella	7	3	37
Escherichia coli	1	2	11
Enterobacter sp	1	–	4
Pseudomonas sp	1	1	7
Serratia sp	1	–	4
Citrobacter sp	1	–	4
Gram positive Bacteria			
Coagulase negative staphylococcus	1	–	4
Staphylococcus aureus	1	–	4
Group B Streptococcus	3	–	11
Streptococcus Group D	2	2	15
	19	**8**	**100**

An individual neonate could have organisms isolated from more than one site

Analysis of sensitivity patterns of the micro-organisms revealed that all *GBS* isolates were sensitive to penicillin. All *Escherichia coli* and *Pseudomonas* isolates were sensitive to gentamicin. However only six (60%) of the isolates of *Klebsiella sp* were sensitive to gentamicin. Two (20%) of the *Klebsiella sp* isolates were resistant to the aminoglycosides, ceftazidime and ceftriaxone. These two isolates were only sensitive to meropenem.

Case fatality rate for VLBW infants with bacterial infections at UHWI was 27%. Case fatality rates were higher for infants weighing less than 1000g (57%) than for infants weighing greater than 1000g (13%). Gram-negative organisms accounted for four (66%) of the deaths. Table 3 shows the organisms causing infection in the non-survivors. Of the non-survivors, one infant developed disseminated intravascular coagulation and died before medical management could be instituted, two died from multisytstem organ failure and three died from respiratory failure.

Table 3: Organisms causing infection in VLBW non-survivors

Organism	EOD 1–6 days	LOD 7–30 days
Klebsiella	0	2
Enterobacter sp	0	1
Pseudomonas sp	1	0
Coagulase negative staphylococcus	0	1
Group B Streptococcus	1	0

Seven (32%) babies were anaemic and thrombocytopenic, three (43%) of these developed bleeding. Three (14%) babies developed acute seizures as a sequel of sepsis, one of these babies had bleeding and went on to develop acute hydrocephalus. Two (9%) VLBW infants with positive cultures developed multi-organ failure. Intensive care unit admission was required for four (18%) of the infants.

DISCUSSION

The mortality rate from sepsis for VLBW infants in this study is similar to that reported in the United States of America (USA) (8). However, in the USA, a greater percentage of babies less than 1000g survive and the weight distribution within the VLBW infants is different from that of this study where the weight distribution is skewed towards the larger babies who have better outcome. A similar cohort in the

USA would have a lower mortality rate. The mortality rate, however, is lower than the rates reported in other developing countries where rates of 40–45% have been quoted (9, 10).

The finding of increased survival with increasing birthweight and gestational age is similar to previous studies (8, 9, 11–13). The predominance of LOD in these VLBW infants is not unexpected as by virtue of their immaturity they are more likely to have an extended hospital stay placing them at prolonged risk for infection. Koutouby *et al* and Moreno *et al* have also documented this finding (10, 14). The association of prolonged rupture of membranes with EOD has been shown in other studies (10, 15). The longer the duration of rupture of membranes, the longer is the period of time the unborn infant is exposed to ascending organisms from the mother's genital tract predisposing to early onset of infection.

The lower haemoglobin levels in infants with LOD may be as a result of their more prolonged exposure to repeated phlebotomy for blood tests in the neonatal unit and anaemia of prematurity. However, half of the infants were both anaemic as well as thrombocytopenic and some of them experienced bleeding. These are all markers of sepsis, particularly thrombocytopenia, which has been shown to occur in gram-negative sepsis (16), which the majority of these infants had.

The common presenting symptoms are similar to those reported by Fanaroff *et al* (8). These illustrate the subtle and non-specific signs of sepsis in VLBW infants. Thus, the physician must have a high index of suspicion for making the diagnosis of sepsis based on clinical signs in these infants.

Several studies from developed countries report coagulase negative staphylococcus as the predominant organism causing LOD in VLBW infants (17–19). In this study, this pattern was not seen. This may be as a result of the limited mechanical ventilation of infants during the study period and the inability to offer total parenteral nutrition in this setting. As such, there was not a high prevalence of indwelling central catheters, a major risk factor for coagulase negative staphylococcal infection. The finding of *Klebsiella sp* as the major pathogen in LOD is similar to studies from other developing countries (10, 20).

The resistance of *Klebsiella sp* to gentamicin and the emergence of multiple antibiotic resistant organisms have important implications in this setting, as *Klebsiella sp* was the most common organism causing nosocomial infection. This means that for infants with LOD, physicians must have a low threshold to switch from empiric antibiotic regimens to more potent antibiotics in the face of sub-optimal clinical improvement. Some parameters that may be used to guide the physician would be if there is persistence of the initial clinical signs of sepsis or the development of new signs after 48 – 72 hours of empiric antibiotics. Also, if there is worsening of laboratory markers of sepsis (anaemia, thrombocytopenia, leucopaenia, deranged PT/PTT) and if there is minimal improvement or deterioration in the clinical status of the infant.

This study has demonstrated an increased incidence of late onset infection in VLBW infants and this represents nosocomial infection. Strategies aimed at prevention of nosocomial infection such as limiting the excessive use of broad-spectrum empiric antibiotics, the development of a hand hygiene programme and periodic review and continuous reinforcement of infection control policies must be instituted.

Development of a hand hygiene programme would include provision of a scrub area at the entrance of the unit. All persons who have patient contact would be required on entering the unit to remove any jewellery *eg* watch, rings and bracelets and wash hands, fingernails and forearms with an antibacterial detergent for at least two minutes. Between handling of patients and after contact with contaminated surfaces, the hands should be washed for at least 15 seconds with soap and water. Every cubicle would be equipped with hands-free, hand-washing sinks so that every bed position is within six metres of a sink. A foot pedal would be used to operate soap dispensers and centre pull towel dispensers would be provided. Pictorial hand washing instructions would be provided above all sinks.

Surveillance for nosocomial infection would be carried out through review of patient charts for clinical evidence of infection and review of microbiologic culture reports. This is routinely done for the monthly perinatal mortality/morbidity conference. This meeting would be an ideal forum for the review and reinforcement of infection control policies. Focussing on these strategies will help decrease the mortality and morbidity associated with hospital acquired infection in the VLBW infant.

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