RISK FACTORS FOR NEONATAL SEPSIS IN TERTIARY HOSPITAL IN JORDAN

Haifa A. Al Dasoky MD, Faten N. Al Awaysheh MD*, Nasser M. Kaplan MD**, Hanadi A. Al Rimawi MD*, Riham M. Agha (BSc)**, Mohammad H. Abu-Setteh MSc***

ABSTRACT

Objectives: To study incidence, mortality, maternal and neonatal risk factors and causative microorganisms for neonatal sepsis.

Methods: A total of 60 neonates with sepsis were studied during the period between January and December 2005. The clinical presentations, maternal, and neonatal risk factors and the time of neonatal death were recorded.

Results: Four hundred ninety nine (10.2%) out of 4902 live neonates were admitted for various reasons to the neonatal intensive care unit at King Hussein Medical Centre. Sixty (12.0%) babies had proven sepsis, 28 (46.7%) of these with early onset and 32 (53.3%) with late onset sepsis. Maternal risk factors associated with neonatal sepsis were: cesarean section in 22 (36.7%) cases, premature rupture of membranes in 4 (6.7%) cases, eclampsia in 4 (6.7%) cases, and maternal urinary tract infection in 3 (5%). Neonatal risk factors observed were: male gender in 40 (66.7%) cases, low birth weight in 38 (63.3%) cases, prematurity in 32 (53.3%) cases, low Apgar score in 10 (16.7%) cases, and mechanical ventilation in 12 (20.0%) cases. Gram positive bacteria were isolated in 44 (73.3%) cases of which four died. However gram negative sepsis was associated with higher morbidity and mortality rates. Twelve (20%) babies died, seven of them due to *Klebsiella sepsis. Candida sepsis* caused three cases of sepsis with one death. Most of deaths occurred out of working hours.

Conclusion: Early recognition and prompt treatment of neonatal sepsis are of paramount importance particularly in the presence of risk factors.

Key words: Neonatal sepsis, Blood culture

JRMS December 2009; 16(3): 16-19

Introduction

Neonatal sepsis: is a clinical syndrome resulting from the pathophysiologic effect of local or systemic infection in the first month of life. Newborns are immunologically immature and are ill-suited to defend themselves against the polymicrobial flora to which they are exposed during and after parturition. Neonatal polymorphonuclear cells demonstrate decreased chemotaxis, opsonization, phagocytosis, and intracellular bacterial killing as well as depressed oxidative responses. Neonatal monocytes have decreased chemotaxis and cytotoxic functions. The most important risk factors for hospital-acquired sepsis are prolonged use of intravascular plastic catheters, exposure to antibiotics, prolonged hospitalization, contaminated respiratory support equipment, and intravascular or parenteral solutions.

Gram positive organisms may be introduced from the environment or patient's skin, while gram

From the Departments of:
*Pediatrics, King Hussein Medical Centre, (KHMC), Amman-Jordan
** Microbiology, Princess Iman Research & Laboratory Sciences Center, (KHMC)
Correspondence should be addressed to Dr. H. Al Dasoky, (KHMC).
Manuscript received March 5, 2006. Accepted September 7, 2006

Table I. The organisms isolated from blood cultures

Number (n=60)	Organism
Staphylococcus epidermidis	40 (67%)
Klebsiella sp.	8 (13%)
Candida albicans	3 (5%)
Streptococcus viridans	3 (5%)
Staphylococcus aureus	2 (3%)
Enterobacter sp.	2 (3%)
Diphtheroids	1 (2%)
Escherichia coli	1 (2%)

Table II. The organisms isolated in cases of death

Number (n=12)	Organism
Klebsiella sp.	7 (58.4%)
Staphylococcus epidermidis	4 (33.3%)
Candida albicans	1 (8.3%)

negative organisms are always derived from patient's endogenous flora which may have been altered by antecedent antibiotic therapy or populated by resistant organisms transferred from the hand of health care workers or contaminated equipments.[1]

Early onset neonatal sepsis is clinically apparent within six hours of birth in >50% of cases, the great majority of this presents within the first seven days of life. Late onset neonatal sepsis usually presents after seven days of age and includes hospital-acquired infections.

The early signs of neonatal sepsis are nonspecific such as hypoactivity, poor sucking, apnea, bradycardia, raised temperature, instability, respiratory distress, peri-umbilical erythema, bulging fontanels, seizures, and coma.

Methods

A prospective study was conducted from 1st of January to 31st of December 2005. This study was conducted in a tertiary referral hospital to determine the frequency of neonatal sepsis, its underlying maternal and neonatal risk factors, and the time of the day in which the highest mortality occurs. There were total of 60 neonates admitted to neonatal intensive care unit (NICU) at King Hussein medical Centre, Amman, Jordan with clinical signs of sepsis as hypoactivity, poor sucking, respiratory distress, and jaundice, in addition to positive blood culture.

The maternal and neonatal data were recorded including age of the mother, parity, maternal disease, method of delivery, time of rupture of membranes, gestational age, birth weight, sex, Apgar Score at one and ten minutes of life consecutively, associated diseases including pneumonia and jaundice, need for respirator, umbilical catheter, and surfactant use.

The duration of hospitalization was recorded as mean length of hospital stay. Sepsis occurring under seven days was defined as "Early", and Sepsis occurring later than seven days was defined as "Late".

Complete blood count including erythrocyte sedimentation rate (ESR), blood chemistry including electrolytes, and C-reactive protein (CRP) were done.

For blood cultures, 1-3 ml of blood was obtained by standard aseptic methods, and injected directly into BACTEC PEDS PLUS/F (Becton Dickinson) blood culture bottle. All bottles were incubated at 35°C in BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems). The system provides continuous incubation and automatic monitoring for microbial growth using a fluorescent-CO_2 sensor. Bottles were inspected by the system every ten minutes and those with undetected microbial growth were flagged negative and displayed on the monitor at the end of five days incubation. Bottles with detected microbial growth were flagged positive and displayed, pulled from the instrument, and Gram stained. According to the organism present, subcultures on aerobic and anaerobic bacteriological media, direct biochemical tests, and direct antimicrobial susceptibility testing were performed according to the established standard procedures. All subcultures were incubated at 35°C in 5% CO_2. For confirmatory purposes, direct identification and susceptibility testing were performed on the microbial colonies using VITEK 120 system (bioMérieux).

The initial empiric antibiotic regimen used in the neonatal intensive care unit is ampicillin and amikacin, and the second line regimen is imipenem and vancomycin.

Results

Out of 499 neonatal admissions during the study period, a total of 60 (12%) were confirmed neonatal sepsis. All cases had positive blood cultures, and the organisms isolated are shown in Table I.

Table III. Maternal risk factors

Risk factor	Number (n=60)
Cesarean section	22 (36.7%)
Premature rupture of membranes >18hr	4 (6.7%)
Pre-eclampsia	4 (6.7%)
Urinary tract infections	3 (5%)

Table IV. Neonatal risk factors

Risk factor	Number (n=60)
Male Gender	40 (66.7%)
Low Birth weight	38 (63.3%)
Prematurity	32 (53.3%)
Mechanical-assisted ventilation	12 (20%)
Umbilical catheters	11 (18%)
Low Apgar score	10 (16.7%)
Surfactant	8 (13%)
Total parenteral nutrition	8 (13%)

Out of the 60 cases, 12 (20%) neonates died and Table II shows the organisms isolated from their blood cultures.

Gram-positive bacteria were isolated from 44 (73.3%) cases, of which four died. Thirty-seven (84%) of the isolated gram positive bacteria were *Staphylococcus epidermidis* of which four were proved to be skin contaminants. Gram-negative bacteria were isolated from 11 (18.3%) neonates, of which seven died.

All mothers were younger than 30 years old and had antenatal care. Thirty-six (60%) mothers were primipara, and 22 (36.7%) delivered by cesarean section. The maternal risk factors are shown in Table III.

Forty neonates (66.7%) were males and twenty were females. Thirty-two (53.3%) had a gestational age of <37 weeks. Thirty eight (63.3%) had birth weight <2.5 kg (maximum weight was 5 kg, and minimum weight was 0.750 kg). Ten (16.7%) had Apgar score <7 in first and ten minutes after birth consecutively. The neonatal risk factors are shown in Table IV.

Ten premature neonates who died because of sepsis and other causes, required the use of respirators and umbilical catheters, and were given surfactant. Two full-term neonates died, one of them had hyperinsulinemia/ hypoglycemia and needed umbilical catheter.

Early infections were detected in 28 neonates mainly due to gram-positive organisms, and late infections were detected in 32 cases mainly due to gram negative organisms.

The twelve neonates who died due to sepsis were mostly premature with low birth weight, and had late sepsis due to gram negative bacteria mainly *Klebsiella sp*. They had leucopoenia, thrombocytopenia, electrolyte disturbances such as hypocalcaemia, and elevated ESR. CRP was positive in most late infections.

For all the 60 neonates, the second antibiotic regimen was used and second blood culture was taken.

Discussion

Neonatal sepsis occurs in 0.5-8.0/1000 live births. The highest rates occur in low birth weight newborns, those with depressed respiratory function at birth, and with maternal prenatal risk factors.[1] In our study, neonatal sepsis occurred in 60/4902 (12.2/1000) with similar risk factors mainly prematurity.

The gram-negative bacteria, specifically entero-bacteriaceae, have been reported by various authors as the major cause of neonatal septicemia.[2-4] In our study, gram-negative bacteria were more common in late onset sepsis and within this group infection with *Klebsiella sp* predominated and was associated with the most serious outcome. Similar to our findings, other authors found that coagulase negative staphylococci were the main cause of late onset sepsis in NICU.[5,6]

The recovery of an organism from blood stream should always be considered significant until proven otherwise. The significance of the isolate should be determined by establishing close liaison and discussion between the microbiologist and the clinician. Although *Staphylococcus epidermidis* had the highest isolation rate (40%) in our study, similar to previous studies[7] more than 94% of these organisms isolated were judged to be contaminants after close discussions and in the light of clinical picture of the patients. Every clinical microbiology laboratory needs policies and procedures designed to ensure that blood cultures are collected in such a way as to minimize contamination. Whether blood cultures are collected by medical technologists, trained phlebotomists, nurses, or other health care workers, an ongoing program to monitor compliance with these policies and procedures is necessary and should be part of the laboratory quality assurance program. Guidelines for proper blood cultures

collection and reduction of contamination have been recently published.[8]

Some authors recorded that 60% of mothers were primipara, 60% of neonates were premature, and 42% with body weight less than 2.5kg at birth.[9] These findings are similar to those reported in other American and European studies.[10-12] Our study showed that 60% of mothers were primipara, thirty two neonates (53.3%) were premature, and 38 neonates (63.3%) had a birth weight less than 2.5 kilograms.

In our study a combination of ampicillin and amikacin was used as initial empiric regimen for early onset neonatal sepsis, while awaiting blood culture results. However, other regimens were used in other studies. Clark and colleagues recommended the use of ampicillin and gentamicin[13] and Flidel-Rimon and colleagues concluded that piperacillin in combination with amikacin are microbiologically and clinically efficient and safe in the treatment of neonatal sepsis.[14]

The increased incidence of nosocomial infection by methicillin-resistant *Staphylococcus aureus* in NICU has led to an increase in the utilization of vancomycin.[15] In our study, a combination of imipenem and vancomycin was used with good outcome in late onset sepsis.

It was reported that the use of pentoxifylline, an anti inflammatory drug, resulted in reduction of neonatal sepsis and its complications.[16] Intraglobulin was given in combination with the antibiotics to all the neonates in our study. As in other studies,[17] we demonstrated a high mortality rate in premature babies who required mechanical ventilation and total parenteral nutrition.

Adequate maternal diagnosis and treatment are necessary to reduce the neonatal morbidity and mortality associated with neonatal sepsis. Since neonatal sepsis may present with non-specific clinical signs and its effect may be devastating, an early diagnosis and prompt therapy are of paramount importance. Antibiotics should be used because they are detrimental to the infant´s flora in the nursery. Depending on the laboratory culture method and rapidity of reporting, almost all bacterial cultures are positive within 72 hours. If negative culture of body fluid is consistent with the clinical course, antibiotic may be discontinued after 72 hours. Adequate number of nursing staff, preferably one nurse for every three neonates, is of great importance in the NICU particularly during night shift. Strict preventive measures particularly hand washing and isolation facilities should be adopted.

References

1. **Beers MH, Berkow R.** Disturbances in newborns and infants. In: Beers MH, Berkow R editors. The Merck manual of diagnosis and therapy. 17th Internet ed., 2005.
2. **Chugh K, Aggarwal BB, Kaul VK, Arya SC.** Bacteriological profile of neonatal septicemia. *Indian J Pediatr* 1988; 55(6): 961-965.
3. **Gupta P, Murali MV, Faridi MM, *et al.*** Clinical profile of Klebsiella septicemia in neonates. *Indian J Pediatr* 1993; 60 (4): 565-572.
4. **Mahapatra A, Ghosh SK, Mishra S, *et al.*** Enterobacter cloacae: A predominant pathogen in neonatal septicemia. *Indian J Med Microbiol* 2002; 20 (2): 110-112.
5. **Lawrence SL, Roth V, Slinger R, *et al.*** Cloxacillin versus vancomycin for the presumed late-onset sepsis in the Neonatal Intensive Care Unit and the impact upon outcome of coagulase negative staphylococcal bacteremia: a retrospective cohort study. *BMC Pediatr* 2005; 5: 49-52.
6. **Bansal S, Jain A, Agarwal J, Malik GK.** Significance of coagulase negative staphylococci in neonates with late onset septicemia. *Indian J Pathol Microbiol* 2004; 47(4): 586-588.
7. **Kaplan NM.** Evaluation of direct light microscopy for rapid detection of microorganisms in blood cultures. *Saudi Med J* 2002; 23(12): 1504-1508.
8. **Ernst DJ.** The right way to do blood cultures. *RN* 2001; 64(3): 28-31.
9. **Vaciloto E, Richtmann R, de Paula Fiod Costa H, *et al.*** A survey of the incidence of neonatal sepsis by group B Streptococcus during a decade in a Brazilian maternity hospital. *Braz J Infect Dis* 2002; 6(2): 55-62.
10. **Lim CT, Thong MK, Parasakthi N, Ngeow YF.** Group B streptococcus: Maternal carriage rate and early neonatal septicemia. *Ann Acad Med Singapore* 1997; 26(4): 421-425.
11. **Weisman LE, Stoll BJ, Cruess DF, *et al.*** Early-onset group B streptococcal sepsis: A current assessment. *J Pediatr* 1992; 121(3): 428-433.
12. **Schuchat A, Deaver-Robinson K, Plikaytis BD, *et al.*** Multistate case-control study of maternal risk factors for neonatal Group B streptococcal disease. The Active Surveillance Study Group. *Pediatr Infect Dis J* 1994; 13(7): 623-629.
13. **Clark RH, Bloom BT, Spitzer AR, Gerstmann DR.** Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics* 2006; 117(1): 67-74.
14. **Flidel-Rimon O, Friedman S, Leibovitz E, Shinwell ES.** The use of piperacillin/tazobactam (in association with amikacin) in neonatal sepsis: efficacy and safety data. *Scand J Infect Dis* 2006; 38(1): 36-42.
15. **Machado JK, Feferbaum R, Diniz EM, *et al.*** Monitoring the treatment of sepsis with vancomycin in term newborn infants. *Rev Hosp Clin Fac Med Sao Paulo* 2001; 56(1): 17-24.
16. **Haque K, Mohan P.** Pentoxifylline for neonatal sepsis. *Cochrane Database Syst Rev* 2003; (4): 4205.
17. **Alaedeen DI, Walsh MC, Chwals WJ.** Total parenteral nutrition-associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants. *J Pediatr Surg* 2006; 41(1): 239-244.