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Clinical Profile of Neonates Admitted with Sepsis: A Study in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh

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Abstract **Original Research Article**

Background: Sepsis is the commonest diagnosis of most neonatal units and is responsible for increasing morbidity, mortality and cost of treatment. A triad of high index of clinical suspicion, early lab diagnosis, with judicious use of antibiotics will lead to favorable outcome. ***Objective:*** To study the clinical presentation, investigative profile and outcome of neonates admitted with sepsis. ***Study Design:*** Prospective observational study. ***Place and Duration of Study:*** Pediatric intensive care unit of Dhaka Shishu (Children) Hospital for a period of six months from April to September 2019. ***Methods:*** This study included data of 109 newborns with clinical diagnosis of septicemia. Clinical suspicion was made on the basis of maternal risk factors like prolonged rupture of membranes, foul smelling liquor, maternal fever or features in the neonates like refusal to feed, lethargy, respiratory distress, jaundice, abdominal distension, vomiting, cyanosis etc. Total WBC, platelet count, C-reactive protein (CRP), blood cultures were sent and all babies were followed up to final outcome either discharge or death. ***Results:*** Amongst the study population, male to female ratio was 1.6:1. Majority of neonates were delivered by vaginal route. Fifty-one (46.8%) neonates had early onset sepsis 58 (53.2%) had late onset sepsis. The major clinical features of sepsis were refusal to feed, respiratory distress, convulsions, jaundice, and lethargy. Blood culture was positive in 24(22%) neonates, gram-negative multidrug resistance were mostly isolated. CRP was positive in 42 (38.6%), leucopenia in 14 (12.8%), leukocytosis in 19(17.4%) and thrombocytopenia was seen in 61(55.9%) enrolled cases. Total deaths were 16(14.7%), of which 9(56.3%) neonates had early onset and 7(43.7%) late onset sepsis. ***Conclusions:*** Septicemia is a major cause of mortality and morbidity in neonates. Prevention is preferable, outcome to a great extent depends upon early identification and prompt intensive treatment.

Keywords: Blood culture, neonatal sepsis, early onset sepsis (EOS), late onset sepsis (LOS).

INTRODUCTION

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections. Sepsis is the commonest cause of neonatal mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries [1, 2]. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes [2]. Sepsis related mortality is largely preventable with rational antimicrobial therapy and aggressive supportive care. The incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD, 2002-03) is 30 per 1000 live births. The database comprising 18 tertiary neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths [3]. Septicemia was the commonest clinical category with an incidence of 23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live births. Neonatal sepsis can be classified into two major categories depending up on the onset of symptoms [4]. It presents within first 72 hours of life. In severe cases, the neonate may be symptomatic at birth. Infants with early onset sepsis (EOS) usually present with respiratory distress and pneumonia [5]. The source of infection is generally the maternal genital tract. It usually presents after 72 hours of age. The source of infection in late onset sepsis (LOS) is either nosocomial (hospital acquired) or community acquired and neonates

usually present with septicemia, pneumonia or meningitis [6, 7]. The main offenders for early onset sepsis are E.coli, Klebsiella and group B streptococcus. The main organisms causing late onset sepsis are Klebsiella pneumoniae, Enterobacteria, Pseudomonas and Staphylococcus aureus. The earliest signs of sepsis are often subtle and nonspecific; indeed, a high index of suspicion is needed for early diagnosis. Neonates with sepsis may present with one or more of the following symptoms and signs; fever or hypothermia, lethargy, poor cry, refusal to suck, prolonged capillary refill time, hypotonia, apnea and metabolic acidosis. Specific features relating to various systems include bulging anterior fontanel, seizures in meningitis, abdominal distension, vomiting, and diarrhea in necrotizing enterocolitis (NEC). Since treatment should be initiated in a neonate suspected to have sepsis without any delay, only minimal and rapid investigations should be undertaken [8]. Blood culture is the gold standard for diagnosis of septicemia and should be performed in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture with sensitivity of the isolated organism is the best guide to antimicrobial therapy. Bacterial growth can be detected within 12-24 hours by using improved bacteriological techniques such as BACTEC and BACT/ALERT blood culture systems. All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis [9, 10]. The various components of the septic screen include total leukocyte count, absolute neutrophil count, immature to total neutrophil ratio, micro-erythrocyte sedimentation rate and C reactive protein. This study was performed to study the clinical presentation, isolated organisms and outcome of neonates admitted with sepsis at ICU of Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh.

MATERIALS AND METHODS

This is a prospective observational study conducted at Dhaka Shishu (children) Hospital, Dhaka, Bangladesh over a period of 6 months from April to September 2019. It is a teaching institution with a tertiary level NICU care. The study population included 109 neonates admitted in ICU with features of sepsis. Clinical suspicion was made on the basis of maternal risk factors like leaking membranes >24 hours, foul smelling liquor, maternal fever or features in the neonates like refusal to feed, lethargy, respiratory distress, jaundice, abdominal distension, vomiting, cyanosis etc. Detailed antenatal, natal and post-natal history was recorded. Thorough physical examination was done. 1-2 ml venous blood samples were collected for blood culture, serum C-reactive protein, total leucocyte count, absolute neutrophil count and platelet count. The results were analyzed using Chi-square test.

RESULTS

During the study period, a total of 109 neonates had clinically suspected sepsis. Among them 68 (62.4%) were male and 41 (37.6%) were female babies. The male female ratio was 1:1.68. Based on the age of onset, the clinically suspected neonatal sepsis group was further categorized into early onset neonatal sepsis for neonates who were 3 days of age or less and late onset neonatal sepsis for those who were >3 days of age but less than 28 days. There were 51 (46.8%) neonates in the early onset sepsis group and 58 (53.2%) in the late onset group (Table-1).

Table-1: Baseline characteristics of the enrolled cases comparing onset of sepsis (N=109)

Characteristics	EOS (N=51)	LOS (N=68)	p-value
Male	31 (60.8%)	37 (63.7%)	0.57
Female	20 (39.2%)	21 (36.3%)	0.09
< 2.5 kg	32 (62.7%)	23(39.7%)	0.86
> 2.5 kg	19(37.3%)	35 (61.3%)	-1.53
Vaginal	37(72.5%)	36 (62.1%)	0.09
Caesarean	14(27.5%)	22 (37.9%)	0.76

Table-2: Clinical presentation of the enrolled cases (N=109)

Clinical Presentation	EOS (N=51)	LOS (N=68)	Total (N=109)
Refusal to feed	5	27	32(29.4%)
Respiratory Distress	22	6	28 (25.7%)
Convulsions	8	14	22(20.2%)
Jaundice	8	13	21(19.3%)
Lethargy	1	17	18 (16.5%)
Abdominal distension	4	5	9(8.3%)
Vomiting	1	8	9(8.3%)
Hepatomegaly	4	5	9(8.3%)

Refusal to feed was the most common clinical presentation (29.4%), followed by respiratory distress (25.7%), convulsion (20.2%), jaundice (19.3%) and lethargy (16.5%). Abdominal distension, vomiting and hepatomegaly was present in 8.3% of cases. Respiratory distress was relatively more common in EOS (43.1%) and refusal to feed in LOS (39.7%) (Table-2). Blood culture positivity was observed in 24 (22%) neonates,

of these 11 (45.8%) were EOS and 13 (54.2%) LOS. Klebsiella was isolated in 50% of culture positive cases followed by CONS and Enterococci. They were mostly resistant to commonly used antibiotics, only sensitive to Vancomyc in and Cefoperazone. The details will be published separately.

Table-3: Laboratory characteristics of the enrolled cases comparing onset of sepsis (N=109)

Onset	EOS 51	LOS 68	p-value
Positive CRP	21	21	0.35
Leucopenia	5	9	0.68
Leukocytosis	10	9	0.86
ANC<1800/mm^3	4	6	0.19
Thrombocytopenia	28	33	0.08

*Absolute neutrophil count.

Table-4: Outcome of the enrolled cases by gender and onset of disease (N=109)

Group	Gender			Discharge			Death			p-value
	Male	Female	Total	Male	Female	Total	Male	Female	Total	
EOS	31	20	51	25	17	42 (82.4%)	6	3	9 (17.6%)	
LOS	37	21	58	33	18	51 (87.9%)	4	3	7 (12.1%)	0.89
Total	68	41	109	58	35	93 (85.3%)	10	6	16 (14.7%)	

In the present study CRP was positive in 42(38.5%) cases with equal distribution between EOS and LOS. TLC less than 5000/mm^3 was observed in 14 neonates. Number of LOS neonates, who had leucopenia, is more compared to EOS, though not statistically significant (p=0.68). TLC more than 20000/mm^3 was observed in 19 neonates. EOS and LOS were almost equal in distribution. Absolute neutrophil count (ANC) <1800/mm^3 was observed in 10 neonates, LOS neonates were more in number; also not statistically significant (p=0.86) Thrombocytopenia was observed in 61 neonates (60.0%), observed more in LOS neonates (54.1% vs. 45.9%) (Table-3). Among the 109 enrolled cases, 16 neonates died, mortality was observed in 16 (14.7%) cases (Table-4). The rest were discharged with an average duration of hospital stay of 7 days.

DISCUSSION

Neonatal septicemia is one of the major factors contributing to the high neonatal mortality and morbidity. The major problem in neonatal infections is the identification of the sick infant. It is desirable to administer appropriate therapy as early as possible to the infected infant. The incidence of septicemia has been reported by several workers to be higher in males than females [11-14]. In the present study, it was found that the incidence of septicemia was higher in males compared to females. Varsha *et al*., in their study reported that 74.6% of neonates evaluated for sepsis were less than 3 days of age and 25.3% were in the late onset sepsis group [11]. In the present study, 51 neonates (46.8%) were aged less than or equal to 3 days of age and the rest 58 neonates (53.2%) belonged to greater than 3 days of age. In studies done by Khatua *et al*., [15] and Klein Jo *et al*., [16] refusal to feed, lethargy, diarrhea, hypothermia were the main clinical features in neonates with sepsis. In the present study, refusal to feed, respiratory distress, convulsions, jaundice, and lethargy were the main clinical features. Despite the increased availability of innovative molecular technologies for detecting and reporting microbial pathogens, most clinicians still regard the isolation of bacteria and antimicrobial susceptibility report as the most important test results generated by clinical microbiology laboratory [17]. However, blood culture may be sterile many a times in spite of presence of clinical and laboratory signs. This could be because the bacterial inoculum may be small, transitory or the blood culture may be unable to pick it up because of preexisting antibiotics. Knowing that up to a third of cultures can be sterile, then it is evident that actual number of infected neonates will be under reported and as a result the positive predictive value of a test used in sepsis screen will be lowered [18]. In the present study, blood culture positivity was observed in 24 (22%) neonates, of these 11 (45.8%) were EOS and 13 (54.2%) were LOS. Klebsiella was isolated in 50% of culture positive cases followed by CONS and Enterococci. They were mostly resistant to commonly used antibiotics, only sensitive to Vancomycin and Cefoperazone. CRP is synthesized within 6 to 8 hours of an inflammatory stimulus. As infection is the most likely cause of inflammation in the neonate, elevation of CRP has been a useful marker for sepsis in many studies, although sensitivity and negative predictive values are not high enough for CRP alone to be a definitive diagnostic test. A single CRP value done at the time of admission may not identify all neonates with sepsis; serial levels done 24 hours apart increase the sensitivity of CRP determinations. In the present study CRP was positive in 42 (38.6%) cases with equal distribution between EOS and LOS. TLC less than 5000/mm^3 was observed in 14 neonates. Number of LOS neonates, who had leucopenia, is more compared to EOS. TLC more than 20000/mm^3 was observed in 19 neonates. EOS and LOS were almost equal in distribution. ANC < 1800/mm3 was observed in 10 neonates. LOS neonates were more in number. A reduction in the number of circulating platelets has been

shown to be an insensitive, a nonspecific and a relatively late indicator of serious bacterial infection during the neonatal period. Thrombocytopenia was observed in 61 neonates. It is observed more in LOS neonates. Mortality was observed in 16 (14.7%) neonates. The rest were discharged with an average duration of hospital stay of 7 days.

CONCLUSION

Neonatal septicemia constitutes an important cause of morbidity and mortality amongst neonates in Bangladesh. Accurate and timely diagnosis of neonatal sepsis is a challenge both to the clinician and the laboratory. A positive blood culture and the antibiotic susceptibility testing of the isolates are the best guide in choosing the appropriate antimicrobial therapy in treating neonatal septicemia.

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