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ORIGINAL ARTICLE

Bacteria Causing Early Onset Sepsis in Neonates Admitted in Neonatal Intensive Care Unit of a Military Hospital in Muzaffarabad, Azad Kashmir

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ABSTRACT

Objective: To determine the burden of early onset of sepsis (EOS) in suspected neonates and to assess the most common causative agents of EOS in these neonates.

Methods: This prospective cross-sectional study was conducted at H.H. Sheikh Khalifa Bin Zayed Al Nahyan Hospital/Combined Military Hospital, Muzaffarabad, Pakistan from January 2020 to June 2021. All neonates admitted in Neonatal Intensive Care Unit (NICU) during first 3 days of life with suspicion of sepsis, based on maternal history or neonatal clinical examination were enrolled. EOS was defined based on the presence of clinical sepsis developed within 72 hours of life or if positive blood/cerebrospinal fluid (CSF) cultures were detected . This information along with the bacteria causing EOS was noted.

Results: Of 109 suspected neonates for EOS, positive blood culture for EOS was observed in 26 (23.9%) neonates. Risk of EOS was 7 times higher among neonates with total leucocyte count (TLC) ≥30,000 per mm as compared to neonates with < 30,000 per mm of TLC (aOR 7.19, 95% CI 2.12 to 24.31, p-value 0.002). Gram positive was the most common bacterial isolates, i.e., 15 (57.69%) whereas gram negative was observed in 11 (42.31%) neonates. Of 15 neonates with gram positive bacteria, all had staphylococcus aureus, i.e., 15 (100%) whereas of 11 neonates with gram negative bacteria, Escherichia coli was observed in majority of the neonates, i.e., 7 (63.64%).

Conclusion: In our study cohort, a significant occurrence of EOS we observed. Specifically, gram-positive organism (staphylococcus aureus) was the predominant cause of sepsis.

Keywords: Early Onset of Sepsis, Escherichia Coli, Neonates, Pakistan, Staphylococcus Aureus.

INTRODUCTION

Early-onset sepsis (EOS) is a serious medical condition that is instigated by the vertical spread of pathogens from the mother to the baby during delivery or from intrauterine infection.[1-3] EOS typically presents within 72 hours after birth[4] and is diagnosed when a blood culture confirms the presence of infection. It is a major cause of mortality and morbidity during the neonatal period and requires prompt diagnosis and treatment to improve outcomes.[5]

Developed countries have observed a noteworthy reduction in EOS among both preterm and term infants due to advancements in clinical practices and the effectiveness of preventive measures.[6] However, in developing country, neonatal sepsis is one of the important health concern. Understanding the epidemiology of infections is crucial in determining the appropriate empirical antibiotic therapy for neonatal care. In addition, with the evolving microbiology of EOS, it is crucial to assess continually the effect of this disease on short- and long-term outcomes along with antibiotic resistance.[7,8]

The rationale of this study is that in country like Pakistan, where financial restrain and limited health care resources is a serious problem, there is a dire need of continuous monitoring of the changes in the pattern of EOS and its associated factors in neonates. The aim of this study is to determine the burden of EOS in suspected neonates and to determine the most common causative agents of EOS in these patients born in Muzaffarabad Military hospital. The determination of the causative agent will help narrow down the most susceptible antibiotic and combat major problems like antibiotic resistance and other related complications.

METHODS

A prospective cross-sectional study was carried out at the pediatric medicine department of H.H Sheikh

Khalifa Bin Zayed AlNahyan Hospital also known as Combined Military Hospital, Muzaffarabad, Pakistan from January 2020 to June 2021.

The ethics committee and relevant authorities were approached for ethical approval. In accordance with the principles of the Helsinki Declaration, parents were informed of the study's risks and benefits before providing written consent for the assessment and intervention of their children.

All neonates admitted in Neonatal Intensive Care Unit (NICU) during first 3 days of life with suspicion of sepsis, on the basis of maternal history or neonatal clinical examination were enrolled. Infants with proven viral illness, perinatal asphyxia, major congenital anomalies like neural tube defects, chest deformities, and congenital heart disease were excluded.

Sample size was calculated using Open Epi sample size calculator using following parameters: confidence interval 95%, margin of error 5%, reported prevalence of early onset of sepsis in neonates 5.6%.[9] The estimated sample size came out to be 82. However, the current study has enrolled 109 neonates with suspected sepsis in this study.

Detailed maternal history was obtained from the mother and medical records. Furthermore, clinical evaluation was carried out and noted in a predesigned proforma along with the demographic characteristics. Neonatal characteristics, such as age, gender, weight, duration of hospital stay, gestational age, term status, mode of delivery, presenting symptoms, and laboratory investigations were observed. Whereas maternal characteristics such as age of the mothers, parity status, and maternal risk factors like Pervaginal leak of >18 hours, intrapartum fever >37 °C, premature onset of labor, chorioamnionitis, "dai" trial and urinary tract infection were observed. Cultures of blood and cerebrospinal fluid (CSF) were obtained. A diagnosis of EOS was made if the cultures came back positive.

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 24. Median inter quartile range (IQR) were calculated for quantitative variables such as age and weight while frequencies and percentages were calculated for gender of the neonates, term status, mode of delivery, presenting symptoms and laboratory investigations. Moreover, maternal age, parity status, and maternal risk factors were also reported in the form of frequencies and percentages. Chi-Square/Fisher-Exact test was applied to see the association of EOS with neonatal and maternal characteristics. The p-value ≤0.05 was considered as significant. Moreover, binary logistic regression was applied on all those variables found significant in chi-square contingency table. Both univariable and multivariable logistic regression were applied.

RESULTS

Of 109 suspected neonates, the median (IQR) age was 2 (1-2) days. There were 56 (51.4%) males and 53 (48.6%) females. The median (IQR) weight of the neonates was 2.4 (2-3 KG). Most of the neonates had gestational age of ≥37 weeks, i.e., 67 (61.5%). Preterm was observed in 47 (43.1%), term in 51 (46.8%), and post-term in 11 (10.1%) neonates. Presenting symptoms showed that fever was observed in 28 (25.7%), hypothermia in 38 (34.9%), fits in 3 (2.8%), moaning in 36 (33%), respiratory distress in 28 (25.7%), cyanosis in 19 (17.4%), apnea in 5 (4.6%), reluctant to feed in 35 (32.1%), lethargy in 38 (34.9%), and excessive cry in 4 (3.7%) of the neonates. Total leukocyte count (TLC) count of <30,000 per mm was observed in 57 (52.3%) and <6 mg/dl C - reactive protein (CRP) was observed in 84 (77.1%) neonates.

Maternal characteristics showed that 60 (55%) of the neonates had a maternal age of 20-30 years whereas primiparous was observed in 51 (46.8%) and multiparous in 48 (44%) of the neonates. Maternal risk factors showed that Pervaginal leak of >18 hours was observed in 27 (24.8%), intrapartum fever of >37°C in 34 (31.2%), premature onset of labor in 23 (21.1%), chorioamnionitis in 3 (2.8%), and urinary tract infection in 18 (16.5%) of the mothers. The frequency of positive blood culture for EOS was observed in 26 (23.9%) of the neonates. A significant association of EOS was observed with age (p-value 0.010), duration of hospital stay (p-value 0.014), term status (p-value 0.003), and TLC count (p-value <0.001) (Table 1). An insignificant association of EOS was observed with maternal age (p-value 0.569), and maternal risk factors (p-value 0.061) (Table 2). The findings of the multivariable analysis showed that after adjusting for other covariates, the risk of EOS was 7 times higher among neonates with TLC ≥ 30,000 per mm as compared to neonates with < 30,000 per mm of TLC (aOR 7.19, 95% CI 2.12 to 24.31, p-value 0.002) (Table 3). Gram positive was the most common bacterial isolates causing EOS observed in 15 (57.69%) of the neonates whereas gram negative bacteria was observed in 11 (42.31%) of the neonates. Among the gram-positive organisms staphylococcus aureus was most frequent 15 (100%), showed more sensitivity to Meropenem 13 (86.7%), Ciprofloxacin 12 (80.0%), Imipenem 11 (73.3%), Vancomycin 9 (60.0%), as compared to Cephalosporins 7 (47.0%), Ampicillin 6

(40.0%), and aminoglycosides 5 (33.3%). While in gram negative organism Escherichia coli was observed in 7 (63.64%) neonates and were mostly sensitive to Meropenem 6 (85.7%), Ceftazidime 6 (85.7%), Imipenem 5 (71.4%), Ceftriaxone 4 (57.1%), and Ciprofloxacin 4 However, 5 (71.4%) of Escherichia coli isolates were resistant to Ampicillin. (Table 4) Multiple resistance (resistance to two or more drugs) was observed in 6 (40.0%) gram positive and 7 (63.6%) in gram negative bacteria respectively.

Table 1: Comparison of sociodemographic and clinical characteristics of neonates with early onset of sepsis (n=109)

Characteristics	Total	Early Onset of Sepsis		p-value
		Yes (n=26)	No (n=83)	
Age, days				
≤2	60	20 (33.3)	40 (66.7)	0.010^*
>2	49	6 (12.2)	43 (87.8)	
Gender				
Male	56	17 (30.4)	39 (69.6)	0.101^
Female	53	9 (17.0)	44 (83.0)	
Weight, kg				
≤3	87	19 (21.8)	68 (78.2)	0.327^
>3	22	7 (31.8)	15 (68.2)	
Duration of Hospital Stay, days				
≤7	72	12 (16.7)	60 (83.3)	0.014^*
>7	37	14 (37.8)	23 (62.2)	
Gestational Age, weeks				
<37	42	10 (23.8)	32 (76.2)	0.993^
≥37	67	16 (23.9)	51 (76.1)	
Term Status				
Preterm	47	11 (23.4)	36 (76.6)	0.003~*
Term	51	8 (15.7)	43 (84.3)	
Post Term	11	7 (63.6)	4 (36.4)	
Mode of Delivery				
Emergency LSCS/ Elective LSCS	53	14 (26.4)	39 (73.6)	0.767~
Normal Vaginal Delivery	40	8 (20.0)	32 (80.0)	
Assisted Vaginal Delivery	16	4 (25.0)	12 (75.0)	
Presented Symptoms				
Fever	28	6 (21.4)	22 (78.6)	0.727^
Hypothermia	38	10 (26.3)	28 (73.7)	0.659^
Moaning	36	11 (30.6)	25 (69.4)	0.249^
Respiratory Distress	28	10 (35.7)	18 (64.3)	0.088^
Cyanosis	19	6 (31.6)	13 (68.4)	0.385~
Reluctant to Feed	35	5 (14.3)	30 (85.7)	0.107^
Lethargy	38	12 (31.6)	26 (68.4)	0.166^
Laboratory Investigation				
TLC count, per mm				
≥30,000	52	22 (42.3)	30 (57.7)	<0.001^*
<30,000	57	4 (7.0)	53 (93.0)	
CRP, mg/dl				
<6	84	23 (27.4)	61 (72.6)	0.113^
≥6	25	3 (12.0)	22 (88.0)	

CRP: C-reactive protein, LSCS: Lower segment cesarean section, TLC: Total leucocyte count, Kg: Kilogram
^Chi-Square/~Fisher Exact test applied,*p-value ≤ 0.05

Table 2: Comparison of maternal sociodemographic and clinical characteristics with early onset of sepsis (n=109)

Characteristics	Total	Early Onset of Sepsis		p-value
		Yes (n=26)	No (n=83)	
Maternal Age, years				
<20	20	3 (15.0)	17 (85.0)	0.569
20-30	60	15 (25.0)	45 (75.0)	
>30	29	8 (27.6)	21 (72.4)	
Parity Status				
Primiparous	51	9 (17.6)	42 (82.4)	0.248
Multiparous	48	13 (27.1)	35 (72.9)	
Grand Multiparous	10	4 (40.0)	6 (60.0)	
Maternal Risk Factors				
Pervaginal Leak >18 hours	27	9 (33.3)	18 (66.7)	0.061
Intrapartum Fever >37°C	34	12 (35.3)	22 (64.7)	
Premature Onset of Labour	23	3 (13.0)	20 (87.0)	
Urinary Tract Infection	18	1 (5.6)	17 (94.4)	
Others	7	1 (14.3)	6 (85.7)	

Fisher Exact test was applied

Table 3: Binary logistic regression analysis for variables predicting early onset of sepsis in suspected neonates (n=109)

	Univariable Analysis		Multivariable Analysis	
	COR (95% CI)	p-value	aOR (95% CI)	p-value
Age, days				
≤2	3.58 (1.31 to 9.83)	0.013*	2.29 (0.76 to 6.89)	0.137
>2	1		1	
Duration of Hospital Stay, days				
≤7	0.32 (0.13 to 0.81)	0.016*	0.67 (0.23 to 1.88)	0.451
>7	1			
Term Status				
Preterm	0.32 (0.07 to 1.37)	0.126		
Term	0.55 (1.35 to 2.29)	0.418		
Post Term	1			
TLC Count, per mm				
≥30,000	9.71 (3.05 to 30.86)	<0.001*	7.19 (2.12 to 24.31)	0.002*
< 30,000	1		1	

COR: Crude odds ratio, aOR: Adjusted odds ratio, CI: Confidence interval, *p-value ≤ 0.05

DISCUSSION

This study was conducted in Muzaffarabad city, which is the capital and largest city of Azad Kashmir, and the 60th largest in Pakistan. Moreover, the study was carried out in one of the largest combined military hospitals of the Muzaffarabad city. The findings of the current study showed that the positive blood culture for EOS was observed in 23.9% of the neonates. This proportion is higher than what is reported in literature. It was observed in previous literature that studies with larger sample size have reported too low prevalence than those with smaller sample size like the current study. Moreover, as reported earlier, the risk of EOS would be higher in low and middle countries than high income countries. Similar to current study findings somewhat same findings were reported in previous studies from Pakistan, Iran, Bangladesh, India, and Indonesia.[9-16]

According to the current study findings, the risk of EOS was 68% lower among preterm status as compared to post-term status. While the risk of EOS was 7 times higher among neonates with TLC ≥ 30,000 per mm as

Table 4: Common bacterial isolates in neonates with early onset of sepsis (n=26)

	Sensitive n (%)	Indeterminate n (%)	Resistance n (%)
Staphylococcus aureus (n=15)			
Meropenem	13 (86.7%)	-	2 (13.3%)
Ciprofloxacin	12 (80.0%)	-	3 (20.0%
Imipenem	11 (73.3%)	-	4 (26.7%)
Vancomycin	9 (60.0%)	-	6 (40.0%)
Cephalosporins	7 (47.0%)	-	8 (53.0%)
Ampicillin	6 (40.0%)	-	9 (60.0%)
Aminoglycosides	5 (33.3%)	-	10 (66.7%)
Escherichia coli (n=7)			
Meropenem	6 (85.7%)	-	1 (14.3%)
Ceftazidime	6 (85.7%)	-	1 (14.3%)
Imipenem	5 (71.4%)	-	2 (28.6%)
Ceftriaxone	4 (57.1%)	-	3 (42.9%)
Ciprofloxacin	4 (57.1%)	-	3 (42.9%)
Ampicillin	2 (28.6%)	-	5 (71.4%)
Acinetobacter Baumannii (n=2)			
Ceftriaxone	2 (100%)	-	-
Meropenem	2 (100%)	-	-
Moxifloxacin	2 (100%)	-	-
Gentamycin	1 (50%)	-	1 (50%)
Tobramycin	1 (50%)	-	1 (50%)
Klebsiella pneumonia (n=2)			
Imipenem	2 (100%)	-	-
Meropenem	2 (100%)	-	-
Ciprofloxacin	1 (50%)	-	1 (50%)
Amikacin	2 (100%)	-	-
Tazobactum-piperacillin	2 (100%)	-	-

compared to neonates with < 30,000 per mm of TLC. Previous literature has reported postnatal age, body weight and parity as independent risk factors for EOS.[17] Various other studies reported parity, delivery method, bleeding issues, and premature rupture of membrane (PROM) as maternal factors in prediction of EOS among neonates. Whereas appearance, pulse, grimace, activity and respiration (APGAR) score in the 1st and 5th minute, resuscitation after delivery, duration of stay in the hospital, and newborn age on admission as neonatal risk factors which predicted the occurrence of sepsis.[17-19]

As per the current study findings, gram positive was the most common bacterial isolates causing EOS in neonates as compared to gram negative bacteria. Neonates with gram positive bacteria, all had staphylococcus aureus while neonates with gram negative bacteria, Escherichia coli was observed more as compared to Acinetobacter Baumannii and Klebsiella pneumoniae. Comparable to our current study findings, a study reported that Staphylococcus aureus was the common bacteriological profile found in neonates.[20] Similar estimates as reported in the current study were also observed in recent studies conducted in

Pakistan.[21,22] However, contrary to the current study findings, gram negative bacteria was the most common cause of EOS in a previously published Pakistani study.[10] Antibiotic sensitivity patterns of the prevalent species must be studied in depth to combat problems such resistance to common antibiotics and to determine the drug that is most suitable to combat the causative organism. Agents along with their sensitivity pattern vary greatly from region to region hence it is of utmost importance to have a clear picture of the drug that will be most effective and to administer it as promptly as possible.

There were certain limitations in the current study. First, certain important predicting variables such as longer duration of invasive mechanical ventilation, longer duration of use of urine catheter, delay in breastfeeding, and longer duration of hospitalization were not reported.[23-25] Secondly, smaller sample size and inclusion of single center study was also one of the limitations. Lastly, this study did not longitudinally follow the patients for longer duration of time due to the limitation of resources and time period. It is believed that reporting of therapeutic outcome could also aid in the improvement of the strength of the study. Despite its limitations, this study is noteworthy because it reports on the current extent of EOS and bacteriological profile in a significant public sector tertiary care hospital in Muzaffarabad. However, further large-scale longitudinal studies are suggested to validate the findings of this study.

CONCLUSION

In our study cohort, a significant occurrence of EOS was observed. Specifically, gram-positive organism (staphylococcus aureus) was the predominant cause of sepsis. In addition, we identified several neonatal risk factors that may cause an increased chance of EOS. A timely detection of these risk factors and with careful probing of antimicrobial sensitivity pattern, may lead to a better management plan for neonates with sepsis.

ETHICAL APPROVAL: The study was approved by the Research ethical committee, SKBZ/ AK CMH Muzaffarabad (Reference Number: DME-225).

AUTHORS' CONTRIBUTIONS: BH, NA, TS: Conception and designing of work, data acquisition and analysis, along with manuscript writing and revision. MA, NR: Conception of work and data acquisition. MS: Conception of work, data analysis and data acquisition. All authors critically reviewed the manuscript and gave final approval of the manuscript.

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