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ORIGINAL ARTICLE

Etiology, risk factors and antibiotic resistance in neonatal sepsis.

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ABSTRACT… Objective: To determine the etiology, risk factors and antibiotic resistance in neonatal sepsis. **Study Design:** Cross-sectional study. **Setting:** Department of Pediatric Medicine, National Institute of Child Health, Karachi, Pakistan. **Period:** October 2023 to March 2024. **Methods:** A total of 174 neonates of both genders, with suspected neonatal sepsis were analyzed. Neonatal and maternal characteristics were noted. Blood sample was collected in aseptic environment and sent to institutional laboratory for blood culture and drug susceptibility testing. **Results:** In a total of 174 neonates, 101 (58.0%) were boys. The mean age, and weight were 9.61±7.86 years, and 2.25±0.85 kg, respectively. Neonatal sepsis on the basis of positive blood culture was reported in 38 (21.8%) neonates. Preterm birth had significant association with neonatal sepsis (44.7% vs. 26.5%, p=0.019). History of maternal UTI during pregnancy had significant linkage with neonatal sepsis (36.8% vs. 11.0%, p<0.001). History of maternal fever during pregnancy had statistically significant association with neonatal sepsis (34.2% vs/ 19.1%, p=0.049). E. Coli, and Klebsiella were the most commonly found bacterial isolates, noted in 8 (21.1%), and 4 (10.5%) neonates, respectively. Most commonly used antimicrobial drugs were found to have high resistance rates against most frequent bacterial isolates. **Conclusion:** E. Coli, and Klebsiella were the most commonly found bacterial isolates in neonatal sepsis. Preterm birth, maternal history of UTI, and maternal history of fever were found to be significant factors linked to neonatal sepsis. Most commonly used antimicrobial drugs were found to have high resistance patterns which should raise alarms.

Key words: E. coli, Fever, Neonate, Preterm, Sepsis.

INTRODUCTION

Neonatal sepsis (NS) is described as a systemic inflammatory response due to a confirmed or suspected infection in neonates.[1,2] Sepsis is among the leading causes of morbidity and mortality in pediatric populations.[3,4] Globally, NS and other infections increased by 12.8%, from 5.6 million in 1990 to 6.3 million in 2019. During the same period, the number of deaths decreased by 12.9%, from 260,000 in 1990 to 227,000 in 2019.[5,6] The prevalence and mortality rates of NS remain high in "low- and middle-income countries (LMICs)", such as Pakistan, likely due to poor hygiene and inadequate infection control practices.[7,8] Recent World Bank data indicates that Pakistan's neonatal mortality rates decreased from 49 in 2011 to 39.4/1000 live-births in 2021.[9]

Early recognition of NS, including understanding its etiology, risk factors, and antibiotic resistance patterns, remains one of the most challenging issues for clinicians today. Delayed diagnosis and inappropriate treatment of NS are linked to systemic and neurological complications, as well as increased mortality.[10,11] Detecting bacteria in the blood is challenging due to factors such as the small number of organisms present at any given time, their intermittent presence in the bloodstream, and the impact of prior antibiotic therapy, which can reduce the likelihood of recovering microorganisms from cultures. Despite these challenges, blood culture remains the gold standard for diagnosing sepsis and determining antibiotic resistance.[12,13]

Early and appropriate diagnosis of NS in very much difficult for physicians and they made NS diagnosis on clinical basis and provide empirical

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treatment protocol that can results in irrational antibiotic use, prolonged hospital stays and cost of therapy but at the same time delay in diagnosis or inappropriate treatment can results in systemic and neurological complication with increased risk of mortality. Therefore, for appropriate diagnosis of sepsis, its pathogen and for antibiotic resistance; blood culture is considered as a gold standard. Therefore, this study was designed in National Institute of Child Health Karachi for finding out the culture-confirmed sepsis in neonates, its etiology, risk factors and antibiotic resistance. Study findings were thought to be helpful in improving management of NS and decrease mortality. The objective of this study was to determine the etiology, risk factors and antibiotic resistance in NS.

METHODS

This cross-sectional study was conducted at the department of pediatric medicine, "National Institute of Child Health, Karachi", from October 2023 to March 2024. Online Open Epi Sample size software was used for calculating sample size by taking proportion of Kabwe M, et al, who reported the culture-confirmed sepsis in 33% of neonates[14], by taking confidential level 95% and margin of error 7%. Calculated sample size was 174 cases. Non-probability consecutive sampling technique was adopted. Inclusion criteria for cases were neonates (0-28 days) of either gender and suspected cases of NS. Neonates born before 32 weeks gestation (as per antenatal record) or birth weight less than 1000 grams were excluded. Neonates who had already received antibiotics in the past 3 days were also not included. NS was suspected if the neonate had any of these two: i) hypothermia (< 36 °C) or hyperthermia (> 38.5 °C), ii) respiratory rate > 60/min, heart rate >190 beats/min at rest. Confirmation of NS was made on the basis of positive blood culture. Early-onset NS (EONS) was labeled among neonates who were aged up to 3 days. Late-onset of NS (LONS) was named if the neonate aged between 4-28. Low-birth weight (LBW) was described as birth weight below 2500 grams (as per medical record).

This study was performed after the permission of "Institutional Ethical and Review Board (IERB)" of NICH (IERB-51/2023, dated: 20-12-2023). Informed consents were sought from parents/ caregivers of all neonates involved in this study. Neonates visiting outpatient department or admitted at NICU of NICH, fulfilling the inclusion criteria and avoiding the exclusion criteria were enrolled. Demographic details of each neonate were obtained including name, age and gender. Weight (kg) of each neonate was measured with the help of digital baby weighing scale. A detailed medical history from the mother or caregivers was obtained such as delivery place (home or hospital), delivery mode, gestational age (weeks) and birth weight (kg). Vitals of each neonate including temperature, respiratory rate and heart rate were obtained. Blood sample of each neonate was collected in aseptic environment and sent to institutional laboratory for complete blood count (CBC), blood culture and drug susceptibility testing. Each neonate was treated according to standard protocols of NICH.

For data analysis, IBM-SPSS Statistics, version 26.0 was used. Mean and standard deviation (SD) were calculated for quantitative variables like age (days), and weight (Kg). Frequency and percentages were calculated for qualitative variables like gender, age groups, delivery place, delivery mode, clinical presentation, NS, type of NS, isolated pathogen and antibiotic resistance. Risk factors such as gender, age, present weight, birth weight, gestational age, delivery place, delivery mode and clinical presentation were controlled through stratification. Chi-square test was applied to compare categorical data taking $p<0.05$ as significant.

RESULTS

In a total of 174 neonates, 101 (58.0%) were boys. The mean age, and body weight were 9.61 ± 7.86 years, and 2.25 ± 0.85 kg, respectively. Low-birth weight was reported in 76 (43.7%) babies. Socio-economic status was low in 89 (51.1%) patients. There were 111 (63.8%) neonates who were born term. Delivery place was hospital among 152 (87.4%) cases. Delivery mode was cesarean section in 97 (55.7%) cases. Table-I is showing neonatal and maternal characteristics of study

participants.

Characteristics			Number (%)
Neonatal	Age (days)	<7	75 (43.1%)
		≥7	99 (56.9%)
	Gender	Boys	101 (58.0%)
		Girls	73 (42.0%)
	Low-birth weight	Yes	76 (43.7%)
		No	98 (56.3%)
Maternal	Socio-economic status	Low	89 (51.1%)
		Middle	66 (37.9%)
		High	19 (10.9%)
	Gestation	Term	111 (63.8%)
		Pre-term	53 (30.5%)
		Post-term	10 (5.7%)
	Delivery place	Home	22 (12.6%)
		Hospital	152 (87.4%)
	Delivery mode	Cesarean section	97 (55.7%)
		Vaginal delivery	77 (44.3%)
	History of maternal UTI during pregnancy		29 (16.7%)
	History of maternal fever during pregnancy		39 (22.4%)

Table-I. Demographic and clinical characteristics (n=174)

NS on the basis of positive blood culture was reported in 38 (21.8%) neonates. Preterm birth had significant association with NS (44.7% vs. 26.5%, p=0.019). History of maternal UTI during pregnancy (36.8% vs. 11.0%, p<0.001), and history of fever during pregnancy (34.2% vs/ 19.1%, p=0.049) had statistically significant association with NS. Details about the association of NS with neonatal and maternal characteristics are shown in Table-II.

In 38 confirmed NS cases, E. Coli, and Klebsiella were the most commonly found bacterial isolates, noted in 8 (21.1%), and 4 (10.5%) neonates, respectively. Yeast candida was found in 6 (15.8%) isolates. Figure-1 is showing distribution frequency of microbial isolates.

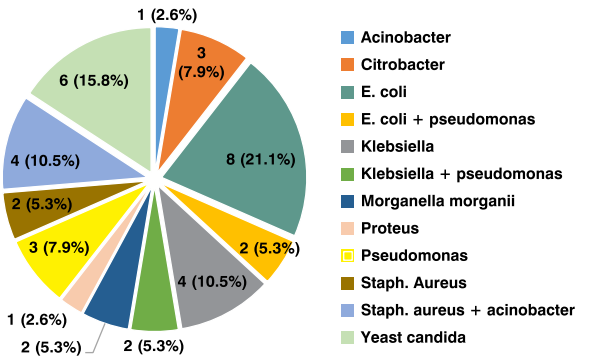

Figure-1. Distribution frequency of causative agents of neonatal sepsis (n=38)

Details about the antimicrobial resistance patterns of most frequently noted bacterial isolates against most commonly used antimicrobials are shown in Table-III.

Characteristics			Neonatal Sepsis		P-Value
			Yes (n=38)	No (n=136)	
Neonatal	Age (days)	<7	12 (31.6%)	63 (46.3%)	0.105
		≥7	26 (68.4%)	73 (53.7%)	
	Gender	Boys	25 (65.8%)	76 (55.9%)	0.274
		Girls	13 (34.2%)	60 (44.1%)	
	Low-birth weight	Yes	21 (55.3%)	55 (40.4%)	0.103
		No	17 (44.7%)	81 (59.1%)	
Maternal	Socio-economic status	Low	19 (50.0%)	70 (51.5%)	0.975
		Middle	15 (39.5%)	51 (37.5%)	
		High	4 (10.5%)	15 (11.0%)	
	Gestation	Term	17 (44.7%)	94 (69.1%)	0.019
		Pre-term	17 (44.7%)	36 (26.5%)	
		Post-term	4 (10.5%)	6 (4.4%)	
	Delivery place	Home	4 (10.5%)	18 (13.2%)	0.657
		Hospital	34 (89.5%)	118 (86.8%)	
	Delivery mode	Cesarean section	22 (57.9%)	75 (55.1%)	0.763
		Vaginal delivery	16 (42.1%)	61 (44.9%)	
	History of maternal UTI during pregnancy		14 (36.8%)	15 (11.0%)	<0.001
	History of maternal fever during pregnancy		13 (34.2%)	26 (19.1%)	0.049

Table-II. Association of neonatal sepsis with neonatal and maternal characteristics (N=174)

Antimicrobial Agents	Coli (n=8)	Klebseilla (n=4)
Penicillins	75.0%	87.5%
Aminoglycosides	87.5%	75.0%
Sulfonamides	75.0%	100%
Macrolides	100.0%	75%
Amphenicol	50.0%	62.5%
Quinalones	75.0%	62.5%
Cephalosporins	75.0%	87.5%
Carbapenems	0%	12.5%

Table-III. Antibiotic resistance patterns against most frequent bacterial isolates (N=38)

DISCUSSION

This study is one of the few ones that evaluated micro-organism spectrum, treatment outcomes, and antibiotic resistance patterns among NS patients at a tertiary care hospital from Pakistan. In suspected NS, 21.8% neonates had confirm NS based on positive blood culture findings. In comparison to the present study, Kabwe et al from Zambia reported the frequency of confirmed NS among suspected NS cases as 33%.[14] Rafi et al from Bangladesh noted the frequency of confirmed NS in suspected noenatal sepsis as 32.0%.[15] Our findings reporting the frequency of NS as 21.8% is also lesser than what was reported by Worku et al from Ethiopia (36.5%).[16] The variation in the frequency of confirmed NS among our study and other developing regions of the world could be due to variation in diagnostic criteria for suspected NS. Sepsis is commonly diagnosed based on clinical observations rather than microbiological evidence.[7]

We noted that preterm birth was significantly associated with NS. These findings correlate well with the local data where Atif et al from South Punjab who reported preterm birth as a significant factors co-existing with NS.[7] The same study also reported LBW, and EONS to have significant linkage with NS but we did resonate these findings.[7] LBW was proportionally high among neonates with confirmed sepsis (55.3% vs. 40.4%) but the difference did not reach statistical significance (p=0.103).

History of fever, as well as UTI during pregnancy turned out to be a significant factor related to NS in the present study. Regional data has reported maternal history of UTI in the 3rd trimester to raise the risk of NS as 5 times.[7] A meta-analysis revealed that maternal infections significantly surged the chances of NS within 1st week of life.[17] Maternal infections can often be transmitted in utero or during birth to the baby, commonly leading to NS.[18] Other maternal risk factors, such as prolonged labor and premature rupture of membranes, which heighten the risk of ascending infection from the birth canal into the amniotic fluid, have been linked to an increased risk of NS in various studies but we did not evaluate these maternal aspects in this study.[19,20] E. Coli and Klebsiella were the most frequent bacterial isolates in this study. Klebsiella species and E. coli have been pointed out to be the most frequently identified gram-negative bacteria, exhibiting high resistance to the initial parenteral antibiotics used from many parts of the world.[17,21] The most treatment adjustments are generally based on the clinician's clinical judgment rather than microbiological reports. The present study reported high resistance rates among commonly used antimicrobials which raises alarms. Antimicrobial resistance among most commonly found bacterial isolates has become a global concern in the recent decades.[22] Regular surveillance and reporting of microbial patterns are required to update existing guidelines about the treatment strategy in NS.

This study accompanies some inherent limitations. As this was a single center study, conducted on a relatively modest sample size, our findings need further verification in large multicentral studies. We were unable to report maternal risk factors of NS like prolonged labor or premature rupture of membranes.

CONCLUSION

E. Coli, and Klebsiella were the most commonly found bacterial isolates in neonatal sepsis. Preterm birth, maternal history of UTI, and maternal history of fever were found to be significant factors linked to neonatal sepsis. Most commonly used antimicrobial drugs were found to have high resistance patterns which should raise alarms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	Muhammad Ashfaq	Concept and design, Critical revisions, Final approval.	
3	Wajid Hussain	Interpretation of data, critical revisions, Final approval.	
4	Fatima Ismail	Interpretation of data, critical revisions, Final approval.	
5	Bader-U-Nisa	Interpretation of data, critical revisions, Final approval.	
6	Mehrunnisa Yasir	Interpretation of data, critical revisions, Final approval.	