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ORIGINAL ARTICLE

Neonatal sepsis – etiological study at the Central Park teaching Hospital, Lahore.

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ABSTRACT… Objective: To identify the causative bacteria responsible for early and late onset neonatal sepsis and to determine their antibiotic susceptibilities at Central Park Teaching Hospital. **Study Design:** Cross-sectional study. **Setting:** Neonatal Intensive Care Unit (NICU) of Central Park Teaching Hospital, Lahore. **Study Period:** Jan to June 2024. **Methods:** Neonates up to 28 days old with clinical features of sepsis were randomly sampled and included in the study. Key maternal and neonatal risk factors were evaluated. Blood cultures were analyzed to identify microbial isolates and assess resistance patterns. Demographic data, clinical features, and blood culture results were collected and analyzed using SPSS version 26.0. **Results:** Out of the cases studied, 55% were male. Early onset sepsis was slightly more prevalent at 51.5%. Significant maternal risk factors for early sepsis included maternal fever, offensive liquor, and prolonged second stage of labor. Blood cultures were positive in 18.8% of cases, with early onset sepsis accounting for 44.7% of positives and late onset sepsis for 55.3%. Gram-positive bacteria were more common in early sepsis (48.1%), with Acinetobacter baumannii and Candida blankii being notable isolates, while Gram-negative bacteria were more prevalent in late sepsis (63.6%), with Bacillus spp. and Burkholderia cenoc as key pathogens. Coagulase-negative Staphylococcus was the most frequently isolated pathogen in both early and late sepsis. **Conclusion:** The study underscores the importance of developing tailored antimicrobial strategies based on the timing of sepsis onset to improve neonatal outcomes. Significant differences in microbial distribution between early and late neonatal sepsis were observed ($p < 0.001$).

Key words: Antibiotic Resistance, Antibiotic Susceptibilities, Early Onset Sepsis, Late Onset Sepsis, Microbial Isolates, Neonatal Sepsis, NICU.

INTRODUCTION

Neonatal sepsis is a serious and potentially life-threatening infection that occurs in infants under 28 days old. In resource-poor countries, neonatal sepsis is a worldwide health issue.[1] Developing countries have the highest incidence, affecting 3 million infants annually. The syndrome is dangerous for neonates, especially in communities without adequate medical care.[2] Preterm and low-birth-weight babies are at higher risk of neonatal sepsis. Prolonged rupture of membranes, maternal fever during birth, and newborn invasive interventions are risk factors. Improved prenatal and neonatal care must address these risk factors to reduce newborn sepsis in vulnerable groups.[3]

Neonatal sepsis can be categorized into early-onset and late-onset sepsis based on the timing of onset. Early-onset neonatal sepsis, occurring within the first three days of life, is most commonly caused by pathogens such as Group B Streptococcus (GBS) and coagulase-negative Staphylococcus.[4] In contrast, late-onset neonatal sepsis, which manifests after three days of life, is attributed to a broader range of pathogens including coagulase-negative Staphylococcus, E. coli, Klebsiella, Enterobacter, Candida, Serratia, Acinetobacter, and various anaerobes.[5]

The risk factors for early-onset sepsis include maternal GBS colonization, premature rupture of membranes, preterm birth, maternal fever during labor, and low Apgar scores at birth. Late-onset sepsis is often associated with factors such as prematurity, the presence of central venous and

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urinary catheters, mechanical ventilation, and gastrointestinal issues.[6] Prompt diagnosis and appropriate antibiotic treatment are crucial for improving outcomes and reducing the mortality rate associated with neonatal sepsis.[7] Effective management is hampered by evolving microbial resistance, necessitating an understanding of local etiological agents and their antibiotic profiles.[8,9]

These results can be used to refine neonatal sepsis management protocols, ultimately improving clinical outcomes and reducing sepsis-related morbidity and mortality. At Central Park Teaching Hospital, there is a lack of recent data on the causative agents and resistance patterns in our NICU. This study aims to identify the bacteria responsible for early and late onset sepsis in neonates and determine their antibiotic susceptibilities. The findings will inform targeted treatment protocols, improve antibiotic stewardship, and enhance neonatal health outcomes by providing essential data for better clinical management and policy formulation.

METHODS

The study was conducted in the Neonatal Intensive Care Unit (NICU) at Central Park Teaching Hospital over a period of six months. A cross-sectional study design was employed, with random sampling of the neonates admitted to the NICU. The study population consisted of neonates up to 28 days old, who were either delivered at the hospital or referred from other hospitals and exhibited clinical features of sepsis. This population was chosen due to the high burden of sepsis in neonates and the growing concern of microbial resistance.

After obtaining approval from the Institutional Review Board (IRB) (CPMC/IRB-No/1451 dated:02-02-2024), transfusion records of all patients meeting the inclusion criteria were reviewed. Demographic data, age of onset of sepsis, and septic profile details were collected. Operational definitions for this study included: neonates (birth to 28 days of life), early onset of sepsis (birth to 72 hours of life), and late onset of sepsis (72 hours to 90 days of life).

Inclusion criteria for the study was: “Newborns up to 28 days of life, delivered in-hospital or referred from other facilities, and presenting with clinical features of sepsis. Exclusion criteria included patients who had already received antibiotics before blood sampling, premature babies, and neonates with intrauterine growth restriction (IUGR) weighing less than 1.5 kg”. A questionnaire was used as the study instrument. Upon meeting the inclusion criteria, babies were enrolled in the study. Informed verbal consent was obtained from the parents. For each neonate, the following data were collected: bio data, medical record (MR) number, physical findings, and septic profile including Complete Blood Count (CBC), C-Reactive Protein (CRP), and blood cultures and sensitivity tests. This data was analyzed to identify the etiological agents causing sepsis and their antibiotic sensitivity patterns.

Participation in the study was ensured as voluntary through the process of obtaining informed verbal consent from the parents. The parents provided consent and basic information, while the neonates underwent standard diagnostic procedures (CBC, CRP, blood cultures). The duration of participation for each subject was brief, limited to the time required for sample collection and data recording. Data collection took place in the Neonatal ICU at Central Park Teaching Hospital. No additional study-related tests were performed beyond the routine workup for sepsis, and hence no extra costs were incurred.

Data analysis was conducted using SPSS version 26.0. No significant risks or discomfort were anticipated for the study participants. The potential benefits of the study included identifying the etiological agents causing sepsis in neonates and determining their sensitivity to specific antibiotics. Informed verbal consent was obtained from the parents, and references were attached for further review.

RESULTS

The demographic and clinical characteristics of neonatal sepsis patients revealed several key findings. Males constituted 55% and females 45% of the cases. Early neonatal sepsis was

slightly more prevalent (51.5%) than late neonatal sepsis (48.5%). Most neonates were delivered via normal vaginal delivery (60.4%), with the rest via cesarean section (39.6%).

Maternal fever during labor was present in 47.5% of cases. Offensive liquor was noted in 50%, and a prolonged second stage of labor occurred in 35.1% of cases. Delayed cry at birth was observed in 45.5% of neonates, meconium staining in 19.8%, and prematurity in 65.8%. Temperature instability was noted in 34.7% of neonates, reluctance to feed in 35.6%, and vomiting or diarrhea in 39.6%. Cessation or rapid breathing occurred in 25.2%, lethargy or seizures in 35.1%, and bleeding or jaundice in 22.4%. Previous hospital admissions were noted in 28.7%.

Blood cultures were positive in 18.8% of cases, with early neonatal sepsis accounting for 44.7% and late neonatal sepsis for 55.3% of the positive cases. There was no significant association between mode of delivery and type of sepsis (p-value = 0.732). However, maternal fever and offensive liquor were significantly associated with early sepsis (p-values = 0.001 and < 0.001, respectively). Prolonged second stage was also significantly associated with early sepsis (p-value < 0.001). Prolonged rupture of membranes showed no significant association with the type of sepsis (p-value = 0.276).

Meconium staining, prematurity, temperature instability, reluctance to feed, vomiting, diarrhea, abdominal distension, bleeding, jaundice, petechiae, purpura, and previous hospital admission did not show significant associations with the type of neonatal sepsis. However, cessation or rapid breathing was significantly associated with late sepsis (p-value = 0.043).

The distribution of microbial isolates revealed no statistically significant difference between early and late neonatal sepsis (p-value = 0.525). Early neonatal sepsis had more Gram-positive bacteria (48.1%) compared to Gram-negative bacteria (36.4%), while late neonatal sepsis had more Gram-negative bacteria (63.6%) compared to Gram-positive bacteria (51.9%). Overall, negative cultures were more common in both early (53%) and late (47%) neonatal sepsis cases.

EOS had more Gram-positive bacteria (48.1%) than Gram-negative (36.4%), while LOS had more Gram-negative bacteria (63.6%) than Gram-positive (51.9%). Coagulase-negative Staphylococcus was the most common isolate in both EOS and LOS. EOS also saw isolates like Acinetobacter baumannii and Candida blankii, while LOS included Bacillus spp. and Burkholderia cenoc. The difference in organism distribution between EOS and LOS was statistically significant (p < 0.001).

In EOS, Coagulase-negative Staphylococcus showed resistance to Oxacillin, Erythromycin, Trimethoprim/Sulfamethoxazole, and Ciprofloxacin, but sensitivity to Vancomycin and Linezolid. Candida blankii was sensitive to Fluconazole, Voriconazole, and Amphotericin B. Gram-negative rods, such as Burkholderia cepacia and Klebsiella pneumoniae, were resistant to several antibiotics but sensitive to Colistin and Meropenem. Similar resistance patterns were observed in LOS, with Burkholderia cenocepacia and Bacillus spp. showing sensitivity to Colistin, Meropenem, Vancomycin, and Linezolid.

Type of Sepsis	Blood Culture Positive	Blood Culture Negative	Total	P-Value
EOS	17(44.7%)	87(53.0%)	104	0.356
LOS	21(55.3%)	77(47.0%)	98	
Total	38	164	202	

Table-I. Comparison of early and late neonatal sepsis cases with blood culture results at Central Park Teaching Hospital, Lahore

Mode of Delivery	Early Neonatal Sepsis	Late Neonatal Sepsis	Total	P-Value
NVD	64 (61.5%)	58 (59.2%)	122 (60.4%)	0.732
C-section	40 (38.5%)	40 (40.8%)	80 (39.6%)	
Maternal Fever >38°C				
Yes	61 (58.7%)	35 (35.7%)	96 (47.5%)	0.001
No	43 (41.3%)	63 (64.3%)	106 (52.5%)	
Offensive Liquor				
Yes	77 (74.0%)	24 (24.5%)	101 (50.0%)	<0.001
No	27 (26.0%)	74 (75.5%)	101 (50.0%)	
Prolonged Second Stage (>3 hours of active pushing)			**Total**	**P-Value**
Yes	52 (50.0%)	19 (19.4%)	71 (35.1%)	<0.001
No	52 (50.0%)	79 (80.6%)	131 (64.9%)	
Temperature Instability			**Total**	
Yes	36 (34.6%)	34 (34.7%)	70	0.991
No	68 (65.4%)	64 (65.3%)	132	
Total	104	98	202	
Reluctant to Feed			**Total**	
Yes	40 (38.5%)	32 (32.7%)	72	0.389
No	64 (61.5%)	66 (67.3%)	130	
Vomiting, Diarrhea, or Abdominal Distension			**Total**	
Yes	41 (39.4%)	39 (39.8%)	80	0.957
No	63 (60.6%)	59 (60.2%)	122	
Total	104	98	202	

Table-II. Mode of delivery and maternal factors associated with early and late neonatal sepsis at Central Park Teaching Hospital, Lahore

Burkholderia cenoc	**0**	**0.00%**	**2**	**9.50%**	**2**
Burkholderia cepacia	1	5.90%	0	0.00%	1
Candida blankii	4	23.50%	0	0.00%	4
Coagulase-negative Staph	0	0.00%	11	52.40%	11

Table-III. Distribution of Early and Late Neonatal Sepsis Cases with Culture Results and Bacterial Isolates at Central Park Teaching Hospital, Lahore

Bacteria Isolated	Early Neonatal Sepsis	Percentage (of 17)	Late Neonatal Sepsis	Percentage (of 21)	Total
Acinetobacter baumannii	2	11.80%	0	0.00%	2
Bacillus spp	0	0.00%	2	9.50%	2
Burkholderia cenoc	0	0.00%	2	9.50%	2
Burkholderia cepacia	1	5.90%	0	0.00%	1
Candida blankii	4	23.50%	0	0.00%	4
Coagulase-negative Staph	0	0.00%	11	52.40%	11
Coagulase-negative Staphylococcus	9	52.90%	0	0.00%	9
E. coli	0	0.00%	2	9.50%	2
Enterobacter	0	0.00%	2	9.50%	2
Klebsiella pneumoniae	1	5.90%	1	4.80%	2
Listeria monocytogenes	0	0.00%	1	4.80%	1
Total	17	100.00%	21	100.00%	38

Table-IV

DISCUSSION

Even with major research and therapeutic developments in this field, newborn sepsis remains challenging to treat due to a lack of good diagnostic tools.[10] In Pakistan, neonatal sepsis is a serious public health concern that raises the morbidity and fatality rates of infants. Neonatal sepsis can occur in 7 to 38 out of

every 1,000 live births, with significant variability caused by different diagnostic standards and healthcare environments. Inadequate healthcare infrastructure, restricted access to high-quality healthcare services, and socioeconomic inequality all contribute to the burden of newborn sepsis by impeding the efficient management and control of neonatal infections.[11,12]

In our study on neonatal sepsis, 55% of the cases were male, with a nearly equal distribution between early-onset (51.5%) and late-onset sepsis (48.5%). The majority of neonates (60.4%) were delivered vaginally. Key maternal risk factors associated with early sepsis included maternal fever (47.5%), offensive liquor (50%), and prolonged second stage of labor (35.1%). Neonatal factors such as delayed cry (45.5%), prematurity (65.8%), and temperature instability (34.7%) were prevalent, though not all were significantly associated with sepsis onset type. Blood cultures were positive in 18.8% of cases, with early sepsis showing a higher incidence of Gram-positive bacteria like Acinetobacter baumannii and Candida blankii, while late sepsis was more frequently associated with Gram-negative bacteria such as Bacillus spp., Burkholderia cenoc, E. coli, and Enterobacter. Our analysis revealed that specific risk factors like cessation or rapid breathing were significantly associated with late sepsis, while early sepsis had more negative blood cultures. The distinct microbial patterns observed between early and late sepsis underscore the importance of tailored antimicrobial strategies to improve clinical outcomes.

Another study of 18,299 newborns without major congenital anomalies at six Kaiser Permanente hospitals in 1996 analyzed the relationship between key predictors and neonatal bacterial infection. Of these, 2,785 (15.2%) underwent sepsis evaluation, with 62 (2.2%) meeting criteria for infection—22 (0.8%) had positive cultures and 40 (1.4%) showed clinical evidence. Rehospitalization occurred in 67 cases (2.4%), including 2 for group B streptococcus bacteremia. Among 1,568 infants without intrapartum antibiotics, asymptomatic status was linked to lower infection risk, while chorioamnionitis, low absolute neutrophil count, and meconium-stained amniotic fluid were associated with higher risk. Similar findings were observed in treated infants, except chorioamnionitis was not significantly associated. The study suggests that the infection risk in asymptomatic newborns is low, and observation and treatment protocols could be optimized based on specific predictors like maternal fever and absolute neutrophil count.[13]

A local study of 100 neonatal sepsis cases found that 58% were male, with 54% having early-onset sepsis (EOS) and 46% late-onset sepsis (LOS). The most common symptoms were failure to feed (31%), lethargy (23%), and fever (19%). Neurological symptoms included seizures (15%) and irritability (13%), while respiratory symptoms were tachypnea (28%), grunting (18%), and cyanosis (12%). Blood cultures were positive in 32% of cases, with E. coli (9 cases) being the most prevalent organism, followed by Klebsiella (8 cases), Pseudomonas (5 cases), Staphylococcus aureus (4 cases), and Staphylococcus epidermidis (2 cases). Group B Streptococcus and Serratia each accounted for one case.[14]

In another hospital-based case-control study was conducted in the NICU, including 174 neonates diagnosed with sepsis (cases) and 348 neonates without sepsis (controls). Significant associations with sepsis risk were found for maternal age, parity, route of delivery, PROM (premature rupture of membranes), prematurity, birth weight, neonatal gender, and age ($p < 0.05$). The bivariate logistic model identified premature rupture of membranes, gestational age, neonatal age, birth weight, and mode of delivery as the most influential predictors of neonatal sepsis.[15]

By determining the antibiotic susceptibilities of these pathogens, the study provide crucial data to inform targeted treatment protocols, improve antibiotic stewardship, and enhance neonatal health outcomes. The findings also contribute valuable insights for healthcare planning and policy formulation in the region, ultimately aiming to reduce the morbidity and mortality associated

with neonatal sepsis.

CONCLUSION

This study reveals significant differences in the microbial profiles and antibiotic resistance patterns between early-onset sepsis (EOS) and late-onset sepsis (LOS) in neonates. EOS is predominantly associated with Gram-positive bacteria, especially Coagulase-negative Staphylococcus, while LOS shows a higher prevalence of Gram-negative bacteria like Burkholderia cenoc and Bacillus spp. Additionally, maternal risk factors such as fever and offensive liquor were strongly linked to EOS, emphasizing the importance of early identification and management of these conditions to reduce the incidence of neonatal sepsis. The findings should guide the development of targeted antimicrobial protocols, with EOS requiring a focus on Gram-positive coverage (e.g., Vancomycin, Linezolid) and LOS necessitating Gram-negative coverage (e.g., Colistin, Meropenem). Enhanced sepsis screening protocols incorporating clinical risk factors and early laboratory markers are recommended to improve early detection and treatment outcomes. Moreover, the observed resistance patterns underscore the need for robust antibiotic stewardship programs to prevent the development of resistance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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