Original Article

Risk Factors and Clinical Outcomes of Early-Onset Neonatal Sepsis among Pre-Term and Full-Term Neonates in Pakistan: Findings and Implications

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ABSTRACT

Objective: The study aims to analyze the early onset neonatal sepsis (EOS) in pre-term and full-term newborns and the clinical outcomes of the antibiotics used for the treatment.

Study Design: Retrospective observational study.

Place and Duration of Study: This study was conducted at the pathology department, in Tertiary Care Hospital, Multan, Pakistan, from March 2023 to February 2024.

Methods: A total of 657 neonates were admitted to the nursery during a period of six months. Based on inclusion criteria, only 100 newborn babies either in-born or out-born, with symptoms of early onset sepsis were included in this study after consulting with child specialists, clinical pharmacists, and the head nurse. The included patients were either treated with cefotaxime plus amikacin or meropenem, plus amikacin. Primary clinical outcome parameters and risk factors were evaluated.

Results: Mean age study cases was 4.13±0.846 years and predominately female gender 63% was observed. Preterm newborns (63%) were affected by EOS greatly as compared to full-term newborns (37%). The occurrence of EOS was higher in low body weight patients (82%). Mothers who had per vaginal (PV) leaking (43%) and PV bleeding (83%) problems, their children were affected by EOS more. The C-reactive protein (CRP) test was positive in 79% of the patients. Results of antibiotics therapy show that 37% of patients recovered, 37% of patients were stable on therapy and 13% of neonatal deaths were reported. However, patients receiving meropenem showed better recovery.

Conclusion: The study found out low body weight, pre-term, PV leaking and PV bleeding as risk for EOS. CRP test and antibiotic therapy were effective but in order to reduce mortality rate and increase recovery rate, but meropenem is more effective, requiring careful prescribing.

Key Words: Onset neonatal sepsis, Neonates, Antibiotic therapy, Mortality.

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INTRODUCTION

Infections are a significant contributor to disease and mortality during the early stages of life, especially in premature and extremely underweight newborns[1]. Preterm delivery is a major cause of neonatal illnesses and deaths, with most studies focusing on pregnancies before 34 weeks. Sepsis, a systemic infection caused by localized inflammatory reactions, is a growing public health threat due to the involvement of various bacteria. Neonatal sepsis, a 28-day-old infant's medical condition, is classified as early-onset or late-onset, and its severity depends on maternal, environmental, and host variables[1]. The WHO reports 48.9 million sepsis cases globally, with one death occurring every 2.58 seconds, with 20 million children affected, with 2.9 million deaths worldwide[2]. The incidence rate of sepsis is 2824 per 100,000 live with an equal prevalence rate of early-onset sepsis (EOS) and late-onset sepsis (LOS)[3]. EOS occurs within 72 hours due to organism presence, prolonged membrane rupture, foul smelling fluid, fever, chorioamnionitis, preterm birth, and uterine muscle relaxants. Furthermore, Pakistan's neonatal mortality rate is 42 per 1000 live births, higher than neighboring countries like India, Bangladesh, Nepal, Sri Lanka, and Afghanistan, with even Afghanistan having a lower rate[4]. Escherichia coli-induced early-onset sepsis is prevalent in premature and extremely low birth weight newborns, increasing the risk of severe gram negative infections and higher mortality rates[5]. A

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study revealed that gram-positive bacteria, specifically Staphylococcus aureus, were more frequently found in neonates with early-onset sepsis compared to gram-negative bacteria[6].

In addition to premature birth and gram negative infections, the risk of LOS is heightened by hematological parameters, ventilator use, central venous catheter, TPN, and hospital environment, along with other risk factors[7]. Low birth weight, low gestational age, low IgG serum levels and male gender of the neonate cannot be ignored as contributors to LOS[8]. Neonatal sepsis is diagnosed on the basis of clinical presentation and by using sepsis diagnostic markers including blood cultures, hematologic abnormalities, white blood cell count, erythrocyte sedimentation rate, pro-calcitonin and C-reactive protein (CRP)[9]. Group B streptococcus is said to be the most persistent pathogens in full-term infants while in preterm infants, E. coli remains the most frequent pathogen[6]. Antibiotics are given during labor to lower the risk of group B streptococcal sepsis and reduce neonatal illness. This is because the microorganism spectrum[10-11]. Comprehensive understanding about spectrum of group B streptococcus infection promotes initiation of guidance of appropriate antibiotic usage[12]. Antibiotics like ampicillin and cefotaxime, which are used as part of routine practice, exhibited poor activity against many microorganisms[13]. Thus, further studies are needed to assess the management of neonatal early onset sepsis, specifically focusing on the endpoints of safety[14]. The study aimed to identify risk factors for early onset sepsis in preterm and full-term newborns and assess the clinical outcomes of antibiotics used for treatment.

METHODS

A retrospective observational study was conducted at pathology department, on neonates admitted to a public tertiary care teaching hospital's intensive care unit, Multan, Pakistan, from March 2023 to February 2024. Ethics committees approved the study, and patient-related information was accessed for analysis. A study involving 657 neonates revealed an unusual increase in sepsis cases over six months. Only 100 newborns with early onset sepsis symptoms were included after consulting specialists and nurses. The study included patients with high body temperature and respiratory rate, excluding newborns with pneumonia, tetanus, jaundice, or birth injuries. Preterm and full-term babies were treated with cefotaxime or meropenem.

Patients received antibiotics twice daily, based on body weight, with data collected from demographics, antenatal and natal history, maternal information, postnatal and past obstetric history, clinical monitoring parameters, serology reports, and medication therapy. Neonatal sepsis was linked to various parameters such as birth weight, WBC count, and respiratory rate, evaluated by a pediatric medical practitioner and consultant physician. The collected data was entered and analyzed using SPSS version 21. Data was collected such as demographics, antenatal and natal history, maternal information, postnatal and past obstetric history, clinical monitoring parameters, serology reports, and medication therapy.

RESULTS

In our study 63% of preterm newborns were significantly affected by EOS compared to 37% of full-term newborns, with males and females in the preterm group and full-term group respectively (Table 1). The preterm group comprised 45 Inborn and 17 Out-born patients whereas the full-term group comprised 17 Inborn and 21 Out-born patients. The incidence of neonatal sepsis significantly differs between male and female patients, with females having a higher incidence (82.0%) and early-onset sepsis more prevalent in newborns with a body weight below 2.5kg (Table 1)

Table No. 1. Demographics Characteristics of early onset neonatal sepsis in pre-term and full-term newborns

Parameters	Pre-Term (n=62)	Full-Term (n=38)	Total (n=100)
Gender			
Female	37 (59.67%)	26 (68.42%)	63 (63.0%)
Male	25 (40.32%)	12 (31.57%)	37 (37.0%)
Age (days)			
Mean ± SD	5.02±1.024	3.24±0.668	4.13±0.846
Weight(kg)			
Mean ± S.E	2.18±0.108	2.68±0.105	2.43±0.106
Place of Birth			
Inborn	45 (72.58%)	17 (44.73%)	62 (62.0%)
Out-born	17 (27.41%)	21 (55.26%)	38 (38.0%)
Birth weight			
Low Below2.5kg	47 (75.80%)	35 (92.10%)	82 (82.0%)

Normal above 2.5kg	15 (24.19%)	3 (7.89%)	18 (18.0%)
Antibiotic therapy			
Meropenem/Amikacin	30(48.4%)	7(18.4%)	37 (37.0%)
Cefotaxime/Amikacin	32(51.6%)	31(81.6%)	63 (63.0%)

The study revealed that vaccinated mothers' children in the preterm group had fewer systemic illness cases than those in the full-term group. The study revealed a preterm group with PV leaking and bleeding, respiratory distress, lethargy, and yellow skin, while the full-term group exhibited no symptoms (Table 2)

Neonatal sepsis, a condition resulting from previous births and abortions, can cause breathing discomfort in preterm and full-term patients, leading to hypothermia and hyperthermia respectively. Preterm infants (n=20) showed slightly higher survival rates, with meropenem treatment being more effective than cefotaxime and more stable on EOS medication compared to full-term infants (n=17) (figure A & B).

The endpoint describes the results of therapy on EOS patients (Figure C). Eight preterm and five full-term patients were shifted to other hospitals, with 11 preterm and 2 full-term patients dying. CRP tests were positive in 48 patients, negative in 14 preterm patients, and negative in 31 full-term patients (Figure D).

Table No. 2. History of early onset neonatal sepsis (EOS) in pre-term and full-term newborns

Parameters	Pre-Term (n=62)	Full-Term (n=38)	OR (CI 95%)	Total
ANTENATAL HISTORY				
Maternal Age				
Mean ± SD	24.53±0.463	24.82±0.719		24.67±0.591
Systemic Illness			1.27(0.51-3.17)	
Yes	15 (24.19%)	11 (28.94%)		26 (26.0%)
No	47 (75.80%)	27 (71.05%)		74 (74.0%)
Maternal Vaccination			0.68(.30-1.52)	
No	25 (40.32%)	19 (50%)		44 (44.0%)
Yes	37 (59.67%)	19 (50%)		56 (56.0%)
Regular Check-up			0.97(.42-2.21)	
No	24(38.7%)	15(39.47%)		39 (39.0%)
Yes	38(61.3%)	23(60.53%)		61 (61.0%)
NATAL HISTORY				
Gestational Age				
Mean ± SD	32.56 ± 0.25	37 ± 0.0		34.78 ± 0.125
PV leaking			0.46(0.12-1.06)	
No	31 (50%)	26 (68.42%)		57 (57.0%)
Yes	31 (50%)	12 (31.57%)		43 (43.0%)
PV bleeding			0.44(0.13-1.47)	
Yes	49 (79.03%)	34 (89.47%)		83 (83.0%)
No	13 (20.96%)	4 (10.52%)		17 (17.0%)
POSTNATAL HISTORY				
Immediate cry at birth			1.04(0.36-2.98)	
Yes	51 (82.3%)	31(81.6%)		82 (82.0%)
No	11 (17.7%)	7(18.4%)		18 (18.0%)
Any illness after birth			1.70(0.74-3.90)	
Yes	42 (67.74%)	21 (55.26%)		63 (63.0%)
No	20 (32.25%)	17 (44.73%)		37 (37.0%)
Resuscitation			0.82(0.32-2.08)	

No	45 (72.58%)	29 (76.31%)		74 (74.0%)
Yes	17 (27.41%)	9 (23.68%)		26 (26.0%)
NEONATAL SYMPTOMS				
Vomiting	61 (98.38%)	36 (94.73%)	0.29(0.02-3.37)	97 (97.0%)
Frequent urination	60 (96.77%)	38 (100%)	1.63(1.39-1.91)	98 (98.0%)
Loose motion	61 (98.38%)	38 (100%)	1.62(1.38-1.89)	99 (99.0%)
Reluctant to feed	61 98.38%)	38 (100%)	1.62(1.38-1.89)	99 (99.0%)
Difficulty in breathing	62 (100%)	38 (100%)	-	100 (100.0%)
Hypothermia	4 (6.45%)	1 (2.63%)	0.39(0.04-3.64)	5 (5.0%)
Hyperthermia	58 (93.54%)	37 (97.36%)	2.55(0.27-23.72)	95 (95.0%)

Table No. 3. Lab values of early onset neonatal sepsis (EOS) in pre-term and full-term newborns.

Parameters	Pre-Term (n=62)	Full-Term (n=38)	Mean¥ Difference	Total
Systolic	80.67±2.482	80.00±2.11	0.667	80.32±2.296
Diastolic	58.67±2.363	58.00±2.00	0.667	58.33±2.181
SPO2	83.57±3.67	66.55±6.99	17.02	75.06±5.33
BSR	86.13±8.44	63.74±8.15	22.39	74.93±8.295
Temp	98.13±0.08	98.17±0.09	-0.045	98.15±0.085
R. R	45.43±2.01	46.34±2.09	-0.906	45.88±2.05
Pulse	116.13±17.44	94.84±4.58	21.29	105.48±11.01
Bilirubin	10.59±2.34	8.18±1.47	2.412	9.38±1.905
TLC	9019±1108	15737±4026	6718	12378±2567
Platelet count	163774±17746	185868±28257	22094	174821±23001.5
HB	15.15±1.88	13.34±1.03	1.812	14.24±1.455
Blood Urea	38.90±3.36	28.53±4.31	10.377	33.71±3.835
Clcr	4.37±2.49	3.51±2.70	0.862	3.94±2.595
Potassium	1.13±0.27	1.19±0.33	-.0642	1.16±0.30
Sod	30.13±7.50	33.07±9.7	-2.945	31.6±8.60
WBCs	7.79±.52	7.81±.85	-0.026	7.8±0.685

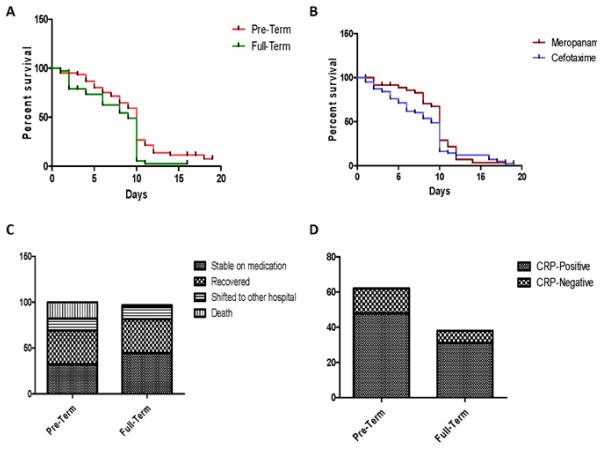

Figure No. 1: (A) Overall Survival of Pre-Term and Full-Term Neonates (B) Survival of Neonates Prescribed Meropenem and Cefotaxime (C) End Points (D) C-Reactive Protein.

DISCUSSION

The prevalence of late-preterm births worldwide is increasing, with South Asia and Africa contributing to more than 60% of pre-term births. A significant portion of the nation's health resources is required to manage late-preterm newborns. Late-preterm neonates are at higher risk of morbidities compared to term neonates, necessitating attention to reduce overall morbidity and mortality[15]. Considerable attempts have been made to reduce the occurrence of early-term deliveries in order to limit the resulting health complications[16]. Although new generations of antibiotics and supportive care are being utilized, infections in infants continue to be a significant problem, particularly in children with low body weight, leading to high morbidity and fatality rates[7].

The USA and Australia have varying rates of neonatal bacterial sepsis, with early-onset and late-onset cases

per 1000 live births, according to a study at Eunice Kennedy Shriver National Institute of Child Health and Human[1]. The incidence of neonatal sepsis significantly differs between male and female patients, with females experiencing a higher incidence in newborns with a body weight below 2.5kg. On the contrary, according to a study[17] conducted in a Nigerian hospital, male gender is at higher risk for LOS and EOS, while female gender is protective in sepsis patients, potentially causing a diminished immune response and cardiovascular functions.

The study reveals that preterm mothers with systemic illnesses are more likely to experience full-term neonatal sepsis, with maternal preeclampsia, premature membrane rupture, and perinatal hypoxia being key risk factors. As per findings of our study, out of 56 vaccinated mothers, 37 patients suffered from preterm neonatal sepsis whereas 19 had full term cases. A retrospective study at Hospital Universitario de la Riberia found that while infected mothers and pregnant women face higher NICU admissions, vaccination does not significantly impact obstetrical outcomes[18].

In this study, it was found out that 31 out of 43 patients with PV leaking linked with pre-term sepsis whereas full term babies had no symptoms. A study in India[19] found common risk factors for neonatal sepsis include leaking PV, meconium stained liquor, multiple vaginal examinations, mixed feeding, and raised maternal TLCs. The present study unveils the relation between previous births and abortions and neonatal sepsis. A similar study[20] also found that mothers with a history of stillbirth or abortion often have low zinc levels, leading to high infection episodes of diarrhea and pneumonia in their infants. Meropenem treatment is more effective than cefotaxime for treating EONS, but a separate study found no superiority in cure visit success, safety, or mortality, suggesting it should be reserved for Gram-negative neonates. CRP, a late indicator of neonatal sepsis, has been confirmed as a specific yet significant marker of infection in neonates[1].

CONCLUSION

Low gestational age, body weight, PV leaking, and bleeding are risk factors for early-onset sepsis. Meropenem, Cefotaxime replacement, supervised hospital delivery, and enhanced neonatal resuscitation may reduce mortality and recovery rates.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Saleha Munir, Sajida Zafar, Sumera Malik
Drafting or Revising Critically:	Kazim Abbas Ali Khan, Sahrish Mumtaz, Ali Abuzar Raza
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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