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# Comparison of Derangement of Cerebrospinal Fluid Markers in Neonates with Early and Late-Onset Sepsis

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## ABSTRACT

***Objective:*** To compare derangement of cerebrospinal fluid markers in neonates with early and late-onset sepsis managed at the Neonatal Intensive Care Unit.

***Study Design:*** Comparative cross-sectional study.

***Place and Duration of Study:*** Neonatology Department, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jul 2021 to Jun 2022.

***Methodology:*** This study was conducted on neonates managed at our Neonatal Intensive Care Unit for late or early-onset sepsis. A consultant neonatologist diagnosed neonatal sepsis based on clinical and laboratory findings. The cerebrospinal fluid routine examination was performed on all the study participants, and the derangement of various markers was compared in neonates with early and late-onset sepsis.

***Results:*** A total of 348 neonates admitted to the neonatal intensive care unit with sepsis were included in the final analysis. The mean age of the newborns included in the study was 5.38±4.53 days. Out of all the neonates in the study, 194(55.7%) had early-onset sepsis, while 154(44.3%) neonates had late-onset sepsis. All the cerebrospinal fluid markers were statistically significantly deranged in patients with late-onset sepsis ($p$-value<0.005).

***Conclusion:*** Derangement of cerebrospinal fluid markers was seen more in patients with late-onset neonatal sepsis admitted to the neonatal intensive care unit. Emphasis should be laid on performing this necessary investigation timely in neonates with late-onset sepsis as chances of meningeal involvement are higher in this group.

**Keywords:** Cerebrospinal fluid, Early onset, Late onset, Meningitis, Neonates, Sepsis.

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## INTRODUCTION

The neonatal intensive care unit usually uses the same principles as the adult unit. It provides organ support to babies with compromised organ systems due to any reason in the first twenty-eight days of life.[1] Situation is quite grave in developing countries like Pakistan, where the load at tertiary care neonatal critical care units is enormous.[2,3] A diverse pattern of complications is seen among neonates who get admitted to intensive care units, and usually, a multidisciplinary team effort is required to ensure the smooth recovery of these patients.[4,5]

Infective conditions of newborn babies may lead to neonatal sepsis, which has been a great concern for neonatologists across the globe. The rising trend of this clinical condition in lower and middle-income countries causes a lot of mortality and morbidity in neonates.[6,7] Involvement of the central nervous system is one of the most lethal complications of septicemia in neonates, and early detection and aggressive management are usually key to saving lives and long-term disability of these little beings.[8,9]

Neonatal sepsis can be a life-threatening condition and may lead to complications, which can be devastating. CSF analysis can give an early clue regarding CNS involvement in the infective process, but it is not routine practice in all the centres. A recent local study assessed the demographic and clinical characteristics of neonates suffering from early or late-onset sepsis.[10] Limited local data has been available regarding CNS involvement and the role of CSF markers in screening high-risk patients among those diagnosed with early or late-onset sepsis. We, therefore, designed this study with the rationale of comparing derangement of cerebrospinal fluid markers in neonates with early and late-onset sepsis managed at the Neonatal Intensive Care Unit of our hospital.

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## METHODOLOGY

The comparative cross-sectional study was conducted at the Neonatal Intensive Care Unit, Pak Emirates Military Hospital, Rawalpindi Pakistan, from July 2021 to June 2022 after ethical approval from the Ethical Review Board Committee (IREB letter no, A/28/180/EC/455/2022). The sample size was calculated by the WHO Sample Size Calculator by using the proportion of early-onset sepsis in neonates as 1.8%.[11]

**Inclusion Criteria:** All neonates with early or late onset sepsis, either born at our hospital or brought from other centres after birth for management of sepsis, were recruited in the study.

**Exclusion Criteria:** The neonates with severe congenital malformations, metabolic disorders, perinatal asphyxia or those neonates with any immuno-compromised condition at the time of birth were excluded from the study. Those patients whose lumbar punctures could not be performed for any reason, including refusal from primary caregivers, were also not included.

Non-probability consecutive sampling technique was used to gather the sample. Written informed consent from the parents or guardians of the potential participants or their caregivers, neonates who were diagnosed with early or late onset sepsis were recruited in the analysis. Early and late-onset neonatal sepsis was diagnosed by a consultant neonatologist based on international paediatric sepsis consensus conference criteria by incorporating clinical and laboratory findings, including blood cultures.[12] Cerebrospinal fluid analysis was carried out in all the neonates included in the study. They underwent lumber puncture by the registrar neonatologist by aseptic techniques as per protocol.[13] CSF routine analysis was performed in the laboratory of our hospital by the Chemical Pathology Department working under a consultant pathologist. Interpretation of CSF white cell count, CSF proteins, CSF glucose and CSF lactate levels was done according to international standards.[14]

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

## RESULTS

A total of 348 neonates admitted to the nursing intensive care unit with sepsis were included in the final analysis. Of them, 238(68.3%) were male, while 110(31.7%) were females. The mean age of the newborns included in the study was 5.38±4.53 days (Table-I). Of all the neonates in the study, 194(55.7%) had early-onset sepsis, while 154(44.3%) neonates had late-onset sepsis. Of all the study participants, 200(57.4%) were delivered by spontaneous vaginal delivery, 110(31.6%) via caesarean section and 38(10.9%) via instrumental delivery. 69(19.8%) babies were preterm, while 279(80.2%) were born at term. Cerebrospinal fluid levels of White cell count (*p*-value<0.001), protein levels (*p*-value-0.015), glucose levels (*p*-value-0.007) and lactate levels (*p*-value-0.003) were statistically significantly deranged more in patients who were diagnosed with late-onset sepsis as compared to those who had early onset sepsis (Table-II).

**Table-I: Characteristics of Neonates with Sepsis included in the Study (n=348)**

| Study parameters | n (%) |
|---|---|
| **Age (days)** | |
| Mean±SD | 5.38±4.53 days |
| Range (min-max) | 1-17 days |
| **Gender of Neonates** | |
| Male | 238(68.3%) |
| Female | 110(31.7%) |
| **Sepsis** | |
| Early onset | 194(55.7%) |
| Late onset | 154(44.3%) |
| **Mode of Delivery** | |
| Normal vaginal | 200(57.4%) |
| Cesarean | 110(31.6%) |
| Instrumental | 38(10.9%) |
| **Gestation** | |
| Pre term | 69(19.8%) |
| Term | 279(80.2%) |

**Table-II: Comparison of CSF Markers in Neonates with Early and Late Onset Neonatal Sepsis (n=348)**

| Cerebrospinal Fluid Markers | Early Onset Sepsis | Late Onset Sepsis | *p*-value |
|---|---|---|---|
| **White Cell Count** | | | |
| <20/mm$^3$ | 167(86.1%) | 99(64.2%) | <0.001 |
| >30/mm$^3$ | 27(13.9%) | 55(35.8%) | |
| **Protein Levels** | | | |
| <2g/l | 163(84.1%) | 113(73.4%) | 0.015 |
| >2g/l | 31(15.9%) | 41(26.6%) | |
| **Glucose Levels** | | | |
| >50% of simultaneous blood glucose | 172(88.6%) | 120(77.9%) | 0.007 |
| <50% of simultaneous blood glucose | 22(11.4%) | 34(22.1%) | |
| **Lactate Levels** | | | |
| <3mmol/l | 169(87.1%) | 115(74.6%) | 0.003 |
| >3mmol/l | 25(12.9%) | 39(25.4%) | |

## DISCUSSION

We planned this study to compare the derangement of cerebrospinal fluid markers in neonates with early and late-onset sepsis managed at the neonatal intensive care unit. Hornik *et al.* compared different parameters between early and late-onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units.[15] They revealed that the types of bacteria found in the culture of these babies were different in early and late-onset sepsis, and the mortality rate was high in culture-positive babies. Mariani *et al*. came up with the findings that different pathogens were involved in patients with early and late-onset sepsis, and empirical treatment, which was effective, was also different in both groups of patients.[16] Our results supported their findings as derangement of cerebrospinal fluid markers was seen more in patients with late-onset neonatal sepsis admitted to the neonatal intensive care unit for management. Emphasis should be laid on performing this basic investigation early in neonates with late-onset sepsis, as the chances of meningeal involvement may be higher in this group.

Baghat *et al*. published a study in our neighbouring country, India, on neonates with late-onset sepsis. Meningitis was found in 16% of the patients included in the study by Baghat *et al.* [17] These statistics highlight the importance of early detection of meningeal and CNS involvement in these children. Our results were similar in this regard, and patients with both early and late-onset neonatal sepsis showed raised CSF markers but were seen more in neonates with late-onset sepsis. You *et al.* published a study on patients from China and highlighted the difference in clinical and laboratory characteristics among neonates suffering from early-onset and late-onset sepsis. Their study concluded that more laboratory derangements and clinical complications were found in neonates suffering from late-onset sepsis.[18] We only compared CSF markers in both groups and found out that they were more deranged in neonates who presented with late-onset sepsis as compared to those who were managed for early-onset sepsis.

## LIMITATIONS OF STUDY

False positive and false negative results of CSF analysis may blur the picture. Moreover, CSF culture was not perfo-rmed to confirm the diagnosis of meningitis, so it cannot be concluded that infection had invaded the meninges or that primary meningitis had led to septicemia.

## CONCLUSION

Derangement of cerebrospinal fluid markers was seen more in patients with late-onset neonatal sepsis admitted to the neonatal intensive care unit for management. Emphasis should be laid on performing this basic investigation early in neonates with late-onset sepsis, as the chances of meningeal involvement are higher in this group.

**Conflict of Interest:** None.

**Author's Contribution:**

Following authors have made substantial contributions to the manuscript as under:

EQ & SAUHS: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZA & NN: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

ZA & FS: Concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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