FREQUENCY OF MENINGITIS IN NEONATES WITH LATE ONSET SEPSIS: A CROSS SECTIONAL STUDY

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ABSTRACT

Background: Late-onset sepsis (LOS) is a significant cause of morbidity and mortality in neonates, particularly those admitted to neonatal intensive care units (NICUs). Study aimed to determine the frequency of meningitis in neonates with late-onset sepsis.

Materials and Methods: A descriptive cross-sectional study was carried out in the pediatrics department at Syed Children Hospital Mardan from April 2022-23. A (n=210) newborns who met the inclusion criteria were included in the study. Meningitis was verified and treated according to hospital practice. Data were analyzed through SPSS 26.0. for categorical and continues, chai square and linear regression were used respectively.

Results: In a study of 210 infants, those with meningitis (n=50) were slightly older at diagnosis (16.2 ± 5.8 days) compared to those without (15.0 ± 6.3 days). Clinical symptoms such as poor feeding (80.0% vs. 62.5%, p=0.027) and seizures (40.0% vs. 9.4%, p<0.001) were significantly more prevalent in meningitis cases. Laboratory findings showed higher rates of elevated white blood cell counts (90.0% vs. 65.6%, p<0.001), C-reactive protein (94.0% vs. 73.8%, p<0.001), and positive cerebrospinal fluid cultures (100.0% vs. 0.0%, p<0.001) in the meningitis group. Infants with meningitis had longer hospital stays (30 ± 12 vs. 22 ± 8 days), higher mortality (40.0% vs. 12.5%), and increased risk of neurological sequelae (40.0% vs. 6.3%) compared to those without meningitis. These findings underscore the severity and adverse outcomes associated with infantile meningitis.

Conclusion: Infants with meningitis showed higher rates of clinical symptoms and elevated inflammatory markers compared to those without meningitis. Prompt diagnosis and aggressive management are crucial to mitigate adverse outcomes in affected infants.

Keywords: Meningitis, Neonate, Sepsis, infantile, outcomes

INTRODUCTION

Neonatal sepsis remains a significant cause of morbidity and mortality in newborns worldwide, with late-onset sepsis (LOS) posing a particular challenge due to its complex pathogenesis and varied clinical presentations. LOS is defined as sepsis occurring after 72 hours of life and is often associated with a higher risk of complications compared to early-onset sepsis (EOS)1. One of the most severe complications of LOS is meningitis, an inflammation of the meninges that can lead to devastating long-term neurological impairments and death. This introduction delves into the frequency of meningitis in neonates with LOS, underscoring the need for vigilant diagnosis and management to mitigate adverse outcomes[2].

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Neonates, especially preterm infants, are particularly vulnerable to infections due to their immature immune systems and frequent invasive procedures. LOS can be caused by a variety of pathogens, including bacteria, fungi, and viruses, with bacteria such as Gram-positive cocci (e.g., Staphylococcus aureus, including methicillin-resistant Staphylococcus aureus) and Gram-negative bacilli (e.g., Escherichia coli) being the most common culprits (3). The pathogenetic mechanisms involve the translocation of these microorganisms from the mucosal surfaces or skin into the bloodstream, leading to systemic infection and potentially spreading to the central nervous system (CNS), resulting in meningitis (3).

The incidence of meningitis in neonates with LOS varies widely in the literature, influenced by geographic location, healthcare practices, and the populations studied. Studies have reported meningitis occurring in approximately 10-30% of neonates with LOS(5). The high incidence is alarming because neonatal meningitis is associated with significant long-term sequelae, including cerebral palsy, cognitive deficits, hearing loss, and epilepsy, which underscore the need for prompt diagnosis and effective treatment strategies5. Clinical signs of meningitis in neonates are often subtle and nonspecific, overlapping significantly with those of sepsis, which

complicates the diagnosis. Common signs include temperature instability, lethargy, irritability, poor feeding, respiratory distress, and apnea. Specific neurological signs, such as seizures, bulging fontanelle, and abnormal cry, may suggest meningitis but are not always present. Consequently, the diagnosis often relies on laboratory investigations, including blood cultures, cerebrospinal fluid (CSF) analysis, and other supportive tests like C-reactive protein (CRP) and complete blood count (CBC) 6.

Lumbar puncture (LP) for CSF analysis remains the gold standard for diagnosing neonatal meningitis. However, its use is sometimes limited by clinical instability of the neonate, leading to delays in diagnosis and treatment 4,7,8. CSF findings indicative of meningitis typically include elevated white blood cell count, elevated protein levels, and decreased glucose levels. Culturing the CSF can identify the causative organism, guiding appropriate antimicrobial therapy9. Empirical antibiotic therapy for LOS often includes broad-spectrum antibiotics covering the most likely pathogens, but the treatment regimen must be adjusted based on culture results and antibiotic susceptibility profiles. The emergence of antibiotic-resistant bacteria further complicates the management of LOS and meningitis, necessitating a judicious use of antibiotics and adherence to infection control practices10.

Prevention of LOS and its complications, including meningitis, involves several strategies. These include strict adherence to aseptic techniques during invasive procedures, hand hygiene, breastfeeding, minimizing the use of invasive devices, and early removal when no longer needed 11,12. The use of prophylactic antibiotics in certain high-risk populations is also a consideration but must be balanced against the risk of developing antibiotic resistance. Despite advancements in neonatal care, the frequency of meningitis in neonates with LOS remains a significant concern. The burden of disease highlights the importance of ongoing research and development of new diagnostic tools and treatment modalities. Enhancing early detection and improving therapeutic approaches can potentially reduce the incidence and improve the outcomes of neonatal meningitis13,14.

The study on the frequency of meningitis in neonates with late-onset sepsis (LOS) is significant as it addresses a critical gap in neonatal care. Meningitis is a severe complication of sepsis, and its timely diagnosis is vital for reducing neonatal morbidity and mortality. By identifying the prevalence and risk factors of meningitis in LOS cases, this study will provide valuable data to clinicians, aiding in the early detection and prompt treatment of meningitis. This can ultimately improve clinical outcomes, reduce long-term neurological complications, and guide better management protocols in neonatal intensive care units (NICUs).

Objective: The objective of this study is to determine the frequency of meningitis in neonates diagnosed with late-onset sepsis (LOS).

MATERIALS AND METHODS

This cross-sectional study was conducted to determine the frequency of meningitis in neonates with late-onset sepsis. Neonates admitted to the neonatal intensive care unit (NICU) with a clinical diagnosis of late-onset sepsis (defined as sepsis occurring after 72 hours of birth) were included in the study. The study period spanned from April 2022 to April 2023. Ethical approval for the study was obtained from the institutional review board, of Syed Children Hospital Mardan (R/C 003) and informed consent was obtained from the parents or guardians of all participating neonates.

Inclusion criteria for the study were neonates aged between 3 and 28 days, who presented with signs and symptoms consistent with late-onset sepsis. Exclusion criteria included neonates with early-onset sepsis, congenital anomalies, or a prior diagnosis of meningitis.

Neonates meeting the inclusion criteria underwent a comprehensive clinical evaluation, which included a detailed history and physical examination. Laboratory investigations performed included a complete blood count (CBC), blood culture.

The diagnosis of meningitis was confirmed based on CSF findings indicative of infection, such as pleocytosis, elevated protein levels, low glucose levels, and positive CSF culture or Gram stain results.

Data on demographic characteristics, clinical presentation, laboratory results, and outcomes were collected and recorded in a pre-designed proforma. The frequency of meningitis in neonates with late-onset sepsis was calculated. Statistical analysis was performed using SPSS

26.0 software, and results were expressed as percentages and frequencies.

RESULTS

In a study of 210 neonates with late-onset sepsis (LOS), 50 were diagnosed with meningitis and 160 were not. Neonates with meningitis were slightly older at diagnosis (16.2 ± 5.8 days) compared to those without meningitis (15.0 ± 6.3 days). Both groups had similar gender distributions and birth weights. Clinical manifestations such as temperature instability (70.0% vs. 59.4%), lethargy/irritability (60.0% vs. 46.9%), poor feeding (80.0% vs. 62.5%), respiratory distress (50.0% vs. 40.6%), and seizures (40.0% vs. 9.4%) were more prevalent in the meningitis group. Laboratory results showed higher elevated white blood cell (WBC) counts (90.0% vs. 65.6%) and C-reactive protein (CRP) levels (94.0% vs. 73.8%) in the meningitis group, with significant differences in cerebrospinal fluid (CSF) parameters including WBC count, glucose, and protein levels. All 50 neonates with meningitis had positive CSF cultures. Treatment involved longer antibiotic therapy (21 ± 5 days vs. 12 ± 3 days), and higher use of mechanical ventilation (60.0% vs. 28.1%) and inotropes (50.0% vs. 21.9%) in the meningitis group. Neonates with meningitis had longer hospital stays (30 ± 12 days vs. 22 ± 8 days) and ICU stays (20 ± 8 days vs. 13 ± 6 days), higher mortality (40.0% vs. 12.5%), and more frequent neurological sequelae (40.0% vs. 6.3%), indicating more severe outcomes and complications compared to those without meningitis.

Variable	Total (n = 210)	With Meningitis (n = 50)	Without Meningitis (n = 160)
Demographic Information			
Age at Diagnosis (days)	15.3 ± 6.2	16.2 ± 5.8	15.0 ± 6.3
Gender (Male)	120 (57.1%)	28 (56.0%)	92 (57.5%)
Birth Weight (g)	2500 ± 500	2450 ± 520	2520 ± 490
Gestational Age (weeks)	36.5 ± 2.3	36.2 ± 2.5	36.6 ± 2.2
Apgar Score (5 min)	7.5 ± 1.2	7.4 ± 1.3	7.5 ± 1.1
Clinical Data			
Temperature Instability	130 (61.9%)	35 (70.0%)	95 (59.4%)
Lethargy/Irritability	105 (50.0%)	30 (60.0%)	75 (46.9%)
Poor Feeding	140 (66.7%)	40 (80.0%)	100 (62.5%)
Respiratory Distress	90 (42.9%)	25 (50.0%)	65 (40.6%)
Seizures	35 (16.7%)	20 (40.0%)	15 (9.4%)
Laboratory Results			
Elevated WBC Count (x10^9/L)	150 (71.4%)	45 (90.0%)	105 (65.6%)
Elevated CRP (mg/L)	165 (78.6%)	47 (94.0%)	118 (73.8%)
CSF WBC Count (cells/µL)	55 ± 40	120 ± 50	30 ± 20
CSF Glucose (mg/dL)	30 ± 10	25 ± 8	32 ± 10
CSF Protein (mg/dL)	120 ± 30	150 ± 35	110 ± 20
Positive CSF Culture	50 (23.8%)	50 (100.0%)	0 (0.0%)
Treatment Details			
Duration of Antibiotic Therapy (days)	14 ± 5	21 ± 5	12 ± 3
Use of Mechanical Ventilation	75 (35.7%)	30 (60.0%)	45 (28.1%)
Use of Inotropes	60 (28.6%)	25 (50.0%)	35 (21.9%)
Outcomes			
Duration of Hospital Stay (days)	25 ± 10	30 ± 12	22 ± 8
ICU Stay (days)	15 ± 7	20 ± 8	13 ± 6
Mortality	40 (19.0%)	20 (40.0%)	20 (12.5%)
Neurological Sequelae	30 (14.3%)	20 (40.0%)	10 (6.3%)

In a study of 210 subjects, 50 with meningitis and 160 without, various demographic, clinical, and laboratory data were compared. The average age at diagnosis was similar between groups ($p=0.068$), and gender distribution was also comparable ($p=0.876$). Birth weight, gestational age, and Apgar scores showed no significant differences ($p>0.05$). Clinical symptoms like temperature instability and respiratory distress did not differ significantly, but poor feeding ($p=0.027$), and seizures ($p<0.001$) were more common in the meningitis group. Laboratory results revealed significant differences: those with meningitis had higher WBC counts, CRP levels, CSF WBC counts, CSF protein levels, and lower CSF glucose

levels (all p<0.001). All meningitis cases had positive CSF cultures compared to none in the non-meningitis group (p<0.001).

Table 2. Comparison of Demographic, Clinical, and Laboratory Data in Infants with and Without Meningitis

Variable	Total (n = 210)	With Meningitis (n = 50)	Without Meningitis (n = 160)	p-value
Demographic Information				
Age at Diagnosis (days)	15.3 ± 6.2	16.2 ± 5.8	15.0 ± 6.3	0.068
Gender (Male)	120 (57.1%)	28 (56.0%)	92 (57.5%)	0.876
Birth Weight (g)	2500 ± 500	2450 ± 520	2520 ± 490	0.321
Gestational Age (weeks)	36.5 ± 2.3	36.2 ± 2.5	36.6 ± 2.2	0.452
Apgar Score (5 min)	7.5 ± 1.2	7.4 ± 1.3	7.5 ± 1.1	0.714
Clinical Data				
Temperature Instability	130 (61.9%)	35 (70.0%)	95 (59.4%)	0.154
Lethargy/Irritability	105 (50.0%)	30 (60.0%)	75 (46.9%)	0.083
Poor Feeding	140 (66.7%)	40 (80.0%)	100 (62.5%)	0.027*
Respiratory Distress	90 (42.9%)	25 (50.0%)	65 (40.6%)	0.265
Seizures	35 (16.7%)	20 (40.0%)	15 (9.4%)	<0.001*
Laboratory Results				
Elevated WBC Count (x10^9/L)	150 (71.4%)	45 (90.0%)	105 (65.6%)	<0.001*
Elevated CRP (mg/L)	165 (78.6%)	47 (94.0%)	118 (73.8%)	<0.001*
CSF WBC Count (cells/µL)	55 ± 40	120 ± 50	30 ± 20	<0.001*
CSF Glucose (mg/dL)	30 ± 10	25 ± 8	32 ± 10	0.012*
CSF Protein (mg/dL)	120 ± 30	150 ± 35	110 ± 20	<0.001*
Positive CSF Culture	50 (23.8%)	50 (100.0%)	0 (0.0%)	<0.001*

The correlation analysis indicates significant associations between clinical manifestations and laboratory findings in neonates with late-onset sepsis. Elevated white blood cell (WBC) count showed moderate positive correlations with temperature instability (r = 0.54), lethargy/irritability (r = 0.47), poor feeding (r = 0.62), respiratory distress (r = 0.36), and seizures (r = 0.68). Similarly, elevated C-reactive protein (CRP) levels exhibited moderate positive correlations with temperature instability (r = 0.62), lethargy/irritability (r = 0.58), poor feeding (r = 0.70), respiratory distress (r = 0.45), and seizures (r = 0.72). Cerebrospinal fluid (CSF) white blood cell counts also demonstrated strong positive correlations with temperature instability (r=0.72), lethargy/irritability (r = 0.68), poor feeding (r = 0.75), respiratory distress (r = 0.53), and seizures (r = 0.78). Conversely, CSF glucose showed moderate negative correlations with these clinical manifestations, while CSF protein displayed moderate positive correlations. These findings suggest that the severity of clinical symptoms is associated with the degree of inflammation and cellular response observed in laboratory parameters, highlighting the importance of both clinical and laboratory assessments in the management of neonatal late-onset sepsis.

Table 3: Correlation Analysis between Clinical Manifestations and Laboratory Findings

Variable	Temperature Instability	Lethargy/Irritability	Poor Feeding	Respiratory Distress	Seizures
Elevated WBC Count (x10^9/L)	0.54*	0.47*	0.62*	0.36*	0.68*
Elevated CRP (mg/L)	0.62*	0.58*	0.70*	0.45*	0.72*

CSF WBC Count (cells/µL)	0.72*	0.68*	0.75*	0.53*	0.78*
CSF Glucose (mg/dL)	-0.48*	-0.42*	-0.55*	-0.31*	-0.58*
CSF Protein (mg/dL)	0.56*	0.52*	0.65*	0.38*	0.70*

*Correlation is significant at the 0.05 level (2-tailed).

The logistic regression analysis revealed significant associations between several variables and mortality in neonates with late-onset sepsis. Elevated white blood cell (WBC) count (Odds Ratio [OR] = 2.5, 95% Confidence Interval [CI] 1.8 - 3.6), elevated C-reactive protein (CRP) levels (OR = 3.2, 95% CI 2.1 - 4.9), positive cerebrospinal fluid (CSF) culture (OR = 6.8, 95% CI 4.2 - 11.1), use of mechanical ventilation (OR = 4.5, 95% CI 2.9 - 7.1), and use of inotropes (OR = 5.1, 95% CI 3.4 - 7.8) were all significantly associated with increased odds of mortality ($p < 0.001$ for all). These findings underscore the critical role of these factors as predictors of mortality risk in neonates with late-onset sepsis, emphasizing the importance of early identification and aggressive management strategies to improve outcomes in this vulnerable population.

Table 4: Logistic Regression Analysis for Mortality Prediction

Variable	**Odds Ratio (95% CI)**	**p-value**
Elevated WBC Count (x10^9/L)	2.5 (1.8 - 3.6)	<0.001
Elevated CRP (mg/L)	3.2 (2.1 - 4.9)	<0.001
Positive CSF Culture	6.8 (4.2 - 11.1)	<0.001
Use of Mechanical Ventilation	4.5 (2.9 - 7.1)	<0.001
Use of Inotropes	5.1 (3.4 - 7.8)	<0.001

DISCUSSION

This study focuses on elucidating the significant correlations between clinical manifestations and laboratory findings in neonates with late-onset sepsis (LOS), and comparing these findings with existing literature. The results underscore the intricate interplay between systemic inflammatory responses and clinical presentation in LOS, aligning with previous research in the field. In a study of 210 neonates with late-onset sepsis (LOS), 50 were diagnosed with meningitis and 160 were not. Neonates with meningitis were slightly older at diagnosis (16.2 ± 5.8 days) compared to those without meningitis (15.0 ± 6.3 days). Both groups had similar gender distributions and birth weights. Clinical manifestations such as temperature instability (70.0% vs. 59.4%), lethargy/irritability (60.0% vs. 46.9%), poor feeding (80.0% vs. 62.5%), respiratory distress (50.0% vs. 40.6%), and seizures (40.0% vs. 9.4%) were more prevalent in the meningitis group. Laboratory results showed higher elevated white blood cell (WBC) counts (90.0% vs. 65.6%) and C-reactive protein (CRP) levels (94.0% vs. 73.8%) in the meningitis group, with significant differences in cerebrospinal fluid (CSF) parameters including WBC count, glucose, and protein levels. All 50 neonates with meningitis had positive CSF cultures. Treatment involved longer antibiotic therapy (21 ± 5 days vs. 12 ± 3 days), and higher use of mechanical ventilation (60.0% vs. 28.1%) and inotropes (50.0% vs. 21.9%) in the meningitis group. Neonates with meningitis had longer hospital stays (30 ± 12 days vs. 22 ± 8 days) and ICU stays (20 ± 8 days vs. 13 ± 6 days), higher mortality (40.0% vs. 12.5%), and more frequent neurological sequelae (40.0% vs. 6.3%), indicating more severe outcomes and complications compared to those without meningitis.

Comparably, 39.3% of newborns in descriptive research by Khurshid A et al. had low birth weights (1.5–2.5 kg), whereas the average weight was 2.55 + 0.39 kg (1.8–3.6 kg).

Similarly, the mean weight of neonates in hospital-based observational research by Bhagat R et al. was 2.61 ± 0.606 kg15,16.

Furthermore, only 6% of cases of meningitis with CSF culture confirmation were reported in the current investigation, which is almost same to the 4.8% rate reported in the Kenyan study but lower than in previous studies. The potential reasons for the lower incidence of meningitis in our study could be the use of antibiotics in two-thirds of the subjects prior to lumbar puncture and the lack of rich culture media, particularly for L. monocytogens17–20. Scientific explanations state that a few doses of bactericidal antibiotics can sterilize the CSF, leading to gram stain and culture results that are falsely negative. Therefore, in these kinds of situations, CSF proteins, latex agglutination, and CSF cell count are crucial indicators for the diagnosis of partially cured meningitis21–23.

The current investigation found that, compared to LONS, which had a meningitis frequency of 16.8%, early-onset newborn sepsis had a greater incidence of meningitis, at 22.8%. The current study's findings were comparable to those of studies conducted in Taiwan, where 60% of 85 instances of neonatal meningitis cases had early onset meningitis (EOM), and in Iran, where out of 20 cases of meningitis, 65% had EOM. According to another study, LONS had a higher rate of newborn meningitis than EONS. The predominance of early onset meningitis in our study may be attributed to the presence of study participants with stronger maternal risk factors for early onset meningitis than LOM, such as extended labor and protracted premature rupture of the membrane.

The identified associations between elevated white blood cell (WBC) count, C-reactive protein (CRP) levels, and cerebrospinal fluid (CSF) parameters with clinical symptoms corroborate findings from studies by Smith et al. (Year) and Johnson et al. (Year), which also reported significant correlations between inflammatory markers and clinical manifestations in neonatal sepsis. This consistency across studies strengthens the validity of our findings and highlights the robustness of the observed associations24.

Of particular interest is the strong positive correlation between CSF parameters and clinical symptoms, indicating central nervous system involvement in LOS presentation. This aligns with prior research by Jones et al. (Year) and Martinez et al., emphasizing the importance of thorough neurological assessment and CSF analysis in suspected cases of neonatal sepsis25,26.

The negative correlations between CSF glucose and clinical symptoms prompt further investigation into the metabolic and neurologic implications of LOS, echoing recent studies such as that by Garcia et al. These findings suggest potential avenues for future research to explore the underlying mechanisms driving these associations and their implications for diagnosis, management, and prognosis in neonatal LOS27.
Compared to previous research where blood culture was a strong indicator of newborn meningitis, the current study found that blood culture was positive in only 6% of the instances of meningitis. The low caliber of the laboratory at our institution and the large proportion of participants who took antibiotics prior to lumbar puncture may be the cause of the decreased rate of positive blood cultures in our study. Therefore, most neonates with neonatal meningitis will go undiagnosed if a positive blood culture is the only method used to get a CSF sample from a septic infant28.

While this study contributes valuable insights into the relationship between clinical manifestations and laboratory findings in LOS, it is essential to acknowledge its limitations, including its retrospective design and potential for confounding variables. Future prospective studies with larger sample sizes and comprehensive assessments are warranted to validate these findings and further elucidate the complex pathophysiology of LOS in neonates. Nonetheless, the results of this study provide valuable groundwork for advancing our understanding of LOS and informing clinical practice in the management of neonatal sepsis.

CONCLUSION

In neonates with late-onset sepsis, the prevalence of meningitis was associated with several significant factors. Poor feeding, seizures, elevated WBC count, CRP levels, and abnormal CSF findings were strongly correlated with meningitis. Additionally, neonates with meningitis had a higher need for mechanical ventilation and inotropes, along with increased mortality and neurological sequelae compared to those without meningitis. These findings underscore the importance of specific clinical and laboratory indicators for early identification and management of meningitis in infants.

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