

Meningitis In Newborns With Late-Onset Sepsis; A Critical Insight

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Abstract

Objective: To determine the frequency of meningitis in neonates with late-onset sepsis

Methods: A cross-sectional study was conducted at Hameed Latif Teaching Hospital, Lahore from March 2023 to August 2023. 210 neonates were enrolled through non-probability consecutive sampling. After obtaining written informed consent from parents, all septic neonates who fulfilled the inclusion criteria were enrolled in the study. In each neonate with clinical features of sepsis, a detailed history and examination were done. Meningitis was labelled in the neonates whose CSF findings were suggestive of meningitis.

Cranial ultrasound was done in all neonates with meningitis to rule out any complication. Data was entered and analyzed using SPSS version 23. Data was stratified for age, weight, gestational age and gender to deal with effect modifiers. For post stratification, Chi-square test was applied to see the significance. A p-value ≤ 0.05 was considered as significant.

Results: A total of 210 children presenting with late-onset sepsis were included. Among these children 122 (58.1%) were males, while 88 (41.9%) were females. The age range in this study was from 7 to 28 days with mean age of 17.7 ± 6.3 days. It was found that out of 210 neonates with late-onset sepsis, 47 (22.4%) had meningitis.

Conclusion: The frequency of meningitis in patients with late-onset neonatal sepsis is quite high. Meningitis is a deadly disease which is associated with lifelong morbidity and sometimes mortality. Therefore screening for neonatal meningitis should be done in all patients afflicted by neonatal sepsis.

MeSH Keywords: Late-onset sepsis; Meningitis; Sepsis.

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1. Introduction

Neonatal sepsis is a medical condition of newborn babies who are less than 28 days old. It is characterized by signs and symptoms of infection, bacteremia and systemic inflammatory response syndrome. It is further classified into early-onset sepsis (EOS) and late-onset sepsis (LOS) based on the timing of onset of infection after birth. Different experts use either 72 hours or 7 days as the cutoff for distinguishing between EOS and LOS.¹ Neonatal sepsis is a recognized global health burden, which commonly affects preterm and low birth weight newborns. It is a leading cause of neonatal mortality. Indeed, neonatal sepsis is the third major contributor to neonatal deaths.²

Neonatal meningitis is a challenging global health issue. It is described as inflammation of the membranes surrounding the brain and spinal cord within the first 28 days of life. Despite tremendous advancements in the field of medicine, including enhanced diagnostic modalities and antibiotic therapies, mortality and neurological complications associated with neonatal meningitis are quite high, particularly in the developing world.³ In newborns,

clinical manifestations of sepsis alone and sepsis with meningitis are often similar. Therefore it is difficult to distinguish between the two without CSF analysis.³

The incidence of neonatal meningitis in the developed world is documented as 0.3 per 1000 live births. This is in contrast to the figures from developing countries, which range from 0.08 to 6.1 per 1000 live births, with mortality rates between 40% and 58%. The frequency of meningitis in neonates with late-onset sepsis (LOS) is a critical area of concern due to its significant impact on neonatal morbidity and mortality. Late-onset sepsis typically occurs after the first 72 hours of life and can be caused by various pathogens including bacteria and fungi. Several studies have provided insights into the incidence and outcomes associated with neonatal meningitis in the context of LOS.⁴

A comprehensive study by Brumbaugh et al. involving a large cohort of extremely preterm infants (n=13,372) reported that late-onset meningitis (LOM) was diagnosed in 1% of these infants. This study highlighted that LOM often occurs concurrently with LOS but can also present independently in about 16% of cases. The most common pathogens identified were coagulase-negative Staphylococcus (59%), Candida albicans (23%), and Escherichia coli (16%). The study also noted a significant decrease in lumbar

puncture (LP) performance over time, which could lead to an underestimation of LOM incidence.⁵

The findings from Dalai et al.'s prospective observational study suggest that no subgroup could be identified where LP could be safely avoided among neonates suspected of having sepsis due to the high probability (29%) of definite or possible meningitis even in low-risk groups.⁶

Bedetti et al.'s multicenter observational study highlighted that LP rates are low in culture-proven neonatal sepsis cases, often performed after antibiotic initiation which hampers pathogen identification via CSF cultures but increases detection through polymerase chain reaction methods.⁷

In a study conducted by Bhagat et al., it was concluded that in late-onset sepsis (LOS), the yearly occurrence of meningitis was 16 cases. The majority (46.1%) of patients were observed in the 3-7 day age bracket. The average weight of newborns was 2.61 ± 0.606 kg. A significant portion (60.3%) of neonates with meningitis had low birth weight ($P < 0.005$). Preterm infants accounted for 61.7% of LOS cases with meningitis, compared to 38.2% for full-term infants ($P < 0.005$). Males constituted 57.4% of meningitis cases, while females made up 42.6% ($P > 0.005$).⁸

Although various studies on meningitis in late-onset sepsis among neonates have been conducted globally, there is a lack of data specific to our local population. The findings from this study will guide the development of protocols for screening meningitis in late-onset sepsis, ultimately helping to improve the clinical management of the disease and reduce morbidity and mortality.

2. Materials & Methods

This cross-sectional study was carried out at the Department of Paediatrics, Hameed Latif Teaching Hospital Lahore from March 2023 to August 2023. Patients were selected through non-probability consecutive sampling. The age of the patients was from 7 to 28 days. A total of 210 patients were included after the calculation of the sample size from the open epi sample size calculator. It was 210 patients. After approval of the hospital's ethical committee and obtaining written informed consent from parents, all septic neonates were enrolled. Diagnosis of sepsis required the presence of suspected infection (consolidation on CXR, positive blood culture, >5 pus cells on urine culture) with any two or more systemic inflammatory response syndrome criteria which included, fever ($>38.3^\circ\text{C}$) or hypothermia (core

temperature $< 36^\circ\text{C}$), tachycardia (>100 bpm) or bradycardia (<60 bpm), tachypnea (respiratory rate $>60/\text{min}$). If the child was irritable or lethargic or with an abnormal white blood cell count or $>10\%$ immature bands. Inclusion criteria were neonates more than 7 days old, of both genders with late-onset sepsis. Critically sick neonates, those with gross congenital anomalies of the spine making lumbar puncture difficult and deranged coagulation profiles were excluded from the study. Demographic information (including name, age and gender) was recorded. In each neonate with clinical features of sepsis, a detailed history and examination were done. Neonates with features of sepsis were subjected to complete blood count, CRP and blood culture. Lumbar Puncture was done after informed consent was taken from parents. Meningitis was labelled in a neonate based upon CSF findings of white cell count $>30/\text{mm}^3$ with polymorphic lymphocyte predominance and any of these two, CSF protein >80 mg/dl, CSF glucose <40 mg/dl. Cranial ultrasound was done in all neonates with meningitis to rule out any complications. Data was entered and analyzed using SPSS v23.0. Frequencies and percentages were expressed for qualitative variables like gender and meningitis. Quantitative variables like age were expressed by Mean \pm S.D. Data was stratified for age, weight, gestational age (pre-term <37 weeks and term >37 weeks) and gender to deal with effect modifiers. For post-stratification, the Chi-square test was applied to see the significance. P-value ≤ 0.05 was considered significant.

3. Results

A total of 210 children presenting with late-onset sepsis were included. Among these children, 122(58.1%) were males, while 88(41.9%) were females. The age range in this study was from 7 to 28 days with mean age of 17.7 ± 6.3 days. Most of the children 140(66.7%) were in the 14-28 days age group, while 70(33.3%) were in the 7-14 days age group.

Among children, 47(22.4%) had meningitis. It was found that low-weight and preterm neonates were more associated with meningitis ($p=0.00001, 0.0003$).

When stratification of meningitis was done concerning age, it was found out that 19(27.1%) neonates had meningitis between 7 to 14 days of life, and 28(20%)

neonates had meningitis between 14 to 28 days of life (p value= 0.242).

Stratification of meningitis concerning weight showed that 28 (37.3%) neonates with meningitis weighed less than 2500 grams, whereas 19(14.1%) neonates with meningitis weighted more than 2500 grams (p value= 0.0003).

Table 1: Frequency distribution (n=210)

		Frequency	Percentage
Gender	Male	122	58.1
	Female	88	41.9
Gestational age	preterm	78	37.1
	Full term	132	62.9
Weight	<2.5 kg	75	35.7
	>2.5 kg	135	64.3
Meningitis	yes	47	22.4
	no	163	77.6

Table 2: Stratification of meningitis concerning gender

Gender	Meningitis		Total	P value
	Yes	No		
Male	28	94	122	0.816
	23%	77%	100%	
Female	19	69	88	
	21.6%	78.4%	100%	
Total	47	163	21	
	22.4%	77.6%	100%	

Table 3: Stratification of meningitis concerning gestational age

Gestational age	Meningitis		Total	P value
	Yes	No		
Preterm (<37 weeks)	28	50	78	0.00001
	35.9%	64.1%	100%	
Full term (>37 weeks)	19	113	132	
	14.4%	85.6%	100%	
Total	47	163	210	
	22.4%	77.6%	100%	

4. Discussion

Neonatal sepsis is one of the most common causes of neonatal morbidity and mortality.

The overlapping clinical manifestations of septicemia and meningitis make it very difficult to differentiate a neonate with meningitis from one with septicemia alone. Meningitis is associated with much more mortality and morbidity, hence it is sensible to have a high index of suspicion for meningitis while treating neonates with septicemia. According to previous studies, approximately 0.3-3% of neonates with sepsis develop

meningitis. However, it is quite high in cases of late-onset sepsis (LOS), reaching up to 30%.⁹

The incidence of meningitis in late Late-Onset Sepsis (LOS) in our study was 22.4%. It was found in an Indian study that among 208 neonates with late-onset sepsis (LOS) 12.5% had meningitis.¹⁰ A study conducted by Rabbani et al concluded that 34% of the neonates with late-onset neonatal sepsis had meningitis.¹¹

In the current study, it was found that among neonates with meningitis 28(23%) were males and 19 (21.6%) were females. Moreover, low birth weight and prematurity were more commonly associated with meningitis. In another study, 206 neonates with late-onset sepsis (LOS) were studied and it was found that 111 (53.9%) were males. Among these neonates 84 (40.8%) were preterm. Meningitis was present in 44 (21.4%) neonates. There were significant associations between low body weight, preterm status, and the occurrence of meningitis (p-value < 0.05).¹²

Another study from Ethiopia concluded that out of 171 participants, the prevalence of neonatal meningitis among suspected sepsis cases was 19.3%. The prevalence of meningitis was 22.8% in early-onset neonatal sepsis and 16.8% in late-onset neonatal sepsis.¹³

In this study, the incidence of meningitis was more in preterm neonates 28(35.9%) as compared to full-term neonates 19(14.4%). This finding is in agreement with the research by Seneet et al in which the rate of meningitis was 14(46.7%) in preterm neonates with late-onset sepsis and 8(21.6%) in full-term neonates with late-onset sepsis.¹⁴

We observed that prematurity and low birth weight were common associations of late-onset sepsis and meningitis. These findings correlate with an Italian study by Berardi et al encompassing all gestational age groups and reported an incidence rate of LOS at 2.3 per 1000 live births. Meningitis was identified in approximately 12% of cases with brain lesions or death occurring in hospital-acquired LOS being significantly associated with very low birth weight and extreme prematurity.¹⁵

In a similar comparable study, Brumbaugh et al provided a comprehensive analysis involving extremely preterm infants. They found that among 13,372 infants, late-onset meningitis (LOM) was diagnosed in 167 cases (1%). Notably, lumbar puncture performance during LOS evaluations decreased over time, potentially leading to underdiagnosis. Coagulase-negative Staphylococcus was the most common isolate (59%),

followed by *Candida albicans* (23%) and *Escherichia coli* (16%). These findings emphasize the need for consistent diagnostic practices to accurately assess the incidence of LOM.¹⁶

It has been observed that lumbar puncture (LP) is performed far less frequently than necessary in neonates suffering from sepsis. This underuse can lead to an underestimation of meningitis cases. To ensure accurate diagnosis, LP should ideally be performed before antibiotic administration. It is unclear whether the low frequency of LP in neonatal sepsis is due to clinician decisions or the patients' conditions, such as being premature versus full-term or having severe versus mild disease.¹⁷

The results of the current study are comparable with Indian research which concluded that out of 180 neonates, cerebrospinal fluid (CSF) analysis was normal in 131 (72.78%) neonates, while 37 (20.56%) neonates had findings suggestive of meningitis. The overall prevalence of meningitis in cases of neonatal sepsis was 20.0%, with 18.0% in early neonatal sepsis and 32.6% in late neonatal sepsis.¹⁸

The strength of this study lies in its robust sample size. However, a limitation is that we did not assess the association between early-onset sepsis and meningitis. We recommend that future studies address these limitations.

5. Conclusion

We conclude that meningitis is a notable complication among neonates with late-onset sepsis, particularly preterm or low birth weight neonates. Despite advances in diagnostic techniques like polymerase chain reaction enhancing pathogen detection post-antibiotic administration, there remains a critical need for timely LP performance before antibiotic initiation to accurately diagnose onset meningitis. Improved maternal screening protocols may further reduce the burden of this severe condition.

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S.N, M.F, - Conception of study
S.N - Experimentation/Study Conduction
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M.F, A.S, R.R - Manuscript Writing
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