Original Article

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Frequency of Meningitis and Associated Risk Factors in Neonates with Late-Onset Sepsis at NESCOM Hospital, Islamabad

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[1,3] Collecting the data, drafting the work or revising it critically for important intellectual content, data interpretation Data Collection , [2]Final approval of the version to be published

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ABSTRACT

Objective: To determine the frequency of meningitis and its associated risk factors among neonates with late-onset sepsis (LOS), defined as sepsis occurring after the first 72 hours of life.

Methodology: This cross-sectional study was conducted in the Department of Paediatrics, NESCOM Hospital, Islamabad, from March 2025 to September 2025. A total of 105 neonates aged >72 hours to 28 days who were admitted with a diagnosis of late-onset sepsis (LOS) were consecutively enrolled in the study. All neonates underwent lumbar puncture for cerebrospinal fluid (CSF) analysis. Meningitis was diagnosed using pre-defined CSF criteria. Demographic, perinatal, and socioeconomic data were recorded on a structured proforma. Effect modifiers were controlled by stratification, and chi-square / Fisher's exact tests were applied; $p \leq 0.05$ was considered statistically significant.

Results: The median age was 18 days (IQR 11) with female predominance (54.3%). Meningitis was diagnosed in 26 of 105 neonates (24.8%; 95% CI 16.9–32.7%). Demographic and socioeconomic factors age group, gender, residence, parental education, parental occupation, and socioeconomic status showed no significant association with meningitis (all $p \geq 0.076$). Low birth weight (50.0% vs. 17.4%, $p = 0.005$) and preterm birth (40.0% vs. 15.4%, $p = 0.005$) were identified as significant risk factors.

Conclusion: Nearly one in four neonates with LOS in our cohort had meningitis, with a strong, statistically robust association with low birth weight and preterm birth. Lumbar puncture should be performed with a low threshold in suspected LOS particularly in preterm or LBW neonates and obstetric care plus hospital infection control must be strengthened to prevent this serious complication.

Key words: Neonatal meningitis, late-onset sepsis, low birth weight, preterm birth, cerebrospinal fluid.

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Introduction

Neonatal sepsis remains a leading cause of newborn morbidity and mortality worldwide. An estimated 3 million neonates are affected annually, with case-fatality rates of 11–19% in low- and middle-income countries (LMICs).[1,2] Neonates are particularly susceptible to infection because of an immature immune system, including reduced neutrophil chemotaxis and phagocytosis, deficient complement activity, low transplacentally acquired immunoglobulin G (particularly in preterm infants), and compromised skin and mucosal barriers.[3] Sepsis in this age group is conventionally classified as early-onset (within the first 72 hours of life) or late-onset (occurring after 72 hours up to 28 days). Although intrapartum antibiotic prophylaxis and culture-based screening have reduced the early-onset burden in developed countries, late-onset sepsis (LOS) — frequently nosocomial — remains a major cause of neonatal morbidity and mortality globally.[3,4]

Neonatal meningitis, defined as inflammation of the membranes of the brain and spinal cord within the first 28 days of life, is among the most feared complications of LOS.[5] The reported frequency of culture-proven neonatal meningitis is 0.3 per 1,000 live births in developed nations, but rises to 0.8–1.6 per 1,000 in developing countries, with case-fatality reaching 58% in the latter and severe long-term complications affecting 20–60% of survivors.[2,5] Among clinically suspected sepsis cases, the prevalence of concurrent meningitis varies widely: 16.8%

in late-onset sepsis at Gondar, Ethiopia (Wondimu et al., 2023),[5] 22.4% from Rawalpindi (Naveed et al., 2024),[6] 28.2% from the Aga Khan University Hospital, Karachi (Ahmed et al., 2024),[7] and 32.6% in a tertiary Indian cohort (Singh & Seep, 2024).[8] This variability reflects differences in case definitions, the threshold for performing lumbar puncture, the proportion of preterm/LBW admissions, and local infection-control practice.

The neonatal predisposition to meningitis arises from a combination of an immature blood-brain barrier, deficient opsonic activity, low transplacental IgG levels (which crosses primarily in the third trimester), and immature cellular immunity. These factors allow circulating organisms during LOS bacteraemia to readily seed the meninges. The highest susceptibility is therefore documented in preterm and low-birth-weight neonates.[3,9] Established risk factors for invasive neonatal infection and subsequent meningitis include prematurity (gestational age < 37 weeks), low birth weight (LBW, < 2500 g), prolonged rupture of membranes, mechanical ventilation, and prolonged NICU stay.[5,10]

Despite an apparently high burden, comprehensive local data on the frequency of meningitis in LOS and its associated risk factors from tertiary care hospitals in the Islamabad/Rawalpindi region of Pakistan remain limited. Most available Pakistani studies have examined overall sepsis or focused on Karachi and Lahore cohorts, leaving an evidence gap for the federal capital region.[6,7,11] The present study was therefore designed to determine the frequency of meningitis among neonates admitted with LOS at NESCOM Hospital, Islamabad, and to identify the demographic, socioeconomic, and clinical risk factors associated with its occurrence — generating local evidence to inform diagnostic thresholds and infection-control protocols.

Methodology

This cross-sectional study was conducted at the Department of Paediatrics, NESCOM Hospital, Islamabad, over a six-month period (1st March 2025 to 30th September 2025), following Institutional Ethical Review Committee approval Ref No NESCOM-44(33)/2023-IMC. Written informed consent was obtained from the parents or guardians of every participant prior to enrolment.

Operational Definitions

Neonatal sepsis was assessed positive when a neonate (≤ 28 days of age) had at least two of the following: (a) clinical signs — any of temperature < 36.5°C or > 37.5°C, respiratory rate > 60/min or apnoea, lethargy, poor feeding, hypotonia, irritability, or bradycardia (<100/min); (b) total leucocyte count < 5,000/mm³ or > 20,000/mm³, or immature-to-total neutrophil ratio > 0.2; (c) C-reactive protein ≥ 10 mg/L; (d) positive blood culture. The neonate was assessed negative if these criteria were not met.

Late-onset sepsis (LOS) was assessed positive when the above sepsis criteria were met after 72 hours of age and up to 28 days of life.

Meningitis was assessed positive when CSF analysis showed any one of: (a) CSF white-cell count > 20 cells/mm³ (or > 30 cells/mm³ if a traumatic tap, after correction); (b) CSF protein > 150 mg/dL; (c) CSF glucose < 30 mg/dL or CSF: blood glucose ratio < 0.5; (d) positive CSF Gram stain or culture; otherwise it was assessed negative.

Low birth weight (LBW) — birth weight < 2500 g (positive) versus ≥ 2500 g (negative). Subcategories were recorded as very LBW (< 1500 g) and extremely LBW (< 1000 g) but, owing to small subgroup numbers, were not analyzed as separate strata.

Preterm birth — delivery before 37 completed weeks of gestation (positive) versus ≥ 37 weeks (negative), per WHO criteria.

Socioeconomic status — classified according to World Bank criteria for lower-middle-income countries, adapted to Pakistan: low (< 28,000 PKR/month household income), middle (28,000–55,000 PKR/month), and high (> 55,000 PKR/month).[12]

The sample size of 105 neonates was calculated using the WHO sample size calculator with a 95% confidence interval, 8% absolute precision, and an anticipated frequency of meningitis of 22.4% among LOS cases (based on Naveed et al., 2024).[6] Participants were enrolled by non-probability consecutive sampling.

Inclusion and Exclusion Criteria

Inclusion criteria: neonates aged > 72 hours to 28 days, of either gender, admitted with a clinical diagnosis of LOS at our institution during the study period.

Exclusion criteria: (i) neonates whose parents or guardians declined consent for lumbar puncture; (ii)

neonates already started on systemic antibiotics prior to enrolment (to avoid CSF sterilization bias).

Demographic and clinical data (age, gender, birth weight, gestational age, residence, parental occupation, maternal education, and socioeconomic status) were collected on a structured proforma. Each neonate underwent lumbar puncture under aseptic technique after a clinical history and physical examination. CSF samples were sent for cell count, biochemistry (protein, glucose), Gram stain, and culture. Concurrent blood culture, CRP, and complete blood count were performed. All neonates were managed in accordance with institutional protocols.

Data were analyzed using SPSS v22.0. Normality of continuous variables was assessed using the Shapiro–Wilk test. Quantitative variables are presented as mean ± SD or median (IQR) according to distribution. Categorical variables are presented as frequencies and percentages. Effect modifiers (age, gender, residence, parental occupation, parental education, and socioeconomic status) were controlled by stratification. Post-stratification chi-square or Fisher's exact tests were used to assess associations between risk factors and meningitis. A p-value of < 0.05 was considered statistically significant.

Results

A total of 105 neonates admitted with LOS were enrolled. The data for age, gestational age, and birth weight were not normally distributed (Shapiro–Wilk p = 0.003, 0.000, and 0.004 respectively). The median age was 18 days (IQR 11), median gestational age 37 weeks (IQR 2), and median birth weight 2,853 g (IQR 747). Female neonates predominated (57/105, 54.3%; Figure I).

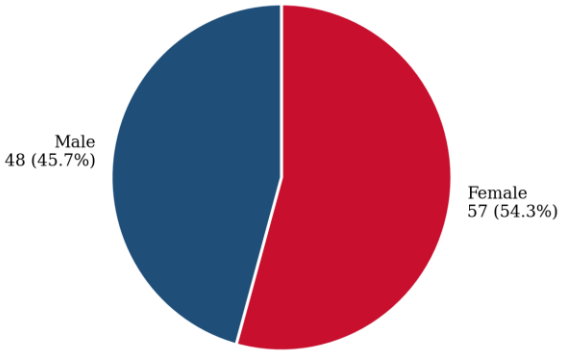

Figure I. Gender distribution among neonates, (n = 105).

Urban residents comprised 48 (45.7%) of the cohort. Maternal education was illiterate in 33 (31.4%) and matriculation or above in 24 (22.9%) (Figure II). Parental occupation was unemployed in 35.2%, salaried in 27.6%, and business in 37.1%. Socioeconomic status was low in 54.3%, middle in 39.0%, and high in 6.7%. Preterm birth was recorded in 40 (38.1%) and LBW in 30 (28.6%) of the cohort. Of the 30 LBW neonates, 24 were LBW (1500–2499 g), 5 very LBW (1000–1499 g), and 1 extremely LBW (< 1000 g).

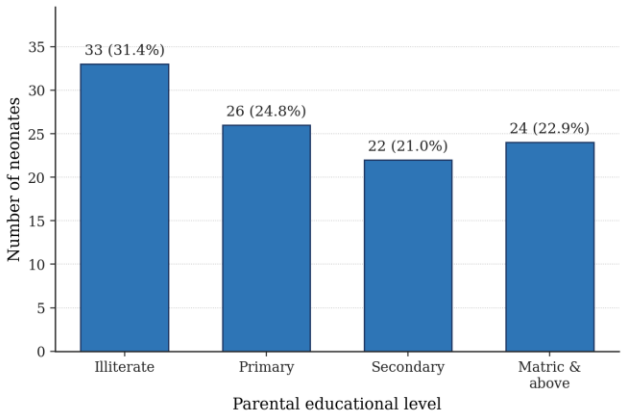

Figure II. Parental educational status. (n = 105)

Meningitis was diagnosed in 26 of the 105 neonates with LOS, giving an overall frequency of 24.8% (95% CI 16.9–32.7%) Figure III.

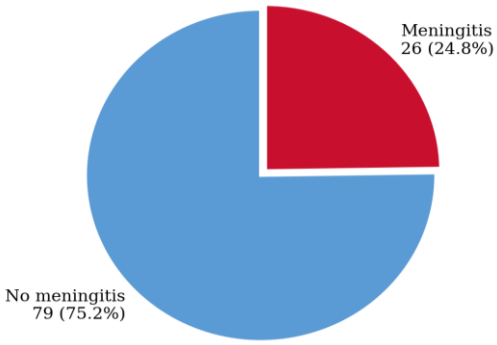

Figure III. Frequency of meningitis in neonates with LOS (n = 105).

After post-stratification analysis, none of the demographic or socioeconomic variables showed a statistically significant association with meningitis (Table I; all p ≥ 0.076). However, the two principal biological risk factors examined were highly significant: meningitis occurred in 50.0% of LBW neonates versus 17.4% of normal-weight neonates (p = 0.005), and in 40.0% of preterm versus 15.4% of term neonates (p = 0.005) (Table II).

Discussion

This single-centre prospective cross-sectional study identified meningitis in nearly one in four neonates admitted with LOS at NESCOM Hospital, Islamabad.

Table I: Meningitis in stratification subgroups (chi-square test).

Stratification group	Subgroup	Meningitis (Yes)	Meningitis (No)	p-value
Age	< 18 days	17 (65.4%)	43 (54.4%)	0.328
	≥ 18 days	9 (34.6%)	36 (45.6%)	
Gender	Male	15 (57.7%)	32 (40.5%)	0.126
	Female	11 (42.3%)	47 (59.5%)	
Area of residence	Urban	13 (50.0%)	35 (44.3%)	0.613
	Rural	13 (50.0%)	44 (55.7%)	
Parental education	Illiterate	6 (23.1%)	27 (34.2%)	0.076
	Primary	3 (11.5%)	23 (29.1%)	
	Secondary	8 (30.8%)	14 (17.7%)	
	Matric & above	9 (34.6%)	15 (19.0%)	
Parental occupation	Salaried	9 (34.6%)	20 (25.3%)	0.648
	Business	9 (34.6%)	30 (38.0%)	
	Unemployed	8 (30.8%)	29 (36.7%)	
Socioeconomic status	Low	13 (50.0%)	44 (55.7%)	0.509
	Middle	10 (38.5%)	31 (39.2%)	
	High	3 (11.5%)	4 (5.1%)	

Table II: Meningitis in potential risk-factor groups (chi-square test).

Risk factor	Status	Meningitis (Yes)	Meningitis (No)	p-value
Low birth weight	Yes	13 (50.0%)	17 (21.5%)	0.005
	No	13 (50.0%)	62 (78.5%)	
Preterm birth	Yes	16 (61.5%)	24 (30.4%)	0.005
	No	10 (38.5%)	55 (69.6%)	

The strong, statistically robust association with low birth weight and prematurity and the conspicuous absence of an association with demographic and socioeconomic variables — has direct implications for the threshold for performing diagnostic lumbar puncture in this setting and for the targeting of obstetric preventive strategies. In the paragraphs that follow, we compare these findings with recent national and international data, examine the pathophysiological underpinnings, and discuss the policy implications and limitations of our work.

Our observed prevalence of meningitis (24.8%) sits in the middle of recently reported Pakistani figures — 22.4% from Rawalpindi (Naveed et al., 2024)[6] and 28.2% from the Aga Khan University Hospital, Karachi (Ahmed et al., 2024)[7] — and is consistent with international LMIC data such as the 32.6% reported in a 2024 Indian tertiary care cohort (Singh & Seep).[8] It is, however, notably higher than the 16.8% reported in late-onset sepsis at the University of Gondar Hospital, Ethiopia (Wondimu et al., 2023).[5] The variability across these settings reflects differences in case definition, the threshold for performing lumbar puncture, the proportion of preterm/LBW admissions, and local infection-control practice. The convergence of three independent Pakistani tertiary centers on a 22–28% range strongly suggests a real and unacceptably high national pattern that warrants coordinated policy attention.

Given this high background prevalence, an aggressive diagnostic approach is justified. Clinical signs of meningitis in the neonate are notoriously nonspecific — temperature instability, irritability, poor feeding, and seizures overlap substantially with sepsis alone — and the predictive value of bedside assessment for culture-proven CNS infection is poor.[13] Lumbar puncture should therefore be performed with a low threshold as part of the routine LOS workup, particularly when neurological features or laboratory markers of severe sepsis are present.

Our finding that 50.0% of LBW neonates and 40.0% of preterm neonates with LOS developed meningitis is consistent with Naveed et al. (LBW 35.7%; preterm 35.9%)[6] and Atif et al. (2021), who reported adjusted odds ratios of 5.13 for LBW and 9.59 for prematurity as predictors of mortality in neonatal sepsis.[11] Mechanistically, the immature blood-brain barrier, deficient transplacental IgG (which crosses primarily in the third trimester), reduced complement activity, and impaired neutrophil chemotaxis in preterm and LBW neonates plausibly explain this strong association.[3,9] A Pakistani outbreak investigation of NDM-producing Burkholderia cepacia in a NICU likewise found that more than half of affected neonates were LBW, underscoring the convergence of biological vulnerability and nosocomial exposure in this group.[14]

Unlike Wondimu et al., who identified prolonged labour and prolonged rupture of membranes as the dominant

maternal risk factors,[5] the present study did not capture these obstetric variables systematically because of incomplete antenatal data for many referred neonates. This is acknowledged as a limitation. Conversely, our finding that none of the demographic and socioeconomic variables showed a significant association with meningitis is consistent with Naveed et al.[6] and supports the hypothesis that, once the proximate biological risk factors (LBW, prematurity) have been established, distal socioeconomic factors do not exert an additional direct effect on meningitis risk within an admitted LOS cohort. Socioeconomic determinants nonetheless remain important upstream contributors to LBW and prematurity themselves, and should not be ignored in policy design.

Although antimicrobial resistance was not an objective of the present study, the implications of our findings cannot be divorced from the local resistance landscape. Atif et al. reported high resistance among common gram-negative pathogens (Klebsiella, E. coli) to amikacin–cefotaxime combinations,[11] and Zahoor et al. documented a high prevalence of Panton-Valentine leukocidin–positive MRSA and multidrug-resistant gram-negative bacteria in neonatal LOS in Pakistan, indicating nosocomial spread.[15] Unusual and inherently resistant organisms (Burkholderia cepacia[14] and Elizabethkingia spp.[16],[17]) have also been described. Empirical antimicrobial regimens for suspected neonatal meningitis must therefore be guided by current local antibiogram data rather than static national guidelines.[18,19]

Several limitations must be acknowledged. This was a single-center study in a tertiary care hospital, limiting generalizability to district-level or community settings. The relatively modest sample size may have produced Type II error for some demographic variables; alternatively, the absence of demographic associations may reflect a genuine null effect once biological risk factors are accounted for. Microbiological identification of causative organisms was not within the scope of this study; CSF cultures, where available, were limited by no-growth and contamination rates and were not analyzed inferentially. We did not capture detailed antimicrobial management or maternal obstetric variables (prolonged labour, PROM, chorioamnionitis), and referral bias is inherent to tertiary care studies. These represent priorities for subsequent multicentre work.

Conclusion

This study confirms a high frequency (24.8%) of meningitis among neonates with LOS at a tertiary care hospital in Pakistan and identifies preterm birth and low birth weight as the only statistically significant risk factors. The findings support the necessity of performing diagnostic lumbar puncture with a low threshold in suspected LOS — particularly in preterm or LBW neonates and in those with any neurological features, clinical deterioration, or laboratory markers of severe sepsis. They further underscore the need for judicious antimicrobial use guided by local resistance patterns and stringent infection-control measures in the NICU. Strengthening antenatal and obstetric care to reduce preterm birth and low birth weight — combined with vigilant clinical and laboratory surveillance for sepsis in admitted neonates — offers the dual benefit of preventing meningitis at source and enabling its early detection where it does occur, thereby reducing associated morbidity, neurodevelopmental sequelae, and mortality.

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