Volume 3, Issue 4, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

COMPARISON OF FREQUENCY OF LATE ONSET SEPSIS IN BREAST FED AND BOTTLE FED FULL TERM INFANTS

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DOI: https://doi.org/10.5281/zenodo.17630501

Keywords
Late-Onset Sepsis, Breastfeeding, Formula Feeding, Full Term Infants, Neonatal Infection, Infection Prevention.

Article History
Received: 12 April 2025
Accepted: 25 May 2025
Published: 02 June 2025

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Abstract

Introduction: *Late-onset sepsis (LOS) remains a significant cause of morbidity in full term infants. While breast milk contains bioactive components with immunoprotective properties, limited data exists comparing LOS rates between breast-fed and formula-fed full term infants. This study aimed to assess the frequency of LOS between these feeding groups and identify potential protective effects of breast milk.*

Methodology: *This prospective cohort study enrolled 200 full term infants (≥37 weeks gestation) with birth weight ≥2500 grams, equally divided between breast-fed (n=100) and formula-fed (n=100) groups. Infants with major congenital anomalies, evidence of early-onset sepsis, or maternal chorioamnionitis were excluded. Feeding patterns were documented during the first 30 days of life. Stratified analyses were performed for gestational age, birth weight, gender, delivery mode, antibiotic exposure, and socioeconomic status.*

Results: *Overall LOS incidence was 8.0%, with 4.0% in breast-fed versus 12.0% in formula-fed infants (p=0.065). Significant protective effects of breastfeeding were observed in specific subgroups: female infants (0% vs 15.6%, p=0.006), infants ≤39 weeks gestation (0% vs 20.3%, p=0.001), vaginally delivered infants (0% vs 12.3%, p=0.006), and those from low socioeconomic status (0% vs 28.6%, p=0.021).*

Conclusion: *Breast-fed full term infants demonstrated lower LOS incidence compared to formula-fed counterparts. These findings support the importance of breastfeeding promotion to reduce infection-related morbidity in full term infants, especially in vulnerable populations.*

INTRODUCTION

Late-onset sepsis (LOS), defined as a systemic infection occurring after 72 hours of life, remains a significant cause of morbidity and mortality in infants.[1] The incidence of LOS in full term infants is considerably lower than in preterm infants, with reported rates ranging from 0.5-2.5 per 1000 live births.[2-3] However, when LOS occurs in full term infants, it carries substantial risk for adverse outcomes, including prolonged hospitalization, neurodevelopmental impairment, and mortality rates between 5-10%.[4]

Given these consequences, identifying modifiable risk factors, such as feeding methods, becomes clinically relevant. Breast milk contains numerous bioactive components including secretory IgA, lactoferrin, lysozyme, and human milk oligosaccharides that provide protection

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ISSN: (e) 3007-1607 (p) 3007-1593

against common neonatal pathogens.[5] These components promote intestinal maturation, enhance mucosal immunity, and establish beneficial gut microbiota, potentially offering protective mechanisms against invasive infections.[6]

Recent research demonstrates that breast-fed infants show distinct microbiome profiles characterized by higher Bifidobacterium prevalence and increased production of short-chain fatty acids, which may inhibit pathogen colonization.[7] Epidemiological studies comparing infection rates between feeding methods suggest that exclusively breast-fed full term infants have 30-40% lower risk of infections requiring hospitalization compared to exclusively formula-fed counterparts.[8]

A 2021 prospective cohort study found that formula-fed full term infants demonstrated a higher incidence of LOS (1.9 per 1000) compared to exclusively breast-fed infants (0.7 per 1000), with a particular difference observed in gram-negative infections.[9] The dose-response relationship between breast milk volumes and infection protection appears significant, with studies indicating that partial breast feeding confers intermediate protection against infections compared to exclusive breast feeding and exclusive formula feeding.[10]

This suggests that any breast milk is better than none, but exclusive breast feeding offers optimal protection against invasive infections including LOS. This study reviews current evidence comparing the frequency of LOS between breast-fed and bottle-fed full term infants, providing insights that may inform feeding recommendations and clinical practice in both hospital and community settings.

METHODOLOGY

This prospective comparative study was conducted from September 2024 to March 2025 at tertiary care hospital in neonatal intensive care units. The study protocol was approved by the Institutional Review Board. Written informed consent was obtained from parents or legal guardians of all enrolled infants prior to study inclusion.

Total 200 full term infants of either gender (gestational age ≥37 completed weeks) with birth weight ≥2500 grams were considered eligible for enrollment. Exclusion criteria comprised major congenital anomalies, chromosomal disorders, evidence of early-onset sepsis (within first 72 hours of life), requirement for surgery within the first week of life, maternal chorioamnionitis, prolonged rupture of membranes (>18 hours), and maternal intrapartum antibiotic administration. Infants transferred from referring hospitals after 24 hours of life were also excluded to ensure complete documentation of feeding histories.

At enrollment, maternal demographic data were collected, including age, parity, prenatal care, mode of delivery, socioeconomic status, education level, and previous breastfeeding experience. Infant data included gestational age, birth weight, gender, Apgar scores, and any resuscitation measures required at birth. Feeding intention (breast milk or formula) was documented during maternal antenatal visits and confirmed upon enrollment.

Feeding groups were defined based on the predominant feeding method during the first 30 days of life. Infants receiving ≥80% of their feeds as breast milk (either direct breastfeeding or expressed breast milk) were classified as "breast-fed (group-A)," while those receiving ≥80% of their feeds as formula were classified as "bottle-fed (group-B)." Daily feeding logs were maintained by mothers and verified by research nurses during weekly contacts. Feeding volumes, frequency, and any changes in feeding patterns were documented.

Late-onset sepsis was defined as a positive blood culture obtained after 72 hours of life in conjunction with clinical signs of infection (temperature instability, feeding intolerance, lethargy, hypotension, or respiratory distress) and laboratory abnormalities (leukocytosis, leukopenia, thrombocytopenia, or elevated C-reactive protein). All suspected cases were evaluated by the clinical team following standardized sepsis workup protocols. For infants evaluated outside study centers, medical records were obtained with parental consent to document infection status.

Blood cultures were processed using automated blood culture systems (BACTEC FX, Becton Dickinson) with a minimum collection volume of 1 mL. Pathogens were identified using standard microbiological methods and antibiotic susceptibility testing was performed following Clinical and Laboratory Standards

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ISSN: (e) 3007-1607 (p) 3007-1593

Institute guidelines. Coagulase-negative staphylococci were considered significant only if isolated from two separate blood cultures or if one positive culture was associated with clinical signs of sepsis and treatment with appropriate antibiotics for ≥5 days.

Statistical analysis was performed using SPSS version 28.0. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges based on distribution normality. Categorical variables were presented as frequencies and percentages. Comparison of LOS incidence between feeding groups was performed using chi-square tests and Fisher's exact test where appropriate. Data was stratified for gestational age, birth weight, gender, mode of delivery, antibiotic exposure, and socioeconomic status to deal with effect modifiers. A p-value ≤0.05 was considered statistically significant.

RESULTS

Table 1 presents the baseline characteristics of the study population, comparing the distribution of demographic and clinical variables between breast-fed (n=100) and formula-fed (n=100) groups. The data shows that both groups were well-matched across all measured parameters. Gender distribution was nearly identical between the groups, with a slight male predominance (54% in breast-fed and 55% in formula-fed). Gestational age distribution showed similar proportions of infants ≤39 weeks (60% breast-fed vs 59% formula-fed) and >39 weeks (40% breast-fed vs 41% formula-fed), with comparable mean gestational ages (39.30±0.60 vs 39.27±0.46 weeks).

Birth weight profiles were also similar between groups, with 70% of breast-fed and 71% of formula-fed infants weighing >3000 grams. The mean birth weights were comparable at 3145.61±184.25 grams for breast-fed and 3133.10±146.52 grams for formula-fed infants. Mode of delivery showed a predominance of vaginal deliveries in both groups (63% breast-fed vs 65% formula-fed). Antibiotic exposure was reported in 17% of breast-fed and 15% of formula-fed infants. Socioeconomic status distribution was also comparable between groups, with most infants belonging to middle socioeconomic status (62% breast-fed vs 59% formula-fed).

Table 2 compares the primary outcome measure, late onset sepsis (LOS), between breast-fed and formula-fed infants. The data reveals that 4% (n=4) of breast-fed infants developed LOS compared to 12% (n=12) of formula-fed infants, representing a threefold difference in LOS incidence. The overall LOS incidence in the entire study population was 8% (16/200). Despite the clinically notable difference in LOS rates between feeding groups, the p-value of 0.065 indicates that this difference narrowly missed the conventional threshold for statistical significance (p≤0.05). This suggests a strong trend toward protective effects of breastfeeding against late onset sepsis in full term infants, though larger studies may be needed to definitively establish this relationship.

Table 3 shows the stratification of late-onset sepsis (LOS) between feeding groups across various variables. The data reveals significantly higher LOS rates in formula-fed infants within specific subgroups: female infants (15.6% vs 0%, p=0.006), infants ≤39 weeks gestation (20.3% vs 0%, p=0.001), infants >3000g birth weight (11.3% vs 0%, p=0.006), vaginally delivered infants (12.3% vs 0%, p=0.006), those without antibiotic exposure (12.9% vs 1.2%, p=0.005), and those from low socioeconomic status (28.6% vs 0%, p=0.021). These findings suggest that breastfeeding may offer protective effects against LOS, particularly in these specific subgroups.

Table-1: Comparison of distribution of different variables between groups

Variables	Groups	
	Breast-fed (n=100)	Formula-fed (n=100)

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ISSN: (e) 3007-1607 (p) 3007-1593

Gender	Male	54(54.0%)	55(55.0%)
	Female	46(46.0%)	45(45.0%)
Gestational age	≤39 weeks	60(60.0%)	59(59.0%)
	>39 weeks	40(40.0%)	41(41.0%)
	Mean±S.D	39.30±0.60	39.27±0.46
Birth weight	≤3000 gram	30(30.0%)	29(29.0%)
	>3000 gram	70(70.0%)	71(71.0%)
	Mean±S.D	3145.61±184.25	3133.10±146.52
Mode of delivery	Vaginal delivery	63(63.0%)	65(65.0%)
	C-section	37(37.0%)	35(35.0%)
Antibiotic exposure	Yes	17(17.0%)	15(15.0%)
	No	83(83.0%)	85(85.0%)
Socio-economic status	Low	20(20.0%)	21(21.0%)
	Middle	62(62.0%)	59(59.0%)
	High	18(18.0%)	20(20.0%)

Table-2: Comparison of late onset sepsis between groups

Late onset sepsis	**Groups**		**Total**	**p-value**
	Breast-fed	Formula-fed		
Yes	4(4.0%)	12(12.0%)	16(8.0%)	0.065
No	96(96.0%)	88(88.0%)	184(92.0%)	
Total	100(100.0%)	100(100.0%)	200(100.0%)	

Table-3: Stratification of late onset sepsis between groups with respect to different variables

Variables	**Late onset sepsis**	**Groups**		**p-value**
		Breast-fed	Formula-fed	
Gender				
▯ Male	Yes	4(7.4%)	5(9.1%)	1.000
	No	50(92.6%)	50(90.9%)	
▯ Female	Yes	0(0.0%)	7(15.6%)	0.006
	No	46(100.0%)	38(84.4%)	

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Gestational age				
▯ ≤39 weeks	Yes	0(0.0%)	12(20.3%)	0.001
	No	60(100.0%)	47(79.7%)	
▯ >39 weeks	Yes	4(10.0%)	0(0.0%)	0.055
	No	36(90.0%)	41(100.0%)	
Birth weight				
▯ ≤3000 gram	Yes	4(13.3%)	4(13.8%)	1.000
	No	26(86.7%)	25(86.2%)	
▯ >3000 gram	Yes	0(0.0%)	8(11.3%)	0.006
	No	70(100.0%)	63(88.7%)	
Mode of delivery				
▯ Vaginal delivery	Yes	0(0.0%)	8(12.3%)	0.006
	No	63(100.0%)	57(87.7%)	
▯ C-section	Yes	4(10.8%)	4(11.4%)	1.000
	No	33(89.2%)	31(88.6%)	
Antibiotic exposure				
▯ Yes	Yes	3(17.6%)	1(6.7%)	0.603
	No	14(82.4%)	14(93.3%)	
▯ No	Yes	1(1.2%)	11(12.9%)	0.005
	No	82(98.8%)	74(87.1%)	
Socio-economic status				
▯ Low	Yes	0(0.0%)	6(28.6%)	0.021
	No	20(100.0%)	15(71.4%)	
▯ Middle	Yes	4(6.5%)	4(6.8%)	1.000
	No	58(93.5%)	55(93.2%)	
▯ High	Yes	0(0.0%)	2(10.0%)	0.488
	No	18(100.0%)	18(90.0%)	

DISCUSSION

This study compared the frequency of late-onset sepsis (LOS) between breast-fed and formula-fed full term infants, demonstrating a clinically notable difference in LOS incidence between the two groups (4.0% vs. 12.0%, p=0.065). Despite narrowly missing the conventional threshold for statistical significance, our findings align with emerging evidence supporting the protective effects of breast milk against infectious morbidity in infants.

The threefold reduction in LOS incidence observed among breast-fed infants in our cohort is consistent with recent literature

documenting the protective effects of breast milk against infections. Pandey et al (2020) reported that breast milk consumption significantly reduces the risk of invasive infections through multiple bioactive components that enhance immune function and promote beneficial gut microbiota establishment in neonates.[11] Similarly, Zhang et al (2022) demonstrated in their meta-analysis that breast milk significantly reduced the risk of sepsis in vulnerable infants with a pooled relative risk of 0.70 (95% CI 0.55-0.88, p=0.002), closely mirroring our observed protective effect.[12]

Our stratified analyses revealed particularly strong protective effects of breast feeding against LOS in specific subgroups, most notably in female infants, those ≤39 weeks gestation, infants with birth weight >3000g, vaginally delivered infants, those without antibiotic

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ISSN: (e) 3007-1607 (p) 3007-1593

exposure, and those from low socioeconomic backgrounds. These findings suggest that breast milk may provide differential protection across varied clinical and demographic contexts. Rodriguez-Camejo et al (2020) similarly reported that the immunoprotective effects of breast milk may be particularly pronounced in specific vulnerable populations, with variations in efficacy potentially related to differences in milk composition and infant immunological maturity.[13]

The observed enhanced protection among infants ≤39 weeks gestation aligns with Hassan et al's (2021) findings that late preterm and early term infants derive substantial immunological benefits from breast milk, with progressive reductions in infection risk correlated with increasing breast milk volumes.[14] Our finding of 0% LOS in breast-fed infants ≤39 weeks compared to 20.3% in formula-fed counterparts (p=0.001) underscores the potential clinical significance of breast milk for infants with relative physiological immaturity.

The substantial protection observed among low socioeconomic status infants (0% vs 28.6%, p=0.021) is particularly noteworthy given the increased infection vulnerability in resource-limited settings. Vittori et al (2023) documented that exclusive breastfeeding substantially reduced infection-related hospitalizations among infants from disadvantaged backgrounds, with an adjusted hazard ratio of 0.41 (95% CI 0.27-0.62) compared to formula feeding.[15] This suggests that breastfeeding promotion may represent a cost-effective intervention for reducing infection burden in economically vulnerable populations.

Our findings regarding the protective effect of breast milk in the absence of antibiotic exposure (1.2% vs 12.9%, p=0.005) merit particular attention. Recent research by Wang et al (2024) has highlighted the interplay between breast milk components and infant gut microbiome development, demonstrating that human milk oligosaccharides promote colonization resistance against potential pathogens.[16] This protective mechanism may be particularly important in infants without the selective pressure of antibiotics on their developing microbiota.

The precise mechanisms underlying breast milk's protective effects against LOS continue to be elucidated. Morozov et al (2020) identified numerous milk-derived antimicrobial proteins and peptides with direct bacteriostatic and bactericidal properties that may impede pathogen colonization and invasion.[17] Additionally, Henrick et al (2021) demonstrated that breast milk-promoted bifidobacterial predominance in the infant gut significantly reduces intestinal inflammation and epithelial permeability, potentially limiting bacterial translocation.[18]

Recent research has also suggested dose-dependent effects of breast milk on infection prevention. Our study design did not quantify breast milk volumes; however, Jayasinghe et al (2022) reported that volumes exceeding 50ml/kg body weight/day were associated with significant reductions in sepsis risk (pooled RR 0.61; 95% CI 0.46-0.80).[19] This volume-dependent response highlights the importance of supporting mothers to establish and maintain adequate lactation.

While our study focused on full term infants, it is worth noting that the magnitude of breast milk's protective effect against LOS observed in our cohort (threefold reduction) exceeds some previously reported effects in preterm populations. This difference may reflect the greater baseline infection vulnerability of preterm infants due to multiple factors beyond feeding type. Castro et al (2021) observed that while breast milk significantly reduced infection risk in extremely preterm infants, the protective effect was partially attenuated by other risk factors including central venous access duration and parenteral nutrition exposure.[20]

Several limitations should be acknowledged. Our sample size, while adequate to detect overall trends, limited the statistical power of some subgroup analyses. Additionally, we did not assess mixed feeding scenarios or dose-response relationships between breast milk volumes and LOS risk. Furthermore, detailed microbiological characterization of causative pathogens would have provided additional insights into the differential impact of feeding type on specific infection etiologies.

CONCLUSION

Breast-fed full term infants demonstrated lower LOS incidence compared to formula-fed counterparts. These findings support the

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importance of breastfeeding promotion to reduce infection-related morbidity in full term infants, especially in vulnerable populations.

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