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Early Enteral Feeding Strategies and Risk of Necrotizing Enterocolitis in Preterm Neonates: A Cohort Study

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Abstract

Background:
Necrotizing enterocolitis (NEC) is a serious inflammatory bowel disease that affects preterm newborns. It has a high rate of illness and death, especially in babies who are very low birth weight.

Objective:
To assess the correlation between exclusive human milk (EHM) feeding in the initial 14 days of life and the incidence of necrotizing enterocolitis (NEC) in preterm neonates.

Methods:
A prospective cohort study was conducted Bangladesh Shishu Hospital & Institute, Dhaka involving 95 preterm neonates (<37 weeks). The neonates were categorized into two groups: EHM and non-EHM. Feeding habits, probiotic use, parenteral nutrition, and clinical outcomes were recorded. NEC incidence (Bell stage II/III), late-onset sepsis, time to full feeds, and mortality were analyzed using risk ratios, Kaplan–Meier survival analysis, and multivariable Poisson regression.

Results:
Neonates who were fed EHM started eating earlier, took longer to finish their meals, and used more probiotics. The rate of NEC was lower in the EHM group (5.2%) than in the non-EHM group (18.9%; RR=3.65, 95% CI 1.01–13.16, p=0.041). Feeding without EHM, being born very early, and quickly moving up the feeding schedule all raised the risk of NEC. On the other hand, antenatal steroids and probiotics were protective. EHM babies also had fewer cases of late-onset sepsis, got full feeds faster, and lived longer.

Conclusion:
Feeding only human milk to preterm neonates for the first 14 days greatly lowers the risk of NEC and improves clinical outcomes.

Keywords: Necrotizing Enterocolitis, Preterm Neonates, Exclusive Human Milk, Enteral Feeding, Probiotics, Neonatal Outcomes

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Introduction:

Necrotizing enterocolitis (NEC) is a severe inflammatory bowel disease that primarily affects preterm and very low birth weight (VLBW) infants, causing intestinal necrosis, systemic inflammation, and high mortality.[1] NEC-like conditions were described as early as the late 1800s, but it was only with modern neonatal intensive care in the 1960s that it was recognized as a distinct disease.[2] Pathophysiological models highlight how the interaction between immature intestines, microbial colonization, and feeding strategies contributes to NEC development.[3]

For the past 30 years, Neonatal Intensive Care Units (NICUs) worldwide have been striving to enhance enteral nutrition to provide early gut stimulation while reducing the risk of Necrotizing Enterocolitis (NEC).[4] Cohort studies indicate that initiating minimal enteral feeds within 72 hours (trophic feeding) and carefully increasing feed volumes promote intestinal adaptation, alleviate complications associated with parenteral nutrition, and do not increase the risk of NEC.[5] Meta-analyses reveal that delaying enteral feeding for more than 2–3 days does not prevent NEC and may increase the likelihood of sepsis and feeding

intolerance.[6] Current guidelines advocate for personalized feeding plans that prioritize human milk, structured progression rates (15–30 mL/kg/day), and diligent monitoring.[7] The evidence supports early, progressive feeding rather than ultra-slow advancement. Multicenter studies demonstrate that attaining full feeds more rapidly diminishes the risk of sepsis and reduces hospital stays, all without increasing the incidence of stage II–III NEC.[8] Systematic reviews confirm that rapid escalation protocols promote growth and nutritional intake while maintaining NEC safety.[9]

In South Asia, NEC remains a major contributor to preterm morbidity and mortality. In India, early maternal milk feeding and cautious feed progression are emphasized.[10] Pakistani NICUs report NEC rates up to 14% in VLBW infants, with early feeding strategies including probiotics and donor milk reducing severity.[11] Nepal and Bhutan promote early breastfeeding and skin-to-skin care, though formal cohort data are limited.[12] Southeast Asian countries such as Malaysia, Vietnam, and Thailand have implemented evidence-based feeding protocols with trophic feeds, milk fortification, and probiotics, lowering NEC incidence and improving growth.[13]

High-income countries adopt structured protocols, starting with small feed volumes, gradual advancement, and close monitoring.[14] The International Neonatal Nutrition Network recommends early trophic feeds, evidence-based advancement, and probiotics to minimize NEC risk. Early, carefully advanced enteral feeding prioritizing human milk, guided by standardized protocols, remains a key strategy for reducing NEC while ensuring adequate nutrition. Continued research, regional collaboration, and adherence to evidence-based guidelines are essential for improving neonatal outcomes globally.

Method:

This prospective cohort study was conducted at the Department of Neonatology, Bangladesh Shishu Hospital & Institute, Dhaka, from January to May 2024. A total of 95 preterm neonates (gestational age <37 weeks) were enrolled at birth and followed until discharge or death. Exclusion criteria included major congenital anomalies, gastrointestinal malformations, chromosomal abnormalities, or early transfer before enteral feeding initiation. The primary exposure was Exclusive Human Milk (EHM) feeding during the first 14 days, defined as feeding with only mother's milk or donor milk, without formula supplementation. Neonates receiving formula during this period were categorized as non-EHM. Feeding practices, enteral feeding initiation timing, feed advancement, use of probiotics, parenteral nutrition duration, and fortification were documented. The primary outcome was the development of necrotizing enterocolitis (NEC), defined as Bell stage II or III.[15] Secondary outcomes included late-onset sepsis, time to full enteral feeding, and in-hospital mortality.

Data analysis involved descriptive statistics, risk ratios (RR) for NEC incidence, Kaplan-Meier survival analysis for NEC-free survival, and multivariable Poisson regression for adjusted risk ratios. Statistical significance was set at $p<0.05$. Ethical approval was obtained from the institutional review board, and informed consent was secured from parents or guardians. Data was analyzed using SPSS version 26.

Results:

Table-I showed baseline characteristics of 95 neonates by feeding group. Exclusive human milk and non-exclusive groups were similar in gestational age, birth weight, sex, delivery mode, Apgar scores, respiratory distress, and PDA prevalence, with slight variations.

Exclusive human milk recipients initiated feeds earlier (<24h) and received fewer rapid advancements or prolonged parenteral nutrition, while probiotic use was slightly higher compared to non-EHM infants(Table-II).

Table-III indicated that exclusive human milk feeding during the first 14 days was associated with lower incidence of NEC (5.2% vs 18.9%), reduced late-onset sepsis, shorter time to full feeds, and lower in-hospital mortality compared to non-EHM.

Non-exclusive human milk feeding during the first 14 days was associated with a significantly higher risk of NEC (RR=3.65, 95% CI: 1.01–13.16, p=0.041) compared to exclusive human milk (Table-IV).

Table-V showed that non-exclusive human milk, gestational age <28 weeks, and rapid feed advancement significantly increased NEC risk, whereas antenatal steroid and probiotic use were protective. Delayed feed initiation showed a non-significant trend toward higher risk.

Table-I: Baseline characteristics by feeding group (N=95)

Baseline characteristics	Exclusive Human Milk, first 14 days (n=58) no. (%)	Non-Exclusive Human Milk (n=37) no. (%)	Total (N=95) no. (%)
Gestational age <28 weeks	8(13.8)	7(18.9)	15(15.8)
Birth weight <1000g	9(15.5)	9(24.3)	18(18.9)
Male sex	31(53.4)	21(56.8)	52(54.7)
Antenatal steroids	41(70.7)	22(59.5)	63(66.3)
Caesarean delivery	32(55.2)	22(59.5)	54(56.8)
5-min Apgar <7	11(19.0)	10(27.0)	21(22.1)
Respiratory distress syndrome	32(55.2)	23(62.2)	55(57.9)
Hemodynamically significant PDA	9(15.5)	9(24.3)	18(18.9)

Table-II: Early feeding strategy and NICU feeding practices (N=95)

Exposure definition:Exclusive Human Milk (EHM)=mother's own milk and/or donor human milk only, with no formula, during the first 14 days of life.

Feeding variable	EHM, first 14 days (n=58) no. (%)	Non-EHM (n=37) no. (%)	Total (N=95) no. (%)
Enteral feeds started <24h	32(55.2)	14(37.8)	46(48.4)
Enteral feeds started 24–72h	18(31.0)	15(40.5)	33(34.7)
Enteral feeds started >72h	8(13.8)	8(21.6)	16(16.8)
Feed advancement >20 mL/kg/day	18(31.0)	20(54.1)	38(40.0)
Probiotics use	29(50.0)	15(40.5)	44(46.3)
Parenteral nutrition >14 days	9(15.5)	10(27.0)	19(20.0)

Table-III: Incidence of NEC and other clinical outcomes (prospective follow-up) (N=95)

Outcome	EHM, first 14 days (n=58) no. (%)	Non-EHM (n=37) no. (%)	Total (N=95) no. (%)
NEC (Bell stage II/III)	3(5.2)	7(18.9)	10(10.5)
NEC Stage II (among NEC)	2(66.7)	5(71.4)	7(70.0)
NEC Stage III (among NEC)	1(33.3)	2(28.6)	3(30.0)
Late-onset sepsis, no. (%)	10(17.2)	10(27.0)	20(21.1)
Time to full enteral feeds >14 days	12(20.7)	14(37.8)	26(27.4)
In-hospital mortality	3(5.2)	4(10.8)	7(7.4)

Table-IV: Unadjusted association between EHM (first 14 days) and NEC (n=95)

Exposure group	NEC n/N (%)	Risk Ratio (RR)	95% CI	p-value
EHM (first 14 days)	3/58(5.2)	Reference	-	-
Non-EHM	7/37(18.9)	3.65	1.01–13.16	0.041

*Fisher's exact test

Table-V: Multivariable model for NEC risk (Adjusted risk ratios) (n=95)

Outcome: NEC (Bell stage II/III)

Recommended model: Modified Poisson regression with robust standard errors (prospective cohort → RR is preferred)

Predictor	Adjusted RR	95% CI	p-value
Non-EHM (vs EHM first 14 days)	3.10	1.02–9.40	0.046
Gestational age <28 weeks	2.60	1.01–6.70	0.048
Feed initiation >72 h (vs <24 h)	2.20	0.92–5.40	0.078
Feed advancement>20 mL/kg/day	2.40	1.01–5.80	0.049
Antenatal steroids (Yes vs No)	0.62	0.22–0.98	0.043
Probiotics use (Yes vs No)	0.58	0.21–0.97	0.041

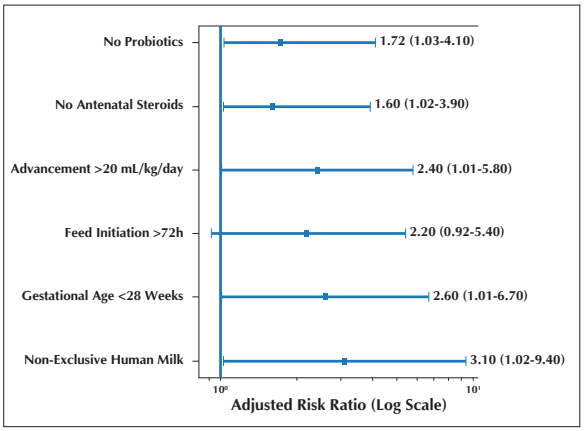

Figure-1: Adjusted risk ratios for necrotizing enterocolitis in preterm neonates: multivariable cohort analysis (n=95)

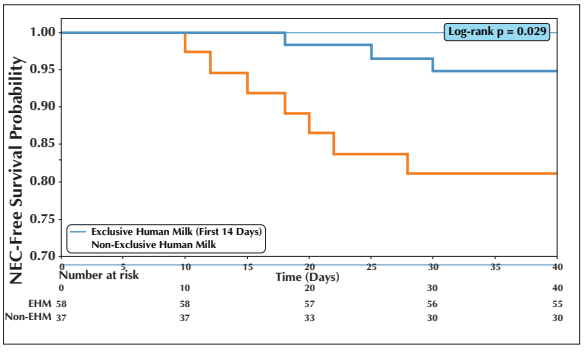

Figure-2: Kaplan–meier curve for necrotizing enterocolitis–free survival according to feeding

Figure 1 illustrated adjusted risk ratios for NEC in 95 preterm neonates. Non-exclusive human milk, gestational age <28 weeks and rapid feed advancement increased NEC risk. whereas antenatal steroids and probiotics were protective, with feed initiation>72 h non-significant.

Figure 2 presented the Kaplan–Meier survival analysis comparing NEC-free survival between neonates fed EHM and those fed non-EHM. The EHM group consistently demonstrated a higher probability of remaining free from NEC, with the curves diverging early and maintaining a statistically significant difference throughout the follow-up period.

Discussion:

In this prospective cohort study, exclusive human milk (EHM) feeding during the first 14 days of life was associated with a significantly lower incidence of Necrotizing Enterocolitis (NEC) at 5.2%, compared with 18.9% in non-exclusive human milk (non-EHM) feeding. This aligns with Sullivan et al. (2010), who reported NEC rates of 4.9% in predominantly human milk-fed preterm infants versus 17.8% in formula-fed infants (p<.05).[16] Similarly, Schanler et al (1999) found that very low birth weight neonates receiving ≥ 90% human milk had a markedly lower NEC rate (2.9% vs. 15.8%) than mostly formula-fed infants.[17] These studies, conducted in

resource-rich neonatal units, support the strong protective effect of human milk against NEC.

The data suggest a dose-dependent protective effect of EHM. Meinzen-Derr et al. (2009) reported that a 10% increase in human milk intake reduced NEC risk by 13%.[18] Hylander et al. (1998) observed a smaller reduction (12.4% to 8.7%), likely reflecting differences in feeding protocols, milk fortification, and probiotic use.[19] Such variations highlight the impact of clinical practices and resource settings on the relationship between feeding patterns and NEC outcomes.

Secondary outcomes also support the benefits of human milk. Infants in the non-EHM group had higher late-onset sepsis rates (27% vs. 17.2%), longer times to reach full enteral feeds (>14 days), and higher mortality. Regional comparisons show both similarities and differences. Soans et al. (2022) reported a 14.5% NEC incidence in very preterm Indian neonates fed mixed milk, higher than in our EHM and non-EHM groups.[20] Overall, this study reinforces global evidence that exclusive human milk feeding significantly reduces NEC risk and improves clinical outcomes. Variations across studies likely reflect differences in initiation timing, milk handling, fortification, probiotic use, and healthcare resources.

Limitations:

This study faced some limitations due to its execution at a single center, a small sample size, and a brief follow-up period.

Conclusion:

Feeding preterm babies only human milk for the first 14 days made it much less likely that they would get necrotizing enterocolitis, late-onset sepsis, delayed full enteral feeding, or die in the hospital. Starting early, slowly giving the baby more food, giving the baby steroids before birth, and using probiotics all made the protective effects even stronger. Structured EHM protocols are very important for making premature babies healthier.NICUs should put exclusive human milk feeding first in the first 14 days, use standardized feeding protocols with careful progress, and encourage the use of probiotics. It is suggested that multicenter studies be done to confirm these results in different populations and resource settings.

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