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Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death

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Abstract

Objective—To determine the association between human milk (HM) intake and risk of necrotizing enterocolitis (NEC) or death among infants 401 to 1000 g birth weight.

Study Design—Analysis of 1272 infants in the National Institute of Child Health and Human Development Neonatal Network Glutamine Trial was performed to determine if increasing HM intake was associated with decreased risk of NEC or death. HM intake was defined as the proportion of HM to total intake, to enteral intake and total volume over the first 14 days. Known NEC risk factors were included as covariates in Cox proportional hazard analyses for duration of survival time free of NEC.

Result—Among study infants, 13.6% died or developed NEC after 14 days. The likelihood of NEC or death after 14 days was decreased by a factor of 0.83 (95% confidence interval, CI 0.72, 0.96) for each 10% increase in the proportion of total intake as HM. Each 100 ml kg^{-1} increase in HM intake during the first 14 days was associated with decreased risk of NEC or death (hazard ratio, HR 0.87 (95% CI 0.77, 0.97)). There appeared to be a trend towards a decreased risk of NEC or death among infants who received 100% HM as a proportion to total enteral intake (HM plus formula), although this finding was not statistically significant (HR 0.85 (95% CI 0.60, 1.19)).

Conclusion—These data suggest a dose-related association of HM feeding with a reduction of risk of NEC or death after the first 2 weeks of life among extremely low birth weight infants.

Keywords

necrotizing enterocolitis; human milk; enteral feeding; extremely premature infants

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Introduction

Necrotizing enterocolitis (NEC) is the most significant gastrointestinal emergency occurring among very low birth weight infants.[1,2] NEC remains a major cause of morbidity and mortality,[1,2] with an incidence of 7 to 13% among very low birth weight infants; extremely low birth weight infants having the highest rates of disease.[3–5]

In 1997 and again in 2005, the American Academy of Pediatrics published position statements recommending human milk (HM) for premature infants.[6,7] Although the mechanism of protection is not completely understood, evidence supports the beneficial effects of HM to reduce the risk for NEC in premature infants.[8–11] In addition, HM may reduce rates of late onset sepsis,[8,12,13] and retinopathy of prematurity,[14] and may have long-term effects on the cognitive development of extremely premature infants.[15]

The objective of this study was to determine the association between amount of HM taken in the first weeks of life and subsequent risk of the combined outcome of NEC or death. This study utilized the cohort of infants that were part of a trial on parenteral glutamine supplementation.[16] These data have also been used in studies evaluating effects of HM on developmental outcomes at 18 months of life[15] and retinopathy of prematurity.[17]

Methods

Study infants

From October 1999 to August 2001, the National Institute of Child Health and Human Development Neonatal Research Network (Network) enrolled infants in a multicenter, randomized, double-masked trial of parenteral glutamine supplementation.[16] Among infants who weighed between 401 and 1000 g at birth, 1433 infants from 15 centers were enrolled during the first 72 h of life. Infants were excluded if they had major congenital anomalies, suspected congenital nonbacterial infection, pH<6.80, hypoxia with bradycardia for >2 h or a decision had been made to withhold aggressive care. Infants were randomized to receive either standard parenteral nutrition or parenteral nutrition supplemented with glutamine. No enteral feeding protocol was mandated; rather enteral feedings were started and advanced as per individual physician and/or center policy.

We used data from the trial and the Network's very low birth weight registry to determine the relationship between amount of HM intake and likelihood of NEC or death. The temporal relationship between early feeding and NEC or death is extremely important, as the infant feedings need to precede the outcome in order to ensure the effect of HM feeding on subsequent outcome. Therefore, infants were excluded from this secondary analysis if they did not remain in the hospital for at least 14 days or developed NEC before 14 days of life. Infants less than 23 weeks estimated gestation were excluded due to their high mortality risk.

Nutrition data were collected daily until the infants were on full enteral feeds (defined as greater than or equal to 110 kcal kg^{-1} per day from enteral nutrition), and then on Monday, Wednesday and Friday until hospital discharge or age 120 days. For the days of the week on which data were not collected, the values were interpolated. As none of the participating centers used banked HM during the trial, all reported feedings with HM were mother's own milk. Institutional Review Board approval and informed consent were obtained as previously described.[16]

Definitions

The primary outcome for this study was NEC, defined as Bell's stage II or III[18] or death occurring between age 14 days and hospital discharge or age 120 days, whichever occurred

earlier. Death was included as a competing outcome because some infants who died may have developed NEC if they had survived. Thus, excluding infants who died assumes that any effect of breast milk feeding on risk of NEC was not observed in those infants. HM intake was defined as the proportion of total intake (enteral and parenteral), proportion of enteral intake and cumulative volume of HM fed in the first 14 days of life. We reasoned that HM intake in the first 2 weeks of life was likely to result in a protective effect after 14 days of life, with 14 days chosen as an arbitrary cutoff. Among infants who received enteral feeds, 90% received their first feed within the first 14 days of life. The relationship between early HM intake and likelihood of NEC or death was determined using multivariable, Cox proportional hazards regression. Covariates in the regression models were chosen because of demonstrated associations with NEC or death or to account for unmeasured center to center variation in infant risk or style of care: birth weight (in grams), small for gestational age, race, antenatal steroids, duration of mechanical ventilation in the first 14 days of life, treatment for patent ductus arteriosus (PDA) defined as either clinical evidence of a left to right shunt and/or echocardiographic evidence of a ductus with left to right shunt and treatment with either indomethacin and/or surgical ligation and center.

Two models were developed to determine the effects of HM intake: (1) as a proportion of total intake (enteral and parenteral) and (2) as a proportion of enteral intake alone. In the latter model, for infants who had no enteral intake in the first 14 days of life, HM intake as a proportion of total enteral intake was assigned as zero. In addition to determining the association between HM as a proportion of total and enteral intake, a third model, including only infants who received HM, was developed to determine whether a dose–response relationship could be observed between amount of HM taken per unit body weight and NEC or death after age 14 days.

Statistical methods

In order to evaluate potential covariates and confounders, unadjusted associations between the outcome (NEC or death) and maternal and neonatal variables were explored using the χ^2-test or the Fisher's exact test when appropriate for categorical variables and the Student's *t*-test or Mann–Whitney *U*-test when appropriate for continuous variables. Variables that were marginally statistically significant ($P<0.1$) in the unadjusted analyses were considered as potential covariates and were further evaluated in a multivariable regression model. To increase confidence in the observed relationship between HM feeding and NEC or death, we attempted to include as many variables as possible that may potentially confound this relationship. The unadjusted relationship of HM intake with NEC or death was assessed by comparing the proportion of intake as HM and the cumulative volume of HM (ml kg^{-1}) received in the first 14 days of life by outcome group using the Student's *t*-test. Multivariable, Cox proportional hazards regression analysis was performed to estimate the effects of the proportions of total and enteral intake as HM in the first 14 days of life on the likelihood of NEC or death after 14 days of life and to estimate the effects of amount of HM taken among those who received HM. Relative risks are expressed as multivariate-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Time to event was calculated from birth to discharge or age 120 days or outcome (NEC or death). For infants who developed NEC and died subsequently, the time to event was calculated from birth to the onset of NEC. Neonatal intensive care unit (NICU) center was included in all regression analyses to control for otherwise unmeasured variability in care and patient characteristics across practice sites. Each model was also run with a second order term included to test for a nonlinear relationship between the feeding variable and the outcome. All second-order terms were nonsignificant, consistent with a linear relationship between the feeding variables and the outcome. The proportional hazard assumptions of all models were tested using the Schoenfeld residuals. All analyses were completed by RTI International using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

Of the 1433 subjects in the original glutamine trial, 1272 infants met the inclusion criteria established for this study. Of the 161 infants who were excluded from the analyses: 32 died within the first 72 h of life; 7 infants were discharged or transferred to another institution before age 14 days; 7 had either gut or heart malformations; and 16 infants were <23 weeks gestation. An additional 99 infants either developed NEC (n = 31) or died (n = 68) within the first 14 days of life and were not included in the analyses. Among the 99 infants who developed NEC or died before 14 days, 46.9% (n = 46) received some enteral feeding before the outcome. Of these, 32% (n = 32) received some HM in the first 14 days of life (mean (s.d.) cumulative volume of HM received 119.6 ml kg^{-1} (190.7)), and 25.3% (n = 25) received some formula (cumulative volume of formula received 127.7 (160.6) ml kg^{-1}). Among the 1272 infants included in this study, 173 (13.6%) either died (n = 75) or developed NEC (n = 98) after day 14 of life, with the mean (s.d.) age of NEC onset or death of 37 (19) days. Most study infants (91%, n = 1153) received some enteral feeding within the first 14 days of life: 31.6% (n = 402) received HM only, 28.3% (n = 360) received formula only, 30.7% (n = 391) received a combination of HM and formula and the remaining 9.4% (n = 119) received no enteral nutrition. There was no association between the amount of HM received in the first 14 days and whether or not the infant received glutamine supplementation as part of the original clinical trial (P = 0.57). There was also no association with glutamine treatment group and NEC.[16] Therefore, glutamine supplementation was not included in any of the statistical models.

Aspects of care, including feeding practices, varied from center to center. Among infants who had a PDA, the proportion of infants treated with indomethacin ranged from 70 to 100%, whereas the proportion of infants who had a ligation ranged from 5.6 to 65.2%. The proportion of infants who received any HM ranged from 36.8 to 94.7%. The incidence of NEC varied by center and ranged from 0 to 12.7%.

The characteristics of the study infants and the unadjusted associations between enteral feeding and NEC or death are summarized in Table 1. Compared to infants who survived free of NEC, infants with NEC or death were fed less HM (mean (s.d.)) cumulative volume (85 (154) vs 154 (250) ml kg^{-1}), and had a lower mean daily HM intake 6 (11.0) vs 11 (17.9) ml kg^{-1} per day) during the first 14 days of life. Over the entire NICU stay, infants who died or developed NEC had a lower mean proportion of total intake as HM (6 (10) vs 10% (16)). Infants with NEC or death were also more likely to receive parenteral nutrition as their only nutritional intake during the first 14 days of life compared to infants who did not develop NEC or death (19 vs 7.8%).

The results of the multivariable Cox analyses, reported as adjusted HRs and 95% CIs, are shown in Table 2. Controlling for birth weight, small for gestational age, race, antenatal steroids, receipt of mechanical ventilation, PDA and center, the HR for NEC or death after age 14 days was 0.87 for every 100 ml kg^{-1} increase in the volume of HM. In other words, the hazard of NEC or death was decreased by 13% for every 100 ml kg^{-1} increase in HM an infant received in the first 14 days of life. As illustrated in Figure 1, increasing amount of HM intake within the first 14 days of life was associated with increased survival time free of NEC.

The results of the multivariable model that only included infants who received some HM in the first 14 days (n = 792), each 100 ml kg^{-1} increase in the cumulative amount of HM fed was associated with a decreased risk of NEC or death, indicating a dose–response relationship (HR 0.87, 95% CI 0.77, 0.97).

An increasing proportion of HM to total intake (enteral plus parental) was also associated with a decreased relative risk of NEC (HR 0.83, 95% CI 0.72, 0.96). As illustrated in Figure 2, increasing proportion of HM to total intake was associated with increased survival time free of NEC. When focusing on enteral feeding only, there appeared to be a trend towards a

decreased risk of NEC or death among infants who received 100% HM as a proportion of total enteral intake (HM plus formula). However, this finding was not statistically significant (HR 0.85 (95% CI 0.60, 1.19)).

Discussion

We examined the dose effect of HM received in the first 14 days of life on the likelihood of NEC or death among extremely low birth weight infants who were over 23 weeks gestational age, were not transferred to another facility, and survived free of NEC to day 14 of life. HM intake was estimated both as the absolute amount of HM as well as a proportion of other types of feeding intakes. The current study findings are consistent with other observational studies that reported on varying doses of HM in relation to a reduced risk of NEC.[8,13,19] We further substantiate and expand the pool of evidence suggesting an inverse relationship between the cumulative amount of HM an infant received and the subsequent risk of NEC or death. We also observed an association between receipt of any type of enteral feeding, including but not limited to HM, and reduced risk of NEC or death. We were unable to distinguish the effects of willingness of clinicians to provide enteral feedings, the infant's ability to tolerate enteral feedings, the mother's intention to breast-feed and the type of enteral feeding used. By excluding infants who developed NEC within the first 14 days, we were able to avoid the majority of cases of spontaneous perforation that could be misclassified as NEC.[20]

Protective effects of HM have been observed with partial, not necessarily exclusive, feeding of HM.[8,9,14,19,21] Although investigators have focused on the potential health contributions of receiving HM, few have evaluated a possible dose–response relationship. Schanler *et al.*[8] reported significantly lower rates of NEC or sepsis in a prospective cohort of 108 very low birth weight infants receiving >50 ml kg^{-1} per day of fortified HM (mean birth weight 1069 g) compared to infants fed preterm formula (mean birth weight 1044 g). Among 119 VLBW infants, Furman *et al.*[13] showed a decrease in the odds of NEC among infants receiving ≥ 50 ml kg^{-1} per day. Sisk *et al.*[21] recently reported a sixfold decrease in the odds of NEC among 202 very low birth weight infants who received feeds with at least 50% HM compared to infants who received <50% HM. We also found a protective effect of HM against NEC when looking at the volume of HM an infant received as well as the proportion of HM received to total intake.

The current study is a secondary analysis of a completed randomized trial of glutamine supplementation[16] and was not designed to address the potential protective effects of HM on outcomes. The primary outcome of the original study was the composite of death or late onset sepsis, with NEC being a secondary outcome of interest. If NEC had been the primary outcome of the glutamine study, the sample size required to detect an effect of glutamine to reduce NEC risk would have been prohibitively higher (as NEC occurs at a lower incidence). The prospective detailed collection of nutrition data as part of the trial allowed us to examine the relationship between the amount of HM provided to the infant in the first 14 days of life and the outcome of interest. We are aware that feeding practices and other aspects of care vary from center to center, with the proportion of infants who received HM ranging from 36.8 to 94.7% in the current study. Most of the infants (67%) who developed NEC or died in our study received some HM during their NICU stay.

Studying the relationship between feeding and any outcome has been both limited and difficult due to the variability in defining HM intake. Various studies have defined important HM intake as receiving any HM,[9,10,14] a daily mean of 50 ml kg^{-1},[8,13] 50% proportion of HM to total enteral intake,[21] early (first 2 weeks of life) full enteral feeds[19] and increasing daily volume.[15] It is also true that when quantifying HM intake as a proportion of enteral intake, infants who are mostly on parenteral nutrition, but receive most of their enteral feeds as HM will have a high proportion of HM to total enteral feeds. This methodological issue may underestimate

the true protective relationship of HM regarding NEC. Therefore, we defined HM intake in several ways, including cumulative volume, proportion of HM to total intake and proportion of HM to total enteral intake all within the first 14 days of life. Our reasoning for these methods are similar to that reported by Furman *et al.*[13]

Variations in HM intake among premature infants may be related to infant illness, infant maturity, clinician practice style and parent preference. In the current study, infants who developed NEC or died received less HM that those who did not. In our multivariable models we, at least partially, adjusted for immaturity (birth weight) and illness severity (duration of mechanical ventilation and PDA) and clinician practice style (center of care). It is possible that factors other than feeding practices, but associated with feeding practices, may have led to higher likelihood of survival time free of NEC. We were unable to adjust for either parent preferences or differences in individual clinician practice style. Healthier infants may be more likely to receive more enteral nutrition. Our analyses may not have fully accounted or controlled for all infant and clinician characteristics related to the amount and type of enteral feedings provided. The issue of potential confounding is not easily addressed. Randomized clinical trials comparing mother's own milk to formula feedings may not be feasible as the decision to provide HM is made by the mother, and other observational studies on infant feeding will have the same limitations as seen in the current study.

The current study findings support a possible dose-dependent, beneficial effect of HM on risk of NEC or death in extremely low birth weight infants. A recommendation to encourage HM feeding to prevent NEC can be supported by evidence presented here in conjunction with other available evidence. We believe that the accumulating evidence from observational studies, including ours, and absence of evidence of harm associated with HM feedings, can be used to guide mothers' infant feeding decisions and NICU policies that encourage provision of HM to premature infants.

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References

1. Stoll BJ. Epidemiology of necrotizing enterocolitis. Clin Perinatol 1994;21:205–218. [PubMed: 8070222]
2. Lin PW, Stoll BJ. Necrotising enterocolitis. Lancet 2006;368:1271–1283. [PubMed: 17027734]
3. Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, LaCorte M, et al. Trends in mortality and morbidity for very low birth weight infants, 1991–1999. Pediatrics 2002;110:143–151. [PubMed: 12093960]
4. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001;107:E1. [PubMed: 11134465]
5. Peter CS, Feuerhahn M, Bohnhorst B, Schlaud M, Ziesing S, von der Hardt H, et al. Necrotising enterocolitis: is there a relationship to specific pathogens? Eur J Pediatr 1999;158:67–70. [PubMed: 9950312]
6. Breastfeeding and the use of human milk. American Academy of Pediatrics. Work Group on Breastfeeding. Pediatrics 1997;100:1035–1039. [PubMed: 9411381]
7. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005;115:496–506. [PubMed: 15687461]

8. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. Pediatrics 1999;103:1150–1157. [PubMed: 10353922]

9. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet 1990;336:1519–1523. [PubMed: 1979363]

10. McGuire W, Anthony MY. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. Arch Dis Child Fetal Neonatal Ed 2003;88:F11–F14. [PubMed: 12496220]

11. Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2007;92:F169–F175. [PubMed: 16556615]

12. el-Mohandes AE, Picard MB, Simmens SJ, Keiser JF. Use of human milk in the intensive care nursery decreases the incidence of nosocomial sepsis. J Perinatol 1997;17:130–134. [PubMed: 9134512]

13. Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. Arch Pediatr Adolesc Med 2003;157:66–71. [PubMed: 12517197]

14. Hylander MA, Strobino DM, Dhanireddy R. Human milk feedings and infection among very low birth weight infants. Pediatrics 1998;102:E38. [PubMed: 9724686]

15. Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Wright LL, Langer JC, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. Pediatrics 2006;118:e115–e123. [PubMed: 16818526]

16. Poindexter BB, Ehrenkranz RA, Stoll BJ, Wright LL, Poole WK, Oh W, et al. Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. Pediatrics 2004;113:1209–1215. [PubMed: 15121931]

17. Heller CD, O'Shea M, Yao Q, Langer J, Ehrenkranz RA, Phelps DL, et al. Human milk intake and retinopathy of prematurity in extremely low birth weight infants. Pediatrics 2007;120:1–9. [PubMed: 17606555]

18. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1–7. [PubMed: 413500]

19. Ronnestad A, Abrahamsen TG, Medbo S, Reigstad H, Lossius K, Kaaresen PI, et al. Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early full human milk feeding. Pediatrics 2005;115:e269–e276. [PubMed: 15687416]

20. Attridge JT, Clark R, Walker MW, Gordon PV. New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. J Perinatol 2006;26:93–99. [PubMed: 16319937]

21. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol 2007;27:428–433. [PubMed: 17443195]

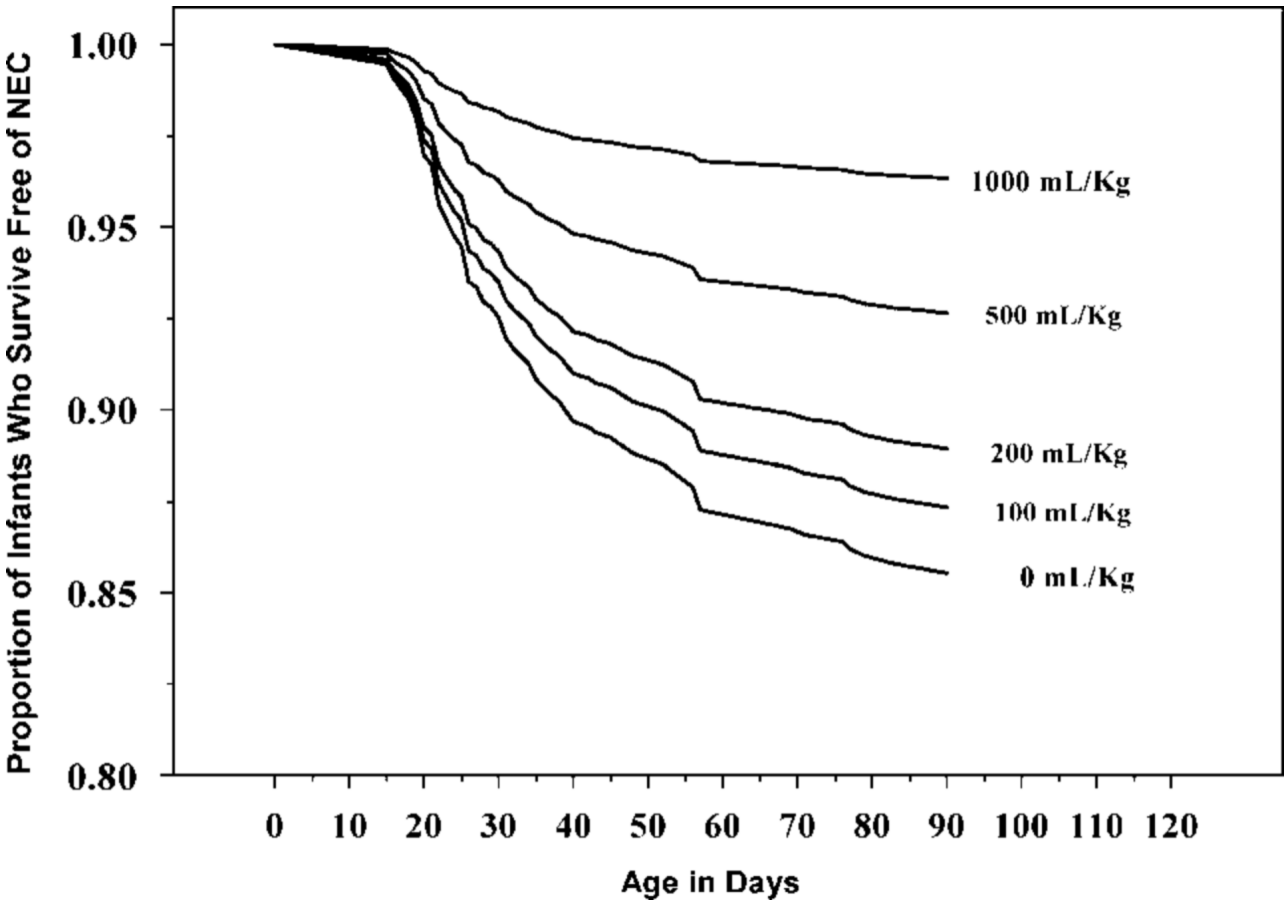

Figure 1.

Adjusted survival curves for necrotizing enterocolitis (NEC) or death by amount of human milk (ml kg^{-1}) over the first 14 days of life. Survival curves adjusted for birth weight, small for gestational age, race, patent ductus arteriosus (PDA), antenatal steroids, duration of mechanical ventilation and Network Center. Survival curves represent predicted survival time free of NEC or death and do not directly correspond to the number of infants.

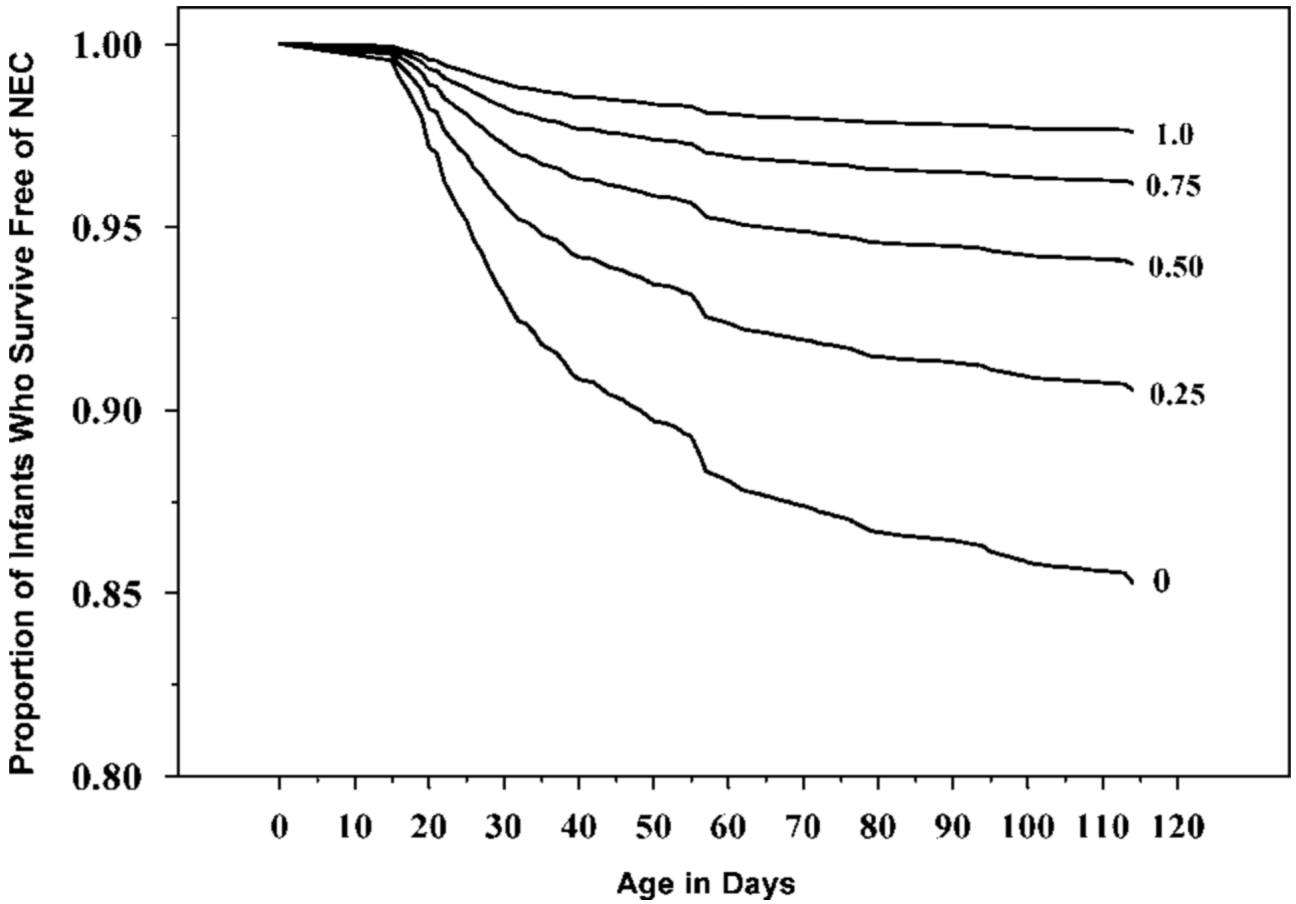

Figure 2.

Adjusted survival curves for necrotizing enterocolitis (NEC) or death by proportion of human milk to total intake over the first 14 days of life. Survival curves adjusted for birth weight, small for gestational age, race, patent ductus arteriosus (PDA), antenatal steroids, duration of mechanical ventilation and Network Center. The numbers on the graph (0, 0.25, 0.50, 0.75 and 1.0) represent the proportion of total intake that is human milk. Survival curves represent predicted survival time free of NEC or death and do not directly correspond to the number of infants.

Table 1

Characteristics of study infants grouped by outcome

Characteristic	*NEC[a] or death (n = 173)*	*Survivors/no NEC (n = 1099)*
Birth weight (g)	722 ± 139	787 ± 133**
Gestational age (weeks)	25 ± 2	26 ± 2**
Race		
Black	51% (88)	45% (491)
White	33% (57)	39% (429)
Hispanic	15% (26)	14% (159)
Other	1% (2)	2% (20)
Male	52% (90)	46% (510)
Multiple birth	26% (45)	21% (231)
5-min apgar <5	19% (32)	12% (132)**
Intrapartum antibiotics	65% (113)	68% (747)
Antenatal steroids	78% (135)	81% (891)
Prophylactic indomethacin[b]	23% (40)	27% (298)
Patent ductus arteriosus[c]	54% (94)	40% (437)**
Feeding characteristic		
Any HM feeding (%)	116 (67)	811 (74)
Daily volume HM (ml kg^{-1}) first 14 days	6.1 ± 11.0	11.0 ± 17.9**
Cumulative volume HM (ml kg^{-1}) first 14 days	85 ± 154	154 ± 250**
Cumulative volume non-HM (ml kg^{-1}) (enteral) first 14 days	70 ± 145	131 ± 246**
Proportion HM/total intake in first 14 days (%)[d]	6 ± 10	10 ± 16**
Proportion HM/total intake for entire NICU stay (%)[d]	10 ± 16	24 ± 32**
Proportion HM/enteral intake in first 14 days (%)	48 ± 46	53 ± 46
Proportion HM/enteral intake for entire NICU stay (%)	41 ± 42	29 ± 37**
First enteral feeding (days)	9 ± 8	7 ± 6**
First HM feeding (days)	10 ± 9	9 ± 10
Received only HM in first 14 days	28% (49)	32% (353)

Abbreviations: NEC, necrotizing enterocolitis; HM, human milk; NICU, neonatal intensive care unit.

Continuous variables reported as mean ± s.d.; categorical variables reported as % (*n*).

** $P<0.05$ when comparing characteristics of infants with outcome NEC or death and those without the outcome.

[a] NEC, $n = 98$; death, $n = 75$.

[b] Defined as indomethacin given within the first 24 h of life.

[c] Defined as PDA treated with either indomethacin and/or surgical ligation.

[d] Total intake defined as enteral plus parenteral nutrition.

Table 2

Results from proportional hazards models for time to NEC or death

Variable	*Hazard ratio*	*95% confidence interval*	P-*value*
Model 1[a]			
Cumulative volume of HM (ml kg^{-1}) days 1–14 (per 100 ml kg^{-1})	0.87	0.77, 0.97	0.015
Model 2			
Proportion of HM to total feeds days 1–14 (per 10% increase)	0.83	0.72, 0.96	0.015
Model 3			
Receiving 100% HM to total enteral feeds days 1–14	0.85	0.60, 1.19	0.34

Abbreviation: HM, human milk.

Each model controls for birth weight, small for gestational age, race, PDA, antenatal steroids, duration of mechanical ventilation, and center.

[a]Among infants who received some HM days 1–14 of life.