An Exclusively Human Milk-Based Diet Is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk-Based Products

Sandra Sullivan, MD, Richard J. Schanler, MD, Jae H. Kim, MD, PhD, Aloka L. Patel, MD, Rudolf Trawöger, MD, Ursula Kiechl-Kohlendorfer, MD, Gary M. Chan, MD, Cynthia L. Blanco, MD, Steven Abrams, MD, C. Michael Cotten, MD, MHS, Nirupama Laroia, MD, Richard A. Ehrenkranz, MD, Golde Dudell, MD, Elizabeth A. Cristofalo, MD, MPH, Paula Meier, PhD, Martin L. Lee, PhD, David J. Rechtman, MD, and Alan Lucas, MD

Objective To evaluate the health benefits of an exclusively human milk–based diet compared with a diet of both human milk and bovine milk–based products in extremely premature infants.

Study design Infants fed their own mothers' milk were randomized to 1 of 3 study groups. Groups HM100 and HM40 received pasteurized donor human milk–based human milk fortifier when the enteral intake was 100 and 40 mL/kg/d, respectively, and both groups received pasteurized donor human milk if no mother's milk was available. Group BOV received bovine milk–based human milk fortifier when the enteral intake was 100 mL/kg/d and preterm formula if no mother's milk was available. Outcomes included duration of parenteral nutrition, morbidity, and growth.

Results The 3 groups (total n = 207 infants) had similar baseline demographic variables, duration of parenteral nutrition, rates of late-onset sepsis, and growth. The groups receiving an exclusively human milk diet had significantly lower rates of necrotizing enterocolitis (NEC; $P = .02$) and NEC requiring surgical intervention ($P = .007$).

Conclusions For extremely premature infants, an exclusively human milk–based diet is associated with significantly lower rates of NEC and surgical NEC when compared with a mother's milk–based diet that also includes bovine milk–based products. *(J Pediatr 2010;156:562-7)*.

The health benefits of human milk for all infants, including those born extremely premature, have been increasingly recognized.[1] When compared with a diet of preterm formula, premature infants have improved feeding tolerance and a lower incidence of late-onset sepsis and necrotizing enterocolitis (NEC) when fed their mothers' milk.[2] It is a challenge for mothers of extremely premature infants, however, to provide sufficient milk to meet their infants' needs. In a recent study, only 30% of such mothers were able to supply 100% of their extremely premature infants' needs.[3] Pasteurized donor human milk would be an attractive proxy for mother's own milk, and donor milk banks have made milk available.[4] Indeed, a review of studies conducted in the 1980s, comparing donor human milk and formula, suggested that donor milk was associated with a significantly lower incidence of NEC.[5] Those studies, however, did not include a large proportion of extremely premature infants, and their nutritional protocols did not evaluate human milk fortifiers (HMF) or contemporary preterm formula.

A randomized trial compared fortified pasteurized donor human milk with preterm formula, both used as supplements when mother's own milk was not available.[3] That study did not find a protective effect of donor human milk on the combined incidence of late-onset sepsis and NEC but did note a significant

BOV	Bovine milk-based human milk fortifier
HMF	Human milk fortifier
HM40	Human milk-based HMF added once feeding volume reached 40 mL/kg/day, and pasteurized donor milk used if no mother's own milk available.
HM100	Human milk-based HMF added once feeding volume reached 100 mL/kg/day and pasteurized donor milk used if no mother's own milk available.
NEC	Necrotizing enterocolitis
PN	Parenteral nutrition
SD	Standard deviation

From the Department of Pediatrics, University of Florida (S.S.), Gainesville, FL; Department of Pediatrics, Schneider Children's Hospital at North Shore (R.S.), Manhasset, NY; Albert Einstein College of Medicine (R.S.), Bronx, NY; Department of Pediatrics, University of Rochester, Golisano Children's Hospital at Strong (N.L.), Rochester, NY; Department of Pediatrics, University of California, San Diego Medical Center (J.K.), San Diego, CA; Children's Hospital and Research Center (G.D.), Oakland, CA; Prolacta Bioscience (M.L., D.R.), Monrovia, CA; Pediatrics, Rush University Medical Center (A.P.), Chicago, IL; Department of Pediatrics, University of Utah Medical Center (G.C., P.M.), Salt Lake City, UT; Department of Pediatrics, University of Texas Health Science Center (C.B.), San Antonio, TX; Department of Pediatrics, Baylor College of Medicine (S.A.), Houston, TX; Department of Pediatrics, Duke University Medical Center (C.C.), Durham, NC; Pediatrics, Yale University School of Medicine (R.E.), New Haven, CT; Department of Pediatrics, Johns Hopkins School of Medicine (E.C.), Baltimore, MD; Department of Pediatrics, Innsbruck Medical University (R.T., U.K.), Innsbruck, Austria; and the MRC Child Nutrition Research Center, Institute of Child Health (A.L.), London, United Kingdom

S.S., R.J.S., J.H.K., A.L.P., R.T., U.K.-K., G.M.C., C.L.B., S.A., C.M.C., N.L., R.A.E., G.D., and E.A.C. received financial support from Prolacta Bioscience. The authors were responsible for the conduct of the study and collection of the data. M.L.L. and D.J.R. are employees of Prolacta Bioscience. A.L. is a paid Consultant of Prolacta Bioscience. P.M. received no support or payment. S.A., C.L.B., E.A.C., R.A.E., M.L.L., A.L., P.M., D.J.R., and R.J.S. were responsible for the design of the study. M.L.L. was responsible for the data analyses. R.J.S. wrote the draft of this manuscript. All of the authors were responsible for review and interpretation of the data and review of the manuscript.

Clinicaltrials.gov reg. # NCT00506584

 10.1016/j.jpeds.2009.10.040

protective effect of mother's own milk. The protocol in that study differed from previous studies in that the pasteurized donor human milk was fortified with bovine milk–based products, and some of the infants in the donor milk group were given preterm formula because of slower rates of growth. Thus no contemporary trial has investigated the effects of an exclusively human milk diet in extremely premature infants.

The technology now exists to collect, pasteurize, and process large quantities of screened donor human milk, labeled with its basic nutrient contents, and prepared as either a HMF or a donor milk alternative to mother's own milk.[6] This technology has prompted a randomized controlled trial in extremely premature infants to evaluate an exclusive human milk–based diet (that includes a human milk–based HMF and donor human milk if no mother's milk is available) compared with the usual feeding protocol comprising a mother's milk diet (that includes a bovine milk–based HMF and preterm formula if no mother's milk is available). We hypothesized that the health benefits (reduced duration of parenteral nutrition [PN], late-onset sepsis, and NEC) of an exclusively human milk–based diet would exceed those of the usual diet containing bovine milk–based products without detrimental effects on growth.

Methods

Infants were recruited from 12 neonatal intensive care units, 11 in the United States and 1 in Austria. Eligibility criteria were as follow: birth weight 500 to 1250 g, intention to receive mother's milk, and ability to adhere to a feeding protocol on the basis of the use of mother's own milk, initiation of enteral feeding before 21 days after birth, and initiation of PN within 48 hours of birth. Infants were excluded if there were major congenital malformations or a high likelihood of transfer to a non-study institution during the study period.

Randomization was performed in blocks of 4 on strata defined by birth weight (500 to 750 g, 751 to 1000 g, and 1001 to 1250 g), and whether the infant was appropriate- or small-for-gestational-age (defined as 2 standard deviations below the mean weight for gestational age on the basis of intrauterine growth charts[7]). Separate block randomization schemes were prepared for each of the strata and performed centrally. The investigators were not aware of the block size. The need to ensure proper handling of mother's own milk precluded true blinding of the infants' caregivers.

Sample size calculation was based on the primary outcome of duration of PN, a surrogate of feeding tolerance and neonatal morbidity. The mean duration of PN in extremely premature infants fed their mother's fortified milk was 18 $\pm$ 11 days (Meier and Blanco, personal communication). To demonstrate a 40% reduction in PN days in either study group, a sample size of 62 infants per group was needed for a 2-sided alpha error of 2.5% and power of 90%. To account for 2 interim analyses by the independent Data Safety Monitoring Board, and an estimated proportion of protocol nonadherence of 5%, the final sample was 69 infants per group. The study was approved by the institutional review boards of each center and written informed consent was obtained from the parents or legal guardians of all subjects before enrollment. Registered with Clinicaltrials.gov reg. # NCT00506584.

Infants were enrolled if their mothers intended to provide their own milk. When enteral nutrition was initiated, all study infants received their own mothers' milk but differed, as randomized, by the type of HMF they received and the type of milk they were given if no mother's own milk was available. Groups HM100 and HM40 received pasteurized donor human milk–based HMF (Prolact+ H^2MF; Prolacta Bioscience, Monrovia, California) when the enteral intake was 100 mL/kg/d and 40 mL/kg/d, respectively, and both groups received pasteurized and standardized 20 kcal/oz donor human milk (Neo20 Prolacta Bioscience) if no mother's milk was available. Group BOV received the usual feeding protocol of bovine milk–based HMF when the enteral intake was 100 mL/kg/d and preterm formula if no mother's own milk was available.

The duration of study participation was the earliest of the following milestones: 91 days of age, discharge from hospital, or attainment of 50% oral feedings (ie, 4 complete oral feedings per day). PN was initiated within 48 hours after birth. Trophic feedings were initiated 1 to 4 days after birth and were continued at 10 to 20 mL/kg/d as tolerated for up to 5 days. Subsequently, milk intake was increased by 10 to 20 mL/kg/d. Donor human milk–based HMF was added in the HM40 group when milk intake reached 40 mL/kg/d and in the HM100 group at 100 mL/kg/day. Bovine milk-based HMF (Enfamil HMF; Mead Johnson, Evansville, Indiana; or Similac HMF; Abbott Laboratories, Columbus, Ohio) was added in the BOV group when milk intake reached 100 mL/kg/d. After the HMF was added, milk intake was increased daily by 10 to 20 mL/kg to a maximum of 160 mL/kg/d. The nutritional content of the fortified milks used in the study is described in **Table I** (available at www.jpeds.com).

Daily body weight and weekly recumbent length and head circumference were recorded. Bronchopulmonary dysplasia was defined as the use of supplemental oxygen at 36 weeks postmenstrual age. Late-onset sepsis was defined as clinical signs and symptoms consistent with sepsis occurring more than 5 days after birth in association with the isolation of a causative organism from a blood culture.[3] In cases of coagulase-negative *Staphylococcus*, at least 2 separate positive cultures were required. NEC was defined as Bell Stage II disease or greater, and abdominal radiographs were read by radiologists unaware of study group assignment.[8] At the conclusion of the study, all cases of NEC were reviewed in a blinded fashion by a panel of 8 of the study investigators. Feeding intolerance was defined as gastric residuals greater than 50% of the prior feeding or more than 2 mL/kg, bile- or blood-stained gastric residuals, emesis, abdominal distention or tenderness, changes in stool pattern or consistency, presence of blood in the stool. Feeding intolerance was quantitated by

the number of days that feedings were withheld for ≥12 hours.

Statistical Analyses

The 3 study groups were compared by use of an intent-to-treat paradigm, any randomized infant remained in their group for the final analyses. Kaplan-Meier[9] estimates for the distribution of PN days were compared among study groups with the log-rank test. The Wilcoxon rank-sum test was used for 2-way comparisons. Three-way comparisons used either the 1-way analysis of variance for normally distributed data or the Kruskal-Wallis test for nonnormal data. Categorical data were compared by use of the χ^2 test with the *P* value determined by an exact procedure (StatXact 7; Cytel Software Corporation, Cambridge, Massachusetts).

Results

During the 14 months of the study, 334 infants were screened, and 207 were enrolled (Figure 1). The baseline characteristics of infants among the 3 study groups were similar (Table II). The ages of attainment of first enteral feeding (15, 11, and 16 days) and full (140 mL/kg/d) enteral feeding (21, 23, and 22 days) were similar among HM100, HM40, and BOV groups, respectively. There were no significant differences among study groups for the duration of PN, length of hospital stay, late-onset sepsis, or growth (Table III). The number of infants below the third percentile[7] at birth and at discharge was similar among groups.

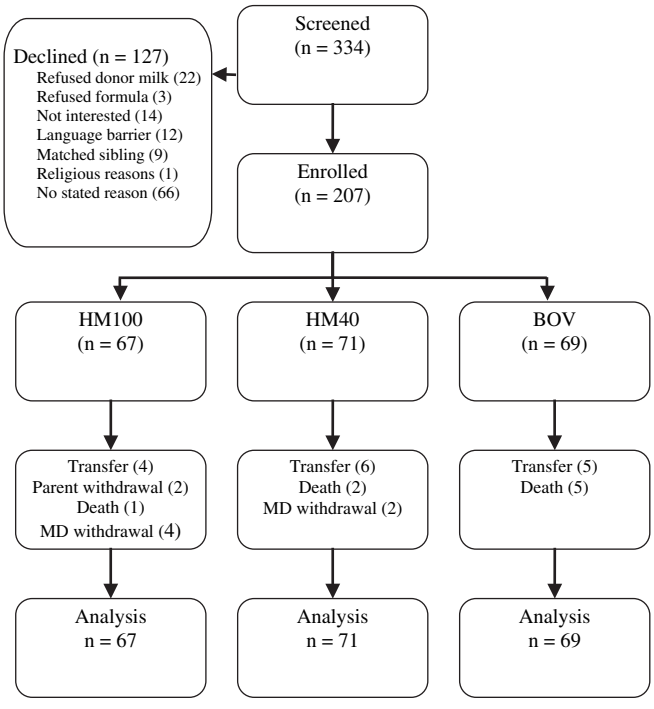

Figure 1. Distribution of study subjects.

Because there were no differences between HM100 and HM40, the exclusive HM group (HM100 + HM40) was compared with the BOV group. This analysis revealed similarities in baseline data and most outcomes, with the exception that there were fewer black infants in the BOV group compared with the combined HM100 + HM40 groups, 14% versus 27%, $P = .046$, and that the rate of weight gain was greater in the BOV group compared with the HM100 + HM40 groups, 16.0 ± 7.8 vs 14.3 ± 3.8 g/kg/d, $P = .051$.

Significant differences, however, were observed among study groups for the incidence of NEC (Figure 2). When compared with the BOV group, there were fewer cases of NEC in the HM100 and HM40 groups and the combined exclusive human milk–based diet groups (HM100 + HM40). A significant difference among groups was observed for the combined outcome of NEC or death in HM100 (6%), HM40 (8.5%), and BOV (20%), respectively, $P = .02$. The onset of NEC was similar among groups, 35 ± 18, 41 ± 18, 28 ± 12 postnatal days and 31 ± 1, 32 ± 3, and 31 ± 2 weeks postmenstrual age, in Groups HM100, HM40, and BOV, respectively. The number of cases of NEC requiring surgical intervention was significantly lower in the HM100 and HM40 groups compared with BOV group (Figure 2). All cases of surgical NEC occurred in infants who received bovine milk-based milk products (either HMF or preterm formula) at some time before the onset of NEC (Table IV; available at www.jpeds.com). Seven of these infants were randomized to the BOV group, but 2 of these infants were in the HM100/HM40 groups who had received bovine milk-based HMF or formula in violation of the protocol.

The 19 cases of NEC were distributed as 1 to 4 cases per site among 9 of the study sites. When rates of NEC were tabulated for only infants who completed the study without any protocol violations, the same distribution of cases was observed: 1.7%, 3.2%, and 15.3%, in HM100, HM40, and BOV groups, respectively; $P = .006$. A multivariate logistic regression that controlled for confounding variables known to affect the incidence of NEC (5-minute APGAR score, quantity of mother's own milk received, gestational age, receipt of prenatal and postnatal steroids, black race, bronchopulmonary dysplasia[10,11]) found an odds ratio for NEC with an exclusive human milk diet of 0.23 (95% confidence interval = 0.08, 0.66), $P = .007$, or a 77% reduction in the odds of developing NEC while receiving an exclusive human milk diet. None of the other variables reached statistical significance.

Infants in all 3 groups received a large volume and proportion of their enteral intake as their own mother's milk (Table III). The BOV group received significantly more own mother's milk because the fortifier was a powdered preparation whereas a liquid fortification regimen was used in the exclusive human milk groups.

Discussion

We conducted a randomized controlled multicenter trial to evaluate the potential health benefits of an exclusively human milk diet in extremely premature infants, 500 to

Table II. Characteristics of study infants

Parameter	HM100 (n = 67)	HM40 (n = 71)	BOV (n = 69)	*P* value
Birth weight, g	945 ± 202*	909 ± 193	922 ± 197	.56
Gestational age, wk	27.2 ± 2.2	27.1 ± 2.3	27.3 ± 2.0	.93
Male/Female, n (%)	32/35 (48/52)	25/46 (35/65)	36/33 (52/48)	.11
Small-for-gestational age, n (%)	6 (9)	6 (8)	8 (12)	.80
APGAR Score < 6, n (%)	9 (13)	4 (6)	8 (12)	.28
Black race n (%)	20 (30)	17 (24)	10 (14)	.10
Antenatal steroids, n (%)	56 (83)	51 (72)	53 (77)	.26
Mechanical ventilation at study entry, n (%)	49 (73)	56 (79)	53 (77)	.73

*Mean ± SD.

1250 g birth weight. This study was unique for its use of human milk–based human milk fortification. We were unable to demonstrate significant differences among the groups for the primary health outcome, PN days, a surrogate measure for feeding tolerance and early morbidity. Furthermore, we did not find significant differences in several other clinical outcomes. We speculate that the lack of differences is a direct result of the overall high intake of mother's own milk, which comprised more than 70% of enteral nutrition across all study groups. The high human milk intake reflects contemporary trends of improved lactation support and caregiver awareness and is consistent with the impact of human milk studies on this measure.[2,12,13]

Surprisingly, the rates of NEC and NEC requiring surgery were markedly lower in the groups fed human milk exclusively (HM100 and HM40) compared with the BOV group. We found a reduction in NEC of 50% and surgical NEC of almost 90% in infants fed an exclusive human milk diet compared with a diet containing bovine milk–based products. We estimate that the number of infants needed to treat with an exclusively human milk–based diet to prevent 1 case of NEC is 10. The number needed to treat to prevent 1 case of surgical NEC or death is 8. No other intervention has been shown to have such a marked effect on the incidence of NEC.[14] The mean incidence of NEC in the Vermont-Oxford Database (2007), approximately 7% to 10%, is in the range observed in this study. A 50% reduction in NEC would prevent between 1300 to 1850 cases annually, with each case leading to a high risk of death and long-term morbidity, and a hospitalization cost estimated at $138 000 to $238 000 per case.[4,15]

The lower incidence and severity of NEC in infants fed an exclusively human milk diet seen in our study are consistent with earlier reports. In 1990, Lucas and Cole[16] reported a reduction in the incidence of NEC among infants who received only human milk when compared with infants who received all bovine milk–based formula. Those infants who received a mixture of formula and human milk had an intermediate level of protection. Lucas[17] also reported a lower incidence of surgical NEC in infants fed unfortified compared with bovine milk-based fortified human milk. Lastly, 3 published meta-analyses concluded that donor human milk feeding was associated with less NEC.[5,18,19]

Our data contrast those reported in 2005,[3] which failed to find a protective effect of donor human milk on the combined incidence of sepsis and NEC, but reported that mother's own milk with bovine milk–based HMF was protective. That study, which also was analyzed on the intent-to-treat principle, included infants randomized to receive donor milk who were given formula because of poor growth, and all infants received a bovine milk–based fortifier. In 1984 Narayanan[20] reported a greater number of infections in premature infants fed pasteurized donor milk when they were also exposed to bovine milk-based formula. She concluded that pasteurized

Table III. Study outcomes

Outcome	HM100 (n = 67)	HM40 (n = 71)	BOV (n = 69)	*P* value
Parenteral nutrition, days	20* (14, 35)	20 (12, 33)	22 (14, 34)	.71
Length of stay, days	74 (61, 107)	79 (64, 110)	78 (67, 99)	.90
Mother's own milk, mL per study	4048 (841, 7479)	4544 (627, 8012)	5676 (1064, 8309)	.71
Mother's own milk, % enteral intake	73 (16, 82)	70 (18, 80)	82 (38, 100)	.002
Late-onset sepsis (LOS), n (%)	19 (28)	15 (21)	13 (19)	.39
LOS and/or NEC, n (%)	22 (33)	20 (28)	21 (30)	.84
Retinopathy of prematurity, n (%)	31 (46)	25 (35)	27 (39)	.41
Ventilator, days	25 (6, 54)	25 (12, 50)	34 (10, 58)	.54
Oxygen therapy, days	41 (24, 63)	48 (12, 78)	45 (19, 74)	.92
Central line, days	21 (15, 36)	22 (14, 30)	22 (16, 30)	.82
Bronchopulmonary dysplasia, n (%)	22 (33)	26 (37)	27 (39)	.74
Weight gain, (g/kg/day)	14.2 (11.9, 15.8)	14.2 (12.3, 16.3)	15.1 (12.8, 17.0)	.13
Length increment, (cm/wk)	0.86 (0.72, 1.08)	0.88 (0.70, 1.03)	0.94 (0.72, 1.16)	.35
Head circumference increment, cm/wk	0.76 (0.62, 0.85)	0.75 (0.61, 0.88)	0.75 (0.62, 0.86)	.99

*Median (25^{th}, 75^{th} percentile).

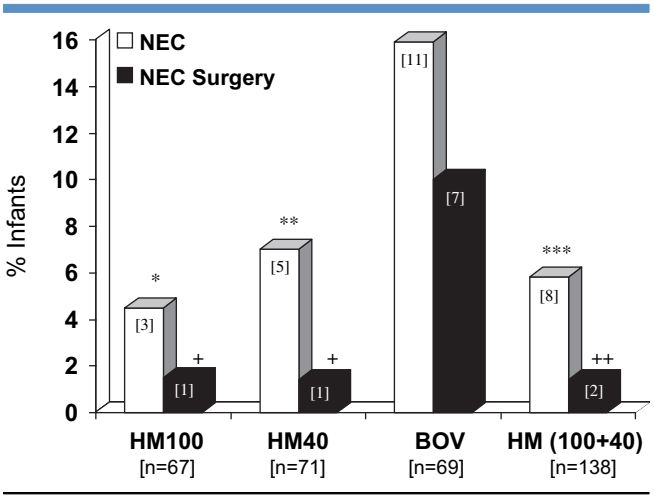

Figure 2. NEC and NEC surgery in study infants. There were significant differences in NEC among the 3 groups ($P = .05$), $^{*}P = .04$ vs BOV, $^{**}P = .09$ vs BOV, $^{***}P = .02$ vs BOV. There were significant differences in NEC requiring surgical intervention among the 3 groups ($P = .02$), $^{\dagger}P = .03$ vs BOV, $^{\dagger\dagger}P = .007$ vs BOV. [ ] refers to number of infants.

donor milk was effective only if it was fed as the total source of enteral nutrition.[21] These data suggest that exclusive human milk diets may exert protective, rather than threshold, effects with respect to NEC. The feeding of a species-specific diet may be important for this protection. However, we cannot exclude the possibility that the protective effect primarily was due to the avoidance of non human milk–based protein. Indeed, an animal model for NEC requires intraluminal bovine casein to produce the enterocolitis.[22]

This study also introduced an earlier fortification strategy with human milk–based human milk fortifier (HM40) to assess, secondarily, if such early fortification could be tolerated without introducing added morbidity. The 71 infants receiving the early fortification strategy appeared to tolerate the feeding well and did not differ significantly in feeding tolerance or other outcomes from the HM100 group. These are encouraging data that suggest the possibility of earlier introduction of human milk–based fortification compared with the usual practice of adding HMF at an enteral intake of 100 mL/kg/d.

The strengths of this study include a randomization and stratification scheme that achieved a balance of patient characteristics across the study groups and good adherence to the protocol as evidenced by a very small number of protocol violations. The control group correctly mimicked how extremely premature infants are fed, by use of combinations of mother's own milk and bovine-based products (HMF and formula). Limitations include the lack of complete blinding, which was not possible because of the obvious physical differences in human milk and formula and the limited power to look at subgroups, including those defined by sex and birth weight.

We conclude that for extremely premature infants, an exclusively human milk–based diet is associated with a significant reduction in the rates of NEC and surgical NEC compared with dietary exposure to bovine milk–based products. The similarities in other outcomes and the lower rate of NEC among study groups add support to the use of an exclusively human milk–based diet. The newer technology that enables an exclusively human milk diet with human milk–based fortification is now available to assist the ongoing efforts of neonatologists in their advocacy of human milk to reduce neonatal morbidity rates. ■

Submitted for publication Apr 8, 2009; last revision received Sep 16, 2009; accepted Oct 29, 2009.

Reprint requests: Richard J. Schanler, MD, Division of Neonatal-Perinatal Medicine, North Shore University Hospital, 300 Community Dr, Manhasset, New York 11030. E-mail: schanler@nshs.edu.

References

1. American Academy of Pediatrics. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2005;115:496-506.
2. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: Beneficial outcomes of feeding fortified human milk vs preterm formula. Pediatrics 1999;103:1150-7.
3. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics 2005; 116:400-6.
4. Arnold LDW. The cost-effectiveness of using banked donor milk in the neonatal intensive care unit: Prevention of necrotizing enterocolitis. J Hum Lact 2002;18:172-7.
5. Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2007;92:F169-75.
6. Wojcik KY, Rechtman DJ, Lee ML, Montoya A, Medo ET. Macronutrient analysis of a nationwide sample of donor breast milk. J Am Diet Assoc 2009;109:137-40.
7. Alexander GR, Himes JH, Kaufman RB. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163-8.
8. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201.
9. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
10. Guthrie SO, Gordon PV, Thomas V, Throp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. J Perinatology 2003;23:278-85.
11. Uauy RD, Fanaroff AA, Korones SB, Phillips EA, Phillips JB, Wright LL. Necrotizing enterocolitis in very low birth weight infants: Biodemographic and clinical correlates. J Pediatr 1991;119:630-8.
12. 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.
13. Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol 2009;29:57-62.
14. Bell EF. Preventing necrotizing enterocolitis: what works and how safe? Pediatrics 2005;115:173-4.
15. Bisquera JA, Cooper TR, Berseth CL. Impact of necrotizing enterocolitis on length of stay and hospital charges in very low birth weight infants. Pediatrics 2002;109:423-8.
16. Lucas A, Cole TJ. Breast milk and neonatal necrotizing enterocolitis. Lancet 1990;336:1519-23.
17. Lucas A, Fewtrell MS, Morley R, Lucas PJ, Baker BA, Lister G, et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. Am J Clin Nutr 1996;64:142-51.
18. 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:F11-4.

19. Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants (review). Cochrane Database of Systematic Reviews 2007;1-41.

20. Narayanan I, Prakash K, Murthy NS, Gujral VV. Randomised controlled trial of effect of raw and holder pasteurised human milk and of formula supplements on incidence of neonatal infection. Lancet 1984;ii:1111-3.

21. Narayanan I, Gupta J. Human milk and neonatal infections. Acta Paediatr Scand Suppl 1989;351:126-30.

22. Koivusalo A, Kauppinen H, Anttila A, Rautelin H, Jusufovic J, Lindahl H, et al. Intraluminal casein model of necrotizing enterocolitis for assessment of mucosal destruction, bacterial translocation, and the effects of allopurinol and N-acetycysteine. Pediatr Surg Int 2002;18:712-7.

Table I. Computed energy and macronutrient contents of milks (per dL)

Component	Mother's own milk*	Mother's own milk fortified with Prolacta fortifier†	Mother's own milk fortified with Similac HMF*	Mother's own milk fortified with Enfamil HMF‡
Energy (kcal)	67	83	79	81
Protein (g)	1.4	2.3	2.3	2.5
Carbohydrate (g)	6.6	7.3	8.2	7
Fat (g)	3.9	4.9	4.1	4.9
Calcium (mg)	25	110	138	115
Phosphorus (mg)	13	59	78	63
Osmolality§ (mOsm/kg H_2O)	290	< 360	est 385	325

*Abbott Nutrition, Columbus, Ohio. Product Description. 2009.
†Prolacta Bioscience, Monrovia, California. Product Description. 2009.
‡Mead Johnson Nutritionals, Evansville, Indiana. Product Description. 2009.
§NEOFAX 2009. Thomson Reuters, Montvale, New Jersey, pages 321-4.

Table IV. Characteristics of the NEC cases

Study group	Birth weight (g)	Gestational age (wk)	First day enteral feeding (day)	First day bovine milk-based HMF or formula (day)	First day human milk-based fortifier (day)	NEC onset (day)	Comment
HM100	720	25	5		32	35	
HM100	560	25	4	47*	20	53	NEC surgery
HM100	1105	28	3		9	18	
HM40	530	22	3		26	58	
HM40	740	25	9		17	38	
HM40	990	27	1	1*	7	22	NEC surgery†
HM40	785	28	1	77	3	60	
HM40	970	29	2	2*	5	25	
BOV	670	25	18	24		46	NEC surgery
BOV	690	25	1	1		17	NEC surgery
BOV	1170	26	1	11		25	NEC surgery
BOV	870	26	10	45	12‡	51	NEC surgery†
BOV	1136	27	1	13		18	NEC surgery
BOV	775	27	3	11		16	NEC surgery†
BOV	1120	28	5	16		38	
BOV	840	28	8	10		29	
BOV	1230	29	2	2		23	
BOV	1100	29	3	30		14	
BOV	817	29	2	12		26	NEC surgery

*Erroneously received formula or bovine milk-based HMF in violation of protocol.
†Died.
‡Erroneously received human milk-based HMF in violation of protocol.