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Decreasing Necrotizing Enterocolitis and Gastrointestinal Bleeding in the Neonatal Intensive Care Unit

The Role of Donor Human Milk and Exclusive Human Milk Diets in Infants ≤1500 g Birth Weight

Robert K. Huston, MD, Andrea M. Markell, RD, LD, Elizabeth A. McCulley, MS, RD, LD, Manoj Pathak, PhD, Stefanie P. Rogers, MD, Sean L. Sweeney, MD, Nancy G. Dolphin, RN, and Stuart K. Gardiner, PhD

Abstract: *Objective: The purpose of this study is to report our experience with an exclusive human milk–based diet (EHM) versus diets of mother's milk supplemented with banked human milk (DHM) or formula (PTF) plus bovine fortifier. Second, we evaluated the cost-effectiveness of using EHM. Design/Methods: This is a retrospective study of infants ≤1500 g birth weight (VLBW) admitted to the NICU from January 1, 2007, to December 31, 2011. Primary outcomes were rates of Bell stage 2 to 3 necrotizing enterocolitis (NEC) and NEC plus significant gastrointestinal bleeding (GIB). There were 3 groups for analysis according to diet: PTF, DHM, and EHM. Binary outcomes were analyzed using a multivariate logistic regression. Linear analysis of covariance was used to analyze continuous outcomes. Cost analysis used costs from a previous study for stage 2 and 3 NEC and from a matched control analysis for infants in our study for stage 1 NEC. Results: Infants who received EHM (n = 44) had higher rates of risk factors for NEC compared with DHM (n = 224) and PTF (n = 93). Rates of NEC were decreased for EHM versus PTF (odds ratio [OR] = 0.060; confidence interval [CI] = 0.003-0.445; P = .019) and NEC plus GIB were decreased for EHM versus DHM (OR = 0.070; CI = 0.004-0.369; P = .012) and EHM versus PTF (OR = 0.062; CI = 0.003-0.366; P = .011). A cost saving was shown when using EHM for VLBW infants with several risk factors for NEC but not all VLBW infants. Conclusions: EHM lowered the incidence of NEC compared with PTF and NEC plus GIB compared with DHM and PTF. Using EHM in VLBW infants at higher risk of NEC appears to be cost-effective.*

Keywords: prematurity; breast milk; cow's milk sensitivity; protein sensitivity

"Mother's own milk (MM) has been associated with improved neurodevelopmental outcome as well as decreased sepsis and NEC [necrotizing enterocolitis] compared with formula in preterm infants."

Introduction

In the newborn intensive care unit (NICU), a major issue for infants with a birth weight ≤1500 g (VLBW) is gastrointestinal morbidity, including

DOI: 10.1177/1941406413519267. From the Division of Neonatology, Randall Children's Hospital at Legacy Emanuel and Northwest Newborn Specialists, PC and Peditatrix Medical Group (RKH, SPR, SLS), the Department of Food and Nutrition Services, Randall Children's Hospital at Legacy Emanuel (AMM, EAM), Devers Eye Institute and Legacy Research Institute (MP, SKG), and NICU, Randall Children's Hospital at Legacy Emanuel (NGD), Portland, Oregon. Address correspondence to Robert K. Huston, MD, Division of Neonatology, Randall Children's Hospital at Legacy Emanuel, 501 N Graham, Suite 265, Portland, OR 97227; e-mail: Robert_Huston@pediatrix.com.

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gastrointestinal bleeding (GIB) and necrotizing enterocolitis (NEC). NEC is a pathological condition that may include GIB, infection, systemic inflammatory response syndrome, intestinal perforation, and death. Clinically significant GIB may be caused by NEC, infection, or protein sensitivity. Mother's own milk (MM) has been associated with improved neurodevelopmental outcome as well as decreased sepsis and NEC compared with formula in preterm infants.[1] In an earlier study of unfortified MM or banked donor human milk (BHM), the incidence of NEC was decreased in infants who were supported with human milk compared with formula; however, although there was a decrease in NEC in infants who were supported with BHM only versus formula, it was not statistically significant.[2] A study comparing outcomes in infants who received MM + BHM with a bovine human milk fortifier (DHM) with outcomes in those who received MM with bovine fortifier plus preterm formula (BOV) also showed a decrease in NEC in the DHM group, which was not statistically significant.[3] The rate of NEC for infants who received the DHM diet was similar to that for infants who received MM only with bovine fortifier. A recent study comparing outcomes for infants who received the BOV diet with that for infants on an exclusive human milk–based diet (EHM) of MM ± BHM with a human milk–based fortifier made from BHM reported a decreased incidence of NEC for infants who received the EHM diet.[4] The most recent Cochrane Review of formula-fed versus BHM-fed preterm infants concluded that there was a decreased rate of NEC but lower short-term growth in infants who were supported with BHM.[5] There were no differences in long-term growth or neurodevelopmental outcome. Except for 1 recent abstract,[6] no study reporting outcomes for infants supported with a DHM diet compared with those for infants supported with an EHM diet has been published.

We began using EHM for selected VLBW infants at increased risk for NEC in May 2008. All other infants continued to be supported with a BOV diet, as defined above. In June of 2009, we changed our standard support for all VLBW infants to a DHM diet while still using EHM for VLBW infants at high risk for NEC. The purpose of this study was to determine whether our use of the EHM diet compared with BOV and DHM diets has been effective in terms of decreasing the rates of NEC and GIB in the NICU at Randall Children's Hospital. A secondary goal was to perform a cost analysis of using the human milk–based fortifier in our NICU.

Methods

This is a retrospective study of infants of 500 to 1500 g birth weight (BW) and ≤32 weeks postmenstrual age (GA) who were admitted to the NICU from January 1, 2007 to December 31, 2011. All infants admitted within the first week of life who survived until they were able to receive fortified MM or 24 cal/oz preterm formula were included in the study. Infants with major anomalies (including complex congenital heart disease) and genetic or metabolic syndromes as well as NEC or GI perforation prior to fortification of MM were excluded.

Infants received unfortified MM, BHM, or 20 cal/oz preterm formula until they reached 80 to 100 mL/kg/d of enteral feeding volume. At that time, MM and BHM were fortified to 24 cal/oz with human milk fortifier or, if receiving formula, were given 24 cal/oz preterm formula. Infants were placed on an EHM diet if they met criteria for increased risk for NEC, which included one of the following: significant patent ductus arteriosus (PDA), defined as moderate to large with left to right shunt on echocardiography or requiring treatment medically or surgically; BW ≤third percentile (SGA); cardiopulmonary resuscitation at birth (CPR); maternal cocaine or methamphetamine use during pregnancy; and GIB without evidence of NEC prior to fortification of MM. Participants were sorted into 3 groups for analysis: group preterm formula (PTF), those who received PTF exclusively or MM fortified with bovine fortifier (Enfamil® Human Milk Fortifier, Mead Johnson & Co, Evanston, IN) plus preterm formula for >48 hours; group DHM, those who received MM or BHM plus bovine fortifier; and group EHM, those who received MM or BHM plus human milk–based fortifier (Prolacta Bioscience Inc, Monrovia, CA). Infants in group DHM must not have received PTF for >48 hours or EHM for >6 days. Infants in group EHM must not have received PTF for >48 hours or EHM for <7 days.

Primary outcomes were the incidence of NEC and the incidence of NEC plus GIB. NEC was defined as Bell stage 2 or 3.[7] GIB was defined as gross rectal bleeding without evidence of fissures that led to discontinuing enteral feedings for ≥48 hours. Secondary outcomes were the incidences of mortality, late-onset sepsis, retinopathy of prematurity (ROP), chronic lung disease, length of stay, and weight gain (WtG; in g/kg/d), length gain (LG; in cm/wk), and head circumference gain (HCG; in cm/wk). WtG velocity was computed from admission to discharge according to the method of Patel et al.[8]

To estimate costs related to stage 1 NEC, a matched control analysis was done of hospital cost for the total length of stay for infants with GIB who did not meet criteria for stage 2 NEC whose enteral feedings were held and were treated with antibiotics for ≥7 days. Cases and controls were matched for BW, GA, CRIB (Clinical Risk Index for Babies) score,[9] PDA, year of birth, and diet for infants in groups PTF and DHM. Hospital costs were estimated from the total hospital billing charge using the hospital cost-to-charge ratio. To estimate the average cost of the human milk–based fortifier, the average daily intake of the fortifier (in mL/kg/d) was computed from dietary intake records of infants who received the EHM diet. Average cost of the fortifier per infant was calculated by multiplying the value (in mL/kg/d) by the total number of days that the infant received the fortifier and the cost per milliliter of the fortifier ($6.25/mL).

Nutritional data were compiled from patient records by neonatal dietitians.

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Table 1.

Baseline Characteristics (Mean ± SD or Percentage).

Group (n)	PTF (93)	DHM (224)	EHM (44)	*P* Value
GA (weeks)	29.1 ± 1.8	28.1 ± 2.2	26.7 ± 2.4	<.0001
BW (g)	1177 ± 222	1104 ± 262	919 ± 269	<.0001
PNS	88%	87%	75%	.1
Male	55%	52%	52%	.88
SGA	3.2%	3.6%	16%	.01
Maternal smoking	30%	18%	16%	.06
Maternal Coc/Meth	5.4%	4.0%	2.3%	.73
APGAR 5 minutes	7.6 ± 1.6	6.7 ± 2.0	4.7 ± 2.8	<.0001
CRIB score	1.6 ± 2.0	2.3 ± 2.9	4.8 ± 3.5	<.0001
CPR	3.2%	5.8%	32%	.0005
Transfusion	16%	31%	73%	<.0001
PDA	18%	20%	73%	<.0001

Abbreviations: SD, standard deviation; PTF, preterm formula or mother's milk plus preterm formula DHM, mother's milk supplemented with banked human milk; EHM, exclusive human milk–based diet; GA, postmenstrual age; BW, birth weight; PNS, prenatal steroids; SGA, BW <third percentile; Coc/Meth, cocaine/methamphetamine; CRIB, Clinical Risk Index for Babies; CPR, cardiopulmonary resuscitation at birth; PDA, patent ductus arteriosus.

Clinical data were compiled from patient records by a neonatal research nurse and a neonatologist. The study was approved by the institutional review board at Legacy Health Systems.

All statistical analyses were performed using *R* version 2.15.1.[10] Baseline characteristics of the study population were summarized using descriptive statistics (mean ± standard deviation) for continuous variables and percentage for categorical variables. Baseline characteristics were compared using analysis of variance for continuous variables and χ^2 or Fisher exact tests for categorical data. Statistical analyses for primary and secondary outcomes were performed using multivariate logistic regression for binary outcomes and linear analysis of covariance for continuous outcomes. Predictors initially included BW, GA, prenatal steroids (PNS), SGA, maternal smoking, maternal cocaine or methamphetamine use, CRIB score, 5-minute APGAR score, CPR, transfusion prior to evidence of NEC or GIB, and PDA. A stepwise selection procedure was used to select appropriate predictors to be included in the analyses. Evaluation of matching criteria for the paired groups in the analysis of cost was done using the Student *t* test after values were entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA). A *P* value of <.05 was considered significant.

Results

Study Results

Baseline characteristics of the study groups are shown in Table 1. As would be expected from our practice guidelines, infants in group EHM were of lower BW and GA, were more often SGA, and had a higher acuity clinically than the other groups. Although the EHM group had a higher incidence of PDA than both the PTF and DHM groups, approximately two-thirds of infants diagnosed with a PDA were treated medically or surgically in each group: 65%, 67%, and 72% for PTF, DHM, and EHM, respectively. In the DHM group, 16 infants (7%) received PTF for ≤48 hours, and 2 (0.9%) received EHM for ≤72 hours. In the EHM group, 5 infants (11%) received PTF for ≤48 hours.

The primary outcomes results were as follows: the incidence of NEC was 8.6%, 4.9%, and 2.3% for PTF, DHM, and EHM, whereas the incidence of stage 3 NEC was 4.3%, 2.7%, and 2.3%, respectively. The incidence of GIB was 4.3%, 8.0%, and 0%, whereas the incidence of NEC + GIB was 12.9%, 12.9%, and 2.3% for PTF, DHM, and EHM, respectively. No infant diagnosed with NEC or GIB in the DHM or EHM groups received PTF. Also, 50% of infants with GIB were diagnosed and treated for stage 1 NEC in both the PTF (2/4) and DHM (9/18) groups, whereas 2 infants in each group were diagnosed with milk protein sensitivity. Results, including predictors tested in the final model of the multivariate logistic regression analyses for the primary outcomes of NEC and NEC + GIB, are shown in Tables 2 and 3. NEC incidence was negatively correlated with EHM versus PTF, and the combined outcome of NEC + GIB was negatively correlated with EHM versus PTF as well as EHM versus DHM. Results also showed that PDA was positively correlated with NEC and NEC + GIB, whereas PNS was negatively correlated with NEC.

Of the secondary outcomes, significant correlations were seen for several predictors. Mortality was negatively correlated with DHM versus PTF (odds ratio [OR] = 0.158; confidence interval [CI] = 0.024-0.854; *P* = .036) and EHM versus PTF (OR = 0.040; CI = 0.001-0.456; *P* = .021). Mortality was positively correlated with CRIB and CPR. Total ROP but not severe ROP (stage 3) was positively correlated with EHM versus DHM. PDA was positively and BW was negatively correlated with severe ROP. No other

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Table 2.

Final Model for the Multivariate Logistic Regression for NEC.

Predictor	OR (95% CI)	*P* Value
DHM vs PTF	0.470 (0.172-1.320)	.141
EHM vs PTF	0.060 (0.003-0.445)	.019
EHM vs DHM	0.127 (0.006-0.846)	.076
SGA	7.17 (0.96-35.66)	.025
PDA	4.78 (1.72-13.35)	.003
Maternal Coc/Meth	3.12 (0.57-12.88)	.143
PNS	0.268 (0.094-0.819)	.016

Abbreviations: NEC, necrotizing enterocolitis; OR, odds ratio; CI, confidence intervals; DHM, mother's milk supplemented with banked human milk; PTF, preterm formula or mother's milk plus preterm formula; EHM, exclusive human milk–based diet; SGA, BW <third percentile; PDA, patent ductus arteriosus; Coc/Meth, cocaine/methamphetamine; PNS, prenatal steroids.

Table 3.

Final Model for the Multivariate Logistic Regression for NEC + GIB.

Predictor	OR (95% CI)	*P* Value
DHM vs PTF	0.897 (0.429-1.966)	.788
EHM vs PTF	0.062 (0.003-0.366)	.011
EHM vs DHM	0.070 (0.004-0.369)	.012
PDA	2.59 (1.17-5.62)	.017
BW	0.999 (0.997-1.000)	.072
Maternal Coc/Meth	2.51 (0.63-8.41)	.153
SGA	2.21 (0.43-8.84)	.290

Abbreviations: NEC, necrotizing enterocolitis; GIB, gastrointestinal bleeding; OR, odds ratio; CI, confidence intervals; DHM, mother's milk supplemented with banked human milk; PTF, preterm formula or mother's milk plus preterm formula; EHM, exclusive human milk–based diet; PDA, patent ductus arteriosus; BW, birth weight; Coc/Meth, cocaine/methamphetamine; SGA, BW <third percentile.

clinical secondary outcomes were correlated with dietary group. Length of stay was negatively correlated with GA and positively correlated with transfusions and SGA. Late-onset sepsis was positively correlated with CPR. Chronic lung disease was negatively correlated with BW and positively correlated with transfusions and PDA.

Nutritional outcomes for PTF, DHM, and EHM, respectively, were as follows: WtG = 14.2 ± 2.4, 13.5 ± 2.2, and 12.8 ± 1.8 g/kg/d; LG = 1.04 ± 0.26, 1.02 ± 0.26, and 0.96 ± 0.12 cm/wk; HCG = 0.80 ± 0.19, 0.76 ± 0.18, and 0.69 ± 0.13 cm/wk. Infants were fortified to 24 cal/oz on day of life (DOL) 10.8 ± 5.1, 13.5 ± 7.2, and 25.2 ± 12.1, respectively. Increased fortification >25 cal/oz was given to 25%, 53%, and 61% of infants in the PTF, DHM, and EHM, groups, respectively, on DOLs 23.6 ± 10.9, 29.8 ± 12.9, and 46.1 ± 23.1. Linear analysis of covariance showed a negative correlation for DHM versus PTF and EHM versus PTF for WtG and HCG, but the models accounted for <25% of variability in growth outcomes (Tables 4 and 5). BW and PDA were also negatively and GA positively correlated with WtG, whereas GA and PDA were negatively and SGA was positively correlated with HCG. LG was only positively correlated with APGAR.

Cost Analysis

Results of the matched-pair analyses for costs of stage 1 NEC are shown in Table 6. The average cost difference for NEC stage 1 compared with controls was $38 386. Human milk–based fortifier intake data were available for 40/44 infants in the EHM group. Median (range) for the number of days that infants received EHM was 27 (8-37). Average total intake of the fortifier per infant was 1137 mL at a cost of $6.25 per mL = $7106 per infant. To evaluate the cost/benefit of a strategy to decrease NEC in high-risk patients, we looked at the incidence of stage 1, stage 2, and stage 3 NEC in the DHM group for infants with the risk factors of PDA, SGA, and maternal methamphetamine or cocaine use. In the 58 infants who met these criteria, the incidences of stage 1, stage 2, and stage 3 NEC were 5.2%, 3.4%, and 5.2%, respectively, versus 4.0%, 2.2%, and 2.7% for all DHM infants. In the EHM group, 40 infants met these criteria, including the 1 infant with NEC (1 stage 3 for a total incidence of 2.5%). For a larger group of infants, we would conservatively assume that no more than 50% of infants receiving an EHM diet who developed NEC would have surgical NEC. Therefore, we used an incidence of 1.3% for both stage 2 and stage 3 NEC. Because there were no infants with stage 1 NEC in our EHM group, we used 0% for the incidence of stage 1 NEC in the EHM group. For the

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Table 4.

Final Model for the Analysis of Covariance for Weight Gain.[a]

Predictor	Estimate	Standard Error	*P* Value
DHM vs PTF	–0.7953	0.2592	.002
EHM vs PTF	–1.3536	0.4147	.001
EHM vs DHM	–0.55	0.37	.13
GA	0.3070	0.0771	<.001
BW	–0.0055	0.0006	<<.001
Transfusion	–0.4704	0.3022	.121
PDA	–0.8682	0.2986	.004

Abbreviations: DHM, mother's milk supplemented with banked human milk; PTF, preterm formula or mother's milk plus preterm formula; EHM, exclusive human milk–based diet; GA, gestational age; BW, birth weight; PDA, patent ductus arteriosus.
[a]Adjusted R^2 = 0.2336.

Table 5.

Final Model for the Analysis of Covariance for Head Circumference Gain.[a]

Predictor	Estimate	Standard Error	*P* Value
DHM vs PTF	–0.0577	0.0224	.010
EHM vs PTF	–0.1030	0.0367	.005
EHM vs DHM	–0.05	0.03	.17
GA	–0.0181	0.0050	<.001
PDA	–0.1060	0.0258	<<.001
SGA	0.0939	0.0444	.035

Abbreviations: DHM, mother's milk supplemented with banked human milk; PTF, preterm formula or mother's milk plus preterm formula; EHM, exclusive human milk–based diet; GA, gestational age; PDA, patent ductus arteriosus; SGA; birth weight <third percentile.
[a]Adjusted R^2 = 0.08459.

cost of NEC and the human fortifier, we used costs found in our study for stage 1 NEC and the fortifier and in the study by Ganapathy et al[11] for stage 2 and stage 3 NEC: stage 1 = $38 386; stage 2 = $74 004; stage 3 = $198 040; fortifier = $7106. The results of our evaluation are shown in Table 7. A cost saving can be demonstrated when an EHM diet is used for VLBW infants at higher risk of NEC (as defined above) but not for all VLBW infants when rates of NEC approach the rates that we experience in our NICU.

Discussion

Our study supports previous findings that an EHM diet decreases the incidence of NEC in VLBW infants compared with a bovine diet of MM supplemented with preterm formula and a cow's milk–based fortifier. It also suggests that an EHM diet decreases the combined incidence of NEC plus GIB compared with a bovine diet or a diet of MM supplemented with BHM and a cow's milk–based fortifier. A recent study by Tuttle et al[6] in VLBW infants has shown a decreased incidence of NEC when comparing DHM versus EHM diets (9.8% vs 1.2%, respectively).[6] Although we showed a 53% decrease in the incidence of NEC for DHM versus PTF in our study, the rate of NEC in the DHM group in our study was low, and therefore, the difference was not statistically significant. The magnitude of the decrease in NEC seen in our study for DHM compared with PTF is similar to that found in a Cochrane meta-analysis, which did show a significant decrease in NEC when comparing banked human milk with formula (OR = 0.47, CI = 0.17-1.32, vs OR = 0.40, CI = 0.20-0.83, for our study vs the Cochrane analysis, respectively).[5] It should be noted that our study and the study of Tuttle et al[6] reported rates of NEC for infants of BW ≤1500 g who survived until they were able to receive fortified milk and not total NEC rates. The average annual rate for total NEC in our NICU for all VLBW infants was 8.2% during the years of this study (2007-2011), whereas the total average annual rate for infants who received fortified milk was 5.5%. The average annual total NEC rate for all VLBW infants after implementation of the EHM diet for high-risk infants and DHM for all others from 2009 to 2012 was 5.1%. Finally, our study is the first to show a significant decrease in mortality for infants who are supported with an EHM diet or a DHM diet compared with PTF.

We used the EHM diet only for infants who we felt had a higher risk for NEC, as defined by our guidelines. These included PDA, SGA, CPR, maternal methamphetamine or cocaine use, or GIB prior fortification. Of these criteria, PDA and SGA were significantly associated with NEC, and PDA was significantly associated with NEC + GIB in our study. Previous studies have associated NEC with PDA[12] and SGA.[13] Hypoxic/ischemic injury has been

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Table 6.

Costs for Infants With Stage 1 NEC (Mean ± SD or n).

Parameter	Stage 1 NEC	Control
n	11	11
GA (weeks)	26.6 ± 2.3	26.8 ± 2.3
BW (g)	931 ± 261	968 ± 246
CRIB	4.6 ± 3.4	4.4 ± 3.3
PDA	4	4
CLD	1	2
IVH	2	1
LOS	2	1
PTF	2	2
DHM	9	9
Stay (days)	79 ± 21	76 ± 25
Cost	$257 837 ± $100 928	$219 451 ± $105 819

Abbreviations: NEC, necrotizing enterocolitis; SD, standard deviation; GA, post menstrual age; BW, birth weight; CRIB, Clinical Risk Index for Babies; PDA, patent ductus arteriosus; CLD, chronic lung disease; IVH, stage 3-4 intracranial hemorrhage; LOS, late onset sepsis' PTF, preterm formula or mother's milk plus preterm formula; DHM, mother's milk supplemented with banked human milk.

implicated in the pathogenesis of NEC but has not been proven to be a risk factor.[14] In our study, there was no significant association between CPR and NEC. A recent study also did not find an association between CPR at birth and NEC.[15] The evidence for a risk of intestinal compromise caused by cocaine and methamphetamine is not clear.[16-18] There were trends in our study for an association of cocaine and or methamphetamine exposure with both NEC and NEC + GIB, but they were not statistically significant. The only other predictor that was found to be significantly correlated with NEC or NEC + GIB in our study was a negative correlation of PNS with NEC. As noted above, our data pertain to VLBW infants who survived until they were fed fortified MM or 24 cal/oz formula.

The study by Ganapathy et al[11] analyzing the cost versus benefit of using an EHM diet has suggested a cost saving of $8167 per extremely preterm infant (≤1250 g BW) compared with the PTF diet.[11] This analysis was based on rates of NEC seen in a previous study in which there was a decrease in the incidence of NEC from 16% to 6% with the use of the EHM diet versus a BOV diet.[4] Added cost associated with using the EHM diet was $10 321 per infant.[11] We found a lower cost per patient for added cost resulting from the use of the human milk–based fortifier in our study. This may be related to fewer days that participants received the EHM diet in our study and differences in the amount of fortification per ounce between the 2 studies. We were also most interested in evaluating the effect of the EHM diet versus a DHM diet because using BHM as a supplement to MM rather than preterm formula is becoming more common. The study by Tuttle et al[6] reported a cost saving comparing an EHM diet with a DHM diet in a study where the rate of NEC decreased from 9.8% to 1.2% and the average cost of the human milk–based fortifier per infant was $5600. With the low rates of NEC in the DHM and EHM groups and an average cost of $7106 per infant for the fortifier in our study, we did not see a statistically significant decrease in the rates of NEC or evidence of cost-effectiveness of using the human milk–based fortifier for all VLBW infants. Our analysis of the cost-effectiveness of using an EHM compared with the DHM diet in VLBW infants with the risk factors of PDA, SGA, and prenatal cocaine or methamphetamine exposure does suggest that a strategy of using the EHM diet versus a DHM diet for infants at higher risk for NEC may be cost-effective in NICUs that have a lower incidence of NEC for all VLBW infants.

Our study and the study by Tuttle et al[6] used values for the excess cost resulting from NEC reported by the study of Ganapathy et al,[11] which reported estimated costs as opposed to total hospital charges. Costs were adjusted for multiple risk factors and morbidities. Bisquera et al[19] previously reported the financial impact of NEC resulting from increased length of stay and total hospital charges.[19] Excess hospital charges for stage 2 NEC were $73 300 and stage 3 NEC were $186 200 based on 1994-1995 rates. Johnson et al[20] have reported significantly lower marginal hospital costs related to NEC, adjusted for other comorbidities and risk factors for adverse outcome, that averaged $13 923 for stage 2 NEC and $22 359 for stage 3 NEC.[20] The average direct costs, however, were $90 209 for stage 2 and $133 888 for stage 3 NEC. The total number of participants with NEC in the study of Johnson et al[20] was 29 of a total of 425 versus 259 of 2560 in the Ganapathy et al[11] study. We feel that direct costs are more relevant because they appear to more accurately reflect the increased total cost for management of patients with NEC compared with those without NEC. Our matched-pair analysis of costs for stage 1 NEC in which GA, BW, and other comorbidities were well matched supports our impression that marginal costs for NEC as reported by Johnson et al[20] understate

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Table 7.

Cost Evaluation of Using EHM Diet Per 100 Infants ≤1500 g Birth Weight.

Parameter	NEC					
	High Risk			All Infants		
	Stage 1	Stage 2	Stage 3	Stage 1	Stage 2	Stage 3
DHM (%)	5.2%	3.4%	5.2%	4.0%	2.2%	2.7%
EHM (%)	0%	1.3%	1.3%	0%	1.3%	1.3%
DHM (n)	5.2	3.4	5.2	4	2.2	2.7
EHM (n)	0	1.3	1.3	0	1.3	1.3
Difference (n)	5.2	2.1	3.9	4	0.9	1.4
Cost	$199 607	$155 408	$772 356	$153 544	$66 604	$277 256
Total cost	$1 127 371			$497 404		
Fortifier	$710 600			$710 600		
Cost saving (excess)	$416 771			($213 196)		

Abbreviations: EHM, exclusive human milk–based diet; DHM, mother's milk supplemented with banked human milk; NEC, necrotizing enterocolitis.

the true financial impact of NEC. It also could be argued that charges rather than costs may be more pertinent to the impact of morbidities such as NEC on society because these are costs that need to be managed by patients and insurance companies.

Growth velocities for WtG and HCG were lower for infants in the EHM group in our study, but these infants also had milk fortified at a later DOL than the other groups. The infants in the EHM group were of lower BW and GA as well as at higher risk for morbidity, which may have influenced the decision by providers to delay fortification. Although we attempted to correct for these factors using linear analysis of covariance, the models evaluating growth parameters accounted for significantly less of the variability than the other models we tested. In the only randomized study comparing EHM with a bovine diet, there were no significant differences among groups in growth parameters.[4] It has also been shown that growth in the NICU for infants receiving an EHM diet can be improved and postdischarge outcomes can compare favorably with published outcomes for VLBW infants, with earlier fortification to 24 cal/oz at 40 to 50 mL/kg/d of enteral feeding volume plus increased fortification at full feeding volume.[21]

Our study is limited by being a retrospective study and by the small numbers in the EHM group. The fact that the EHM group had decreased NEC and NEC + GIB in spite of the fact that this group included infants with a higher incidence of possible risk factors for NEC may increase the plausibility of our results. The cost analysis for infants with stage 1 NEC is also limited by small numbers of participants. The average NICU cost for our control group is close to the average cost reported by Ganapathy et al[11] for extremely premature infants without NEC, however ($219 451 vs $207 378, respectively). The strength of our study is that it does include a large total number of participants and that we have corrected for many factors that have been associated with the occurrence of NEC in our statistical analyses.

Conclusion

Our study supports findings from a previous study that suggests that the incidence of NEC can be decreased in VLBW infants when they are fed an EHM diet versus a diet that contains bovine products. In addition, we found that the incidence of NEC plus significant GIB can be decreased when using an EHM diet versus a diet of MM and/or BHM plus a bovine fortifier or a diet supplemented with bovine products. In an NICU with lower overall rates of NEC, an EHM diet also appears to be cost-effective when used in VLBW infants who may be at higher risk of NEC but not for all VLBW infants. Although we did not see a significantly decreased incidence of NEC with the DHM diet compared with PTF, the trend for a decrease in NEC with DHM is consistent with findings from a Cochrane meta-analysis[5] that showed a significant decrease in NEC when supporting preterm infants with BHM versus formula. We also found that both the EHM and DHM diets were

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associated with decreased mortality compared with PTF.

Authors' Note

Data from this study were presented in part at the Pediatric Academic Societies Annual Meeting, May 4 to May 7, 2013, in Washington, DC. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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