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ORIGINAL ARTICLE

Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet

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OBJECTIVE: Human milk is the best form of nutrition for preterm infants and has been associated with a lower incidence of necrotizing enterocolitis (NEC). Infants that develop NEC have a higher incidence of feeding intolerance and longer hospitalizations. The combination of a donor milk bank and donor milk-derived fortifier has changed feeding practices in neonatal intensive care units (NICU). The purpose of this study is to assess the benefits and cost of an exclusive human milk (EHM) diet in very low birth weight (VLBW) infants in a community level III NICU.

STUDY DESIGN: This is a retrospective study including preterm infants ⩽28 weeks and/or VLBW (⩽1500 g) who were enrolled from March 2009 until March 2014. Infants were grouped as follows: group H (entirely human milk based, born March 2012 to 2014), group B (bovine-based fortifier and maternal milk, born March 2009 to 2012), group M (mixed combination of maternal milk, bovine-based fortifier and formula, born March 2009 to 2012) and group F (formula fed infants, born March 2009 to 2012). Baseline characteristics among the four groups were similar.

RESULT: The study included 293 infants between gestational ages 23 to 34 weeks and birth weights between 490 and 1700 g. Feeding intolerance occurred less often ($P < 0.0001$), number of days to full feeds was lower ($P < 0.001$), incidence of NEC was lower ($P < 0.011$), and total hospitalization costs were lower by up to $106,968 per infant ($P < 0.004$) in those fed an EHM diet compared with the other groups. Average weight gain per day was similar among the four groups (18.5 to 20.6 g per day).

CONCLUSIONS: Implementing an EHM diet in our VLBW infants has led to a significant decrease in the incidence of NEC. Other benefits of this diet include: decreased feeding intolerance, shorter time to full feeds, shorter length of stay, and lower hospital and physician charges for extremely premature and VLBW infants.

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INTRODUCTION

Neonatal intensive care has long been associated with high health-care costs, both economic and social. Prematurity and low birth weight contributes significantly to these costs. Health care providers continue to look for safe ways to improve outcomes for the smallest of infants and this hopefully translates to a decrease in cost. Prematurity as well as being very low birth weight (VLBW) < 1500 grams places an infant at a higher risk of developing feeding intolerance, necrotizing enterocolitis (NEC) and sepsis due to an immature gastrointestinal tract.[1] NEC affects ~ 10% of VLBW infants.[2] The etiology of the development of NEC is multifactorial with ischemic injury, aberrant microbial colonization, diet and other factors having an integral role in the disease process.[1,2] Neonates that develop NEC may require surgical management placing them at a higher risk for poor growth, neurodevelopmental impairment and other long-term effects.[2–7] Infant diet is one of the many factors contributing to the development of NEC and feeding intolerance. Human milk is the preferred form of nutrition for premature infants owing to better feeding tolerance and lower incidence of NEC.[1,2,8] The development of NEC at any gestational age (GA) may not only be related to the choice of milk but also the timing of its introduction.[9] Many studies have recently shown that being fed a human milk diet is beneficial from an immunologic and gastrointestinal standpoint.[10,11] Simultaneously, there has been an increase in the push for breast feeding after delivery owing to guidelines established by the WHO (World Health Organization).[12] According to these guidelines a mother should initiate pumping or breast feeding within 2 h after vaginal delivery and 4 h after cesarean section.[12] The American Academy of Pediatrics also recommends human milk over formula for the initiation of feeds in premature infants.[13,14] Many studies have shown that donor human milk is associated with a decreased incidence of NEC when compared with those infants who are formula fed.[15,16] The multitude of health benefits of a human milk diet for VLBW has been well documented.[17] In addition, standardized feeding protocols are also associated with infants attaining full feeds sooner and less total parenteral nutrition use.[13] Recent studies have found that elimination of all bovine-based products, including fortifiers, could be a possible explanation for a reduction in NEC.[15,16] Infants fed an exclusive donor milk diet without fortification have had slower growth rates.[9,15,18,19] Only recently have neonatal intensive care units (NICU) been able to provide premature infants with an exclusive human milk (EHM) diet with the development of donor milk-derived fortifiers. Preterm infants that develop NEC have been shown to have a higher incidence of feeding intolerance and longer hospitalizations.[20] One study demonstrated infants with NEC are hospitalized 60 days longer than preterm infants who did not develop NEC.[20] Longer hospitalization also means increased cost. One study estimated yearly hospitalization costs at $6.5 million or

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Table 1. Demographics

	Human	*Bovine*	*Mixed*	*Formula*	P-*values*
Total	87 (30%)	127 (43%)	49 (17%)	30 (10%)	
Male	53 (60%)	63 (50%)	29 (59%)	9 (30%)	
Female	34 (39%)	64 (50%)	20 (40%)	21 (70%)	
Caucasian	24 (27%)	36 (28%)	14 (28%)	9 (30%)	
African American	53 (61%)	85 (67%)	32 (65%)	21 (70%)	
Other	10 (11%)	6 (5%)	3 (6%)	0 (0%)	
ROP	11 (14%)	40 (32%)	19 (40%)	4 (14%)	< 0.001
Sepsis	1 (14%)	3 (43%)	3 (43%)	0 (0%)	0.545
BPD	13 (15%)	30 (24%)	21 (42%)	3 (10%)	< 0.001
Average gestational age in weeks (s.d.)	27.7 (±2.7)	28.3 (±2.8)	27.6 (±2.8)	29.8 (±2.5)	< 0.002
Average growth velocity g kg^{-1} per day (s.d.)	11.6 (±2.7)	11.6 (±2.5)	11.2 (±3.0)	12.1 (±3.2)	0.377

Abbreviations: BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.

$216,666 per surviving infant.[20] Total annual estimated cost of caring for babies with NEC is between $500 million and $1 billion in the United States.[2] The combination of donor human milk and donor milk-derived fortifier has changed practices in NICUs allowing preterm infants to be fed an EHM diet.

This primary purpose of this study is to examine the benefits of such a diet. This study adds to current research by comparing feeding intolerance, time to full feeds, length of stay, weight gain and total cost of hospitalization in VLBW infants receiving an EHM diet to those receiving a more typical bovine supplemented diet.

METHODS

This is a single center retrospective chart review study at a level III community NICU at The Herman & Walter Samuelson Children's Hospital at Sinai located in Baltimore, MD, USA. Currently, there are ~2300 live births at Sinai Hospital per year, 50 of those with a GA < 29 weeks and/or $\leqslant 1500$ g. All infants $\leqslant 28$ weeks GA and/or $\leqslant 1500$ g from 2009 to 2014 were included in our study. Infants were excluded if they died before the initiation of feeds or were transferred to an outside hospital before a GA of 34 weeks. In March of 2012 we began providing infants with an EHM diet using donor milk-derived fortifier (Prolact+H^{2}MF Prolacta Bioscience, City of Industry, CA, USA) and donor milk (as needed). Two hundred and ninety-three infants were identified as eligible and all data were collected retrospectively for all cohorts from electronic medical records. The infants were divided into four feeding groups as follows: B = bovine, H = human, M = mixed and F = formula. All infants in group H were born March 2012 to 2014, as that is when our institution initiated the EHM diet. Groups B, M and F were born March 2009 to 2012. No significant changes to clinical practice, feeding strategies, respiratory management or attending physician staffing occurred during the study period. All groups had similar feeding schedules, including slow advances (10 to 20 ml kg^{-1} per day) and subsequent fortification with either bovine-based human milk fortifier (Similac HMF liquid, Abbott Nutrition, Columbus, OH) or donor milk-derived fortifier (Prolacta) after reaching ~120–150 ml kg^{-1} per day (full enteral feeds). Our primary aim was to compare each group by length of time to full feeds, length of stay, incidence of feeding intolerance, incidence of NEC, growth velocity, bronchopulmonary dysplasia (BPD) and hospital and physician charges. Approval for this study was obtained from the hospital's institutional review board.

Study outcomes

The primary objective was to examine the effect of an EHM diet on length of stay, incidence of feeding intolerance and time to full feeds.

The secondary objectives were to determine the effect of the diet on the incidence of NEC and to determine the cost effectiveness of an EHM diet.

Primary explanatory variables

Time to full feeds was defined as time from birth until receiving 150 ml kg^{-1} per day of fortified (24 kcal oz^{-1}), enteral feeds. Feeding was initiated within the first 48 h of life. Length of stay was calculated by subtracting the date of birth from the date of discharge. Feeding intolerance was defined as feeds being interrupted and held for 24 h or longer due to emesis, abdominal distension, bloody stools or suspicion of NEC. The feeding intolerance variable was divided into three groups: 0 interruptions, 1 interruption, or 2 or more interruptions in feeding for 24 h or more. NEC was defined using Bell staging criteria, stage 2 or greater.[3,21] Estimated growth velocity (g kg^{-1} per day) was calculated to assess weight gain from birth to discharge using the two point average weight $GV = [1000 \times (W_n - W_1)] / \{(D_n - D_1) \times [(W_1 + W_n)/2]\}$.[22] Where W = weight in grams, D = day, 1 = beginning of time interval and n = end of time interval in days.[22] Discharge criteria were defined as gaining 20 to 30 g per day, tolerating feedings by mouth, maintaining adequate temperature control, and having no apnea and bradycardia. BPD is defined as requiring oxygen at 36 weeks GA. Total cost of hospitalization was defined as the total hospital charges plus physician charges per day, multiplied by days hospitalized. In addition, group H included the cost of donor milk-derived fortifier plus the cost of donor human milk (if needed). Total cost information was unavailable for 10 infants, five in the bovine group, three of whom developed NEC, three in the formula group and two in the mixed group. Those infants were excluded from the total cost of hospitalization analysis. Therefore, a second cost analysis including all study infants was done comparing the physician charges alone. Physician charges were the total physician charges based on billing codes listed by the provider daily for each infant for the length of hospitalization. The cost of donor milk-derived fortifier and donor milk (if needed) was added to the physician charges analysis for the EHM group.

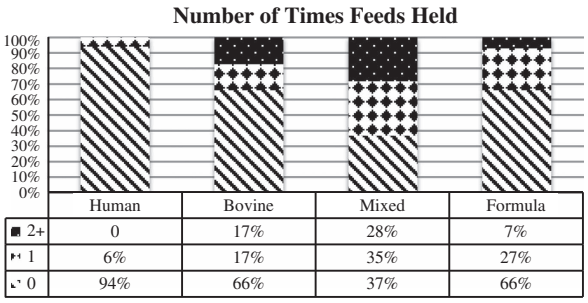
Statistical analysis

All statistical analysis was done using STATA statistical software version 13 (College Station, TX, USA).

Descriptive statistics for infant characteristics in each of the four groups is shown in Table 1. Fisher's exact test was used to examine the association between feed type and feeding intolerance. Linear regression analysis was used to examine the association between time to full feeds and feed type adjusted for GA. To adjust for down-weighting observations with undue influence a robust regression was performed. Linear regression with robust standard error estimation was performed to examine the association between length of stay and feed type adjusted for GA. Fisher's exact test was performed to examine the association between feed type and incidence of NEC. Mean weight gain per day was examined using a one way analysis of variance. The association between feed type and development of BPD, retinopathy of prematurity (ROP) and sepsis was examined using Fisher's exact test and adjusted for GA. The association between total cost of hospitalization and feed type when adjusted for GA was examined using linear regression with standard error estimation. Since the individual groups were small the bovine and mixed groups were combined and the association between feed type and cost was also examined using linear regression. This study had Cox statistical power of 95% with the sample size for each group being a minimum of 50 for analysis with a s.d. of 0.5.

RESULTS

There were 293 preterm infants born at The Herman & Walter Samuelson Children's Hospital at Sinai, with GA between 23 and 34 weeks and birth weights 490 to 1700 g from March 2009 to



	Human	Bovine	Mixed	Formula
2+	0	17%	28%	7%
1	6%	17%	35%	27%
0	94%	66%	37%	66%

Figure 1. Fisher's exact test ($P < 0.001$) for all groups, $N = 293$.

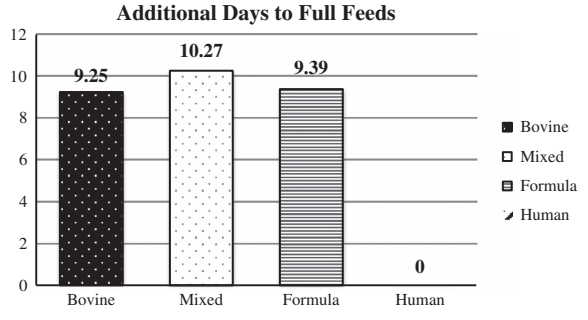


Figure 2. Linear regression analysis adjusted for gestational age ($P < 0.001$) for all groups, $N = 293$.

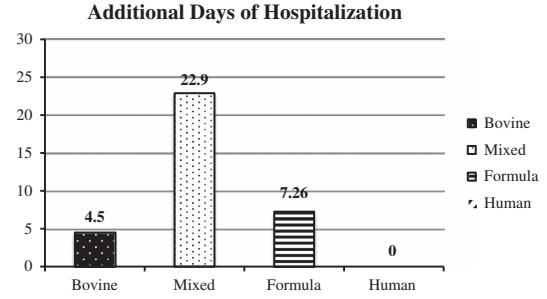


Figure 3. Analysis using linear regression adjusted for gestational age, $R^2 = 0.35$, $P < 0.04$, $N = 293$.

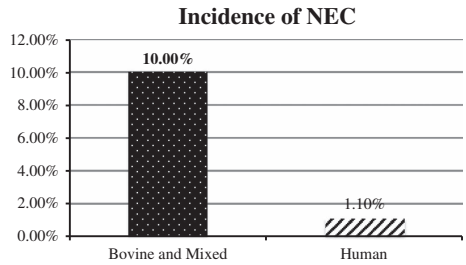


Figure 4. Using Fisher's exact test ($P < 0.011$), $N = 263$. Formula group excluded from analysis (statistically older group), medical NEC represents 1% of bovine and mixed group, all others were surgical.

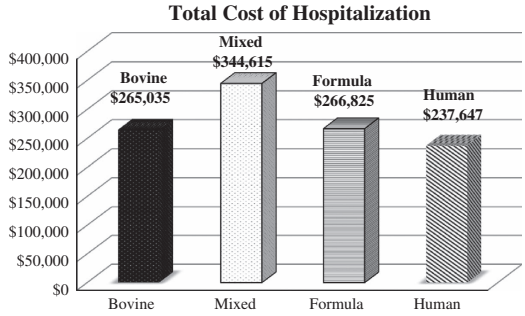


Figure 5. Linear regression analysis adjusted for gestational age $P < 0.001$, between human and mixed group, $R^2 = 035$, $N = 283$.

March 2014. Each group was divided based on dietary status and date of birth. In March of 2012 our NICU was able to provide infants with an EHM diet with donor milk and donor milk-derived fortifier. Thirty percent of the 293 preterm infants were fed an EHM diet using either mother's own or donor milk and donor milk-derived fortifier, 43% received mother's milk with bovine-based milk fortifier, 17% had a few days of formula and as well as mother's milk with bovine-based milk fortifier, and 10% were fed an exclusive formula diet. The average GA in each group was not statistically different except for the exclusively formula fed group, which was statistically more mature (29.8 weeks compared with 27.7 weeks in group H, 28.3 in group B and 27.6 in group M (Table 1).

Feeding intolerance was significantly worse in all groups compared with the human milk group ($P < 0.0001$, Figure 1). Ninety-four percent of preterm infants fed an EHM diet never had feeds held compared with 66%, 37% and 66% for groups B, M and F, respectively. The number of additional days to full feeds was also significantly higher for all groups compared with human milk ($P < 0.001$, Figure 2). It took 9.25 to 10.27 days longer to achieve full feeds in those groups not fed an EHM diet (Figure 2). Length of hospitalization was significantly longer in the mixed group by 22 days compared with the EHM group ($P < 0.04$, Figure 3). The incidence of NEC decreased statistically when infants received an EHM diet. Incidence of NEC included both surgical and medical NEC. Spontaneous intestinal perforation, diagnosed by visual diagnosis at the time of surgery, was not included in this study. The incidence of NEC in group H was significantly lower than that of study infants of the same GA (1.1 versus 10%, $P < 0.011$, Figure 4). Average weight gain was similar in the four groups at 18.5 to 20.6 g per day or growth velocity 11.2-12.1 g kg^{-1} per day ($P < 0.377$, Table 1). Unexpected but positive findings in the study included decreased incidence of BPD, ROP and sepsis in the human milk group. Eighty-five percent of infants in group H had no BPD compared with 57 to 76% in the bovine and mixed group, respectively ($P < 0.001$, Table 1). Incidence of ROP was 14% in group H, 32% in group B and 40% in group M ($P < 0.001$). Sepsis incidence was 14% in group H, 43% in group B and 43% group M. The formula group (group F) was more mature and had the lowest rates of BPD, ROP and sepsis.

The total hospital charges per infant were found to be statistically higher in the mixed group (Figure 5). Total overall charges were the lowest when fed an EHM diet despite adding the cost of donor milk and donor milk-derived fortifier. Total cost (hospital charges plus physician charges per patient) for the EHM group were $237,647, compared with $265,035, $344,615 and $266,825 for groups B, M and F, respectively (Figure 5). Cost savings between the groups ranged from $27,388 to $106,968 per infant. Hospital charges for 10 infants (three in group F, five in group B and two in group M) were unavailable. Three of those infants developed surgical NEC, and all infants without total cost data were not included in the hospital charges analysis. Therefore, a second analysis was performed using only physician charges as an indirect marker for cost. The cost of the donor milk and donor

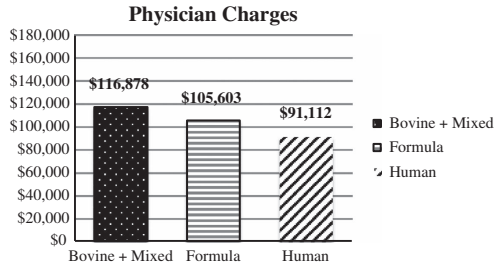


Figure 6. Linear regression analysis adjusted for gestational age, $P < 0.001$ between bovine+mixed and human, $R^2 = 0.45$, $N = 293$.

milk-derived fortifier was added to the physician charges in the EHM group. Charges were significantly higher by $25,765 for the B+M group, compared with group H ($P < 0.001$, Figure 6).

DISCUSSION

This is an unsponsored study in a level III community NICU comparing the clinical and fiscal outcomes of an EHM diet compared with bovine-based diets among VLBW infants. This study has the advantages of having stable attending physicians and nurses with consistent feeding practices throughout the length of the study, active lactation consultants and a single center patient population. Many hospitals vary in feeding protocols used and in maternal lactation consultant availability.[15,18,19] Lactation support is an important component of our multidisciplinary care in the NICU. Our institution has the advantage of consistent feeding methods in our attending physician staff throughout the study period and a NICU dedicated lactation consultant. An important limitation is the overall small sample size and the combination of groups B and M for comparison analysis.

In our NICU we have ~3 to 5 cases of NEC (medical and surgical) per year. This is an incidence of NEC 8 to 10% of VLBW infants, a statistic that has been stable at our institution for the past 15 years, but which is slightly high compared with other NICU's. Since starting an EHM diet in our VLBW infants, we have seen the rate of NEC decrease to 1%. This is associated with decreased feeding intolerance and was significantly lower in those fed an EHM diet. Ninety-four percent of the EHM group did not have feeds held during hospitalization when compared with 66% for the bovine and formula groups, and 37% for the mixed group. This demonstrates decreased feeding intolerance and incidence of NEC with an EHM diet, adding support to previous studies.[16,20] Due to the small numbers of NEC cases this study lacked statistical power for this variable. Despite this there was a notable decrease of NEC in our institution.

Feeding intolerance is associated with increased length of stay and increased cost.[20] Infants reached full feeds significantly faster in the EHM group. All other groups took 9 to 10 days longer to achieve full feeds. In addition, length of stay was shorter in the EHM group by 4.5 to 22 days. Discharge criteria were unchanged for the study time period. Length of hospitalization was longest in the mixed group. This observation deserves further study, as the negative effect of a mixed formula/breast milk diet has not been well described. Possible interference of bovine products on the biologic advantages of human milk would be an interesting area to target future research.

Weight gain is important for neurocognitive development.[23] Many studies have shown that those fed an EHM diet without fortification have poor weight gain.[9,15,18,19] This study did not show a significant difference in weight gain between the groups, supporting the nutritional adequacy of a 100% human milk diet. Earlier initiation of fortification would most likely improve weight gain in the EHM group. Long-term benefits such as decreased incidence of BPD and ROP were also seen. The study was not powered for these outcomes. As there were no significant respiratory management changes or oxygen-targeting protocol changes implemented during the study period, the findings are worth noting. Infants who have shorter lengths of stay and who reach full feeds more rapidly could be presumed to be healthier overall. The lower incidences of BPD and ROP may be simply due to babies who do better overall.

The development of NEC has been shown in past studies to lead to an increase in direct health-care costs and increased cost to the hospital, although it has varied by institution and by year.[20,24] Total hospitalization charges, which included physician charges, were higher by $27,388 to $106,968 in all other groups compared with those fed an EHM diet. Total hospital charges were unavailable for 10 infants (three in group F, five in group B and two in group M), three of whom had surgical NEC. Total hospital charges in our study would theoretically be even higher if the costs for those infants were included in our total cost analysis. Physician charges were available for all 293 infants. Therefore a second cost analysis was performed using provider charges as an indirect marker for cost. All infants were included in the second cost analysis. In the EHM group, we included the cost of donor milk and donor milk-derived fortifier that can range from $125 to $250 per 100 ml bottle. The hospital is currently assuming this added cost. Physician charges as well as hospital charges do not reflect reimbursements. The analysis of physician charges showed significantly higher charges in the bovine and mixed group ($14,490 to $25,765), despite adding the cost of the fortifier and donor milk to the EHM group. Increased length of stay secondary to increased feeding intolerance is most likely the main contributor to these increased costs. A previous study showed a total cost of $10,989 for donor human milk only not including the cost of fortifier.[25] Our study indicates that, despite this high price of donor milk and donor milk-derived fortifier, it is still cost effective to provide an EHM diet.

CONCLUSION

This study demonstrates the benefits of providing an exclusive human milk diet and adds confidence to previous studies showing an association of such a diet with decreased morbidities such as sepsis, BPD and ROP. Hospitals have been hesitant to implement an EHM diet due, in part, to the cost of the human milk products themselves. Our study shows that our level III NICU actually had overall lower costs when providing this EHM diet. An EHM diet has led to decreased feeding intolerance, shorter time to full feeds, shorter length of hospital stay, lower incidence of BPD, and lower hospital and physician charges for extremely premature and VLBW infants.

What is known about this subject:

- Studies have shown many benefits of an exclusive human milk (EHM) diet, however, the impact of this diet and its cost is being investigated in a community level III NICU independently of pharmaceutical company financial support.

What this study adds:

- This study supports previous research and demonstrates that, despite the added cost of donor human milk and donor milk-derived fortifier, an EHM diet is cost effective.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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