Human Milk Feedings and Infection Among Very Low Birth Weight Infants

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ABSTRACT. *Background.* **Preterm infants are immunologically immature at birth. Previous studies have demonstrated that human milk protects against infection in full-term infants, but there are few studies of its effect for preterm infants.**

Objective. **To examine the effect of human milk feedings on infection incidence among very low birth weight (VLBW) infants during their initial hospitalization.**

Study Design. **The sample consisted of 212 consecutive VLBW infants admitted to the Georgetown University Medical Center neonatal intensive care unit (NICU) during 1992–1993 and surviving to receive enteral feeding. Type of feeding (human milk vs formula), presence of infection and sepsis/meningitis (clinical signs and positive cultures for pathogenic organisms), and potential confounding variables were abstracted from medical records. Multiple logistic regression was used to control for confounders.**

Results. **The incidence of infection (human milk [29.3%] vs formula [47.2%]) and sepsis/meningitis (human milk [19.5%] vs formula [32.6%]) differed significantly by type of feeding. Major risk factors for infection were similar in both groups. Human milk feeding was independently correlated with a reduced odds of infection (odds ratio [OR] = 0.43; 95% confidence interval [CI]: 0.23–0.81), controlling for gestational age, 5-minute Apgar score, mechanical ventilation days, and days without enteral feedings; and was independently correlated with a reduced odds of sepsis/meningitis (OR = 0.47, 95% CI:0.23–0.95), controlling for gestational age, mechanical ventilation days, and days without enteral feedings.**

Conclusions. **The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants.** *Pediatrics* **1998;102(3). URL: http://www.pediatrics.org/cgi/content/full/102/3/e38;** ***infection, sepsis, infant, low birth weight, human milk, breastfeeding.***

ABBREVIATIONS. AAP, American Academy of Pediatrics; IgA, immunoglobulin A; VLBW, very low birth weight; NICU, neonatal intensive care unit; IV, intravenous; NPO, without enteral feedings; OR, odds ratio; CI confidence interval; EBM, expressed breast milk.

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In a recent policy statement, the American Academy of Pediatrics (AAP) strongly advocated breastfeeding for full-term infants and for the first time extended this recommendation to premature infants.[1] This statement from the AAP's Work Group on Breastfeeding cited the compelling advantages of human milk, which include immunologic benefits. Studies comparing human milk from preterm mothers with that from term mothers suggest that these immunologic benefits may be even greater for preterm infants because secretory immunoglobulin A (IgA), lysozyme, lactoferrin, and interferon are found in greater concentrations in preterm human milk compared with term milk.[2–4] Very low birth weight (VLBW) infants do not benefit from the transplacental transfer of maternal immunoglobulins that occurs primarily after 34 weeks of gestation.[5] These infants are exposed to abundant pathogenic organisms during neonatal intensive care unit (NICU) hospitalization and may benefit from the host defense factors present in preterm human milk.[6–9]

Although researchers have investigated the role of infant feeding type on the development of infection in full-term infants,[10–15] the relation between type of infant feeding and infection among preterm infants has received less attention in the literature. This study was designed to examine the effect of human milk feedings on the incidence of infection and sepsis/meningitis among hospitalized, VLBW infants controlling for potential confounding variables.

METHODS

Study Population

The study sample consisted of all preterm infants weighing up to 1500 g at birth and hospitalized in the NICU at the Georgetown University Medical Center from January 1992–September 1993 (n = 283). Infants who died before the start of enteral feedings (n = 65) and infants whose medical records were not available from the medical records department (n = 6) were excluded. The total sample for which the effect of the provision of human milk on infection could be studied was 212 VLBW infants. This study was reviewed and approved by the Institutional Review Board at the Georgetown University Medical Center.

Study Site

The Georgetown University Medical Center NICU is a tertiary care center and accepts maternal and infant transports. The National Capital Lactation Center and the Milk Bank at the Georgetown University Medical Center provide support to mothers who choose to provide expressed breast milk to their infants. As a result, the rate of breastfeeding among mothers of VLBW, preterm infants is relatively high: 59.0% for this study sample.

Source of Data

The medical records of all consecutive admissions of VLBW infants during the study period were reviewed. Daily feedings were routinely recorded for all infants (human milk vs infant formula). Cases of infection and sepsis/meningitis were also routinely documented in the chart. For our analyses, we considered only infections that occurred after the start of enteral feeding. Medical records of infants who had been transported were also abstracted at reverse transport hospitals to obtain complete data regarding infection outcomes. Potential confounding variables including major risk factors for infection, maternal demographic characteristics, obstetric factors, and infant risk factors were also abstracted from the medical record.

Definition of Study Variables

All human milk-fed infants received milk from their own mothers with supplemental formula feedings when human milk was not available. Expressed human milk was provided fresh or frozen for future use at −20°C. Frozen milk was thawed for each use. Human milk was fortified with Human Milk Fortifier, Polycose, or MCT oil, as clinically indicated. Most mothers who initiated human milk feedings continued for the duration of their infant's hospitalization.

Human milk feeding was defined as any human milk, regardless of supplementation with formula. Categories of high human milk consumption (80% or greater human milk) and partial human milk consumption (79% or less human milk) were also constructed based on a standard international classification of human milk feedings.[16] Formula feeding was defined as exclusive formula feeding.

Only cases of infection occurring after the start of enteral feeding that could be potentially affected by the type of feeding were included. Infection was documented by the presence of clinical signs of sepsis and by positive cultures for pathogenic organisms at one or more of the following sites: blood, spinal fluid, urine, stool, pleural fluid, umbilicus, or surgical wound. In all cases of infection, infants received at least 7 to 10 days of parenteral antibiotic therapy. Multiple infections in the same infant were only counted as one case of infection. Cases of necrotizing enterocolitis (Bell's classification) and pneumonia (abnormal chest roentgenogram with worsening clinical signs) were also included. Sepsis/meningitis was documented by the presence of clinical signs of sepsis and by positive cultures for pathogenic organisms in blood or spinal fluid.

Data Analysis

The bivariate analysis was conducted to determine the degree of comparability between the human milk-fed and formula-fed infants and to identify differences between these groups. Significant ($P < .05$) differences were determined through unpaired t tests for continuous variables and χ^2 tests for categorical variables. Associations between potential confounding variables and the presence of infection and sepsis/meningitis were also identified through this bivariate analysis. Unadjusted incidence rates for infection and sepsis/meningitis were then compared between the human milk and formula-fed infants. Logistic regression analysis was used to adjust for potential confounding variables. A confounding variable was defined for analysis as one for which there was at least a 5% difference in the regression coefficient estimates for type of feeding in regression models with and without the potential confounding variable.

RESULTS

Characteristics of the Population

The human milk-fed and exclusively formula-fed infants were similar with respect to major risk factors for infection including gestational age (Table 1). Rates of respiratory distress syndrome, surfactant administration, bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage (grades 3 or 4) and seizures (after 24 hours of life) were also similar between human milk and formula-fed infants. Factors related to nutrition and feeding including duration of intravenous (IV) fluid therapy, total parenteral nutrition, days without enteral feedings (NPO), days to first enteral feeding, and days to full feeding (without IV fluids requirements)—and factors related to growth including days to regain birth weight, discharge weight, and length of stay did not differ significantly between the two feeding

TABLE 1. Characteristics of Study Population*

	Human Milk (n = 123)	Formula (n = 89)	P Value
Infant factors			
Gestational age (wk)	28.2 ± 2.3	27.8 ± 2.4	NS
Birth weight (g)	1061 ± 251	988 ± 242	.03
Apgar score at 1 minute (median)	5.0	5.0	NS
Apgar score at 5 minutes (median)	8.0	8.0	NS
Respiratory distress syndrome	86.0	91.0	NS
Bronchopulmonary dysplasia	52.2	61.7	NS
Patent ductus arteriosus	62.0	58.4	NS
Intraventricular hemorrhage (grades 3 or 4)	13.7	15.1	NS
NPO (days)	11.4 ± 10.5	11.1 ± 12.2	NS
Total parenteral nutrition (d)	18.4 ± 15.6	19.9 ± 21.3	NS
Days to first enteral feeding	9.5 ± 10.1	11.5 ± 15.2	NS
Days to regain birth weight	17.0 ± 7.8	17.1 ± 7.1	NS
Blood transfusions	7.1 ± 10.0	6.5 ± 9.9	NS
Mechanical ventilation (d)	16.9 ± 22.1	15.9 ± 21.2	NS
Supplemental oxygen (d)	34.6 ± 36.8	30.6 ± 29.3	NS
Length of NICU stay (d)	75.8 ± 36.6	70.7 ± 30.6	NS
Maternal factors	%	%	
Married	74.6	43.4	<.0001
Prenatal care	92.2	77.8	.004
Pregnancy-induced hypertension	14.7	18.5	NS
Gestational diabetes	6.6	5.0	NS
Premature rupture of membranes before 37 weeks gestation	45.9	39.1	NS
Prolonged premature rupture of membranes (>24 h)	32.8	28.7	NS
Smoking (any or none)	6.2	31.2	<.0001
Alcohol use (any or none)	1.7	12.1	.003
Illegal drug use (any or none)	1.7	25.9	<.0001

* All continuous data are mean ± SD. Categorical data are expressed as percents.

groups. The only infant variable that differed significantly between the two groups was mean birth weight, which was higher by 73 g in the human milk-fed group (Table 1). A frequency distribution of birth weight by infant feeding type is presented in Fig 1.

Several maternal demographic variables were found to differ between the human milk and the formula-fed groups (Table 1). Mothers who chose to provide human milk were more likely to be nonblack, married, employed, and to have insurance or health maintenance organization coverage for medical care, receive prenatal care, and report avoiding alcohol, smoking, or drug use during pregnancy compared with mothers who provided infant formula exclusively.

Incidence of Infection and Sepsis/Meningitis

The overall incidence of infection for all VLBW infants in the study sample was 36.7%. The unadjusted incidence of infection was significantly higher for formula-fed infants (47.2%) compared with infants who received human milk (29.3%; Table 2). The overall incidence of sepsis/meningitis was 25.0%, and was also significantly higher for formula-fed infants (32.6% vs 19.5%; Table 2). An analysis of the number of cases of infection among formula and human milk-fed infants indicated a higher rate of multiple infections among formula-fed infants (8.0%) compared with human milk-fed infants (3.3%; $P = .009$). There was no dose-response effect between the proportion of human milk provided and the number of infections (Table 3). The specific organisms reported for infants with sepsis/meningitis are described in Table 4; they are generally similar for the two groups. *Staphylococcus epidermidis* was a leading pathogen in this group of infants, a finding noted in other studies.[17]

Logistic Regression

A logistic regression analysis was conducted to adjust for the effects of variables identified through the bivariate analysis to be associated with either type of feeding or the presence of infection or sepsis/meningitis. The variables included in the multiple regression analysis are listed in Table 1. To avoid major loss of data, missing values were imputed for all confounding variables: infants with missing values for categorical data were included in the reference category (the most commonly occurring category), and those with missing values on continuous variables were assigned the group median. Through this imputation process, 5% of cases required imputation, and as a result, all eligible cases were included in the analysis.

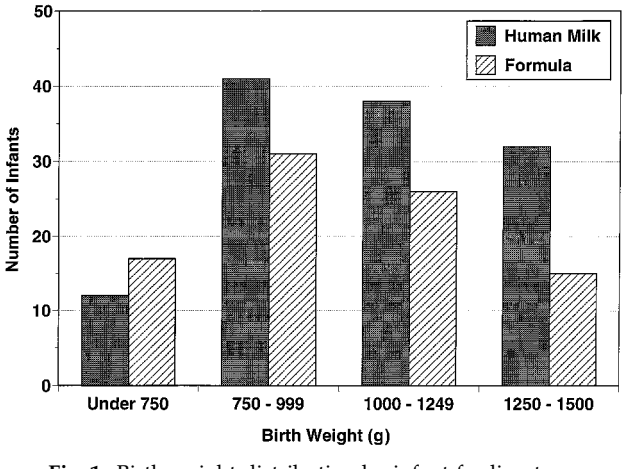

Fig 1. Birth weight distribution by infant feeding type.

TABLE 2. Association Between Type of Feeding and Infection

	Human Milk ($n = 123$)	Exclusive Formula ($n = 89$)	P Value
Total infants with infection	36(29.3%)	42(47.2%)	0.01
Sepsis/meningitis:	24(19.5%)	29(32.6%)	0.04
Blood	22	25	
Cerebrospinal fluid	2	4	
Other sites of infection	12(9.8%)	13(14.4%)	NS
Urine	2	3	
Stool	1	3	
Necrotizing enterocolitis	1	1	
Pneumonia	2	1	
Pleural fluid	1	0	
Nasopharyngeal	0	2	
Intravascular catheter	1	0	
Umbilicus	1	0	
Eye	3	2	
Surgical wound	0	1	

Logistic regression models were constructed by a heuristic stepwise process that started by considering all factors directly associated with either type of feeding or the presence of infection or sepsis/meningitis. In sets of highly correlated variables, the variable most strongly associated with infection was included in the analysis as assessed by the magnitude of the odds ratio. Moreover, variables not significantly predictive of the outcome ($P > .1$) were excluded. The remaining variables were then removed one at a time starting with the least strongly associated with infection. Variables were retained in the reduced logistic regression model when their presence was determined to confound the association between human milk feeding and infection or sepsis/meningitis, as defined by a change of >5% in the regression coefficient for type of feeding when the variable was removed from the full regression model. The results from the full model, which included maternal demographic variables, are not presented here but are available upon request from the authors.

Type of feeding remained an independent predictor of both infection (Table 5) and sepsis meningitis after adjusting for potential confounders. Human milk feeding was associated with a 57% reduction in

TABLE 3. Percentage of Infants With Infection by Human Milk Groups

Human Milk	Infection % (Count)	No. of Infants
100%	33.3 (9)	27
80–99%	35.5 (11)	31
20–79%	25.5 (12)	47
<20%	22.2 (4)	18
Formula	47.2 (42)	89
Totals	36.8 (78)	212

TABLE 4. Sepsis/Meningitis: Type of Organism by Type of Feeding

Site	Human Milk	No.	Exclusive Formula	No.
	(n = 24/123)		(n = 29/89)	
Blood	*S epidermidis*	9	*S epidermidis*	13
	Candida	5	*Candida*	5
	Enterococci	3	*Enterococci*	2
	Enterobacter	2	*Bacillus spp*	1
	E coli	1	*Bacteroids*	1
	S aureus	1	*S aureus*	1
	Klebsiella	1	*Group B strep*	1
			H influenzae	1
Cerebrospinal fluid	*Candida*	1	*Candida*	1
	S epidermidis	1	*S epidermidis*	3

TABLE 5. Reduced Logistic Regression Model for Infection in Relation to Confounding Variables*

Variable	Odds Ratio	95% CI	*P* Value
Gestational age (wk)	0.80	(0.68–0.95)	.009
Apgar score at 5 minutes	0.93	(0.77–1.14)	.494
Days without enteral feedings (NPO)	1.03	(0.99–1.07)	.153
Mechanical ventilator days	1.01	(0.99–1.03)	.184
Human milk-fed	0.43	(0.23–0.81)	.010

* The total for the regression model is 212 cases. The number of cases with imputed values on any single variable is 11 (5.0%).

the odds of infection, in general, controlling for gestational age, mechanical ventilation days, 5-minute Apgar score, and days without enteral feedings and a 53% reduction in the odds of sepsis/meningitis, in specific, controlling for gestational age, mechanical ventilation days, and days without enteral feedings. Reduced logistic regression models with birth weight substituted for gestational age were also estimated. Human milk feeding was independently associated with a reduced odds of infection (odds ratio [OR] = 0.46, 95% confidence interval [CI]: 0.24–0.87; $P = .016$), controlling for birth weight, 5-minute Apgar score, mechanical ventilation days, and days without enteral feedings. For sepsis/meningitis, the OR was 0.50, (95% CI: 0.25–1.02; $P = .056$), controlling for birth weight, mechanical ventilation days, and days without enteral feedings.

When categories of human milk were entered into the logistic regression models, a dose-response effect was not observed. This finding may be attributable to the small numbers of VLBW infants in the categories of high human milk consumption (80% or greater human milk feedings) in this sample.

DISCUSSION OF STUDY FINDINGS AND CONCLUSION

In our study, limited to VLBW infants, the incidence of any infection or sepsis/meningitis was significantly reduced in human milk-fed infants compared with exclusively formula-fed infants. The protective effect of human milk persisted even after adjustment for potential confounding variables. In this sample, being human milk-fed decreased the odds of infection by 57%, controlling for gestational age, mechanical ventilation days, 5-minute Apgar score, and days without enteral feedings; as well as the odds of sepsis/meningitis by 53%, controlling for gestational age, mechanical ventilation days, and days without enteral feedings.

There are a few other studies of VLBW infants and human milk feedings; their findings are similar to ours. A prospective, controlled study of the effect of breast milk on infection among low birth weight infants was conducted in India in 1981.[18] Although the sample size was small, 62 infants, the study design was a randomized block design in which feeding schedules for breast milk or formula were randomly allocated within groups of infants that were determined to be relatively homogeneous with respect to factors predisposing to infection. The infection rate was lower among infants who received expressed breast milk (EBM) and no major infection occurred among infants who received EBM.

More recently, Lucas and Cole,[19] in a large, prospective, controlled study reported a lower incidence of necrotizing enterocolitis among VLBW infants fed human milk compared with formula-fed infants. In our study there was one case of necrotizing enterocolitis in each feeding group. A reduction in the incidence rates of sepsis among human milk-fed infants admitted to an intensive care nursery has also been recently reported.[20] The study sample included 178 infants ranging in gestational age from 25 to 40 weeks. The investigators also compared stool colonization in human milk-fed and formula-fed infants; and reported that the frequency of *Escherichia coli* and *Enterococcus sp* colonization was increased in human milk-fed infants.

The immunologic components of breast milk that include secretory IgA, lysozyme, lactoferrin and interferon, may have protected the hospitalized VLBW infants in our study against the development of infection. One of the three major classes of immunoglobulin occurring in human colostrum and milk, secretory IgA, has been found in significantly higher concentrations in the milk of mothers of preterm infants compared with milk from mothers of term infants.[3] Skin-to-skin contact between mothers and preterm infants in this sample may have promoted maternal production of protective antibodies specific to the nosocomial flora of the NICU.[9] The provision of human milk may enable preterm, VLBW infants to compensate for their inherently immature immune status.

The protective effect of human milk feedings demonstrated in this study is consistent with findings from studies of full-term infants. Previous studies

investigating the relation between human milk feeding and infection, however, have sometimes been criticized for failing to control for confounders.[12,21] Maternal selection of type of feeding may introduce confounding based on inherent differences between mothers who choose to provide human milk and mothers who choose to provide formula to their infants. These maternal differences may contribute to differences in infant risk factors with respect to the development of morbidity, specifically infection in this case. We found, however, that the benefit of human milk feedings persisted even after accounting for such confounders.

Previous studies of the effect of breastfeeding on morbidity among full-term infants have not always accounted for selection bias that may result if infants who are breastfed are inherently healthier than bottle-fed infants.[22] In the current study, the VLBW infants' ability to breastfeed did not reflect better health status as both human milk and infant formula were provided via gavage feeding especially during early enteral feedings. Detection bias has also been cited as a significant methodologic problem in studies of the relation between breastfeeding and infection among full-term infants.[21] Detection bias may occur when breastfed and bottle-fed infants do not have an equal chance of being identified with an illness. Reliance on maternal reports to identify cases of infection may also contribute to detection bias. Detection bias has been avoided in this study by equal surveillance of clinical outcomes between the two feeding groups by the NICU staff and physicians.

In previous studies of full-term infants, ascertainment of morbidity status occurred after discharge from the hospital, increasing the potential for confounding related to the home environment, parental socioeconomic status, parental smoking, and differential access to health care. In the current hospital-based study design, VLBW infants were exposed to a similar NICU environment and had equal access to medical care, removing these potential sources of confounding. Finally, we have attempted in our study to address the methodologic limitations of previous studies including selection bias, detection bias, and lack of control for differences between human milk-fed and formula-fed infants through our study design and statistical adjustment.

The follow-up period of the study was limited to initial NICU hospitalization and did not extend beyond hospital discharge. Accordingly, the observed protective effect of human milk feedings only applies to the limited period after birth when preterm infants are at highest risk for infection. Future research is needed to investigate whether the protective effect of human milk feedings against infection among VLBW infants extends beyond hospital discharge.

Our study was limited by our definition of infant feeding in that it did not include the duration of feeding. Data on the actual adjusted (per kg) volume of human milk provided to VLBW infants would be useful to detect a potential dose-response relationship between the amount of human milk provided and either the incidence or the number of infections per infant. More detailed data regarding the timing of the occurrence of cases of infection after the start of enteral feeding should also be considered. Our study also did not address the frequency of infection after human milk feeding was discontinued and whether infections occurred at an earlier age in formula-fed infants. A multicenter study or an extension of the enrollment period with a larger sample would enable researchers to expand their focus beyond the presence or absence of infection and examine the possible effect of human milk feedings on the severity of infection.

One final limitation of our study relates to the generalizability of the findings. The study was limited to one tertiary center where several resources were available to mothers who provided human milk to their VLBW infants. This limitation, however, also increases the ability to assess the effects of human milk feeding on infection incidence for two reasons: 1) there was a higher prevalence of human milk feeding among mothers of VLBW infants in this sample; and 2) as a result, there were fewer differences between mothers who provided human milk and mothers who formula-fed their VLBW infants than would likely be found in hospitals with less resources.

The findings from this study contribute to the information currently available to neonatologists, nurses, lactation consultants, and other health care providers, as well as to parents, regarding the provision of maternally expressed human milk to VLBW infants and infectious morbidity. These findings demonstrate a protective effect of human milk feedings against infection and sepsis/meningitis for VLBW infants during NICU hospitalization and further underscore the potential immunologic benefit of providing maternally expressed human milk to hospitalized VLBW infants.

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