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Impact of breast milk on respiratory outcomes in infants with bronchopulmonary dysplasia

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Abstract

Background—The objective of our study was to examine whether outpatient respiratory morbidities in infants with bronchopulmonary dysplasia (BPD) are influenced by the human milk consumption.

Methods—Caregivers of subjects recruited from a BPD clinic completed questionnaires regarding breast milk intake and respiratory outcomes.

Results—One-hundred eighty-eight caregivers completed the questionnaire. Of these, 173 (92.0%) reported that the child received some breast milk. Infants who received breast milk for fewer months were more likely to be non-white, and have a lower household income, public insurance, and secondhand smoke exposure. A longer receipt of breast milk was associated with reduced likelihoods of emergency department visits, systemic steroid courses, and cough or chest congestion, and a trend towards a lower risk of re-hospitalizations.

Conclusions—Longer duration of breast milk intake was associated with markers of higher socio-economic status, and reduced likelihood of acute and chronic respiratory morbidities among preterm infants with bronchopulmonary dysplasia.

Keywords

breast milk; bronchopulmonary dysplasia (BPD); epidemiology; neonatal pulmonary medicine

1 | INTRODUCTION

Bronchopulmonary dysplasia (BPD) is an important cause of respiratory illness in infants and children born prematurely that results in significant morbidity and mortality.¹ BPD leads to longer initial hospitalization stays, independent of prematurity. In a population-based observational study, the mean initial length of stay for preterm infants with BPD was 84.1 days, compared to 58.1 days for preterm infants without BPD.² Another study reported that after initial hospital discharge, almost 50% of infants with BPD were re-hospitalized within the first year of life, compared to 23% of infants without BPD.³ Other complications and comorbidities associated with BPD include increased risk for respiratory tract infections,

neurodevelopmental impairment, poor growth, and death.^{4,5} BPD is also associated with an estimated annual economic burden of \$1.7 billion in the USA.⁶ Despite the significant health and economic burdens associated with BPD, our understanding of the factors affecting outcomes in BPD remains incomplete. Our knowledge of the pathophysiology and evolution of BPD is further complicated by changes in the characteristics of the disease process, as much smaller and more extremely premature babies are surviving with the help of ongoing advances in medical care. Many factors contribute to the progression of BPD, including ongoing need for positive pressure ventilation, exposure to high FIO₂, and infection.⁷ It is important to identify modifiable factors that may reduce these complications in the BPD population.

Adequate nutrition has been shown to play a major role in modulating lung development and maturation.^{8–10} In vivo studies in mice have demonstrated that caloric restriction reduces the number of alveoli as well as the alveolar surface area.¹¹ As the majority of alveolar growth occurs during the first 2 years of life,¹² it is important to optimize nutrition during this crucial postnatal period. However, optimization of nutrition is particularly challenging in preterm infants with BPD, due to their increased caloric needs secondary to tachypnea and healing of lung injury. Common problems in preterm infants that may preclude adequate intake of calories include immaturity of bowel function/gastrointestinal motility, necrotizing enterocolitis, and poor suck-and-swallow function.

Many studies have emphasized the advantage of a diet of human milk over a formula diet for both preterm and full-term newborn infants. Human milk contains various immune system factors, including immunoglobulins, antioxidant agents, and anti-inflammatory mediators, that improve gastrointestinal activity and protect both full term and preterm infants from various infections.^{13–17} Human milk has also been shown to improve psychomotor development of full term and preterm infants later in life, including cognitive, social, language, gross motor, and fine motor skills.^{18–23} Specifically among preterm infants, breast milk has also been associated with a decreased incidence of common neonatal complications, including necrotizing enterocolitis,^{24–27} retinopathy of prematurity,^{28,29} and sepsis.³⁰

The mechanisms underlying the effects of human breast milk on the immune system are likely multifactorial. Human breast milk contains varying levels of IgA, immune cells and microbiome and all of these components may help to mitigate the development of asthma, allergies and respiratory and gastrointestinal infections in breast fed infants.³¹ It has also been demonstrated that human milk oligosaccharides 2'-fucosyllactose can attenuate LPS-inflammatory responses in intestinal epithelial cells by attenuating CD14 expression.³² In addition, longer duration of human breast milk intake in infants has been associated with a greater thymic size³³ along with greater numbers of CD4⁺ and CD8⁺ cells at 8–10 months of age.³⁴

The objective of this study was to examine whether or not outpatient respiratory morbidities in premature infants are influenced by the consumption of human milk versus formula. We hypothesized that infants with BPD who receive breast milk for a greater length of time have improved outpatient respiratory outcomes during the first 3 years of life. To test this

hypothesis, we studied 188 premature infants from an outpatient BPD clinic using questionnaire data and chart review.

2 | METHODS

2.1 | Study design

All subjects ($n = 188$) were recruited from the Johns Hopkins Bronchopulmonary Dysplasia Clinic between January 2016 and January 2018. Patients were referred to the clinic by area Neonatal Intensive Care Units (NICUs) across the state of Maryland or pediatricians on the basis of prematurity and having the diagnosis of BPD. Patients were included if they were accompanied by a consenting caregiver and met the inclusion criteria, which were: (i) a diagnosis of BPD by the referring NICU or staffing pediatric pulmonologist; (ii) born at <36 weeks gestation; and (iii) 36 months of age and younger at the time of questionnaire completion to minimize caregiver recall bias. Maternal recall for estimating breastfeeding duration has been shown to be a valid and reliable method.³⁵ This study was approved by the Johns Hopkins University Institutional Review Board (NA_00051884). All caregivers were orally consented per the IRB.

2.2 | Analytic methods

Retrospective chart review was conducted to collect demographic and clinical data. Breast milk intake was assessed by questionnaire through interview. Only one questionnaire was completed if the patient had discontinued breast milk at the time of the initial visit. Otherwise, questionnaires were completed at subsequent clinic visits until the child was weaned off breast milk. The total duration of breast milk intake was also assessed; 23 subjects were still receiving breast milk at the time of analyses. Acute respiratory outcomes (eg, emergency department visits and hospitalizations for respiratory symptoms, steroid courses, antibiotic courses for respiratory illnesses over the preceding 2 months) and chronic respiratory symptoms (eg, cough, congestion, wheezing, coughing with feeds, nighttime cough, use of short-acting beta-agonists at home, tolerance of physical activity over the past week) were collected on the first questionnaire only for all subjects. Our study also examined the role of confounders (eg, gender, attendance in daycare, primary caregiver's working status, gestational age and weight at delivery, socioeconomic status, presence of gastrostomy tube $\pm$ Nissen fundoplication, need for supplemental oxygen) and their potential impact on respiratory outcomes. Demographic and clinical factors were assessed for confounding using Cox univariate regression, specifically testing for any association between a specific demographic or clinical factor (independent variable) and the total duration of breast milk received (dependent variable). To test whether breast milk duration was associated with respiratory outcomes multivariate logistic regression was employed with the respiratory outcome of interest (dependent variable) and duration of breast milk at the time of questionnaire completion (independent variable) with adjustment for confounders. All potential confounders for the multivariate model identified through univariate Cox regression as above were adjusted for; in addition, all multivariate regression models were adjusted for the age at the time of form completion. The adjusted odds ratios and P values represent the increased (or decreased) odds of a specific respiratory outcome for every

additional month of breast milk. STATA IC 14.0 was used for statistical analysis. *P* values <0.05 were considered significant.

3 | RESULTS

3.1 | Demographics

A total of 188 caregivers completed the questionnaire and of these, 173 (92.0%) indicated that the child received some breast milk after birth. Of these 173 infants who received some breast milk, 7 (4.0%) received breast milk exclusively, while the remaining 166 (96.0%) received a combination of breast milk and formula. Of the 173 infants who received some breast milk, 36 (20.8%) were nursed, while the remainder were not. One-hundred thirty-one infants (75.7%) received mothers' milk only, 16 infants (9.2%) received donor milk only, and 26 infants (15.0%) received both mothers' milk and donor milk.

Of the 188 subjects, 55.9% were male and 62.8% were self-identified as non-white. The mean gestational age was 27.4 weeks. At the time of their initial BPD clinic visit 41.5% of subjects were on home supplemental oxygen, and 28.7% of subjects had a gastrostomy tube. The median estimated household income of the study population was \$66 200, and 46.8% of subjects had public insurance. In Table 1, we divided the population into two groups based on duration of breast milk intake. We found that 127 (67.6%) received breast milk for less than 6 months, while 61 (32.4%) received breast milk for 6 months or longer (See Figure 1 for Kaplan-Meier plot of breast milk intake duration). By Cox regression, patients who received breast milk for fewer months were more likely to be non-white ($P < 0.001$), have a lower median household income ($P = 0.001$), have public insurance ($P < 0.001$), and have a smoker living in the home ($P = 0.005$). There was no difference in breast milk duration between subjects with a mother who worked outside the home and subjects with a mother who did not work outside the home. Sex, gestational age, birthweight, and daycare attendance were not associated with breast milk duration. When comparing clinical characteristics, breast milk duration was not associated with home mechanical ventilator use, home supplemental oxygen use, gastrostomy tube placement, Nissen fundoplication, or inhaled corticosteroid use before 2 years of age.

3.2 | Acute respiratory outcomes

Acute respiratory outcomes over 2 months preceding the questionnaire were assessed in all subjects (Table 2). Of all 188 subjects, 14.9% reported having at least one visit to the emergency department, 9.0% were hospitalized, 25.5% had an outpatient sick visit, 17.6% completed at least one course of systemic steroids, and 14.4% had at least one course of antibiotics. After adjusting for socio-economic factors using logistic regression, children who had a longer receipt of breast milk were less likely to have had a visit to the emergency department ($P = 0.045$) and less likely to have been prescribed a systemic steroid course ($P = 0.046$). They also tended to have a lower risk of re-hospitalizations ($P = 0.054$). Breast milk duration was not associated with a risk of an outpatient sick visit or antibiotic use.

3.3 | Chronic respiratory outcomes

Chronic respiratory outcomes over 1 week prior to questionnaire administration were assessed in all subjects (Table 2). Of all 188 subjects, 36.7% had cough or chest congestion, 13.3% had wheezing, 18.1% had cough with feeds, 43.6% had vomiting or reflux symptoms, 12.8% had nighttime cough, 29.3% used a short-acting bronchodilator, and 11.7% had shortness of breath with exertion. After adjusting for socio-economic factors using logistic regression, children who had a longer receipt of breast milk were less likely to have cough or chest congestion ($P = 0.045$). There was no association between any of the other chronic respiratory outcome parameters and breast milk duration.

4 | DISCUSSION

In this study, we found that 92.0% of children with BPD seen in an outpatient clinic received some breast milk after birth. This figure is higher compared to that reported in a Centers for Disease Control and Prevention (CDC) study,³⁶ which found that 81.1% of infants born in the United States received some breast milk, and likely reflects the use of donor milk in our population. In our study, 32.4% of infants were still receiving breast milk at 6 months of age, which is lower than the US average of 51.8%.³⁶ Longer duration of breast milk intake was associated with fewer emergency department visits, fewer systemic steroid courses, and fewer episodes of cough or chest congestion, and trended toward fewer hospitalizations.

Demographic analysis of our BPD population showed that BPD infants who received breast milk for fewer months were from a socioeconomically disadvantaged group and were more likely to have a smoker living in the home, which may further increase their vulnerability to poor outcomes. These results are consistent with previous research which have shown racial and socioeconomic disparities in breastfeeding practices.^{37–39} There was no association between duration of breast milk intake and daycare attendance or having a mother who did not work outside the home.

Children who received breast milk for a longer duration were less likely to have had a visit to the emergency department with a trend towards having fewer hospitalizations. This may have implications for the cost effectiveness associated with breast milk intake in decreasing hospitalization costs after discharge from the NICU. One study conducted in very low birth weight infants in the NICU found a dose-dependent relationship between the amount of breast milk feedings and the reduction in odds of BPD and subsequent reduction in cost of newborn intensive care.⁴⁰ Further studies are needed to determine whether breast milk intake is associated with decreased healthcare costs in infants with BPD after they are discharged from the hospital.

The factors underlying a protective effect against respiratory morbidities in preterm infants with BPD receiving breast milk are unclear; some potential mechanisms may include differences in lung growth/development and/or immune function, given many of the respiratory morbidities we studied can be attributed to respiratory viral infections. It is well established that breast milk contains a variety of immune factors, including humoral factors,⁴¹ but also factors that affect T-cell memory.⁴² Alternatively, breast milk does contain an array of microbiota that may foster development of the infant's immune system, which may

be influenced by levels of oligosaccharides in the milk determined by maternal genetic and environmental factors.^{43,44} Breast milk also contains a variety of other factors that may influence lung growth and development, including macro- and micro-nutrients, hormones, and growth factors, and of note, human milk can vary greatly in the composition of these factors.⁴⁵

There are several limitations associated with this study. First, the duration of breast milk intake does not reflect the percent of breast milk intake. It is also uncertain as to whether or not the benefits obtained from consuming donor breast milk is similar to that of mother's own milk, and we did not assess whether donor milk was received outside the NICU setting. The role of donor milk and its effect on the growth and development of preterm infants are unclear. Previous studies have found that preterm infants fed donor milk either had the same neurodevelopmental outcomes as preterm infants fed formula,⁴⁶ or had worse neurodevelopmental outcomes and poorer weight gain compared to preterm infants fed formula or mother's own milk.⁴⁷ In our population the number of subjects solely on donor milk was too small to conduct a meaningful analysis. Other limitations include potential varying definitions of BPD across NICU sites, potential recall bias and retrospective assessment of outcomes. Our study is not large enough to determine the effects of breast milk in specific sub-populations; retrospectively, the study is powered (70%) to detect a 15% difference in outcomes between 127 subjects receiving breast milk for at least 6 months versus 61 subjects who did not without accounting for confounders ($\alpha = 0.05$).

In conclusion, our study involving infants with bronchopulmonary dysplasia showed that a longer duration of breast milk intake was associated with fewer emergency department visits, fewer systemic steroid courses, and fewer episodes of cough or chest congestion. We would advocate for additional studies to examine the long term respiratory consequences of breast milk over time (eg, development of asthma, resolution of pulmonary hypertension, weaning off of oxygen, etc.) with respect to the percentage of breast milk received and the use of donor milk in infants with BPD. In the meantime, our findings suggest that NICUs and primary care physicians should continue to promote breast milk consumption in preterm infants with BPD.

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Abbreviations

BDP Bronchopulmonary dysplasia

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FIGURE 1. Kaplan-Meier Plot depicting duration of receiving breast milk for 188 preterm infants. Subjects who never received any breast milk were assigned an arbitrary duration of 0.01 months for graphing purposes only

TABLE 1

Demographics

Mean±S.D. [Range]	Entire study population (n = 188)	Received breast milk for <6 months (n = 127) ^a	Received breast milk for >6 months (n = 61)	P-value ^b
Age at questionnaire completion (months)	12.0 ±8.1 [2.5, 35.0]	11.1 ±7.7 [2.5, 35.0]	14.0 ± 8.5 [2.6, 34.6]	0.28
Sex (% male)	55.9	50.4	67.2	0.18
Race/Ethnicity (% non-white)	62.8	73.2	41.0	<0.001
Gestation (weeks)	27.4 ±3.0 [23.0, 36.0]	27.1 ±2.8 [23.0, 36.0]	28.0 ±3.4 [23.6, 36.0]	0.38
Birthweight (grams)	1018 ±485 [380, 3125]	982 ±444 [380, 3125]	1093 ±558 [530, 2869]	0.36
Birthweight (percentile)	40.8 ± 25.3 [1, 94]	43.1 ±25.4 [1, 94]	35.8 ±24.6 [2, 90]	0.51
Median household income (\$ '000s)	66.2 ± 23.7 [15.6, 132.7]	63.7 ±23.3 [15.6, 132.7]	71.5 ±23.9 [21.9, 132.7]	0.001
Public insurance (% yes)	46.8	56.7	26.2	<0.001
Attends daycare (% yes)	12.2	11.0	14.8	0.49
Mother is primary caregiver and does not work outside home (% yes)	50.5	53.5	44.3	0.28
Smoker lives in the home (% yes)	23.4	29.1	11.5	0.005
Home supplemental oxygen (% yes)	41.5	39.4	45.9	0.92
Home ventilator (% yes)	5.9	5.5	6.7	0.66
Gastrostomy tube (% yes)	28.7	22.1	42.6	0.39
Nissen fundoplication (% yes)	16.5	13.4	23.0	0.93
Inhaled steroid use <2yo (% yes)	75.0	74.0	77.1	0.23

^aFor this table 8 subjects under 6 months of age and still receiving breast milk were categorized as having received less than 6 months of breast milk.

^bThe reported P values for the association between a specific demographic factor (independent variable) and the duration of breast milk received (dependent variable) were derived using univariate Cox regression.

TABLE 2

Breast milk duration and respiratory outcomes

(% Reporting Yes)	Entire study population (n = 188)	Received breast milk for <6 months (n = 127) ^a	Received breast milk for >6 months (n = 61)	Adjusted odds ratio [95% C.I.] ^b	Adjusted OR P-value
Acute respiratory outcomes over the past 2 months					
Emergency department visit	14.9	20.5	3.3	0.84 [0.70, 1.00]	0.045
Hospital admission	9.0	12.6	1.6	0.79 [0.62, 1.00]	0.054
Outpatient sick visit	25.5	25.2	26.2	0.94 [0.86, 1.03]	0.20
Systemic steroid use	17.6	19.7	13.1	0.88 [0.77, 1.00]	0.046
Antibiotic	14.4	15.0	13.1	0.90 [0.79, 1.02]	0.11
Chronic respiratory outcomes over the past week					
Cough or chest congestion	36.7	41.7	26.2	0.91 [0.82, 1.00]	0.045
Wheeze	13.3	15.0	9.8	0.91 [0.78, 1.05]	0.20
Cough with feeds	18.1	16.5	21.3	1.05 [0.95, 1.15]	0.37
Vomiting or reflux symptoms	43.6	46.5	37.7	1.01 [0.92, 1.10]	0.90
Nighttime cough	12.8	14.2	9.8	0.93 [0.82, 1.05]	0.26
Short-acting bronchodilator use	29.3	27.6	32.8	0.98 [0.90, 1.06]	0.58
SOB with exertion	11.7	14.2	6.6	0.89 [0.76, 1.05]	0.17

^aFor this table 8 subjects under 6 months of age and still receiving breast milk were categorized as having received less than 6 months of breast milk.

^bThe adjusted odd ratios and P-values represent the increased (or decreased) odds of a specific outcome (dependent variable) for every additional month of breast milk (independent variable) derived using multivariable logistic regression; regressions were adjusted for age at the time of outcome reporting, race/ethnicity, median household income, insurance status, and a smoker living in the home.