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Influence of own mother's milk on bronchopulmonary dysplasia and costs

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Abstract

Background—Human milk from the infant's mother (own mother's milk; OMM) feedings reduces the risk of several morbidities in very low birthweight (VLBW) infants, but limited data exist regarding its impact on bronchopulmonary dysplasia (BPD).

Objective—To prospectively study the impact of OMM received in the neonatal intensive care unit (NICU) on the risk of BPD and associated costs.

Design/methods—A 5-year prospective cohort study of the impact of OMM dose on growth, morbidity and NICU costs in VLBW infants. OMM dose was the proportion of enteral intake that consisted of OMM from birth to 36 weeks postmenstrual age (PMA) or discharge, whichever occurred first. BPD was defined as the receipt of oxygen and/or positive pressure ventilation at 36 weeks PMA. NICU costs included hospital and physician costs.

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Results—The cohort consisted of 254 VLBW infants with mean birth weight 1027 ± 257 g and gestational age 27.8 ± 2.5 weeks. Multivariable logistic regression demonstrated a 9.5% reduction in the odds of BPD for every 10% increase in OMM dose (OR 0.905 (0.824 to 0.995)). After controlling for demographic and clinical factors, BPD was associated with an increase of US \$41 929 in NICU costs.

Conclusions—Increased dose of OMM feedings from birth to 36 weeks PMA was associated with a reduction in the odds of BPD in VLBW infants. Thus, high-dose OMM feeding may be an inexpensive, effective strategy to help reduce the risk of this costly multifactorial morbidity.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a common and costly morbidity in very low birthweight (VLBW; birth weight <1500 g) infants.¹² Defined as the need for oxygen at 36 weeks postmenstrual age (PMA), BPD is categorised as mild, moderate or severe, based on the level of respiratory support required.³ BPD prolongs the neonatal intensive care unit (NICU) hospitalisation⁴ and increases the risk of long-term complications, rehospitalisations and neurocognitive impairment.⁵⁶ Furthermore, BPD is the single most costly NICU morbidity with an estimated annual economic burden of US\$1.7 billion in USA.⁴ Reducing the risk of BPD is a clinical and economic priority for the care of VLBW infants.

The pathogenesis of BPD is multifactorial and includes exposure of the immature lung to oxidative stress, inflammation and inadequate nutrition.⁷⁸ Common strategies to reduce the risk and/or incidence and severity of BPD include volume-targeted ventilation, vitamin A, caffeine and post-natal steroids.⁷⁹ Own mother's milk (OMM) has potent protective mechanisms that target oxidative stress,¹⁰ inflammation^{11–13} and inadequate nutrition.^{14–16} However, investigations of the impact of human milk (OMM±donor milk supplementation) on BPD are limited.^{17–19} The purpose of this study was to investigate the dose-dependent impact of OMM feedings received from birth to 36 weeks PMA on BPD and associated NICU healthcare costs in a contemporary cohort of VLBW infants.

METHODS

This was a prospective cohort study of VLBW infants admitted to the Rush University Medical Center (RUMC) NICU between 2008 and 2012. Inclusion criteria for the study were birth weight (BW) <1500 g, gestational age (GA) <35 weeks, enteral feedings initiated by day of life (DOL) 14, absence of major congenital anomalies or chromosomal disorders and negative maternal drug screen.²⁰²¹ Infants were excluded if they died prior to NICU discharge or were transferred to another hospital, resulting in incomplete NICU hospitalisation cost data. The study was approved by the RUMC Institutional Review Board, and signed informed consent was obtained from the parent/legal guardian.

Standard NICU nutritional practices were followed and uninfluenced by the study. All VLBW infants received parenteral nutrition (PN) upon admission. Freshly expressed colostrum was administered oropharyngeally once available.²² Feedings were initiated at 20 mL/kg/day, and then advanced daily by 20 mL/kg as tolerated, with PN decreased concomitantly. Initial feedings consisted of unfortified OMM or 20-calorie preterm formula

if OMM was unavailable; donor milk feedings were only available through a separate study, and those subjects were excluded from this analysis. OMM was fortified with powdered bovine human milk fortifier when feeding volume reached 100 mL/kg/day; formula was switched to 24-calorie formula at 140 mL/kg/day. Freshly expressed OMM was preferentially fed instead of refrigerated or frozen OMM. In December 2009, a BW-based feeding protocol was instituted for all VLBW infants.²³

Maternal and infant demographic and clinical data were collected prospectively. Chorioamnionitis was clinically diagnosed by the attending perinatologist. Infant nutritional data were collected daily as intake (mL) of intravenous fluids (including PN and clear fluids), OMM and formula. BPD was defined as oxygen requirement >21% or continuous positive airway pressure or mechanical ventilation at 36 weeks PMA.³ Other neonatal morbidities included late-onset sepsis (sepsis, a positive blood culture after DOL 3 with antibiotic treatment $\geq$ 5 days), necrotising enterocolitis (NEC, stage $\geq$ 2)²⁴ and patent ductus arteriosus (PDA, echocardiographic documentation with medical and/or surgical treatment). Daily level of ventilator support and typically prescribed medications were collected prospectively. Data abstracted retrospectively from the medical record for each infant included: mean airway pressure and FiO₂ to quantify the degree of respiratory failure with the respiratory severity score (RSS=mean airway pressure $\times$ FiO₂),²⁵ the number of surfactant doses received and the highest level of delivery room respiratory support. The dose of OMM, as a proportion or percentage of total enteral feedings (HM-PCT), was calculated from birth until 36 weeks PMA or discharge, whichever came first, in order to avoid inclusion of feeding data after the diagnosis of BPD. Due to the partial retrospective data collection required for this analysis, infants were included in this analysis if they were born during a 3-year period (March 2009–March 2012) when data were available through an electronic medical record (figure 1).

Direct and total hospital costs and physician costs were collected from RUMC's clinical and financial data repositories that provided the direct cost of care for each chargeable item (eg, room and board, clinical and non-clinical personnel time) used during each infant's hospitalisation. The direct costs for each chargeable item were summed to calculate the hospital direct cost for each NICU hospitalisation. *Total hospital costs* included direct and indirect (overhead) costs, and *physician costs* were estimated using physician payments. Then, total hospital costs and physician costs were summed to calculate the *total NICU costs*. All costs were adjusted to 2014 US\$ using the Bureau of Labor Statistics Consumer Price Index for medical care.²⁶

Data analysis

Data were analysed using χ^2 or Fisher's exact test as appropriate, the Mann-Whitney U test and t-test. A two-step logistic regression analysis was conducted to identify variables associated with BPD. In the first step, BPD was regressed on potential covariates demonstrated in the literature to be associated with BPD^{7,27} or that were associated with BPD in the current sample. Backward elimination was used to select the final covariates that remained associated with BPD at $p < 0.10$. Then, these final covariates were used to create the propensity score for BPD which was used in the economic analysis. In the second step, HM-

PCT was added to the model which included the final covariates to determine the effect of OMM on BPD.

A generalised linear regression model with a log link function and gamma distribution was fit to test the association of total NICU costs with BPD, HM-PCT, race/ethnicity, gender, GA, small for GA (SGA) at birth²⁸ and the propensity score for BPD to control for unobserved heterogeneity related to the risk factors for BPD. The appropriate mean–variance relationship was selected using a modified Park test, a statistical test for selecting the appropriate distribution when the distribution of the outcome is skewed.²⁹ We computed the marginal economic effect of BPD by computing $[\exp(\beta)-1]$ multiplied by the mean predicted NICU costs for infants without BPD.³⁰ A similar approach was used to test the association of BPD and HM-PCT with total NICU cost per day. Analyses were performed using SPSS V.19.0 (Chicago, Illinois, USA) and SAS V.9.3 (Cary, North Carolina, USA). Type 1 error was set at $p < 0.05$, unless stated otherwise.

RESULTS

OMM and BPD

During 2008–2012, 430 VLBW infants were enrolled into the original prospective cohort, of which 254 infants were included in this analysis (figure 1). Demographic, maternal and neonatal characteristics and outcomes are detailed in table 1.

Infants who developed BPD were significantly different from infants who did not develop BPD with lower BW and GA, higher rate of intubation and surfactant administration, greater intravenous fluid administration, later initiation of enteral nutrition and lower OMM proportion. BPD infants were also more likely to have other neonatal morbidities, longer NICU hospitalisation and greater weight, but no difference in length or head circumference at 36 weeks PMA.

In step 1 of the multivariate logistic regression, 17 variables previously demonstrated to be associated with BPD or identified in the bivariate analyses (BW, GA, SGA at birth, gender, race/ethnicity, chorioamnionitis, antenatal steroids, 5-min Apgar, maximal delivery room respiratory support, surfactant, caffeine, RSS DOL 14, sepsis, NEC, PDA, DOL first feeding and DOL 1–7 intravenous fluids) were entered into the logistic regression model. Five variables (GA, gender, NEC, PDA and SGA) were retained as significant ($p < 0.10$) factors associated with BPD (table 2) and comprised the propensity score for BPD that was used in the cost analysis. In step 2, HM-PCT was added to these five retained variables, and HM-PCT demonstrated an independent effect with reduction in the odds of BPD (adjusted OR (aOR) 0.905, $p = 0.04$).

Cost analysis

Median total cost of the NICU hospitalisation was US\$269 004 (IQR US\$204 606–US\$331 552) for BPD infants and US \$117 078 (IQR US\$90 496–US\$162 017) for infants without BPD ($p < 0.001$). Median total NICU cost per day was US\$2445 (IQR US\$2243–US\$2623) for BPD infants vs US\$2195 (IQR US\$2064–US\$2352) for infants without BPD ($p < 0.001$) (table 3).

Hospital costs represented 88% of total NICU costs for BPD infants and 90% of total NICU costs for infants without BPD. The largest category of hospital direct costs for BPD infants was room and board, followed by respiratory care and pharmacy. BPD infants had significantly higher direct hospital costs in all but one cost category and significantly higher physician costs compared with infants without BPD.

After adjusting for the propensity score for BPD, race/ethnicity, gender, GA and SGA, BPD was associated with US\$41 929 additional costs for the NICU hospitalisation ($p<0.001$). The propensity score for BPD was not associated with NICU costs, suggesting that the model had no unobserved heterogeneity related to the risk factors for BPD. Additionally, HM-PCT was not associated with total NICU costs. In the analysis for total cost per day, BPD was not associated with an increase in cost per day, but HM-PCT was associated with a small but significant increase in cost per day of US\$11 per 10% increment ($p=0.009$).

DISCUSSION

To our knowledge, this is the first prospective study to examine the dose-dependent effect of OMM received during the NICU hospitalisation on the risk of BPD and its associated NICU costs in VLBW infants. Our findings reveal a 9.5% reduction in the odds of BPD for each 10% increase in enteral feedings consisting of OMM received from birth to 36 weeks PMA. This is significant, since this would yield a 63% reduction in odds of BPD with 100% OMM compared with no OMM. Until recently, there were limited data suggesting a beneficial impact of human milk feedings on BPD. In a randomised trial of premature infants fed OMM supplemented with donor milk or formula, Schanler *et al*¹⁷ demonstrated a reduced incidence of BPD in the donor milk group; however, the study was not designed to evaluate BPD as a primary outcome or examine costs. A recent large prospective cohort study of German VLBW infants demonstrated that infants who received exclusive formula feedings had a 2.6-fold increase in the odds of developing BPD compared with those who received exclusive human milk feedings (OMM±donor milk); however, the investigators were unable to calculate a dose effect.¹⁸ Another recent retrospective study demonstrated an exclusive human milk diet (OMM±donor milk fortified with human milk-based fortifier) reduced the incidence of BPD compared with a diet of human milk supplemented with bovine products.¹⁹

Multiple direct and indirect mechanisms support a role for OMM as part of a targeted bundle of NICU practices to reduce the risk of BPD in VLBW infants. Their immature lungs are exposed to noxious stimuli including oxidative stress, inflammation and inadequate nutrition, which result in lower lung weight, reduced number of alveoli and reduced collagen deposition.³¹ High-dose OMM feedings, especially when fed fresh rather than frozen, may provide nutritional and bioactive components that mitigate oxidative stress,¹⁰ inflammation^{11–13} and nutritional inadequacies.^{14–16,32,33} Furthermore, these protective OMM components are highly concentrated in colostrum and transitional milk, and are optimally preserved in fresh versus frozen milk.³⁴

OMM may also impact the risk of BPD indirectly by reducing the incidence of NEC and sepsis, morbidities which have been linked to subsequent development of BPD.^{35,36} The

protective impact of OMM on NEC and sepsis and associated costs is well established.¹⁷²⁰²¹³⁷ However, we found no association between sepsis and BPD, and the final regression model demonstrated an independent dose-dependent effect of OMM on BPD after adjusting for NEC.

The prevalence of BPD was 30% in our cohort, similar to the Vermont Oxford Network rate of 26% during 2008–2009¹ and the California Perinatal Quality Care Collaborative rate of 33% for 2007–2011.² Unexpectedly, BPD infants weighed more than infants without BPD at 36 weeks PMA in contrast to previous reports.³⁸ Since no significant differences in length or head circumference at 36 weeks PMA were detected, the greater weight in BPD infants may reflect fluid retention or greater fat mass rather than lean mass gains.

In our analysis of infants who survived to discharge, we found that BPD infants incurred US \$41 929 in additional costs compared with infants without BPD, but that the impact of OMM dose on NICU costs was indirect, meaning that high OMM dose reduced the risk of BPD, which then translated into significant cost savings. The impact of BPD on total NICU costs was larger than that in our prior work (US\$31 565 in 2010 US dollars vs US\$41 929 in 2014 US dollars).²¹ These differences may be due to our current analysis capturing both the direct cost of BPD and indirect costs of BPD that are associated with other morbidities such as NEC and sepsis. Future work will evaluate the impact of OMM on the overall costs of combinations of these morbidities. Given the link between BPD and subsequent long-term morbidities in this population, it is likely that the NICU costs represent only a portion of the total societal costs incurred as a consequence of BPD. In contrast, the acquisition of OMM by the NICU is less expensive than either formula or donor human milk, provided that the mother produces >100 mL of OMM each day.³⁹

We found no association between BPD and total NICU cost per day, suggesting that BPD principally increased costs by increasing the length of NICU hospitalisation rather than significantly increasing daily resource use. However, since the NICU hospitalisation was nearly twice as long for infants with than those without BPD, the BPD costs per day may have been minimised even with greater resource use. Additionally, we found an unexplained small but significant association between HM-PCT and total NICU cost per day, although there was no significant association with total NICU cost over the hospitalisation.

Our analysis excluded four infants who were initially enrolled in the study but died prior to NICU discharge. We hypothesise that infants who die during the NICU stay have lower overall healthcare costs due to shorter NICU hospitalisation,⁴⁰ but higher cost per day due to additional services and treatments prior to death. Future analyses of morbidities and healthcare costs should address the impact of death.

Limitations of our study include the baseline differences in subjects who did and did not develop BPD, as reported previously.²⁵ Our statistical analyses adjusted for these differences; however, it is possible that all differences between these groups could not be controlled for statistically. Additionally, our data originate from a single institution which may limit generalisability, although the collection of OMM dose and hospital cost data,

instead of hospital charges, enabled more detailed analyses than that possible in larger multicentre studies.

In conclusion, a 9.5% reduction in the odds of BPD was noted for each 10% increase in OMM feedings from birth to 36 weeks PMA. Infants without BPD had reduced associated costs principally due to a shorter duration of hospitalisation. Thus, high-dose OMM feeding may be an inexpensive, effective strategy to include in a targeted bundle of NICU care to reduce the risk of BPD.

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What is already known on this topic?

- ▶ Bronchopulmonary dysplasia (BPD) is a multifactorial, serious and costly morbidity in very low birthweight infants with long-term consequences.
- ▶ Adequate nutrition is an important aspect of prevention and/or therapy for BPD; however, human milk's impact on BPD has been minimally studied to date.

What this study adds?

- ▶ Human milk from the infant's own mother is associated with a dose-dependent reduction in the odds of developing bronchopulmonary dysplasia (BPD).
- ▶ Reduction of BPD translates into a substantial reduction in the cost of newborn intensive care.

Figure 1.

Flow diagram of subject recruitment. DOL, day of life; EMR, electronic medical record; NICU, neonatal intensive care unit; SGA, small for gestational age; VLBW, very low birth weight.

Table 1

Subject characteristics

Variable	BPD N=77	Without BPD N=177	p Value
Birth weight (g)	831±194	1112±233	<0.001
Birth length (cm)	33.2±2.8	36.8±2.9	<0.001
Birth head circumference (cm)	23.4±1.8	25.9±2.1	<0.001
Gestational age (weeks)	26.0±1.7	28.7±2.3	<0.001
Male	52 (68)	81 (46)	0.001
Multiple gestation	11 (14)	22 (12)	0.686
Any antenatal steroids	70 (91)	159 (90)	0.791
Complete antenatal steroid course	48 (62)	119 (67)	0.378
Vaginal delivery	29 (38)	61 (35)	0.624
Inborn	65 (84)	158 (89)	0.278
Maternal race/ethnicity			0.075
Black	39 (51)	93 (53)	
White/other	24 (31)	32 (18)	
Hispanic	14 (18)	52 (29)	
Maternal chorioamnionitis	12 (16)	20 (11)	0.344
Small for gestational age at birth	18 (23)	37 (21)	0.660
Apgar 1 min	6 (3.75–7)	7 (4–8)	0.004
Apgar 5 min	7 (7–8)	8 (7–9)	<0.001
Maximal delivery room support *			<0.001
Room air	0 (0)	7 (4)	
Oxygen	0 (0)	10 (6)	
Mask CPAP	6 (9)	52 (30)	
Mask PPV	12 (17)	27 (16)	
Intubation and PPV	52 (74)	77 (45)	
Surfactant	69 (90)	108 (61)	<0.001
Surfactant—number of doses			<0.001
0 dose	7 (9)	69 (39)	
1 dose	38 (49)	92 (52)	
2 doses	19 (25)	14 (8)	
3 doses	13 (17)	2 (1)	
Caffeine	77 (100)	155 (88)	<0.001
RSS DOL 14	3.4 (2.1–4.5)	0 (0–1.6)	<0.001
Ventilation duration up to 36 weeks PMA (days) †	22 (9–35)	1 (0–4)	<0.001
DOL 1–7 intravenous fluid mL/kg/day	126±19	114±19	<0.001
DOL first feeding	5 (3–8)	4 (3–5)	<0.001
DOL full feeding	29 (22–36.5)	16 (13–21.75)	<0.001
HM-PCT at 36 weeks PMA (%) †	45±39	57±41	0.027
Early onset sepsis	49 (64)	69 (39)	<0.001

Variable	BPD N=77	Without BPD N=177	p Value
Late onset sepsis	9 (12)	22 (12)	0.868
PDA	59 (77)	60 (34)	<0.001
NEC	13 (17)	10 (6)	0.004
IVH grades 3 or 4	2 (3)	9 (5)	0.371
Weight at 36 weeks PMA (g) [†]	2183±455	2033±358	0.011
Length at 36 weeks PMA (cm) [†]	42.5±2.9	42.9±2.4	0.318
Head circumference at 36 weeks PMA (cm) [†]	30.7±1.9	30.9±1.6	0.229
NICU length of stay (days)	110±28	59±25	<0.001
Discharge PMA (weeks)	42.0±3.8	37.7±2.2	<0.001

Data are reported as n (%), median (IQR) or mean±SD as appropriate.

* Available for 244 infants.

[†] At discharge, if discharged before 36 weeks PMA.

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; DOL, day of life; HM-PCT, human milk dose as a proportion of enteral feedings; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PMA, postmenstrual age; PPV, positive pressure ventilation; RSS respiratory severity score.

Table 2

Relationship between OMM and BPD: binary logistic regression models

Variable	Step 1		Step 2	
	Adjusted OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
GA per week	0.429 (0.329 to 0.560)	<0.01	0.424 (0.327 to 0.549)	<0.01
Female	0.474 (0.215 to 1.047)	0.07	0.430 (0.198 to 0.936)	0.03
NEC	6.317 (1.852 to 21.550)	<0.01	6.740 (2.083 to 21.806)	<0.01
PDA	3.296 (1.411 to 7.699)	<0.01	3.061 (1.338 to 7.002)	<0.01
SGA	15.115 (4.407 to 51.836)	<0.01	13.115 (3.974 to 43.285)	<0.01
HM-PCT per 10% increase	–	–	0.905 (0.824 to 0.995)	0.04
Model ROC area under the curve	0.892		0.899	
Pseudo-R ² (Nagelkerke)	0.533		0.550	

Step 1: BW, GA, SGA at birth, gender, race/ethnicity, chorioamnionitis, antenatal steroids, 5-min Apgar score, maximal support received in delivery room, surfactant, caffeine, respiratory severity score DOL (day of life) 14, sepsis, NEC, PDA, DOL first feeding and DOL 1–7 intravenous fluids entered in the logistic regression model to identify and retain the significant variables with p values <0.1.

Step 2: The five significant variables (GA, gender, NEC, PDA and SGA) and HM-PCT entered in the logistic regression model.

BPD, bronchopulmonary dysplasia; DOL, day of life; GA, gestational age; HM-PCT, human milk dose as a proportion of enteral feedings; NEC, necrotising enterocolitis; OMM, own mother's milk; PDA, patent ductus arteriosus; ROC, receiver operating characteristic; SGA, small for GA at birth.

Table 3

Comparison of direct cost categories by presence of bronchopulmonary dysplasia, in 2014 US\$, N=254

Variable	With BPD N=77 Median (IQR)	Without BPD N=177 Median (IQR)	p Value
Total NICU costs, hospital and physician	269 004 (204 606–331 552)	117 078 (90 496–162 017)	<0.001
Hospital costs (direct+indirect)	230 153 (185 540–290 469)	107 749 (80 083–144 645)	<0.001
Hospital direct costs	144 588 (117 030–185 695)	68 823 (51 109–92 009)	<0.001
NICU room and board	115 580 (92 976–141 959)	59 620 (43 416–78 231)	<0.001
Respiratory care	11 662 (7935–17 214)	1460 (365–4043)	<0.001
Pharmacy	7983 (6225–12 059)	3731 (2294–4983)	<0.001
Laboratory and pathology	5349 (4247–7451)	2200 (1406–2954)	<0.001
Diagnostic testing	2284 (1730–3373)	819 (521–1360)	<0.001
Surgery	912 (0–1843)	0 (0–902)	<0.001
Cardiology and echocardiography	1005 (493–1645)	238 (0–627)	<0.001
Therapy services (speech, physical, occupational)	572 (379–909)	311 (246–419)	<0.001
Psychology	230 (148–280)	230 (148–280)	0.312
Hospital indirect costs	85 564 (65 651–106 107)	40 096 (30 020–52 423)	<0.001
Physician costs	26 046 (19 067–40 187)	10 018 (6228–15 592)	<0.001
Neonatology	21 323 (16 208–34 037)	8466 (5400–12 797)	<0.001
Cardiology	331 (208–518)	80 (0–182)	<0.001
Paediatric surgery	312 (0–936)	0 (0–670)	<0.001
Paediatric subspecialties	155 (0–291)	0 (0–0)	<0.001
Other surgeries	426 (229–1250)	142 (101–324)	<0.001
Total NICU costs, hospital and physician, per day	2445 (2243–2623)	2195 (2064–2352)	<0.001
Hospital cost per day	2179 (2017–2282)	1994 (1877–2102)	<0.001
Physician cost per day	217 (185–363)	173 (135–246)	<0.001

Analyses performed using Mann-Whitney U tests.

BPD, bronchopulmonary dysplasia; IQR, IQR, 25 percentile–75 percentile; NICU, neonatal intensive care unit.