The Economic Impact of Donor Milk in the Neonatal Intensive Care Unit

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Objective To assess the cost-effectiveness of mother's own milk supplemented with donor milk vs mother's own milk supplemented with formula for infants of very low birth weight in the neonatal intensive care unit (NICU).

Study design A retrospective analysis of 319 infants with very low birth weight born before (January 2011-December 2012, mother's own milk + formula, n = 150) and after (April 2013-March 2015, mother's own milk + donor milk, n = 169) a donor milk program was implemented in the NICU. Data were retrieved from a prospectively collected research database, the hospital's electronic medical record, and the hospital's cost accounting system. Costs included feedings and other NICU costs incurred by the hospital. A generalized linear regression model was constructed to evaluate the impact of feeding era on NICU total costs, controlling for neonatal and sociodemographic risk factors and morbidities. An incremental cost-effectiveness ratio was calculated for each morbidity that differed significantly between feeding eras.

Results Infants receiving mother's own milk + donor milk had a lower incidence of necrotizing enterocolitis (NEC) than infants receiving mother's own milk + formula (1.8% vs 6.0%, P = .048). Total (hospital + feeding) median costs (2016 USD) were $169 555 for mother's own milk + donor milk and $185 740 for mother's own milk + formula (P = .331), with median feeding costs of $1317 and $936, respectively ($P$ < .001). Mother's own milk + donor milk was associated with $15 555 lower costs per infant (P = .045) and saved $1812 per percentage point decrease in NEC incidence.

Conclusions The additional cost of a donor milk program was small compared with the cost of a NICU hospitalization. After its introduction, the NEC incidence was significantly lower with small cost savings per case. We speculate that NICUs with greater NEC rates may have greater cost savings. *(J Pediatr 2020;224:57-65)*.

Infants with very low birth weight (VLBW, <1500 g) are at increased risk of severe morbidities in the neonatal period. Necrotizing enterocolitis (NEC), one of the most devastating conditions, which affects up to 7% of infants with VLBW, is associated with prolonged hospitalizations, poor neurodevelopmental outcomes, and lifelong health problems.[1-4] Although the pathophysiology of NEC remains poorly understood, the use of mother's own milk is recognized as a standard strategy to reduce the risk of NEC.[5] Mother's own milk feeding, compared with formula feeding, is associated with reduced rates of NEC,[6-9] late-onset sepsis,[6,7,10-12] bronchopulmonary dysplasia (BPD),[13,14] and retinopathy of prematurity.[15] Not all infants with VLBW are able to receive exclusive mother's own milk, and the use of pasteurized donor human milk is recommended as an alternative to formula when mother's own milk pumped volume is insufficient.[16,17]

Although a systematic review of 11 trials demonstrated that donor milk reduced the risk of NEC in infants born preterm,[18] the American Academy of Pediatrics recognizes that the cost of donor milk is a major limitation to its universal availability for high-risk infants.[17] It has been argued that the greater cost of providing pasteurized donor milk compared with formula would be offset by the cost savings incurred by improved outcomes and reduced rates of NEC. We have previously shown that a single case of NEC increased hospital costs by an estimated $30 681.[8] Studies have modeled the cost-effectiveness of donor milk based on costs of obtaining and providing donor milk with the estimated reductions in NEC and length of hospitalization.[19-23] However, there is a paucity of data to inform how donor milk directly affects hospital costs in a tertiary neonatal intensive care unit (NICU) in the US.[24] The study objective was to determine the cost-effectiveness of supplementing mother's own milk with donor milk rather than with formula for infants with VLBW in a single tertiary NICU.

BPD	Bronchopulmonary dysplasia
DOL	Days of life
ICER	Incremental cost-effectiveness ratio
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
USD	US dollars
VLBW	Very low birth weight

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Methods

This study included a total of 319 infants with VLBW, 150 of whom were enrolled in the prospective LOVE MOM (**L**ongitudinal **O**utcomes in **V**ery Low Birthweight Infants **E**xposed to **M**other's **O**wn **M**ilk) cohort[25] born before the donor milk program was implemented in the study NICU (January 2011-December 2012, mother's own milk + formula era) and 169 who were admitted after the donor milk program was implemented (April 2013-March 2015, mother's own milk + donor milk era). The sample excluded infants with early deaths (death <7 days of life [DOL]) or gestational age ≥32 weeks. The institutional review board approved this study and the original LOVE MOM cohort study.

Nutritional Practices

Feeding practices were per the established NICU nutritional guidelines in place during each era. In the mother's own milk + formula era, infants were maintained nil per os (NPO, nothing by mouth) until mother's own milk was available, which may have delayed feeding initiation up to 3-5 days. If mother's own milk was unavailable, preterm formula was used for feedings. Mother's own milk and formula caloric density were increased once feedings reached 140 ml/kg/d with the addition of bovine human milk fortifier (Generation 1 Similac, Abbott Laboratories, Columbus, OH) to mother's own milk or by changing to a 24 kcal/oz preterm formula. The donor milk program was implemented in April 2013 for infants with birth weight <1500 g or gestational age <32 weeks. Pasteurized donor milk (from The Milk Bank, Indianapolis, Indiana) was used to supplement insufficient mother's own milk through 34 0/7 weeks of corrected gestational age, at which time donor milk was transitioned to preterm formula over a 1-week interval. In the mother's own milk + donor milk era, feedings also were initiated preferentially with mother's own milk, but if mother's own milk was not available by day 2 or 3 postbirth, then donor milk consent was obtained, and feedings were started with donor milk. Both mother's own milk and donor milk were fortified once feedings reached 140 mL/kg/d with the addition of bovine human milk fortifier, using powdered formulation in the mother's own milk + formula era and liquid non-acidified formulation during the majority of the mother's own milk + donor milk era (starting in July 2013). Infants receiving donor milk also received an additional modular protein (Similac; 0.5-1 g/kg/d). All infants in both eras received parenteral nutrition starting on the day of birth. There were no other changes in NICU lactation or nutritional practices during the study periods.

Feeding Outcomes and Feeding Characteristics

Feeding outcomes included the proportion of enteral feedings at NICU discharge that were human milk (mother's own milk or donor milk) vs formula, any formula feedings during the NICU stay, initiation of mother's own milk feedings during the NICU stay, exclusive mother's own milk feedings through the NICU stay, and any mother's own milk feedings at NICU discharge. Other feeding outcomes for the first 14 DOL included the proportion of enteral feedings that were mother's own milk, donor milk and formula, any mother's own milk feedings during the first 14 DOL, and any formula feedings during the first 14 DOL. Feeding characteristics included DOL of feeding initiation, DOL at full enteral feedings defined as 140 mL/kg/d, days to full enteral feeding (DOL of full enteral feeding-DOL of feeding initiation), and number of days parenteral nutrition was received.

Neonatal Morbidities and Death during the NICU Hospitalization

Neonatal morbidities included NEC (modified Bell criteria stage ≥2)[26]; culture-proven late-onset sepsis; BPD, defined as the receipt of oxygen or positive pressure ventilation at 36 weeks of postmenstrual age[27]; severe brain injury, defined as grades 3-4 intraventricular hemorrhage, periventricular leukomalacia, or post hemorrhagic hydrocephalus[28]; and retinopathy of prematurity stage ≥3. We evaluated the presence or absence of each morbidity and created a composite variable that indicated whether the infant had any of the 5 morbidities or died during the NICU stay.

NICU Costs

NICU total cost represented the cost incurred by the hospital and included the cost of all hospital and feeding (ie, mother's own milk, donor milk, formula) resources. Except for feeding-related costs, each resource used during the NICU hospitalization and its associated per-unit cost were collected from the organization's cost accounting system.[11,29] These costs included the following resource categories: NICU room and board (inclusive of nursing care), diagnostic testing, laboratory and pathology, pharmacy, respiratory care, cardiology, surgery, developmental psychology, and therapies. To account for changes in costs over time, all costs were held constant at their 2016 US dollar (USD) values by creating a list of all resources used and their 2016 per-unit costs. For resources that did not have a 2016 cost value, costs were inflated to 2016 USD using the Bureau of Labor Statistics Consumer Price Index for medical care (Series ID: CUSR0000SAM).[30] The resource-level costs in 2016 USD were summed to calculate the hospital cost.

Feeding costs were calculated separately for mother's own milk, donor milk, and formula, and these costs were summed to calculate the total feeding cost. Formula feeding costs were calculated as the total volume of formula consumed in the NICU stay × \$0.033 per mL, based on the median formula cost from published studies, inflated to 2016 dollars.[22,31,32]

Mother's own milk feeding costs included evidence-based educational materials, hospital-grade electric breast pump rental and supplies needed to support mother's own milk expression, breastfeeding peer counselor support, freezer space, waterless warmers and liners, a creamatocrit to individualize mother's own milk feedings, and infant scales (**Table I**; available at www.jpeds.com).[21,30-33] Because donor milk was not a billable cost for hospitals in Illinois during the study time period, donor milk feeding costs were calculated separately using a bottom-up costing approach and included the cost to purchase donor milk (direct cost) and cost of resources needed to store and prepare the donor milk, including personnel, freezer space, waterless warmer and liners (indirect costs) (**Table I**).

Neonatal and Sociodemographic Risk Factors

Neonatal risk factors included infant gestational age, birth weight, sex, Apgar score at 5 minutes, small for gestational age at birth,[34] singleton or multiple birth, mode of delivery (vaginal vs cesarean), and surfactant use. Sociodemographic risk factors included maternal race/ethnicity and primary insurance (Medicaid or commercial).

Statistical Analyses

Continuous variables were expressed as means and SD or medians and IQR, depending on their distribution, and categorical variables are expressed as frequencies and percentages. Independent samples *t* tests, Mann–Whitney *U* tests, χ^2 tests, and Fisher exact tests were used to compare variables between feeding eras, as appropriate. A generalized linear regression model with a log link function and gamma distribution was constructed to determine the relationship between feeding era and NICU costs, adjusting for neonatal (infant gestational age, infant sex, birth small for gestational age, surfactant use) and sociodemographic risk factors (maternal race/ethnicity, primary insurance) and DOL of first feeding. Another model was constructed with the same covariates that included neonatal morbidities as additional covariates. A modified Park test was used to select the appropriate mean–variance relationship for the regression models.[35] The average marginal effect in 2016 USD was computed for feeding era by calculating the adjusted cost for each infant, assuming all infants were in the mother's own milk + formula era, holding all other infant characteristics constant, then calculating the adjusted cost for each infant, assuming all infants were in the mother's own milk + donor milk era, and computing the difference in costs between feeding eras for each infant. The average marginal effect was calculated using a similar approach for all other independent variables. Secondary analyses were conducted for NICU length of stay and NICU total cost per day using a similar approach.

The cost-effectiveness analysis was conducted from the hospital's perspective and evaluated the cost per percentage point reduction in the incidence of NEC. The incremental cost-effectiveness ratio (ICER) was computed as $(\widehat{C}_{\text{mothers own milk + donor milk}} - \widehat{C}_{\text{mothers own milk + formula}})/(p_{\text{mothers own milk + donor milk}} - p_{\text{mothers own milk + formula}})$, where $\widehat{C}$ is mean adjusted NICU total cost, p is the proportion of infants with NEC, and subscripts mother's own milk + donor milk and mother's own milk + formula indicate the respective feeding era. To assess uncertainty in costs and effectiveness (ie, NEC incidence), 1000 bootstrapped replicates were created using random sampling of the full sample size (n = 319) with replacement of the original data set. For each bootstrapped replicate, the ICER was calculated for the mother's own milk + donor milk era vs mother's own milk + formula era and plotted, for a total of 1000 bootstrapped replicate ICERs. The 95% CI for the ICER was computed from the 2.5th and 97.5th percentiles of the 1000 bootstrapped replicates.[36,37] The bootstrapped ICERs were plotted graphically to display the variation in costs vs effectiveness. SAS version 9.3 (Cary, NC) was used for all analyses.

Results

Neonatal and sociodemographic risk factors, feeding characteristics, incidence of morbidities, and unadjusted costs for the 150 infants in the mother's own milk + formula era and 169 in the mother's own milk + donor milk era are reported in **Table II**. Infants in the mother's own milk + donor milk era had shorter times to first feeding, achieved full feeds sooner, and had fewer days with parenteral nutrition. In addition, the proportion of infants in the mother's own milk + donor milk era with any formula use by DOL14 was significantly lower than for infants in the mother's own milk + formula era, although the proportion of infants with exclusive mother's own milk at DOL14 was lower for infants in the mother's own milk + donor milk era. The cumulative proportion of total enteral feedings that consisted of formula for the NICU stay was significantly lower for infants in the mother's own milk + donor milk era, whereas the proportion of infants with any mother's own milk at NICU discharge was not significantly different between the 2 groups.

NEC incidence was significantly lower in the mother's own milk + donor milk era compared with the mother's own milk + formula era (1.8% vs 6.0%, P = .048; difference, 4.2% [95% CI, −0.7% to 8.5%]), with fewer infants receiving surgical treatment for NEC in the mother's own milk + donor milk era (**Table II**). The occurrence of other neonatal morbidities was not significantly different between feeding eras, and one-half of infants in each feeding era had at least 1 major morbidity or died during their NICU hospitalization.

Median NICU length of stay, total cost, and cost per day were not significantly different between groups (**Table II** and **Figure 1**). Median feeding costs were significantly greater in the mother's own milk + donor milk era ($1317 vs $936, P < .001). The median cost per 100 mL was $3.30 for formula and $12.35 for mother's own milk (**Table I**). The median donor milk cost was $21.18 per 100 mL, with the direct cost to purchase donor milk from a milk bank representing 68% ($14.37) of the cost and the indirect cost (eg, supplies, staff time) representing the remaining cost ($6.81). Mean costs for each component were similar between feeding eras (**Table III**; available at www.jpeds.com), with the exception of feeding, laboratory/pathology, and pharmacy costs. The difference in pharmacy costs was primarily driven by differences in parenteral nutrition costs (median cost, $4323 [IQR: $2797, $6612] in the mother's

Table II. Description of the sample, N = 319

Variables	Mother's own milk + formula* N = 150 (47%)	Mother's own milk + donor milk† N = 169 (53%)	*P* value
Gestational age, wk, mean ± SD	27.3 ± 2.1	27.1 ± 2.3	.299
Birth weight, g, mean ± SD	986 ± 246	989 ± 268	.923
Race/ethnicity, n (%)			.881
Black/African American	84 (56.0)	90 (53.3)	
Non-Hispanic white	34 (22.7)	40 (23.7)	
Hispanic	32 (21.3)	39 (23.1)	
Female, n (%)	66 (44.0)	81 (47.9)	.482
5-min Apgar, median [IQR]	8 [7, 8]	8 [7, 9]	.642
Birth SGA, n (%)	27 (18.0)	21 (12.4)	.165
Multiple gestation, n (%)	24 (16.0)	47 (27.8)	.011
Cesarean delivery, n (%)	100 (66.7)	126 (74.6)	.122
Primary payer			.917
Medicaid/self-pay	102 (68.0)	114 (67.5)	
Commercial	48 (32.0)	55 (32.5)	
DOL first feeding, median [IQR]	3.5 [3, 5]	3 [2, 3]	<.001
DOL full feeding, median [IQR]	21 [15, 29]	15 (12, 24)	<.001
Days to full feeding, median [IQR]	16 [11, 23]	11.5 [9, 20]	<.001
Days with parenteral nutrition, median [IQR]	17 [11, 26]	11 [9, 18]	<.001
Mother's own milk initiation during NICU stay, n (%)	145 (96.7)	168 (99.4)	.072
DOL 14, percent mother's own milk, median [IQR]	100.0 [92.9, 100.0]	100.0 [62.0, 100.0]	.010
DOL 14, any formula, n (%)	44 (29.3)	6 (3.6)	<.001
DOL 14, exclusive mother's own milk, n (%)	106 (70.7)	90 (53.6)	.002
Cumulative % of formula for NICU stay, median [IQR]	82.6 [7.8, 96.3]	40.4 [0.3, 70.9]	<.001
Any mother's own milk at discharge, n (%)	53 (35.3)	74 (43.8)	.124
Surfactant, n (%)	120 (80.0)	100 (59.2)	<.001
Any neonatal morbidities or death, n (%)	75 (50.0)	84 (49.7)	.958
NEC, n (%)‡	9 (6.0)	3 (1.8)	.048
NEC, with surgical treatment, n (%)‡	5 (3.3)	1 (0.6)	.103
ROP, stage 3 or greater, n (%)	0 (0)	0 (0)	
Late-onset sepsis, n (%)	15 (10.0)	16 (9.5)	.873
BPD, n (%)	64 (42.7)	75 (44.4)	.758
Severe brain injury, n (%)	7 (4.7)	9 (5.3)	.788
In-NICU death, n (%)	5 (3.3)	3 (1.8)	.374
NICU length of stay, median [IQR]	79 [59, 107]	78 [51, 110]	.851
NICU total cost, hospital + feeding, median [IQR]	185 740 [130 626, 250 469]	169 555 [110 186, 254 472]	.331
Hospital cost, median [IQR]	184 784 [129 833, 249 666]	168 184 [109 541, 251 356]	.309
Feeding cost, median [IQR]	936 [721, 1199]	1317 [875, 2123]	<.001
NICU cost per day, median [IQR]	2254 [2183, 2394]	2232 [2159, 2368]	.077
Parenteral nutrition cost, median [IQR]	4323 [2797, 6612]	2798 [2289, 4578]	<.001

ROP, retinopathy of prematurity; *SGA*, small for gestational age.
*n = 149 for DOL of full feeding and days to full feeding.
†n = 167 for 5-min Apgar; n = 164 for DOL of full feeding; n = 168 for DOL14, percent mother's own milk, and DOL14, exclusive mother's own milk.
‡Differences between groups were compared with the Fisher exact test; otherwise, χ^2 tests were used to test differences between groups of categorical variables.
Independent samples *t* tests were performed for continuous variables when normally distributed; otherwise, Mann–Whitney *U* tests were performed for continuous variables.

own milk + formula era vs $2798 [IQR: $2289, $4578] in the mother's own milk + donor milk era).

After we adjusted for neonatal and sociodemographic risk factors and feeding characteristics, infants in the mother's own milk + donor milk era had 7% lower NICU total costs, translating into –$15 555 in NICU costs per infant relative to the mother's own milk + formula era (*P* = .045) (**Table IV** and full results reported in **Table V** [available at www.jpeds.com]). Model 2 also adjusted for neonatal morbidities, and the mother's own milk + donor milk era remained significant, with –$14 599 in NICU costs per infant relative to the mother's own milk + formula era. In addition, NEC was associated with $66 015 greater costs per infant (*P* < .001), and BPD was associated with $74 084 greater costs per infant (*P* < .001).

The ICER for NEC was $1812 (95% CI –$7010 to $14 542) or a cost savings of $1812 per percentage point reduction in NEC (**Table VI**). In the 1000 bootstrapped replicates, 80.3% of the replicates had mean adjusted costs that were lower in the mother's own milk + donor milk era, 97.6% of the replicates had a lower incidence of NEC in the mother's own milk + donor milk era, and 78.6% had ICERs where both the mean adjusted cost and incidence of NEC were lower in the mother's own milk + donor milk era (**Figure 2**, quadrant A).

In the secondary analysis of the relationship between feeding era and NICU length of stay, mother's own milk + donor milk era was associated with a mean reduction of 5.8 (SD 2.4) days after controlling for neonatal morbidities and other risk factors (*P* = .031) (**Table VII**; available at www.jpeds.com). Feeding era was not significantly associated with NICU total cost per day.

Discussion

In this retrospective analysis of NICU outcomes and costs for infants with VLBW, both the incidence of NEC and NICU

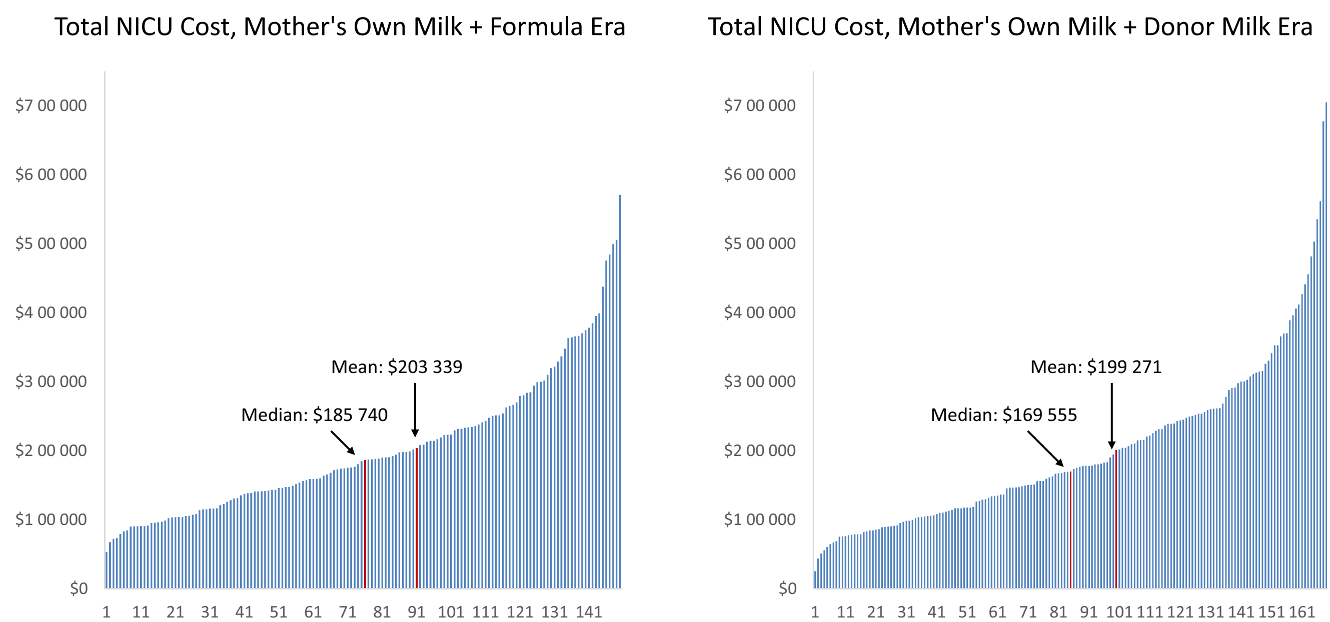

Figure 1. Distribution of NICU costs by feeding era. Shown is a histogram of total NICU costs, with each *bar* representing 1 NICU discharge.

costs were significantly lower after implementation of a donor milk program. Contrary to concerns regarding the cost of donor milk, we found that NICU costs were not significantly greater after implementing the donor milk program, even after accounting for both the direct cost of donor milk and the associated indirect costs. The incidence of NEC was 4.2 percentage points lower and adjusted NICU costs were $15 555 lower in the mother's own milk + donor milk era compared with the mother's own milk + formula era. In the cost-effectiveness analysis, donor milk was associated with a cost savings of $1812 per percentage point reduction in the incidence of NEC, with 98% probability that the NEC incidence would be lower with the donor milk program and 79% probability that both the incidence of NEC and NICU costs would be lower with the donor milk program.

This study comprehensively calculated the cost of donor milk in the NICU for donor milk acquired through an independent milk bank, including both direct and indirect costs of donor milk. Although the direct cost or "purchase price" of donor milk ($14.37/100 mL) was similar to the cost of acquiring mother's own milk feedings ($12.37/100 mL) in our study, the purchase price represents only 68% of the cost of donor milk feedings in the NICU. Thus, the cost estimates for donor milk that do not include the staff time and resources required to manage and prepare donor milk will underestimate its true cost in the NICU setting. However, even after comprehensively accounting for these costs, the additional feeding costs were miniscule relative to the cost of the NICU hospitalization. We found that the median feeding cost in the mother's own milk + donor milk era was only $381 greater than the feeding cost in the mother's own milk + formula era. In a study of 64 infants born preterm in an Australian NICU, Carroll and Herrmann estimated that the mean donor milk cost per infant was $237 (in 2011 USD), taking into account only the purchase price of donor milk.[38] In a systematic review of the cost and cost-effectiveness of donor milk, Buckle and Taylor found that the cost per infant of donor milk as an adjunct to mother's own milk ranged from $224 to $319, also based exclusively on the donor milk purchase price.[24] These estimates based on the donor milk purchase price are remarkably consistent with our direct cost calculations for donor milk

Table IV. Generalized linear regression model results for NICU total cost, N = 319

	Model 1			Model 2		
Variables	RR* (95% CI)	Average marginal effect	*P* value	RR* (95% CI)	Average marginal effect	*P* value
Donor milk feeding era	0.93 (0.86-1.00)	−15 555 ± 6654	.045	0.93 (0.87-0.99)	−14 599 ± 6886	.027
NEC				1.33 (1.13-1.57)	66 015 ± 30 259	<.001
Late-onset sepsis				1.08 (0.97-1.20)	15 921 ± 7313	.148
BPD				1.46 (1.35-1.56)	74 084 ± 24 975	<.001
Severe brain injury				1.11 (0.97-1.27)	21 744 ± 10 160	.132

*RR = relative risk; Models adjust for gestational age, maternal race/ethnicity, infant sex, birth SGA, primary payer, DOL of feeding initiation, and surfactant use.

Table VI. ICER for mother's own milk + donor milk relative to mother's own milk + formula

Feeding eras	N	Mean adjusted cost	Δ Cost	Proportion of infants with NEC	Δ NEC	ICER
Mother's own milk + formula	150	$205 899 ± 83 700		6.000%		
Mother's own milk + donor milk	169	$198 244 ± 88 169	−$7655	1.775%	−4.225%	$1812 (−7010 to 14 542)

(median = $259 or 68% of $381). Although these previous studies underestimate the actual cost of donor milk due to the omission of indirect costs associated with donor milk, all of these estimates are quite low in comparison with the NICU hospitalization. This is likely due to the relatively small volumes and short time frame during which infants with VLBW receive donor milk at most institutions, namely when enteral feedings are being advanced and although total volumes of intake are low during the first 2-8 weeks that donor milk is commonly used.[39,40]

In our detailed analysis of the direct and indirect cost of donor milk feedings, we found that the average cost per 100 mL of donor milk was $21.18. In a similar study of the hospital costs of infant feedings in the NICU, Fengler et al calculated the cost of donor milk feedings in a German hospital with an internal milk bank, including the acquisition and preparation of donor milk.[41] They calculated a total cost of 8.29 EUR (approximately $9.20 USD) per 100 mL of donor milk, which is substantially lower than the cost in our study. A portion of the cost difference is likely due to the acquisition costs of donor milk in the two studies (through an in-hospital milk bank vs independent milk bank). The "purchase price" of donor milk in our study was $14.39, more than the entire cost of donor milk feedings in the study by Fengler et al. Future work should evaluate differences in the processes and associated costs for acquiring and feeding donor milk in the NICU.

Our findings differ from those of Trang et al in the direction of the cost-effectiveness of donor milk feedings.[22] Trang et al evaluated the cost-effectiveness of donor milk for infants with VLBW enrolled in a randomized controlled trial of donor milk vs formula as supplements to mother's own milk in 4 Canadian NICUs.[42] In this randomized controlled trial, costs of enteral feeding (direct cost or "purchase price" of donor milk, fortifier and formula) were significantly greater for infants with donor milk supplementation ($41 Canadian Dollars for infants with formula supplementation vs $921 Canadian Dollars for infants with donor milk supplementation), with both groups receiving similar proportions of enteral intake as mother's own milk. Although not the primary outcome, infants randomized to the supplemental donor milk arm had significantly lower incidence of stage ≥2 NEC than infants in the supplemental formula arm (1.7% vs 6.6%), similar to the 3-fold difference in the

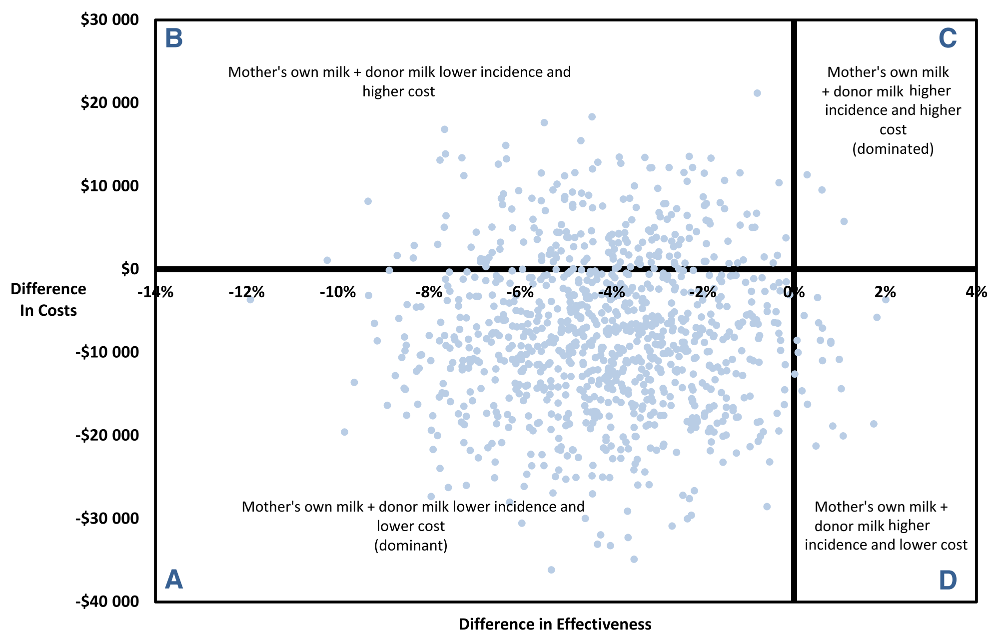

Figure 2. ICER for the incidence of NEC. Scatterplot of 1000 bootstrap samples of cost-effectiveness (ie, NEC incidence) pairs. Quadrant A indicates samples with mean differences in cost and effectiveness favoring mother's own milk + donor milk era; Quadrant B indicates samples with mean difference in cost favoring mother's own milk + formula era and mean difference in effectiveness favoring mother's own milk + donor milk era; Quadrant C indicates samples with mean differences in costs and effectiveness favoring mother's own milk + formula era; Quadrant D indicates samples with mean differences in costs favoring mother's own milk + donor milk era and differences in effectiveness favoring mother's own milk + formula era.

incidence of NEC that we report. Analyzing the reported data from Trang et al in a similar manner to our analytic plan by only including NEC stage ≥2 and costs through NICU discharge (excluding caregiver and physician expenses), we can better compare the results from these 2 studies. Their reduction of 4.9 percentage points in the incidence of NEC stage ≥2 would translate into $1691 (CAD) in *additional* costs per percentage point reduction in NEC stage ≥2 (difference in costs = $8287 CAD, difference in proportion of infants with NEC = −4.9%).[22] In contrast, we found mother's own milk + donor milk *saved* $1812 USD per percentage point reduction in NEC stage ≥2. This difference in direction is due to the substantially greater costs through discharge for infants in the supplemental donor milk arm in the study by Trang et al. Infants in their supplemental donor milk arm had greater enteral feeding costs and greater hospital case costs, likely due in part to a substantially longer hospital length of stay, whereas we had lower overall hospital costs through discharge for infants in the mother's own milk + donor milk feeding era.

Another potential difference may relate to differences in the timing of the first feeding between the 2 studies. Although the Canadian randomized controlled trial did not report a difference in median day of first feedings between study groups,[42] we found a significant difference, with earlier first feedings in the mother's own milk + donor milk era. Although no formal feeding initiation guideline changes were made, the availability of donor milk likely resulted in clinicians' comfort in starting feeds earlier, thus resulting in the shortened duration to full feeds and decreased parenteral nutrition days observed in the donor milk era in our NICU. Correspondingly, pharmacy costs, specifically related to parenteral nutrition, were significantly lower in the donor milk era and may confer some of the cost savings observed in the donor milk era as a whole.

This study also differs from a previous study that compared the costs and benefits of donor milk for infants who received exclusive formula vs exclusive human milk diets that demonstrated greater costs with exclusive formula,[19] in that we did not compare the subset of infants in our cohort who received exclusive formula vs a combination of mother's own milk and donor milk. Given that the majority of NICUs have reported stable or increased rates of mother's own milk feedings after instituting donor milk programs, indicating donor milk is primarily being used as a supplement to mother's own milk,[43-45] our goal was to conduct a cost-effectiveness analysis that was representative of current donor milk practice.

Several factors will impact the cost-effectiveness of donor milk in other settings. For example, the use of donor milk as exclusive nutrition or for a longer duration would clearly increase acquisition cost and impact cost-effectiveness. Similarly, cost-effectiveness would be affected by an individual NICU's incidence of NEC. Institutions with greater NEC rates may garner a greater cost savings if the absolute reduction in NEC is greater than in our study. Finally, the relative costs of resources used during the NICU stay may differ across countries, and application of our findings to other settings should take these potential differences into account.

The current study has several limitations, including the fact that it was retrospective, with a pre–post intervention design spanning several years in a single tertiary NICU. The design precluded our controlling for all factors that might be associated with NICU total costs, including clinical practice changes between eras. For example, surfactant usage was significantly lower in the postdonor milk era, coinciding with an effort to decrease invasive ventilation and to give less prophylactic surfactant in infants with VLBW. However, it is important to note that the rates of BPD were similar between groups, and the costs associated with respiratory care were not significantly different between the feeding eras. Another clinical practice change was the conversion from powdered to liquid bovine fortifier, which occurred almost simultaneously with donor milk introduction. Although we were unable to adjust for this confounding, a randomized trial of these same 2 fortifiers did not reveal any difference in feeding outcomes.[46] In addition, we did not account for costs due to fortification of mother's own milk or donor milk. Given that the formula usage was nearly halved in the donor milk era, the additional fortification may have resulted in increased enteral feeding costs. Baseline characteristics and clinical outcomes outside of NEC were similar between eras suggesting a comparative pre–post population; however, we cannot exclude the possibility of other unaccounted confounding factors that could impact NICU costs.

Another limitation of this study is that costs only included those incurred directly in the NICU. Our calculations did not account for medical costs incurred after the initial hospitalization or for the opportunity costs incurred by the family and society. Trang et al found that caregiver expenses, including productivity losses due to foregone labor market earnings, did not differ for infants in the supplemental donor milk vs formula arms during the infant's initial NICU stay, but caregiver productivity losses were 20% lower for infants in the supplemental donor milk arm in the 18 months postdischarge.[22] In addition, the mother's time (ie, opportunity cost) spent pumping is a cost currently incurred by the mother rather than the NICU and should be considered in future cost-effectiveness analyses. Based on previous work on the maternal cost of providing mother's own milk for infants in the NICU, the maternal opportunity cost could add $2.44 per 100 mL of mother's own milk, based on a federal minimum wage of $7.25 per hour.[47] Future research should examine the cost-effectiveness from a societal perspective, taking into account maternal opportunity cost due to time spent pumping and other costs incurred by the mother. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Revolutionary Changes in the Management of Juvenile Idiopathic Arthritis

Calabro JJ. Management of juvenile rheumatoid arthritis. J Pediatr 1970;77:355-65.

This comprehensive Medical Progress report outlines the subtypes of juvenile rheumatoid arthritis (JRA), clinical manifestations, complications, and prognosis, with an emphasis on management. Unfortunately, the medical management options were few and largely not effective. The mainstay of therapy was high dose aspirin (90-130 mg/kg/day) divided 4 to 6 times per day; this was associated with many adverse effects. Other options included gold injections for polyarthritis, which was effective in ~20% of patients, also with many adverse effects, particularly hematologic and renal. Phenylbutazone was associated with agranulocytosis, especially in younger children. Corticosteroids were offered for systemic features (high fever, uveitis, peri/myocarditis, vasculitis), but once started were difficult to wean. Chloroquine was associated with severe potential cardiotoxicity in younger children. The report emphasized physical therapy, including range-of-motion exercises, splints, and avoiding bed rest, although this was often difficult in patients with severe arthritis. A large part of this report was devoted to orthopedic surgical therapies for the many complications of chronic arthritis and a debate on the effect of early synovectomy.

Although we still cannot cure JIA, modern therapies, when used in a timely fashion in accordance with new guidelines, can prevent joint damage, deformities, and disability.[1] The need for surgery in newly diagnosed patients is extremely rare. Current treatments include corticosteroid injections for oligoarthritis, also mentioned by Calabro, but this is combined with newer, longer-acting agents, methotrexate, and other synthetic disease-modifying drugs and a growing list of biologic medications targeting an increasing list of cytokines, T and B cell antigens, and intracellular trafficking pathways of inflammation.

A vivid example of the results of this revolution was demonstrated in a talk I heard from Dr Daniel Lovell, one of my mentors and principal investigator of many of the studies of the new therapies. The opening slide showed, side by side, children who attended the annual arthritis camp run by Cincinnati Children's Hospital Medical Center (Camp Wekandu) in 1987 and in 2011. In the former photo, most of the children were pictured in wheelchairs or using walkers, whereas in the latter photo, only 1 child was using a walker. We can do even better in 2020.

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Table I. Feeding components, per unit costs, and median and mean feeding costs per infant by type of feeding

Feeding components	Description	Source	Type of cost*	Cost per unit	Median cost: per 100 mL in 2016 USD	Median cost: per infant	Mean cost: per 100 mL in 2016 USD	Mean cost: per infant
Formula feeding	*Cost per infant with any formula feeding (n = 278)*							
Formula product cost	Hospital cost to purchase formula	Median cost per published studies[21,30,31]	Variable	$0.033 per mL	$3.30	$321.70	$3.30	$477.34
Total formula feeding cost					**$3.30**	**$321.70**	**$3.30**	**$477.34**
Mother's own milk feeding	*Costs per infant with any mother's own milk feeding (n = 313)*							
Evidence-based materials	Evidence-based materials targeting importance of mother's own milk for infants born preterm + monitoring of mother's own milk volume and mother's own milk feeding goals	Meier et al[32]	Fixed	$15.80	$0.35	$15.80	$6.06	$15.80
Hospital-grade electric breast pump rental	Pump rental for number of months infant received any mother's own milk (days infant received any mother's own milk, rounded up to next month)	Meier et al[32]	Variable	$40.51/month	$1.56	$81.02	$16.12	$84.00
Provision of pump kit	1 kit per infant	Meier et al[32]	Fixed	$33.33	$0.74	$33.33	$12.78	$33.33
Custom-fitted breast shields	1 set per infant	Meier et al[32]	Fixed	$7.09	$0.16	$7.09	$2.72	$7.09
Hospital-grade storage containers for pumped mother's own milk	Containers in sets of 3 per day (mL mother's own milk per day * 1.2)/120 = number of containers rounded up to multiple of 3	Meier et al[32]	Variable, cost per average mL of mother's own milk/d	$0.21 per container	$0.56	$23.61	$1.48	$30.24
Breastfeeding peer counselors	Provision of NICU-specific lactation support from NICU-based certified breastfeeding peer counselors; 2 h/d for DOL 1-2 (and DOL 3, if cesarean delivery) + 3 h for first 2 wk; 1 h/wk until last 2 wk of NICU stay; for infants discharged on mother's own milk, 2.5 h/wk for last 2 wk	Meier et al[32]	Variable, cost per day infant received any mother's own milk	$18.23 per hour	$5.63	$244.79	$64.11	$270.31
NICU freezers for safe storage of pumped mother's own milk	Cost of $7.01 per infant per 71-d NICU stay	Meier et al[32]	Variable, cost per day infant received any mother's own milk	$0.10 per day	$0.09	$3.65	$0.23	$4.48
Waterless warmers for mother's own milk	$783 per warmer; 1 warmer per infant per 71-d NICU stay	Meier et al[32]	Variable, cost per day infant received any mother's own milk	$0.43 per day	$0.38	$15.87	$0.99	$19.46
Liners for waterless warmer	1 liner per day	Meier et al[32]	Variable, cost per day infant received any mother's own milk	$3.29 per day	$2.91	$121.78	$7.60	$149.34
Creamatocrit	Basic creamatocrit to individualize mother's own milk feedings and mother's own milk collection strategies; $1519 per creamatocrit and 1 per NICU for 5-year lifespan	Meier et al[32]	Fixed	$0.38	$0.01	$0.38	$0.15	$0.38
Infant scale	Measurement of mother's own milk intake during breastfeeding; 1 scale per 15 infants	Meier et al[32]	Variable, cost per day infant received any mother's own milk	$3.94	$0.09	$3.94	$1.51	$3.94
Total mother's own milk feeding cost					**$12.35**	**$555.67**	**$113.74**	**$618.38**

(*continued*)

Table I. Continued

Feeding components	Description	Source	Type of cost*	Cost per unit	Median cost: per 100 mL in 2016 USD	Median cost: per infant	Mean cost: per 100 mL in 2016 USD	Mean cost: per infant
Donor milk feeding	*Costs per infant with any donor milk feeding (n = 122)*							
Donor milk product cost	Hospital cost to purchase donor milk from milk bank	Actual 2016 cost	Variable	$0.14 per mL	$14.37	$361.62	$14.37	$516.77
Donor milk peer counselors	Provision of NICU-specific donor milk support and management of donor milk supply in NICU; 2.5 h per day for preparation, assuming 10 infants with donor milk per day	Actual 2016 cost	Variable, cost per day infant received any donor milk	$4.56 per day	$3.70	$97.40	$20.26	$115.07
NICU freezers for safe storage of donor milk	Cost of $7.01 per infant per 71-day NICU stay	Meier et al[32]	Variable, cost per day infant received any donor milk	$0.10 per day	$0.08	$2.11	$0.44	$2.49
Waterless warmers for donor milk	$783 per warmer; 1 warmer per infant per 71-day NICU stay	Meier et al[32]	Variable, cost per day infant received any donor milk	$0.43 per day	$0.35	$9.17	$1.91	$10.83
Liners for waterless warmer	1 liner per day	Meier et al[32]	Variable, cost per day infant received any donor milk	$3.29 per day	$2.67	$70.34	$14.63	$83.11
Total donor milk feeding cost					**$21.18**	**$561.31**	**$51.60**	**$728.28**

*The cost per 100 mL for feeding components that have a fixed cost is calculated by dividing the fixed cost by the total mL of nutrition (mother's own milk, donor milk) for each infant.

Table III. Mean costs, N = 319

Costs	Mother's own milk + formula N = 150 (47%) Mean ± SD	Mother's own milk + donor milk N = 169 (53%) Mean ± SD	*P* value	Difference in means (95% CI)
Hospital cost	202 340 ± 100 916	197 701 ± 117 960	.708	4638 (−19 701 to 28 977)
NICU room and board	165 273 ± 71 218	164 805 ± 87 678	.958	468 (−17 269 to 18 204)
Cardiology	1922 ± 1954	1819 ± 1874	.632	103 (−319 to 525)
Diagnostic testing	3151 ± 2941	2786 ± 2755	.254	365 (−263 to 993)
Laboratory/pathology	7939 ± 6490	6356 ± 5008	.016	1583 (293-2872)
Pharmacy	12 266 ± 11 080	9201 ± 7949	.005	3065 (915-5215)
Parenteral nutrition	6039 ± 5667	3966 ± 3244	<.001	2073 (1037-3109)
Nonparenteral nutrition	6227 ± 5914	5235 ± 5461	.120	992 (−261 to 2245)
Psychology	687 ± 332	735 ± 287	.169	−48 (−116 to 20)
Respiratory care	9254 ± 12 778	9919 ± 15 921	.680	−664 (−3830 to 2501)
Surgery	1054 ± 1928	1098 ± 2385	.855	−44 (−520 to 431)
Therapies	794 ± 734	982 ± 1065	.064	−189 (−388 to 11)
Feeding costs	1000 ± 414	1570 ± 907	<.001	−571 (−724 to −418)
Mother's own milk	574 ± 297	637 ± 334	.069	−63 (−133 to 7)
Formula	425 ± 415	408 ± 591	.755	18 (−94 to 129)
Donor milk	0	526 ± 628	<.001	−526 (−621 to −43)
Total NICU cost	203 339 ± 101 235	199 271 ± 118 571	.741	4068 (−20 150 to 28 286)
Total NICU cost per day	2329 ± 259	2288 ± 183	.106	41 (−8 to 91)

Table V. Generalized linear regression model results for NICU total cost, N = 319

	Model 1			Model 2		
Variables	RR (95% CI)	Average marginal effect	*P* value	RR (95% CI)	Average marginal effect	*P* value
Gestational age	0.83 (0.81-0.84)	−35 179 ± 15 000	<.001	0.86 (0.85-0.88)	−27 440 ± 12 844	<.001
Female	1.09 (1.02-1.17)	17 673 ± 7457	.015	1.09 (1.03-1.16)	17 664 ± 8233	.004
Birth SGA	1.19 (1.08-1.32)	37 509 ± 16 305	<.001	1.16 (1.07-1.26)	31 692 ± 15 050	<.001
Surfactant	1.08 (1.00-1.18)	16 075 ± 6615	.061	1.02 (0.94-1.09)	2984 ± 1388	.688
Black	0.97 (0.89-1.07)	−5665 ± 2398	.554	0.96 (0.89-1.03)	−8984 ± 4178	.260
Hispanic	0.92 (0.83-1.03)	−16 344 ± 6920	.141	0.93 (0.85-1.02)	−14 986 ± 6969	.109
Medicaid	0.97 (0.90-1.05)	−5688 ± 2420	.494	0.96 (0.90-1.03)	−7381 ± 3451	.286
DOL of first feeding	1.00 (0.99-1.02)	442 ± 188	.804	1.00 (0.98-1.01)	−562 ± 263	.708
Donor milk feeding era	0.93 (0.86-1.00)	−15 555 ± 6654	.045	0.93 (0.87-0.99)	−14 599 ± 6886	.027
NEC				1.33 (1.13-1.57)	66 015 ± 30 259	<.001
Late-onset sepsis				1.08 (0.97-1.20)	15 921 ± 7313	.148
BPD				1.46 (1.35-1.56)	74 084 ± 24 975	<.001
Severe brain injury				1.11 (0.97-1.27)	21 744 ± 10 160	.132

Table VII. Generalized linear regression model results for other NICU outcomes, N = 319

	Model 1			Model 2		
Variables	**RR (95% CI)**	**Average marginal effect***	***P* value**	**RR (95% CI)**	**Average marginal effect***	***P* value**
Outcome: NICU length of stay						
Donor milk feeding era	0.95 (0.88-1.01)	−4.8 ± 1.9	.110	0.93 (0.88-0.99)	−5.8 ± 2.4	.031
Outcome: cost per day						
Donor milk feeding era	0.99 (0.97-1.00)	−24 ± 1	.274	1.00 (0.98-1.01)	−4.9 ± 0.3	.800

*Model 1 adjusts for neonatal risk factors (gestational age, birth SGA, surfactant), sociodemographic risk factors (race/ethnicity, sex, payer), and DOL of the first feeding. Model 2 also adjusts for the presence of morbidities.