

# Commentary

## Donor Human Milk for Preterm Infants

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As survival rates for preterm infants improve, more attention is being focused on improving the quality of survival through optimal nutritional management. The benefits of human milk for term infants are well recognized, with current research suggesting that human milk may especially benefit the preterm infant. Some mothers are unable or unwilling to provide breastmilk for their infants. Although not as well studied as mother's own milk, pasteurized donor human milk can provide many of the components and benefits of human milk while eliminating the risk of transmission of infectious agents. Pasteurization does affect some of the nutritional and immunologic components of human milk, but many immunoglobulins, enzymes, hormones, and growth factors are unchanged or minimally decreased. In California donor human milk costs approximately \$3.00 per ounce to purchase. A reduction in length of stay, necrotizing enterocolitis and sepsis may result in a relative saving of approximately \$11 to the NICU or healthcare plan for each \$1 spent for pasteurized donor milk.

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### INTRODUCTION

As survival rates for preterm infants improve, more attention is being focused on improving the quality of survival through optimal nutritional management. Early total parenteral nutrition (TPN) and minimal enteral nutrition are being strongly recommended, along with mother's own milk, to decrease morbidity, shorten duration of hospitalization and improve overall health and long-term outcome.<sup>1–4</sup>

The benefits of human milk for term infants are well recognized.<sup>5,6</sup> Current research suggests that human milk may *especially* benefit the preterm infant<sup>5,7</sup> (Tables 1 and 2). Human milk provides nutrition, digestive enzymes, immunologic factors of many types, growth factors, hormones, and other bioactive factors, with new components being discovered regularly. Research to date supports, and the consensus is growing, that human milk [with appropriate fortification for the very low-birth-weight (VLBW) infant] is the standard of care for preterm, as well as term infants.<sup>2,8,9</sup>

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What about those mothers who cannot provide their own milk for their preterm infants? Should their infants be denied the considerable benefits of human milk? Although not as well studied as mother's own milk, pasteurized donor breastmilk can provide many of the components and benefits of human milk while eliminating the risk of transmission of infectious agents and of graft versus host disease.

### BENEFITS OF HUMAN MILK FOR PRETERM INFANTS

The benefits and concerns regarding the use of human milk for preterm infants have been recently reviewed,<sup>2,9</sup> with more factors, actions, and interactions being discovered frequently. Breastmilk empties from the stomach faster,<sup>10,11</sup> reduces intestinal permeability faster,<sup>12</sup> and results in less residuals and faster realization of full enteral feedings.<sup>3,13,14</sup> Many factors in human milk may stimulate gastrointestinal growth, motility and maturation.<sup>15,16</sup> Reaching full feedings faster means fewer days of IVs, less side effects from TPN, less infections and infiltrations from IVs, and less costly and fewer hospital days.<sup>3</sup> Breastmilk-fed infants have a reduced incidence of necrotizing enterocolitis (NEC),<sup>3,13,17–24</sup> sepsis,<sup>3,21,25–27</sup> and other infections such as urinary tract infections.<sup>28–30</sup> Infants fed breastmilk tend to have higher IQ scores (Table 3),<sup>31–33</sup> and improved visual development,<sup>34–37</sup> with less retinopathy of prematurity.<sup>38,39</sup> Enzymes in breastmilk help immature infants absorb and utilize nutrients more efficiently<sup>40</sup> and may also improve absorption of nutrients when breastmilk and artificial milks are combined.<sup>41</sup>

Protective effects of human milk on infection rates have been observed with the use of *both* fresh and pasteurized milk.<sup>13,22</sup> Lucas and Cole<sup>13</sup> found a dose–response decrease in NEC with both mothers' own and pasteurized donor human milk. In a randomized, controlled trial of 226 high-risk neonates, Narayanan et al.<sup>22</sup> demonstrated that infants given only raw human milk or pasteurized human milk had similar (10.5% vs 14.3%) infection rates. However, when formula was added to each, the heat-treated milk had less protective effect than the raw human milk on infection rates (33% vs 16%). Kangaroo Care, which is associated with an increased maternal milk supply and longer duration of breastfeeding post discharge, is also thought to help protect infants from infection through the enteromammary pathway.<sup>42,43</sup> Through skin-to-skin contact with her premature infant, a mother can be exposed to, and make specific antibodies

**Table 1** American Academy of Pediatrics

Human milk is the preferred feeding for all infants, including premature and sick newborns with rare exceptions . . . . When direct breastfeeding is not possible, expressed human milk, fortified when necessary for the premature infant, should be provided.

AAP, Work Group on Breastfeeding.<sup>5</sup>

against, the nosocomial pathogens in the neonatal intensive care unit (NICU) environment.

### COMPOSITION OF PRETERM VERSUS TERM HUMAN MILK

Milk from mothers who deliver prematurely (preterm milk) has been shown to be different from milk of mothers who deliver at term (term milk). Since the first report of higher concentrations of nitrogen in preterm milk in 1978,<sup>44</sup> many publications have described differences in milk composition relative to gestational age at birth. Preterm milk has been noted to have increased amounts of nitrogen, total protein, immune proteins, total lipids, medium-chain fatty acids, total energy, some vitamins and minerals as well as trace elements.<sup>45–53</sup> The long-chain polyunsaturated fatty acids (especially docosahexaenoic acid and arachidonic acid) found in both term and preterm milk have been implicated in optimal brain development and retinal maturation.<sup>32,34–37</sup> The degree of prematurity and whether infants are born appropriate or small for gestational age may also play a role in milk composition.<sup>46,48</sup> Some studies did not find a difference between term and preterm milk,<sup>54,55</sup> but no studies have found lesser concentrations of nutrients in preterm milk at similar stages of lactation.<sup>2</sup> The lack of agreement between studies may reflect small sample size because of the greater

**Table 2** British Paediatric Association

Breastfeeding is particularly important for low birth-weight infants in whom both reduced mortality associated with necrotizing enterocolitis and advantages in cognitive function have been associated with provision of breastmilk.

Standing Committee on Nutrition of the British Paediatric Association.<sup>7</sup>

**Table 3** Breastmilk and Subsequent Intellectual Performance in Premature Infants at 8 Years

Factor affecting IQ	IQ points
Breastmilk	+ 8.3
Social class	– 3.5/class
Mother's education	+ 2.0/group
Female gender	+ 4.2
Mechanical ventilation	– 2.6/week

From Lucas et al.,<sup>31</sup> p. 261.

interindividual variability of milk composition in preterm milk, but also milk sample collection methods, and inclusion of wide ranges of gestational age.<sup>56</sup>

In addition, preterm milk seems to have a higher concentration of growth factors and hormones to aid in the development of the gut and other organs. Preterm milk has more live infection-fighting cells, immunoglobulins like secretory IgA, anti-inflammatory factors and immunomodulators than term milk.<sup>16,57</sup> There is a trend for nutrient and immunologic factor concentrations in preterm milk to decrease as lactation progresses, a pattern also observed in term milk.<sup>2</sup> However, as infants gain in weight and postnatal age, they consume increasing volumes of milk containing these immunologic factors.

### CHANGES IN HUMAN MILK WITH PASTEURIZATION AND FREEZING

Pasteurization (56 or 62.5°C for 30 minutes) does affect some of the nutritional, immunologic and other components of human milk. Heat treatment at 56°C (133°F) or greater for 30 minutes reliably eliminates all functional white blood cells and bacteria, inactivates human immunodeficiency virus (HIV)<sup>58</sup> and human T-lymphotrophic virus,<sup>59</sup> and decreases the titers of other viruses, but in one study did not eliminate cytomegalovirus (CMV).<sup>60</sup> Holder pasteurization [62.5°C (144.5°F) for 30 minutes] reliably inactivates HIV and CMV, and will eliminate or significantly decrease titers of most other viruses.<sup>60,61</sup>

Immunologic factors are variously affected by heat treatment. With Holder pasteurization most of the secretory IgA, bifid growth factor, and lysozyme remain (0% to 30% destroyed), lipids are unaffected, but 57% of the lactoferrin, and 34% of the IgG are destroyed.<sup>61–64</sup> The reader is referred to a more detailed recent review.<sup>65</sup>

In general, the nutritional components are altered somewhat, resulting in slightly slower growth when compared to infants fed unpasteurized raw human milk.<sup>66–69</sup> Holder pasteurization does not appear to influence nitrogen absorption or retention in LBW infants.<sup>67</sup> Most enzymes, growth factors, vitamins, and minerals are unchanged or minimally decreased.<sup>70,71</sup> Heat treatment of donor milk appears to foster more rapid growth of intestinal epithelial cells by inactivating heat-labile inhibitory cytokines, allowing heat-stable epidermal growth factor to act.<sup>72</sup> Freezing inactivates milk cells and most

**Table 4** Human Milk Banks

Human Milk Banking Association of North America (HMBANA) <i>www.hmbana.org</i>	
Mothers' Milk Bank, Newark, DE	302-733-2340
Mothers' Milk Bank at WakeMed, Raleigh, NC	919-350-8599
Mothers' Milk Bank, Denver, CO	303-869-1888
Mothers' Milk Bank, San Jose, CA	408-998-4550
Mothers' Milk Bank at Austin, Austin, TX; <i>www.mmbaustin.org</i>	512-494-0800
C&W Milk Bank, Vancouver, BC, Canada	604-875-2282
Banco de Leche, Veracruz, Mexico	52-55-14-4551

viruses, but does not appear to effect the nutritional or anti-infective quality of the milk.<sup>61</sup> Microwaving clearly decreases the anti-infective properties of human milk; the higher the temperature, the greater the effect.<sup>73</sup>

**HUMAN BREASTMILK DONORS AND BANKS**

Although mothers' own milk is clearly best, human milk banking has a long tradition in many countries and a recognized role in the care of preterm and sick infants.<sup>69,74,75</sup> Currently, five US donor milk banks, one Canadian, and one Mexican milk bank belong to the Human Milk Banking Association of North America (HMBANA) (Table 4). All voluntarily follow guidelines drafted in consultation with the Food and Drug Administration (FDA) and the Center for Disease Control and Prevention (CDC).<sup>60,76</sup> These guidelines include screening of all donors for antibodies to HIV-1, HIV-2, HTLV-1, HTLV-2, HBsAg, hepatitis C, and syphilis. Breastmilk donors also receive a full health and risk history and a tuberculosis skin test (PPD) if appropriate. Although most donors to milk banks deliver at term, some do not. "Preterm" milk is usually processed separately and reserved for the smallest, most immature infants. Donor milk is shipped frozen, thawed to a slurry, cultured, then pooled for pasteurization.

Donor milk is released after it is heat-treated and bacterial cultures reveal no growth at 2 days. The San Jose Mothers' Milk Bank and all members of the HMBANA currently use Holder pasteurization. Donor milk is dispensed only on prescription. Lot numbers are recorded and the milk is shipped frozen, overnight. Although pasteurized donor milk is sterile, until further research is available, it should be handled the same as mothers' own milk in the hospital setting.<sup>77</sup>

**BENEFICIARIES OF BANKED DONOR MILK**

The usual recipients of banked human breastmilk are the VLBW (<1500 g) infants whose mothers cannot provide breastmilk for various reasons: maternal illness, medications, substance abuse, or poor social support and resources.<sup>1-4,56,78</sup> Other potential recipients are infants with severe allergies, feeding intolerance, short gut syndrome,

malabsorption and other GI problems, who cannot tolerate formulas.<sup>74</sup> Postsurgical infants can often have feedings advanced more quickly when human milk is used as the initial feeding.<sup>79,80</sup> As pasteurized human milk is devoid of functional cells, infants with immune deficiencies can often benefit from the immunoglobulins and other immune factors in pasteurized human milk without worrying about graft versus host disease.<sup>81</sup>

**FINANCIAL IMPLICATIONS**

Although human milk is donated and not purchased, the costs of screening, processing, and shipping the milk are considerable. To remain financially solvent, breastmilk banks have had to rely on charitable donations, as well as billing approximately \$2.50 to \$3.00 per ounce (plus shipping) for the milk provided. It is, however, the policy of all of the milk banks that no infant shall go without milk for financial reasons. New York State enacted a law to promote and support donor milk availability and quality.<sup>82</sup> The World Health Organization/UNICEF has also supported the establishment and use of donor milk banks as part of international efforts to promote breastfeeding<sup>75</sup> (Table 5).

In California, medically necessary donor human milk is covered by MediCal (Medicaid) for outpatients and noncontracting hospital inpatients. MediCal-managed care plans are mandated to provide medically necessary donor human milk for infants as well as prenatal and postnatal breastfeeding education, breast pump rental and supplies, and lactation consultation services.<sup>83</sup> However, many hospitals contract with MediCal for an NICU per diem rate that was negotiated long ago, without considering the need for donor milk. At present, the cost of donor milk and the cost of supporting mothers who provide their own milk (pumps, containers, miscellaneous supplies, lactation consultant services) must come out of low NICU per diem rates.

The cost effectiveness of human milk can be estimated through the use of medical utilization and cost data derived from published literature and experience at Sharp Mary Birch Hospital for Women (SMBHW). Each year the SMBHW NICU cares for approximately 140 VLBW (<1500 g) infants of whom about 15% (21 infants/year) do not receive their mothers' milk, predisposing them to higher risk for NEC, sepsis, and a longer stay in the NICU.<sup>3</sup> For this group of 21

**Table 5** WHO/UNICEF Joint Resolution, 1980.<sup>75</sup>

Where it is not possible for the biological mother to breastfeed, the first alternative, if available, should be the use of human milk from other sources. Human milk banks should be made available in appropriate situations.

**Table 6** Morbidity: Fortified Human Milk Versus Preterm Formula\*

	FHM	PTF	Difference	<i>p</i>
Length of stay (days)	73	88	15	0.03
NEC (#/infant)	0.02	0.13	0.11	≤0.01
Late-onset sepsis (#/infant)	0.3	0.6	0.3	0.03
Duration of TPN (days)	25	35	10	0.01

\*Schanler et al.<sup>3</sup>  
 FHM, fortified human milk.  
 PTF, preterm formula.

VLBW infants, the use of preterm formula, instead of human milk, is expected to result in 315 additional hospital days, 2.3 additional cases of NEC, 6.3 additional episodes of late-onset sepsis, and 210 additional days of TPN (Table 6).

This added morbidity due to lack of human milk is associated with additional and preventable healthcare costs. The direct medical costs for 1 day of NICU hospitalization, one case of NEC, and one

**Table 7** Estimated Direct Costs of Hospitalization, NEC, Late-Onset Sepsis, and PDHM

<i>Estimated costs of hospitalization</i>	
NICU nursing care	\$600/day
TPN	\$160/day
Antibiotic therapy	\$50/day
Radiology	\$10/film
Lumbar puncture tray	\$9 ea
Bacteriologic culture	\$15 ea
PTF	No cost at present*
Human milk fortifier	No cost at present*
<i>Estimated cost of one case of nonsurgical NEC</i>	
Antibiotic therapy × 10 days	\$500
TPN × 10 days	\$1600
Additional X-rays (10)	\$100
Bacteriologic cultures (4)	\$60
Total	\$2260
<i>Estimated cost of one case mild sepsis</i>	
Antibiotic therapy × 10 days	\$500
TPN × 5 days	\$800
Additional X-rays (3)	\$30
LP tray (1)	\$9
Bacteriologic cultures (4)	\$60
Total	\$1399
<i>Estimated costs of PDHM per VLBW infant</i>	
\$3.00/oz + shipping	
1 month PDHM ~70 oz = \$210 + 50 = \$260	
2 months PDHM ~250 oz = \$750 + 100 = \$850	

\*The WHO/UNICEF and the US Baby-Friendly Committee strongly recommend all hospitals purchase formulas at market rates to avoid the appearance of endorsement of formula brands and conflict of interest in promoting a product inferior to breastmilk.

**Table 8** Cost of Not Using Human Milk

15 extra days LOS × \$600/d	\$9000
0.11 extra cases NEC/infant × \$2260/case	\$ 249
0.3 extra cases of sepsis/infant × \$1399 per case	\$ 420
Total extra cost/infant	\$9669
\$9669 ÷ \$260 = \$37.19 (1 month donor milk).	
\$9669 ÷ \$850 = \$11.37 (2 months donor milk).	

episode of sepsis have been estimated from costs, not charges, at SMBHW (Table 7). Actual cost estimates were obtained from the finance and purchasing departments of SMBHW and do not include indirect costs and overhead. Estimates for the costs of pasteurized donor human milk (PDHM) were derived from the San Jose Mothers' Milk Bank and average milk intakes of our SMBHW VLBW infants. It is clear that one episode of sepsis or NEC would more than pay for donor breastmilk for a given infant.

Using these utilization and conservative cost data, estimates can be calculated for the total direct medical costs attributable to the use of preterm formula rather than human milk (Table 8). Assuming the increased length of stay of infants fed preterm formula is at least partly due to the concomitant increase in NEC and late-onset sepsis in these infants, the increase in cost of not using human milk is \$9669 per infant. Indeed, assuming purchase of 2 months of donor human milk for each NICU VLBW infant not receiving his/her own mother's milk, the NICU could save approximately \$11 for each \$1 spent on donor milk. Assuming the more usual 1 month (or less) of donor milk per infant, the savings would be \$37 for each \$1 spent on donor milk. Research suggests that pasteurized human milk is nearly as effective as fresh human milk in reducing infection and NEC in preterm infants.<sup>13,22</sup> Even if donor milk is only half as effective as mothers' own milk, the savings can be dramatic. At SMBHW, donor human milk for 21 VLBW infants could save almost \$200,000 per year.

### SUMMARY

While neonatologists and others work at the state and federal level to update policy, increase NICU rates to cover newer, but proven, therapies, and educate insurance companies and health plans, we need to take advantage of donor milk for our infants. Although fresh mothers' milk is best, banked donor human milk can save lives, reduce morbidity, and save NICU and healthcare dollars, while helping to insure optimal physical and neurologic development.

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