Milk Banking and Donor Milk: Experience, research & innovation in the NICU and beyond

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Donor Human Milk
Not a new idea...

Ancient Egypt
Relief from the tomb of King Tut’s wetnurse (~1340 BC)

More Ancient Milk Donors

Maia, one of the Pleiades, mother of Hermes by Zeus. Wet-nurse to Zeus’s son Arca after Hera turned his mother into a bear

Greek terracotta, 2nd century AD

Louis XIV and his wetnurse
27th Century France
Famous Donor Milk Recipients

Who are these babies and their poor mother?

Dionne Quintuplets

- Born in Ontario in 1934
- ~32 weeks, 735-1200g
- Fed drops of water for first day, then cow milk + corn syrup on 2nd day
- Donated milk started on day 3
- 120 shipments of milk from Toronto, over 5 mo
- 8000 estimated oz

Donor Human milk and milk banking

- Donor milk introduction
- HMBANA
- Donor screening process
- Donor Milk Use in North America
- Pasteurization process
- Effects of pasteurization
- Donor milk for preterms
- Donor milk for other newborns
- Cost of donor milk

Human Milk Banking Association of North America: HMBANA

HMBANA advances the field of nonprofit milk banking through member accreditation, development of evidence-based best practices, and advocacy for breastfeeding and human lactation to ensure an ethically sourced and equitably distributed supply of donor human milk.

- 26 member banks, 5 more in development
- (up from 6 in 2003, when we opened in Iowa)
- Minnesota – became a member bank a few weeks ago 😊

Minnesota Milk Bank for Babies – recent HMBANA certification – will have a pin here soon!

https://www.mnmilkbank.org/
Human Milk Banking Association of North America: HMBANA

- 4.2 million ounces (126,000 liters) dispensed in 2015 doubled from 2011,
- 6.5 million ounces in 2018 (12% increase from 2017)
- 11,672 donors in 2018

Mother’s Milk Bank of Iowa

- Founded in 2002 by Jean Drulis and Ekhard Ziegler
- Dispensed first milk in 2003
- 216,688 oz pasteurized in 2017 (about 225k in 2018)
  - 15.5% increase over 2016
- 20% of milk dispensed to Stead Family Children’s Hospital
- 80% elsewhere
- 79% of total dispensed to inpatients, 21% to outpatients
- Milk dispensed to 17 states, 61 hospitals, and 117 cities
- Dispensed to 15 hospitals in Iowa
- 35 milk depots around the state and surrounding states
- 1st milk dispensary opening in Dubuque, IA, May 2019

Milk Collection Depots (35), Mother’s Milk Bank of Iowa

Comparison – Inpatient, Outpatient
Mother’s Milk Bank of Iowa

https://uichildrens.org/mothers-milk-bank-iowa
Donor human milk is on the rise

- Collected, pooled, and pasteurized by the member banks of HMBANA
- 26 banks, 5 more in development (up from 6 in 2003, when we opened in Iowa)
- 4.2 million ounces dispensed in 2015 (doubled from 2011, quadrupled since 2007)
- Smaller contributions from Prolacta and now Medolac commercial banks.
- CDC MPINC: 25% usage in 2007, 45% in 2011 in level 3-4 NICUS
- Recent survey of medical directors: 75% usage in level 4, 53% in level 3 units in the US

Milk Donors: Screening

- Volunteer, healthy, lactating women
- Health and behavioral screening in person or via phone
- Mother’s medical provider must sign off on her suitability as a donor
- Infant’s medical provider must sign off that mother may donate (unless donor is bereaved or infant not in her care)
- Serologic screening for infectious disease performed prior to donation
- Ongoing behavioral screening every 2 months

Milk Donors: requirements

- Non-smokers
- Light alcohol use only (<2oz per 24hrs)
- No illegal drug use (or medical marijuana)
- No chronic use of herbals or megadose vitamins
- No tattoos or piercings within past 8 days if from licensed provider
- No blood products (except Rhogam) within 12 months

Safety of Donor Milk

- There has never been a case of a disease transmitted by donor milk in the history of HMBANA
- Theoretical risk similar to blood transfusion, but should be lower
  - Milk is ingested vs. intravenous exposure
  - In addition to the donor screening (identical to blood donors), Pasteurization and freezing inactivate HIV, CMV, and hepatitis, and other viruses
Tracking and Recall of Donor Milk

- System of tracking is maintained until every recipient of milk from a batch is 21 years old
- A mock recall to test the bank’s ability to track a donation from donor to recipient in less than 6 hours is carried out every 3 years

Milk Donors, exclusions

- No sexual partners in the past 12 mo at risk for HIV/HTLV/hepatitis infection via needle use or sexual contact
- Not more than 3 mo spent in the UK between 1980 and 1996
- Not more than 5 years spent in Europe since 1980
- Cannot be native of or traveled in Africa since 1977 (or sex partner of same)
- Cannot have been (or sexual partner) incarcerated for more than 72 hours in past 12 mo

Milk Donors, temporary exclusions

- Any acute infection of the breast or nipple (yeast, mastitis, impetigo, etc)
- 4 weeks after household case of rubella or varicella
- During reactivation of any HSV or zoster of the chest
- 12 hours after any alcohol consumption > 1 drink (6 hrs for 1 drink)
- Waiting periods after all drugs, including Tylenol and Ibuprofen, homeopathic remedies, herbal remedies, prescription drugs
- 28 days after Ebola exposure

Milk Donors: allowed medications

- Human insulin
- Thyroid replacement
- Progestin-only contraceptives
- Low-dose estrogen contraceptives
- Nasal sprays, topical medications, asthma inhalers, eye drops
- Non sedating antihistamines
- Fluvoxamine, paroxetine, sertraline
- Antacids (Tums, H2 blockers, PPI)
- Ibuprofen, acetaminophen
Blood Screening of Donors

- HIV 1 and 2, HTLV I/II antibody tests
- Hepatitis B surface antigen and Hepatitis C antibodies
- Syphilis (RPR) (most common false positive)

May use previously obtained tests within past 6 months (IA bank does testing for each donor regardless of previous testing)

All above tests are screening tests

Confirmatory tests can be ordered for indeterminate or positive screening tests and if negative, the bank may allow the donor

- PCR (nucleic acid) tests for HIV, HTLV, Hepatitis B and C
- FTA (florescent treponemal antibody) confirmatory test for Syphilis

Milk Processing/Pooling Procedure

- Milk delivered by donors, typically frozen, to bank or depot
- Kept at -20ºC until processed
- Milk thawed and pooled, 3-10 donors per batch

Holder Pasteurization: HMBANA procedure

- Milk containers submerged in shaking water bath at 62.5ºC for 30 minutes
- Milk rapidly cooled, aliquoted into 100ml bottles, and frozen at -20ºC until use
- Milk from each batch cultured for bacteria, any growth is unacceptable

Effects of Holder Pasteurization on Human Milk

- White blood cells are inactivated
  - Human milk has 4000 cells/ml in the first three months
  - Milk WBCs are bioactive, and survive into the intestine intact
  - Inactivates HIV, CMV, and many other viruses
  - Kills bacteria
Pasteurization Effects on Anti-infective compounds in human milk

- Secretory IgA: opsonizes viral and bacterial pathogens in the gut
  - Up to 40% inactivated
- Lactoferrin: bacteriostatic iron-binding protein
  - Up to 66% inactivated

Pasteurization effects on Anti-infective compounds in human milk

- Lysozyme: enzyme that disrupts bacterial cell walls
  - Not affected by Holder Pasteurization
- Oligosaccharides: bind to bacterial receptors, making them unable to invade intestinal mucosal cells
  - Total amount less in donor milk
  - Different structures than in preterm infant mother’s own milk

Effects of handling on donor milk nutritional content

<table>
<thead>
<tr>
<th>Step in Process</th>
<th>Fat g/dl</th>
<th>Protein g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw*#</td>
<td>2.17 ± 1.47</td>
<td>1.03 ± 0.39</td>
</tr>
<tr>
<td>Post-Pasteurization*#</td>
<td>2.05 ± 1.46</td>
<td>0.99 ± 0.42</td>
</tr>
<tr>
<td>Thawed*#</td>
<td>2.00 ± 1.45</td>
<td>0.97 ± 0.41</td>
</tr>
<tr>
<td>p value, ANOVA* (5 conditions)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fed by NG bolus #</td>
<td>1.88 ± 1.22</td>
<td>0.94 ± 0.38</td>
</tr>
<tr>
<td>Continuous infusion #</td>
<td>1.00 ± 0.99</td>
<td>0.89 ± 0.41</td>
</tr>
<tr>
<td>p value, ANOVA* (all 5 conditions)</td>
<td>&lt; 0.001</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Study of milk donated to Brazilian milk bank, assessed protein and fat by infrared Analyzer 87 milk samples, unknown # of donors
The more times you handle milk, the more you lose

Adapted from Viera et al, Early Human Development 2011; 87:577

Donor Milk Use: preterm and term infant populations
Hierarchy of VLBW feeding

1. Mother’s own milk
   - Clearly established as gold standard
   - Compared to preterm formula, decreases risk of short term morbidity (sepsis, NEC, perhaps ROP and BPD)
   - Direct comparisons to donor milk are limited, but suggest superiority
   - Requires nutrient fortification to support growth needs for VLBW, primarily protein and minerals
   - “hindmilk” is not the solution to the increased needs of very preterm infants
   - Total volume of human milk required to achieve target nutrition is often excessive for VLBWS (> 180 ml/kg/d needed, <1.5 kg infants often need to be limited to ~150 ml/kg/d)
   - Fat is not always the growth limiting nutrient

2. Pooled, Pasteurized donor milk
   - AAP Section on Breastfeeding recommends use of donor milk when maternal milk unavailable
     - [AAP Section on Breastfeeding](http://pediatrics.aappublications.org/content/129/3/e827.full.html)
     - “The potent benefits of human milk are such that all preterm infants should receive human milk.” “If mother’s own milk is unavailable...pasteurized donor milk should be used.”
   - Also requires nutrient fortification, often at higher levels than mother’s own milk

More society recommendations re: donor milk in VLBWs

- **Royal College of Paediatrics and Child Health, 2018:**
  - [https://www.rcpch.ac.uk/statement-donor-breast-milk](https://www.rcpch.ac.uk/statement-donor-breast-milk)
  - “There is an insufficient evidence base to recommend pasteurised human donor milk over formula for preterm and full-term babies in modern neonatal care when maternal breast milk is insufficient or unavailable.”
- **ESPHGAN Committee on Nutrition, 2013**
  - “When OMM is not available, DHM is the recommended alternative.”

These positions from professional societies are all based on the same body of evidence

Donor Milk vs Preterm Formula for VLBW infants

- Few randomized trials
- Most frequent outcome studied is necrotizing enterocolitis and other infections
- Growth a secondary outcome in all trials
- Developmental outcomes

Greek sarcophagus, British Museum
Meta-analysis of trials comparing feeding with formula versus donor breast milk—effect on risk of necrotising enterocolitis (adapted from Quigley et al.).

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Formula</th>
<th>DBM</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross (1983)</td>
<td>3/26</td>
<td>1/41</td>
<td></td>
</tr>
<tr>
<td>Lucas (1984a)</td>
<td>4/76</td>
<td>1/83</td>
<td></td>
</tr>
<tr>
<td>Lucas (1984b)</td>
<td>5/173</td>
<td>2/170</td>
<td></td>
</tr>
<tr>
<td>Schanler (2005)</td>
<td>10/88</td>
<td>5/76</td>
<td></td>
</tr>
<tr>
<td>Tyson (1983)</td>
<td>1/44</td>
<td>0/37</td>
<td></td>
</tr>
</tbody>
</table>

Pooled RR: 2.46 [95% CI 1.19-5.08]

Heterogeneity: $\chi^2 = 0.99$ (p = 0.69); $I^2 = 0.0\%$

Donor milk and growth for VLBW infants

- Schanler 2005:
  - donor milk resulted in lower weight gain than either maternal milk or preterm formula (17.7 g/kg/d vs. 18.8 vs. 20.1)
  - Head circumference and length gains were similar for donor milk and preterm formula

Donor milk, maternal milk, and preterm formula: growth at Iowa


- Infants born between 1/1/03 and 6/1/05
- <1251 g at birth
- Admitted to UICH NICU in first 24 hours of age
- 171 eligible infants, fed maternal milk, donor milk, and preterm formula in varying proportions
Type of human milk may be related

- Infants fed donor milk had more fall off in growth, were more often SGA at discharge than those fed maternal milk, not significant

Weight 2-scores decrease across hospitalization

- Infants are AGA at birth, and AGA at discharge in general, but have not maintained in-utero growth rate

- More human milk resulted in greater fall off in growth rate, but not significant, and better than historical comparison

Growth Outcomes by Type of Human Milk

<table>
<thead>
<tr>
<th>Type of Human Milk</th>
<th>Median (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;75% DM</td>
<td>(2320, 2720)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;75% MM</td>
<td>(2710, 3050)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mixed MM/DM</td>
<td>(2875, 3200)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Donor milk (+/- MM) vs. Preterm Formula: Studies including 2 year developmental outcomes

- 1 Retrospective cohort study
- 2 completed RCTs of donor milk vs. preterm formula as supplement to MM
- 1 ongoing large RCT of donor milk as primary diet vs. preterm formula

Retrospective cohort study of developmental outcomes of infants fed donor milk

- Retrospective cohort study of infants fed DM vs. MM vs. PF, in the first 30 days of life
- Pre and post DM protocol comparison
  - MM group = 100% MM
  - DM and PF = > 50% of indicated diet
- DM infants identified first, then admission logbooks used to identify MM and PF groups matched for GA and birthweight (non-specific)
- 27 fed DM, 29 fed MM, 25 fed PF, about 65% followed to age 2
- Infants fed DM grew more poorly in the first month of life than those fed MM or PF


Paul Cezanne, Hortense Breastfeeding Paul
DoMINO Trial Results

- 363 VLBWs in Ontario
- Randomized to DM or PF if mother’s milk unavailable
- 28% of infants received no study diet
- Proportion of feeds as study diet ~60% in both groups
- Used milk from donors <3mo post-partum and with at least 20kcal/oz, milk from Ohio

Other DoMINO outcomes

- Growth similar: both groups lost about 0.5 sd z-score for weight
- NEC Stage II or greater
  - Formula group 6.6%
  - Donor milk group 1.7% p = 0.02
- Editorial by TTC published along with trial
  - JAMA, 2016 Nov 8;316(18):1875-1876
- Reinforces the importance of ongoing research

No difference in BSID III scores

Increased risk of Cog < 85

No difference in Risk of Cog < 70
Donor milk and term infant populations

Donor milk for healthy term newborns: recommendations

Academy of Breastfeeding Medicine (Protocol #3: Suppl feeding in healthy term neonate)

• "If the volume of mother’s own colostrum/milk does not meet her infant’s feeding requirements... donor human milk is preferable to other supplements."

American Academy of Pediatrics

• Recommended for preterm infants, and high risk term infants “is acceptable”

Donor milk for healthy term newborns

Survey of NE US hospitals: Belfort et al; Breastfeeding Med. 13:34-41; 2018

• 71 hospitals, 73% used donor milk, 55% had level III/IV NICUs, 50% BFH or working toward
• 32% reported use of donor milk for healthy term infants

Donor milk use in healthy newborns increasing


• Survey of Massachusetts birth hospitals
  • 29% of all respondents used DM in the normal nursery, 43% of hospitals served by a milk bank for NICU used DM in the normal nursery
  • DM use associated with higher rates of exclusive BF at discharge
    • 77% vs 56% p = 0.02
    • 83% of respondents felt DM increased exclusive BF

Kair and Flaherman, J Hum Lact 2017 33(4) 710-16

• Qualitative Study of Iowa moms using DM at UIHC
  • Moms saw DM as temporary compared to formula as ongoing plan
  • Donor milk is ‘healthier’

Donor milk for healthy term newborns associated with:

• Higher “exclusive breastfeeding” at discharge per Joint Commission PC05
  • 77% vs 56% p = 0.02
• Increased odds of BFHI participation

*78% of respondents answered “agree or strongly agree” to the statement: “studies show health benefits of providing donor milk to healthy full term infants.”
Donor milk use for healthy newborns

Donor Milk Utilization for Healthy Infants: Experience at a Single Academic Center
Sen et al, Breastfeed Med 13:28-33, 2018;

Use increased as availability increased
Displaced formula supplementation

Indications similar to formula supplementation

Donor milk for healthy term newborns: RCT


- RCT of donor milk vs. no supplementation for ≥ 37 week infants with ≥ 4.5% (but < 10%) weight loss at 24-36 hrs of age
- Donor milk intervention: 10 ml supplement via syringe feed after each breastfeed until mature milk production established. If not established prior to discharge (dc), 200 ml donor milk provided to continue supplement at home.
- Control: continued exclusive breastfeeding unless supplement ordered by physician team
- Primary outcome: formula use at 1 week of age
- Secondary outcomes: Any human milk and human milk only at 1, 2, and 3 months


RESULTS

Note: breastfeeding outcomes better in non-supplemented group
Not statistically significant, but all outcomes go in the same direction

Table 3. Infants Feeding Outcomes

<table>
<thead>
<tr>
<th>Feeding Outcomes</th>
<th>Donor Mil (Intervention)</th>
<th>No Supp (Control)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any formula use</td>
<td>6 (21)</td>
<td>2 (7)</td>
<td>.15</td>
</tr>
<tr>
<td>1 month</td>
<td>5 (17)</td>
<td>3 (10)</td>
<td>.23</td>
</tr>
<tr>
<td>2 months</td>
<td>4 (14)</td>
<td>2 (21)</td>
<td>.88</td>
</tr>
<tr>
<td>3 months</td>
<td>1 (5)</td>
<td>2 (33)</td>
<td>.37</td>
</tr>
<tr>
<td>4 months</td>
<td>1 (4)</td>
<td>1 (33)</td>
<td>.20</td>
</tr>
<tr>
<td>5 months</td>
<td>1 (5)</td>
<td>3 (33)</td>
<td>.69</td>
</tr>
<tr>
<td>6 months</td>
<td>1 (5)</td>
<td>3 (33)</td>
<td>.69</td>
</tr>
<tr>
<td>Feeding at breast</td>
<td>30 (100)</td>
<td>28 (93)</td>
<td>.35</td>
</tr>
<tr>
<td>1 week</td>
<td>32 (107)</td>
<td>29 (97)</td>
<td>.55</td>
</tr>
<tr>
<td>2 weeks</td>
<td>21 (70)</td>
<td>17 (58)</td>
<td>.18</td>
</tr>
<tr>
<td>3 weeks</td>
<td>9 (30)</td>
<td>7 (24)</td>
<td>.20</td>
</tr>
<tr>
<td>Feeding at breast at hospital</td>
<td>30 (100)</td>
<td>28 (93)</td>
<td>.35</td>
</tr>
<tr>
<td>Any breast milk feeding</td>
<td>26 (69)</td>
<td>18 (46)</td>
<td>.20</td>
</tr>
<tr>
<td>1 month</td>
<td>25 (83)</td>
<td>17 (46)</td>
<td>.20</td>
</tr>
<tr>
<td>2 months</td>
<td>24 (82)</td>
<td>15 (46)</td>
<td>.20</td>
</tr>
<tr>
<td>3 months</td>
<td>22 (73)</td>
<td>17 (46)</td>
<td>.20</td>
</tr>
</tbody>
</table>

*Feeding at breast means the infants were breastfed directly to breast within the last 24 hours

**Feeding at breast means the infants were breastfed directly to breast within the last 24 hours"
Use of DM in late preterm infants outside of NICU

- Decreased length of stay in 35-36 week infants in mother-baby units compared to use of formula supplementation, ~ 1 day shorter
- Mean LOS for formula 3.19 days, for BF + DM 2.86 day; for BF only 2.58 days, p 0.001 for formula vs BF; p 0.06 for DM vs no supplement
- Improved breastfeeding rate at discharge
  - Infants receiving formula supplement 16% less likely to continue breastfeeding (RR 0.84, 0.77, 0.92, p = 0.01)

DM cost is not excessive

Spatz, Robinson, Froh; JOGNN 47:583-88, 2018
Cost and use of pasteurized donor human milk at a Children’s Hospital

- CHOP study of use in 281 infants < 1 yr old
  - 70% NICU, 30% other hospital units
- Diagnoses: 21% cardiac; 17% NEC; 29% complex surgical anomaly (CDH, etc); preterm 9%; other 23%
- Mean volume used 195ml per patient
- Mean days of use 23 (range 1-134)
- Mean cost $29.19 per day of use ($4.50 per oz)

CHOP study of annual cost: Spatz and Edwards, Adv Neon Care 12(5) 2012
- $155,000 per year for donor milk
- $18.4 million for TPN in same time period in same population

Cost of Donor milk vs. other diets for VLBW infants

The Institutional Cost of Acquiring 100ml of Human Milk for VLBW infants in the NICU

- Prospective cohort study of 157 mothers (Rush University)
- Cost of DHM and PF compared to MM – cost of pump rental, collection kit, storage containers

Cost dependent on mom’s milk supply
- $0.51 per 100 ml in moms >700ml/d
- $7.93 per 100 ml in moms <100 ml/d
- >100ml per day volume was cut point for cheaper than DM

<table>
<thead>
<tr>
<th>Intervals (Days) Infants Were Fed Donor Breastmilk and Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of DM use</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>All infants 12 (1–84)</td>
</tr>
<tr>
<td>Discharge feeding Breastmilk only 4 (1–32)</td>
</tr>
<tr>
<td>Breastmilk and formula 9 (2–23)</td>
</tr>
<tr>
<td>Formula (MOM during admission) 13 (2–84)</td>
</tr>
<tr>
<td>Formula (no MOM during admission) 29 (12–60)</td>
</tr>
</tbody>
</table>
Final Thoughts

- Donor milk is commonly used in preterm populations, with use increasing in other infant groups.
- Theme of donor milk being not exactly like mother’s milk emerges
  - Different cytokine profile, different HMO profile
  - Different macronutrient composition (mostly lower protein)
  - Lower concentration of LC-PUFAs
  - Use may result in growth compromise compared to MM, although not universally
  - "Lacto-engineering" can help – fortification to help growth
- Support Milk Banks – human milk matters
- NEC is much less in babies fed donor milk – improved health outcomes and huge cost savings in NICUs
- The cost of donor milk for hospital use in infant populations is not excessive and can be cost effective.

Final Final thoughts

- The optimal diet for VLBWs is their own mothers’ milk, appropriately fortified
- But what if we don’t have enough?
  1. We need to focus on mothers, to support their efforts to provide milk
     - Interventions such as: free access to hospital grade pumps for home use, peer support, professional support, payment?
  2. Donor Milk is recommended, and likely is the better of the two alternatives, with the most evidence for NEC prevention, less for other outcomes.
  3. Lack of prospective studies of EHM vs. human milk + bovine HMF without formula make it difficult to recommend EHM as superior choice when using DM