Human Donor Milk: Current Experience

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Objectives

• Rationale for donor milk
• Donor milk processing
• Ongoing donor milk trial

• "Banked human milk may be a suitable feeding alternative for infants whose mothers are unable or unwilling to provide their own milk."

• "Human milk banks in North America adhere to national guidelines for quality control of screening and testing of donors and pasteurize all milk before distribution."

• "Fresh human milk from unscreened donors is not recommended because of the risk of transmission of infectious agents."

The Canadian Paediatric Society: Position Statement (Nov 2010)

- Pasteurized human donor milk is a recommended alternative when mother’s own milk is not available
- Should be prioritized to compromised preterm and selected ill term newborns
- Informed consent


The Canadian Paediatric Society: Position Statement

- Milk banking should be adopted as a cost effective nutritional source for hospitalized neonates
- There is a need for prospective studies to evaluate the benefits of banked human milk
- The CPS does not endorse the sharing of unprocessed human milk


Media coverage

- television, radio, print, on-line
- Postmedia news: Got breast milk? Doctors say milk bank would save babies’ lives
- The Canadian Newswire: Donations of human milk could help sick, hospitalized newborns
- The Toronto Star: Pediatricians call for breast milk banks across Canada
- The Ottawa Citizen: A different kind of bank
- The Edmonton Journal: Donations of breast milk save lives of premature babies: MDs
- The Toronto Star: Donor breast milk is ‘greatest gift’ for sick babies
Media Coverage: Milk Sharing

• Postmedia News: Breast milk sharing ‘very dangerous’ but Canadian moms persist
• The Toronto Star: Breast-milk banks latch on to social media
• The Toronto Star: Health Canada urges caution in sharing breast milk if source is unknown
• The Vancouver Sun: Sharing breast milk not easy; Langley woman rebuffed in attempts to advertise on Craigslist

FDA U.S. Food and Drug Administration

• “If you are considering feeding a baby with human milk from a source other than the baby’s mother, you should know that there are possible health and safety risks for the baby. Risks for the baby include exposure to infectious diseases, including HIV, to chemical contaminants, such as some illegal drugs, and to a limited number of prescription drugs that might be in the human milk, if the donor has not been adequately screened. In addition, if human milk is not handled and stored properly, it could, like any type of milk, become contaminated and unsafe to drink.”
• “FDA recommends against feeding your baby breast milk acquired directly from individuals or through the Internet”

http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm235203.htm

Health Canada Raises Concerns About the Use of Unprocessed Human Milk

Information Update 2010-202 November 25, 2010 For immediate release

OTTAWA - Health Canada advises Canadians to be aware of the potential health risks associated with consuming human breast milk obtained through the Internet or directly from individuals.

Donor Milk: Rationale

- Increased survival of smaller VLBW infants
  - > 90% survive

- However, serious morbidity (eg. NEC, sepsis) and neurodevelopmental sequelae are inversely related to gestational age at birth

  *Interventions to reduce morbidity and promote normal brain development for VLBW infants are urgently required*

Neurodevelopment of the VLBW Infant

- Factors in addition to gestational age shown to be prognostic of neurodevelopmental outcome:
  - sepsis
  - NEC
  - chronic lung disease
  - suboptimal nutrient intake
  - poor growth
  - human milk feeding

Association Between Human Milk Intake and Development of ELBW Infants

- National Institute of Child Health and Development Glutamine Trial
- Extremely LBW infants
  - 775 breast milk
  - 260 no breast milk
- Bayley Scales of Infant Development
  - 18-22 months

For each 10 mL/kg/d of breast milk:


Neurodevelopmental Outcomes Of VLBW Infants And The Role Of Mothers’ Own Milk

- Mothers’ own milk is thought to improve neurodevelopment because:
  - It is well tolerated facilitating optimal nutrient intake and substrate for brain development
  - Indirectly via a myriad of bioactive components in breast milk that may reduce the incidence of sepsis, NEC, and other infections

Donor milk and sepsis

- 226 infants <2500g at high risk for infections (prolonged labour, prolonged ROM, maternal infection, unhygienic vaginal exam, birth asphyxia)
  - Randomized to raw human milk, pasteurized human milk, raw milk with formula, pasteurized milk with formula
  - Unethical to feed formula exclusively!

An Exclusively Human Milk-Based Diet Is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk-Based Products.

- 12 participating NICU’s (11 in US and 1 in Austria)
- Financially supported by Prolacta Biosciences
- Used donor milk and fortifier from Prolacta Biosciences
  - Fortifier provides minimum of 24 cal/oz (82 cal/100 mL)
  - Fortifies to a target of 2.3g of protein in 100mL of nutrition
- Eligibility criteria:
  - BW 500 to 1250g
  - Intention to receive EBM


<table>
<thead>
<tr>
<th>Patient assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HM100: EBM+donor milk+HMF at 100 mL/kg/day</td>
</tr>
<tr>
<td>• HM40: EBM+donor milk+HMF at 40 mL/kg/day</td>
</tr>
<tr>
<td>• BOV: EBM+preterm formula+bovine fortifier at 100 mL/kg/day</td>
</tr>
</tbody>
</table>

NEC + death:
HM100= 6%
HM40= 8.5%
BOV= 20%
P=0.02

OR for NEC with exclusively human milk diet of 0.23 (CI=0.08-0.66, p=0.007)

Discussion

• Number needed to treat to prevent 1 case of NEC is 10 and to prevent 1 surgical case or death is 8.
• Vermont Oxford rate of NEC: 7-10%
• Lucas has reported a reduction in NEC in infants fed unfortified compared to fortified human milk
• An animal model for NEC requires intraluminal bovine casein

Mothers of VLBW babies (Toronto)

• >97% of mothers of VLBW babies wish to provide expressed breast milk for their baby
• Only 30-50% of mothers have a full volume
Inadequate milk volumes

- Maternal factors: stress, illness, endocrine, unable to access medical care (for mastitis, domperidone)
- Infant factors: illness, continuous feeds, speciality formula
- Physical barriers: geographical distance, cost of pump, language barriers
- NICU factors: barriers between mom and baby, lack of privacy to pump at bedside, multi-patient rooms

History of Donor Milk Use

- Wet Nursing
- 1909: 1st milk bank established in Vienna, Austria
- 1910: 1st North American Milk bank founded (Boston)
- 1943: AAP established standards for milk bank operations (collection, processing, storage and dispensing)
- Early 1980’s 23 banks in Canada and 30 in the United States
- Late 1980’s many milk banks closed 2^ due to concerns of viruses transmission
- 1985: Human Milk Banking Association of North America (HMBANA) established
- 2005: Prolacta (commercial entity)

Donor Milk Banking Worldwide

- Brazil: 186+
- Norway: 15
- United Kingdom: 15
- United States: 11
- Canada: 1
- Additional countries include: Argentina, Australia, Bulgaria, Cameroon, Chile, China, Costa Rica, Cuba, Czech Republic, Denmark, Dominican Republic, Finland, France, Germany, Greece, India, Italy, Kuwait, Mexico, Netherlands, Nicaragua, Panama, Poland, Spain, Russia, Slovakia, South Africa, Spain, Sweden, Switzerland, Uruguay, Venezuela

http://www.internationalmilkbanking.org
Milk Donor Qualifications

- Must be healthy and provide milk beyond own baby’s needs
- Non-smokers
- Other than limited list (e.g., asthma inhalers, eye drops), no medications or illicit drug use
- Screened serologically for HIV-1, HIV-2, HTLV I/II, hepatitis C, hepatitis surface antigen, and syphilis no more than 6 months prior to 1st donation
- Donors not paid

Processing Donor Milk

- To remove the potential for transmission of infectious agents that could harm VLBW infants, donor milk is usually pasteurized (62.5°C for 30 minutes)

Flowchart:

1. Freezing, storage, and transport
2. Thawing and Bacterial culture
3. Batching
4. Pasteurization
5. Culture of batch
6. Milk analysis
7. Freezing
8. Courier to institution
Impact of the Pasteurization Process

• Additional freeze/thaw and multiple container changes impact the energy and protein content of donor milk
  
  – donor milk protein ~0.9 g/dl
  – mother's own milk ~1.0-1.2 g/dl

Impact of Holder Pasteurization: Nutrients

<table>
<thead>
<tr>
<th>Protein</th>
<th>Minimal (one study a reduction; another a reduction in the essential amino acid lysine [30%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat (50% of energy in human milk)</td>
<td>Minimal</td>
</tr>
<tr>
<td>Hemeolic acid</td>
<td>Minimal</td>
</tr>
<tr>
<td>Hemeolic acid</td>
<td>Minimal</td>
</tr>
<tr>
<td>Monoglycerides</td>
<td>Minimal</td>
</tr>
<tr>
<td>LCPUFA</td>
<td>Minimal</td>
</tr>
<tr>
<td>Lactose</td>
<td>Minimal</td>
</tr>
<tr>
<td>Minerals</td>
<td>Minimal</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Water Soluble, some significant reductions (e.g. vitamin C, folate); Vitamin A, Minimal</td>
</tr>
</tbody>
</table>

Impact of Pasteurization: Bioactive Components

| Amylase                        | 15% loss of activity                                                                    |
| T-cells, B-cells               | Abolished                                                                                |
| bile salt dependent lipase     | Abolished                                                                                |
| CD14 (soluble)                 | Significantly reduced                                                                    |
| Extracellular growth factor    | No effect                                                                                |
| Erythropoietin                 | Significantly reduced                                                                    |
| Immunoglobulins                | Significantly reduced                                                                    |
| TGF-1, TGF-2, TGF-β3, 3         | Significantly reduced                                                                    |
| IL-10                          | Significantly reduced                                                                    |
| Lactoferrin/iron-binding capacity | Significantly reduced                                                                  |
| Lactoferrin/iron-binding capacity | Significantly reduced                                                                  |
| Lysozyme activity              | No effect                                                                                |
| Slightly reduced               | Slightly reduced                                                                         |
| Oligosaccharides               | No effect                                                                                |
| TGF-α, TGF-β                  | No effect                                                                                |
Cytokine concentrations in raw and pasteurized donor milk

Heparin-binding epidermal-like growth factor (HB-EGF), hepatocyte growth factor (HGF), and granulocyte colony-stimulating factor (GCF)

Gangliosides in raw and pasteurized donor milk
Potential Risks and Benefits of Using Donor Milk as a Supplement: Cochrane Review

- A higher incidence of NEC among infants fed formula vs. donor milk (Relative Risk of 2.5 [95% CI, 1.2, 5.1])
- No longer significant when analysis restricted to trials where donor milk was provided as a supplement

Effect on NEC

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Formula milk</th>
<th>Donor milk</th>
<th>Rate Ratio</th>
<th>Weight</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gwee 1998</td>
<td>256</td>
<td>(141)</td>
<td>2.5</td>
<td>472 (52.4, 519)</td>
<td></td>
</tr>
<tr>
<td>Lopez 1994</td>
<td>676</td>
<td>(163)</td>
<td>1.9</td>
<td>107 (244, 3923)</td>
<td></td>
</tr>
<tr>
<td>Lynn 1996</td>
<td>517</td>
<td>(217)</td>
<td>2.0</td>
<td>246 (245, 1.49)</td>
<td></td>
</tr>
<tr>
<td>Sauger 2005</td>
<td>1300</td>
<td>(179)</td>
<td>3.3</td>
<td>177 (234, 463)</td>
<td></td>
</tr>
<tr>
<td>Tunc 1996</td>
<td>144</td>
<td>93</td>
<td>3.7</td>
<td>53 (10.6, 48.9)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>667</td>
<td>445</td>
<td>3.0</td>
<td>2.56 (1.35, 5.16)</td>
<td></td>
</tr>
</tbody>
</table>


Potential Risks and Benefits of Using Donor Milk as a Supplement: Cochrane Review

- Infants fed donor milk experienced slower weight (P<0.0001, length (P<0.0003) and head circumference gains (P<0.0001).
- Mean rate of weight gain was sub-optimal in 6 of 8 trials for donor milk
Limitations of Studies in the Cochrane Review

- Studies not blinded
- 7 of 8 studies in meta-analysis do not reflect current clinical practice
  - >25 years ago
  - Larger babies
  - Predominance of formula versus mothers’ own milk feeding
  - No nutrient fortification of mothers’ own milk
  - Only two studies looked at long term follow-up

Donor Milk for Improved Neurodevelopmental Outcomes

DoMINO Project

Hypotheses:

Primary:
- Improve cognitive development at 18-24 months CA

Secondary:
- Reduce neonatal mortality and morbidity
- Support growth
- Improve visual development at 4 and 6 months CA
Study Design

- Multi-centered double-blinded RCT
- Infants randomized within 4 days of birth
- Duration of 90 days or until hospital discharge

Inclusion Criteria

- <1500 g birth weight
- Singleton or multiples

The Intervention

- Receive either pasteurized donor human milk (PDM) or preterm formula when mothers’ own milk is unavailable
- Infants will continue to receive PDM or preterm formula after transfer to a participating Level II NICU in the GTA for 90 days after randomization or discharge home, whichever occurs first
- PDM will be purchased and shipped on ice from the Mothers’ Milk Bank of Ohio
  - Backup: Bronson Mothers’ Milk Bank
  - Transition to Ontario Human Milk Bank as comes on line
Overall Study Design, Frequency and Duration of Follow-up

Health Economics

Objectives:

- Measure relevant and non-health costs of neonatal care to 18 months CA
- To use measured costs in conjunction with trial efficacy data to estimate the cost of a 5-point improvement in the Bayley through use of PDM in VLBW infants
- To use decision-analytic modeling and secondary literature to estimate long-term health and non-health costs, as well as quality of life outcomes per quality adjusted life year.
Economic gains resulting from the reduction in children’s exposure to lead in the US
• IQ increase 2.2 to 4.7 points in 20 years of lead reduction
• Each IQ point raises worker productivity 1.76-2.38%
• 2 y/o lifetime earnings in 2000 dollars (US): $723,300
• 3.8 million children per year
• $110 to $319 billion per year’s cohort


Conclusion

- Strategies are required to reduce morbidity and improve neurodevelopment of VLBW infants
- Strong evidence that human milk (mothers’ own, donor milk) may be an important strategy
- Order of benefit: Mothers’ own milk >> donor milk >> formula
- First priority to promote mother’s own milk production

Conclusion

- Meta-analysis suggests donor human milk:
  - Reduces NEC
  - Slows both linear and head growth
- To promote expansion and on-going support of the use of donor milk:
  - Need studies that include smaller babies, mixed feeding and current clinical practices
  - With growing health care costs, a systematic approach to understanding the cost associated with feeding type is required
Future directions

- Better pasteurization methods for donor milk that are effective in eliminating known pathogens while preserving bioactive components?
- Should donor milk not be pasteurized?
- Human milk fortifiers?