Human Donor Milk: Current Experience

Dr Sharon Unger, MD, FRCP
University of Toronto
Mount Sinai Hospital

UNIVERSITY OF TORONTO

MOUNT SINAI HOSPITAL
Joseph and Wolf Lebovic Health Complex

Objectives

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

AAP Policy

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN

- "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."

Pediatrics 2005;115(2): 496-506.

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

Paediatr Child Health 2010;15(9):595-598.

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

Paediatr Child Health 2010;15(9):595-598.

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

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.

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2010/2010_202-eng.php

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

Vohr et al. Pediatrics. 2006;118(1):e115-23.

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

TABLE 4 Effect of Breast Milk Feeding (mL/kg per day) on Developmental Outcomes and Rehospitalization: Multiple Regression Results

Outcomes	Parameter Estimate	P
MDI	0.53	.0002
PDI	0.63	<.0001
BRS	0.82	.0025
Logistic regression	OR	95% CI
Rehospitalization for infection or respiratory morbidity	0.94	0.90–0.98

Estimates are adjusted for standard covariates listed previously. OR indicates odds ratio; CI, confidence interval.

Vohr et al. Pediatrics. 2006;118(1):e115-23.

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!

Narayanan et al. Lancet 1984;17(2):1111-3.

TABLE III—OCCURRENCE OF INFECTIONS

	I Raw EHM	II Pasteurised EHM	III Raw EHM + formula	IV Pasteurised EHM + formula
Number in group	57	56	56	57
Number infected	6 (10·5%)	8 (14·3%)	9 (16·1%)	19 (33·3%)
Infections				
Septicaemia	4	4	5	9
Diarrhoea	..	..	2	3
Pneumonia	..	..	..	2
Conjunctivitis	2	4	1	8
Pyoderma	..	..	..	1
Thrush	..	..	..	1
Umbilical sepsis	2	..	1	2

Narayanan et al. Lancet 1984;17(2):1111-3.

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.

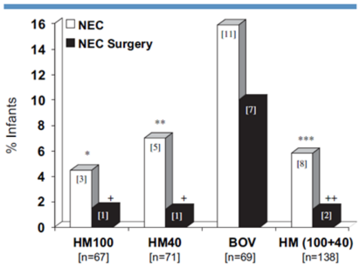
- 12 participating NICU's (11 in US and 1 in Austria)
- Financially supported by Prolacta Biosciences
- Used donor milk and fortifier from Prolacta Biosciences
  - Fortifier provides minimum of **24 cal/oz** (**82** cal/100 mL)
  - Fortifies to a target of **2.3g of protein** in 100mL of nutrition
-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

Sullivan S et al. J Pediatr 2010;**156**(**4**):562-7

Patient assignment

- HM100: EBM+donor milk+HMF at 100 mL/kg/day
- HM40: EBM+donor milk+HMF at 40 mL/kg/day
- BOV: EBM+preterm formula+bovine fortifier at 100 mL/kg/day

Sullivan S et al. J Pediatr 2010;**156**(**4**):562-7



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)

Sullivan S et al. J Pediatr 2010;**156**(**4**):562-7

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

Sullivan S et al. J Pediatr 2010;**156**(**4**):562-7

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

Image from SickKids Archives

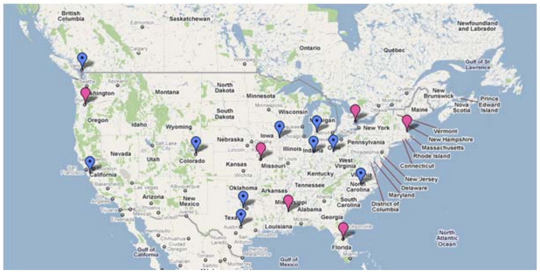
- Wet Nursing
- 1909: 1st milk bank established in Vienna, Austria
- 1910: 1st North American Milk bank founded (Boston)
- 1943: AAP established standards for milk bank operations (collection, processing, storage and dispensing)
- Early 1980's 23 banks in Canada and 30 in the United States
- Late 1980's many milk banks closed 2º 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

HUMAN milk banking ASSOCIATION OF NORTH AMERICA

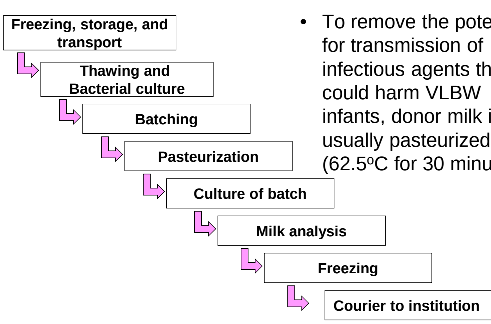


http://www.hmbana.org/

Milk Donor Qualifications

- Must be healthy and provide milk beyond own baby's needs
- Non-smokers
- Other than limited list (eg. 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 (62.5ºC for 30 minutes)

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

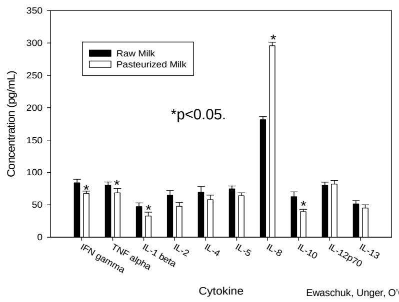
Impact of Holder Pasteurization: Nutrients

Protein	Minimal (one study a reduction; another a reduction in the essential amino acid lysine [30%])
Fat (50% of energy in human milk)	Minimal
•linoleic acid	Minimal
•linolenic acid	Minimal
•Monoglycerides	Minimal
•LCPUFA	Minimal
Lactose	Minimal
Minerals	Minimal
Vitamins	Water Soluble, some significant reductions (e.g vitamin C, folate); Vitamin A, Minimal

Impact of Pasteurization: Bioactive Components

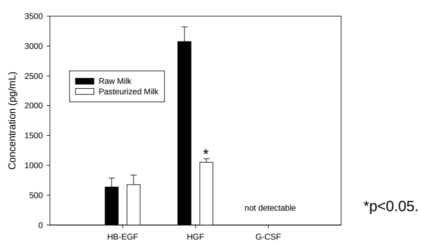
Amylase	15% loss of activity
B-cells, T-cells	Abolished
Bile salt dependent lipase	Abolished
CD14 (soluble)	Significantly reduced
Epidermal growth factor	No effect
Erythropoeitin	Significantly reduced
Immunoglobulins	Significantly reduced
IGF-1, IGF-2, IGF-BP2, 3	Significantly reduced
IL-10	Significantly reduced
Lactoferrin/iron-binding capacity	Significantly reduced
Lipoprotein lipase	Abolished
Lysozyme activity	No effect Slightly reduced
Oligosaccharides	No effect
TGF-α, TGF-β	No effect

Cytokine concentrations in raw and pasteurized donor milk



Ewaschuk, Unger, O'Connor et al; J Perinatol, Feb 2011

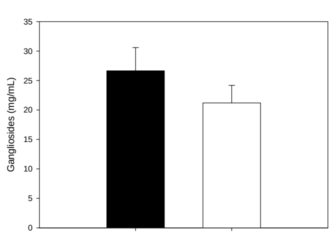
Heparin-binding epidermal-like growth factor (HB-EGF), hepatocyte growth factor (HGF), and granulocyte colony-stimulating factor (GCF)



*p<0.05.

Ewaschuk, Unger, O'Connor et al; J Perinatol, Feb 2011

Gangliosides in raw and pasteurized donor milk



Ewaschuk, Unger, O'Connor et al; J Perinatol, Feb 2011

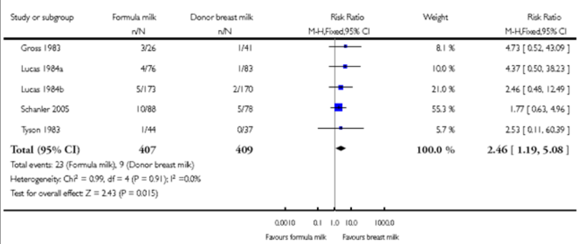
Potential Risks and Benefits of Using Donor Milk as a Supplement: Cochrane Review

- 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

Author	Year	Subjects	Comparison	Blind	Primary outcome	Notes
Davies	1977	68 preterm (28-30 weeks)	Term formula vs Donor Milk	No	Slower growth first month for Donor Milk	Uncertain group for 2 infants with mothers' own milk
Gross	1983	67 preterm (27-33 weeks)	Term formula vs Donor Milk	No	Slower growth for term Donor Milk (not preterm Donor Milk)	Infants with feed intolerance or NEC withdrawn from growth analysis
Lucas	1984	159 LBW (<1850g)	Preterm formula vs Donor Milk	No	Slower growth for Donor Milk; no neurodevelopmental difference	
Lucas	1984	343 LBW (<1850g)	Preterm formula vs Donor Milk	No	No neurodevelopmental difference	
Raiha	1976	106 LBW (<2100g)	Term formula vs Donor Milk	No	No difference in growth	
Schanler	2005	173 preterm (<30 weeks)	Term formula vs fortified Donor Milk	Yes	Slower growth for Donor Milk, no difference in infection events	Only fortified Donor Milk study; 20% cross-over from Donor Milk to Formula
Schultz	1980	20 preterm	Term formula vs Donor Milk	No	No difference in weight gain	
Tyson	1983	81 LBW (<1500g)	Preterm formula vs Donor Milk	No	Slower growth for Donor Milk	Donor Milk not pasteurized ; Randomized day 10; 5 affected infants withdrawn

Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2007:CD002971

Effect on NEC



McGuire, Anthony. Arch Dis Child Fetal Neonatal Ed 2003;88:F11-F14.

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<0003) and head circumference gains (P<0.0001).
- Mean rate of weight gain was sub-optimal in 6 of 8 trials for donor milk

Author	Year	Subjects	Comparison	Blind	Primary outcome	Notes
Davies	1977	68 preterm (28-30 weeks)	Term formula vs Donor Milk	No	Slower growth first month for Donor Milk	Uncertain group for 2 infants with mothers' own milk
Gross	1983	67 preterm (27-33 weeks)	Term formula vs Donor Milk	No	Slower growth for term Donor Milk (not preterm Donor Milk)	Infants with feed intolerance or NEC withdrawn from growth analysis
Lucas	1984	159 LBW (<1850g)	Preterm formula vs Donor Milk	No	Slower growth for Donor Milk; no neurodevelopmental difference	
Lucas	1984	343 LBW (<1850g)	Preterm formula vs Donor Milk	No	No neurodevelopmental difference	
Raiha	1976	106 LBW (<2100g)	Term formula vs Donor Milk	No	No difference in growth	
Schanler	2005	173 preterm (<30 weeks)	Term formula vs fortified Donor Milk	Yes	Slower growth for Donor Milk, no difference in infection events	Only fortified Donor Milk study; 20% cross-over from Donor Milk to Formula
Schultz	1980	20 preterm	Term formula vs Donor Milk	No	No difference in weight gain	
Tyson	1983	81 LBW (<1500g)	Preterm formula vs Donor Milk	No	Slower growth for Donor Milk	Donor Milk not pasteurized ; Randomized day 10; 5 affected infants withdrawn

Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2007:CD002971

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

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

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

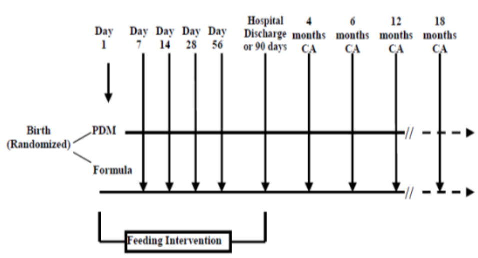
- ❑Receive either pasteurized donor human milk (PDM) or preterm formula when mothers' own milk is unavailable
- ❑ Infants will continue to receive PDM or preterm formula after transfer to a participating Level II NICU in the GTA for 90 days after randomization or discharge home, whichever occurs first
- ❑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

Table 1. Guidelines for Feeding During Intervention Phase of Trial

	Pasteurized Human Donor Milk	**Preterm Formula*** (Similac Special Care 20 or 24 kcal/ oz [3.0 g protein/100 kcal] [Abbott Laboratories] or Enfamil Premature Formula 24 kcal/oz [3.0 g protein/100 kcal] [Mead Johnson Nutritionals]
Initiation of enteral feeding	Day 1-7	Day 1-7
Volume of feeding at initiation	10-20 ml/kg/d (hold volume for 3-5 days)	10-20 ml/kg/d (hold volume for 3-5 days)
Rate of feed advancement	10-20 ml/kg/day	10-20 ml/kg/day
Fortification to commence at ≥120 ml/kg/day using milk pumped ≥ 10 days after parturition+	Human milk fortifier ([Enfamil Human Milk Fortifier, Mead Johnson Nutritionals] **or** [Similac Human Milk Fortifier, Abbott Laboratories])	Not Applicable
Volume	150-200 ml/kg/d to achieve a weight gain of ≥ 15 g/kg/day	150-200 ml/kg/d to achieve a weight gain of ≥ 15 g/kg/day
Minimum protein dose to be provided once (or up to 3 days after) volume reaches ≥ 150 ml/kg/d	3.0 g/kg/d	3.0 g/kg/d
At 24 kcal/oz, and weight gain < 10 g/kg/d, for 7 days	Concentrate feeding using a multi-nutrient modular to 26-27 kcal/oz	Concentrate feeding using a multi-nutrient modular to 26-27 kcal/oz
At 27 kcal/oz and weight gain < 10 g/kg/d for 7 days	Concentrate feeding using a multi-nutrient modular to 30 kcal/oz	Concentrate feeding using a multi-nutrient modular to 30 kcal/oz
At 30 kcal/oz and weight gain < 10 g/kg/d, for 7 days	Remove from feeding protocol	Remove from feeding protocol

*A low or high iron formula will be used for study infants at each NICU depending on the iron content of the human fortifier in use to avoid unblinding of feeding assignments.
+Commence supplementation with 200-400 IU vitamin D and 2-4 mg/kg/d elemental iron.

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

Grosse et al. Environ Health Perspect **2002**;110(6):563-9.

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?