

# Donor Milk: Not a Panacea

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## DISCLOSURE STATEMENT Speaker: Josef Neu

Dr. Neu has disclosed the following relevant financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

Affiliation/Financial Interest	Organization
Infant Bacterial Therapeutics	Scientific Advisory Board Research Grant
Medela	Scientific Advisory Board Research grant
National Institutes of Health	Research Grant
Astarte	Scientific Advisory Board

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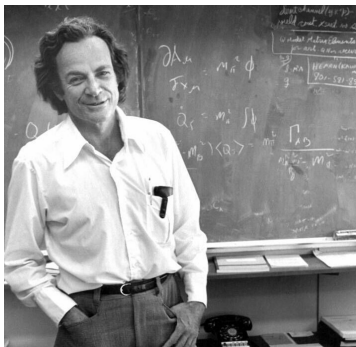
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**"We must be careful not to believe things simply because we want them to be true. No one can fool you as easily as you can fool yourself!"**

**"Religion is a culture of faith; science is a culture of doubt."**

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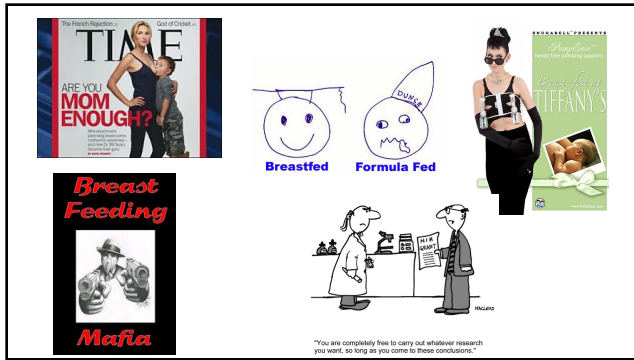
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**Association versus Causality**

**PLOS MEDICINE**

**RESEARCH ARTICLE**  
**Breastfeeding during infancy and neurocognitive function in adolescence: 16-year follow-up of the PROBIT cluster-randomized trial**

**Sharon Luby<sup>1</sup>, Richard B. Meade<sup>1\*</sup>, Emily Olson<sup>1</sup>, Mikael Haines<sup>1</sup>, Glen Dangor<sup>2</sup>, Sharmistha Laha<sup>3</sup>, and Pooja Chaturvedi<sup>4,5,6,7,8,9,10</sup>, Sheryl L. Hillier<sup>11</sup>, Christopher F. Powell<sup>12</sup>, Richard S. Kovacs<sup>13</sup>**

**OPEN ACCESS**  
 Citation: Luby S, Meade RB, Olson E, Haines M, Dangor G, Laha S, et al. (2018) Breastfeeding during infancy and neurocognitive function in adolescence: 16-year follow-up of the PROBIT cluster-randomized trial. *PLOS ONE* 13(10): e0202811. doi:10.1371/journal.pone.0202811

**Abstract**

**\* sharon.luby@pitt.edu**

**“In conclusion, our randomized intervention to promote prolonged and exclusive breastfeeding showed little evidence on beneficial effect of breastfeeding on overall neurocognitive function at age 16 years. However, we observed slightly higher verbal function at age 16 years, suggesting limited but persistent benefit to verbal ability. Nevertheless, these benefits were small in magnitude compared to other family and birth factors and appeared to decrease with age from childhood to adolescence.”**

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**American Academy of Pediatrics Guidelines 2012**

**“The potent benefits of human milk are such that all preterm infants should receive human milk. Mother’s own milk, fresh or frozen, should be the primary diet, and it should be fortified appropriately for the infant born weighing less than 1.5 kg. If mother’s own milk is unavailable despite significant lactation support, pasteurized donor milk should be used. Quality control of pasteurized donor milk is important and should be monitored.”**

Pediatrics  
 March 2012, VOLUME 129 / ISSUE 3

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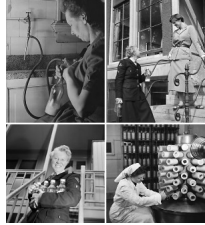
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## History of Donor Milk Use

- In Europe after WW2, many countries started a human milk bank: collected at home, brought to a central place (blood bank or hospital) and vacuum dried.
- In 1990's, HIV stimulated preterm formula use.
- In 1990, Lucas and Cole reported that in exclusively formula-fed babies, NEC was 6–10 times more common than in those fed breast milk alone.
- Numerous papers report also an association with a lower incidence of nosocomial infections when own mother's milk is fed instead of preterm formula.
- The use of donor milk as substitute for own mother's milk became increasingly popular again



From Van Goudesvoort, J.B.,  
Ann Nutr Metab. 2018 Apr; 72(Suppl 3): 25–31

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## Questions to be Addressed

- Can these guidelines lead to harm?
- Is there a rationale to use mother's own milk versus donor milk?
- What components are lost with routine pasteurization for banked donor milk and what is their importance?
- How can we make donor milk more like own mother's milk?
  - Transfaunation
  - Improving "pasteurization" techniques.

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## QUIZ: For this 25 week gestation, 2 day old preterm infant, which of the following is FALSE?

1. Enteral feeds should be initiated.
2. Donor milk should always be the first feeding because the mother is often only able to produce small amounts.
3. Banked donor milk composition is similar to that of baby's own mother's milk.
4. It has clearly been shown in head to head randomized trials that banked donor milk provides similar benefits to babies own mothers' milk.




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### Mother's Own Milk vs. Donor Milk: Head to Head Trials??=0



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### QUIZ

- The average protein content of unfortified term donor human milk is:
  - a. The same as preterm baby's own mothers milk.
  - b. Adequate for optimal growth of the ELBW infant.
  - c. Approximately 2.2 grams/dL
  - d. Approximately 0.9 grams/dL

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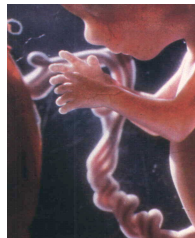
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### Protein Requirement

- Estimated at 3.5-4.0 g/kg/d for the human fetus.
- ELBW infant would require 330 ml/kg/d of term donor human milk to meet this requirement.



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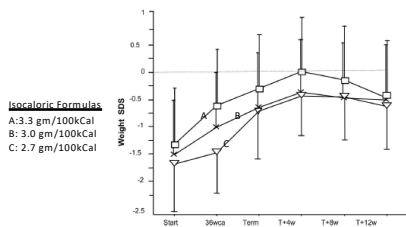
## Composition

Table 1  
Macronutrient (g/dL) and energy (kcal/dL) composition of human milk from specified references

Author <sup>a</sup> (year), N	Protein Mean (±2 SD)	Fat Mean (±2 SD)	Lactose Mean (±2 SD)	Energy Mean (±2 SD)
Term infants, 24 h collection, mature milk				
Nomensen et al <sup>18</sup> (1991), N = 58	1.2 (0.8, 1.5)	3.6 (2.2, 5.0)	7.4 (7.2, 7.7)	70 (57, 83)
Donor human milk samples				
Wojcik et al <sup>19</sup> (2009), N = 415	1.2 (0.7, 1.7)	3.2 (1.2, 5.2)	7.8 (6.0, 9.6)	65 (43, 87)
Michaelsen et al <sup>20</sup> (1990), N = 253	0.9 (0.6, 1.4) <sup>b</sup>	3.6 (1.8, 8.9) <sup>b</sup>	7.2 (6.4, 7.6) <sup>b</sup>	67 (50, 115) <sup>b</sup>
Representative values of mature milk, term infants				
Reference standard <sup>18</sup>	0.8	3.5	6.7	65 to 70
Preterm, 24 h collection, first 8 wk of life				
Escher and Gross <sup>21</sup> (2011)				
Term >29 wk, n = 52	2.2 (1.3-3.3)	4.4 (2.6-6.2)	7.6 (6.4-8.8)	75 (61-90)
Term <29 wk, n = 20	1.9 (1.3-2.9)	4.8 (2.8-6.8)	7.5 (6.5-8.5)	77 (64-89)
Preterm donor milk				
Landers and Hartmann <sup>9</sup> (2012), N = 47	1.4 (0.8, 1.9)	4.2 (2.4, 5.9)	6.7 (5.5, 7.9)	70 (53, 87)

Ballard O., Morrow, A.L. Pediatric Clinics of North America 60(2013)49-74

## Preterms Grow Better with Protein Supplementation



Embleton and Cooke Pediatric Research 2005

## Calcium and Phosphorus in Human Milk, Term and Preterm Formulas

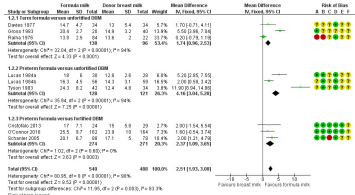


	Required per Kg/day	Required per 100 kcal	Human Milk per 100kcal	Fortified human milk per 100kcal	Term Formula/100kcal	Preterm formula /100kcal
Ca, mg	184	170	45	156	75	170
P, mg	126	116	21	94	50	85

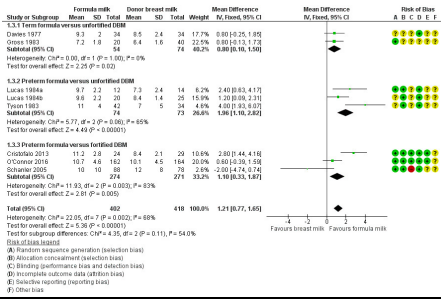
Ziegler, E. Nutritional Care of Preterm Infants, 2014



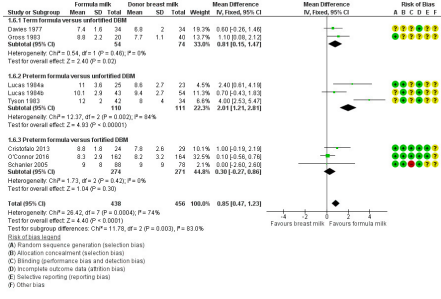
## Weight Gain



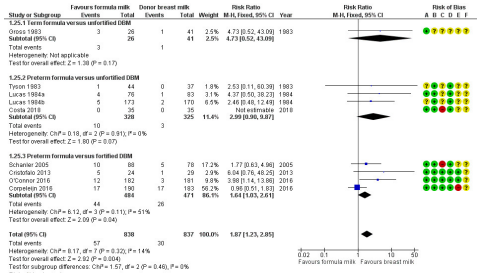
## Linear Growth



## Head Growth



# Necrotizing Enterocolitis




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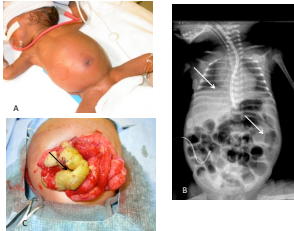
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## NEC: Why such a dilemma? Can NEC be a discrete outcome?



Neu, J. and Walker, W. A. New England Journal of Medicine, Jan. 2011

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## NEC "Imposters"

- Stage 1, 2 and 3<sup>rd</sup> NEC
- Cardiogenic Ischemia
- Variants of Food Protein Induced Enterocolitis Syndrome
- Spontaneous Isolated Intestinal Perforations
- Misrepresentation of pneumatosis— "poopatosiis"
- Placement of Drain for pneumoperitoneum without direct visualization of bowel
- Congenital bowel anomalies (e.g., Hirschsprung's aganglionosis)




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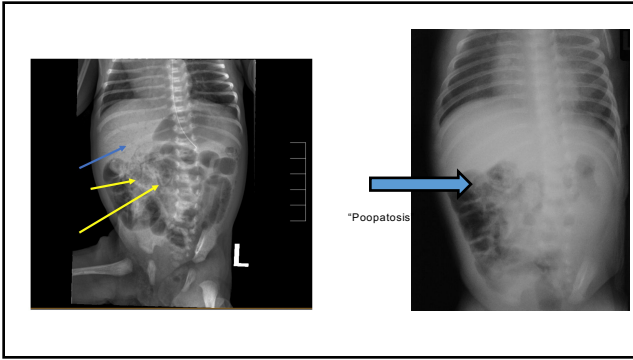
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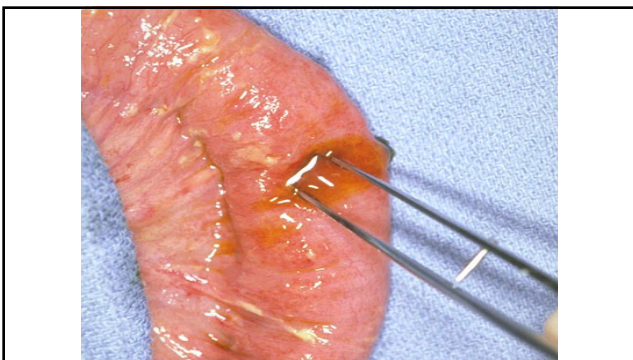
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### NEC: Be careful of how it is used in studies

- Studies where “NEC” is adjudicated by non-biased observers can lead to different results than when diagnosed by the clinical team or a radiologist asked to rule out NEC on an abdominal radiograph.
- Can medical “NEC” as currently most commonly diagnosed be feeding intolerance or food protein intolerance syndrome?

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### Consumption of Mother's Own Milk by Infants Born Extremely Preterm Following Implementation of a Donor Human Milk Program: A Retrospective Cohort Study

Leslie A. Parker, PhD<sup>1</sup>, Nicole Cacho, DO, MPH<sup>1</sup>, Clara Engelmann, MBA<sup>2</sup>, Jasmine Benedict, BSN<sup>1</sup>, Susan Wymier, MSN<sup>1</sup>, Weaver Michael, PhD<sup>1</sup>, and Josef Neu, MD<sup>1</sup>

Table III. Generalized mixed model analysis incorporating GEE results for high-proportion MOM feedings

Effect	P value	OR (95% CI)		
Group (across weeks)	.027	2.21 (1.34-3.65)	0.878 (0.587-1.35)	0.987 (0.629-1.55)
Week (across groups)	<.001			
Group* week	.017			
Single main effects		Group 1	Group 2	Group 3
Week 1	.001	2.77 (1.45-5.30) <sup>a</sup>	1.22 (0.66-2.14) <sup>a</sup>	0.514 (0.291-0.908) <sup>b</sup>
Week 2	.208	3.07 (1.55-6.07)	1.60 (0.915-2.80)	1.44 (0.834-2.50)
Week 3	.068	2.82 (1.55-5.06)	1.26 (0.730-2.18)	1.24 (0.719-2.15)
Week 4	.022	2.46 (1.29-4.69) <sup>a</sup>	0.793 (0.459-1.37) <sup>a</sup>	1.26 (0.731-2.18) <sup>a</sup>
Week 5	.112	1.39 (0.745-2.55)	0.569 (0.325-0.971)	0.963 (0.596-1.71)
Week 6	.007	1.37 (0.737-2.54) <sup>a</sup>	0.374 (0.197-0.707) <sup>a</sup>	1.19 (0.683-2.08) <sup>a</sup>
Custom contrasts				
Day 1-14		2.81 (1.61-4.92) <sup>a</sup>	1.42 (832-2.42) <sup>a</sup>	0.799 (0.490-1.30) <sup>a</sup>
Day 1-28		2.79 (1.63-4.76) <sup>a</sup>	1.20 (0.749-1.93) <sup>a</sup>	0.971 (0.608-1.55) <sup>a</sup>

<sup>a</sup> Post hoc paired comparisons using modified Bonferroni adjustment (P < .0025 within week. Shared letter indicates paired comparison P > .05. For example, week 1, least squares mean for groups 1 and 2 and 2 and 3 are similar; 1 is different from 3.

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### Microbes in Mother's Milk



Hunt, et al. PLoSOne 2011

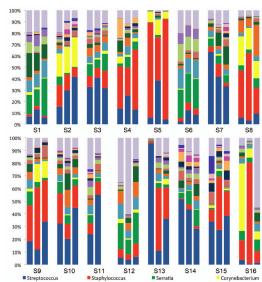


Figure 1. The taxonomic composition of the 18 most abundant bacterial genera in each of 8 milk samples from 18 subjects was shown. The taxonomic domain was used to describe the phylogenetic relationships and the composition of the bacterial community in the milk samples. Legend: B = Bacterium, F = Firmicutes, P = Proteobacteria, C = Cyanobacteria, M = Mollusca, O = Other.

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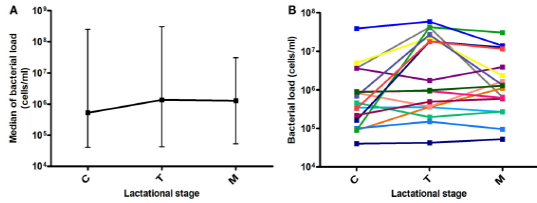
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### Bacterial Load over Lactational Stages: FusA Gene PCR



Boix-Amaros, A. Frontiers in Microbiology, 20 April, 2016

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### Microbial Dose from Human Milk

- Assume intake of 800 ml/day
- Assume 10<sup>5-6</sup> bacterial cells/ml
- This will provide 10<sup>7-8</sup> bacterial cells (personalized?) daily, close to the dose in most probiotic studies.

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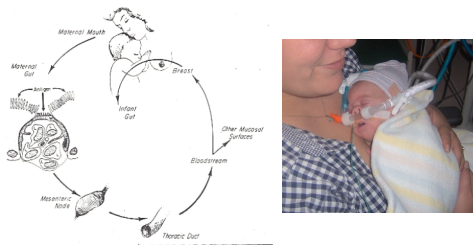
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### Human Milk Personalization and Dynamic Interactions: Enteromammary Immune System



Kleinman, RE and Walker, WA. Dig Dis Sci. . 1979

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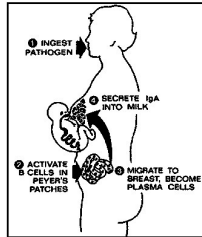
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**Changes in immunomodulatory constituents of human milk in response to active infection in the nursing infant**

- Twelve infants with viral disease vs. controls. Milk samples taken 7 days apart while infants were recovering:
  - CD45 leukocyte, macrophage counts, TNF-alpha decreased.
  - Lactoferrin drop was borderline.

**Conclusion: Results support dynamic nature of immune defense in breastfeeding infants.**



Riskin A., et al. *Pediatr Res.* 2012, Feb;71(2):220-5

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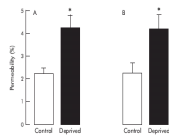
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**Maternal Separation: Rat Pups and Subsequent Intestinal Permeability**



**Figure 2** Effect of maternal stress on small gut (A) and colonic (B) permeability in 12-week old rats. Values are mean (SEM). n=8 in each group. \*p<0.05 between deprived and control rats.

Barreau, F. *Gut*, 2004

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**Some Caveats!!**

- Simply providing pumped mother's milk is not the same as breastfeeding!
- Does babies' own mothers' milk pumping and freezing and lack of direct maternal infant contact ameliorate some of the beneficial effects of breastfeeding?
- Can we personalize donor milk?

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**Personalization of the Microbiota of Donor Human Milk with Mother's Own Milk**

**Abstract**

The American Academy of Pediatrics recommends that extremely preterm infants receive mother's own milk (MOM) when available or pasteurized donor breast milk (DBM) when MOM is unavailable. The goal of this study was to determine whether DBM could be inoculated with MOM from mothers of preterm infants to restore the live microbiota (LM). Culture dependent and culture independent methods were used to analyze the fluctuations in the overall population and microbiome, respectively, of DBM, MOM, and LM samples over time. Using MOM at time 0 (T0) as the target for the restoration

Frontiers in Microbiology, August 2017

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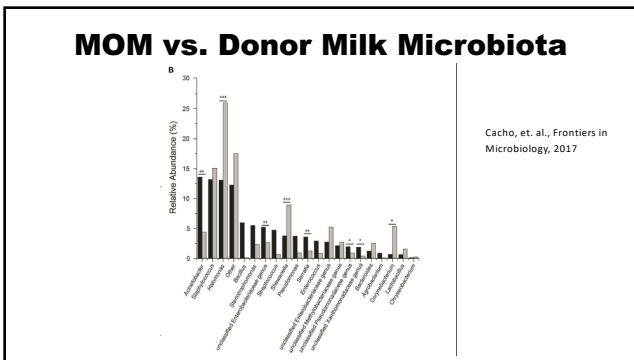
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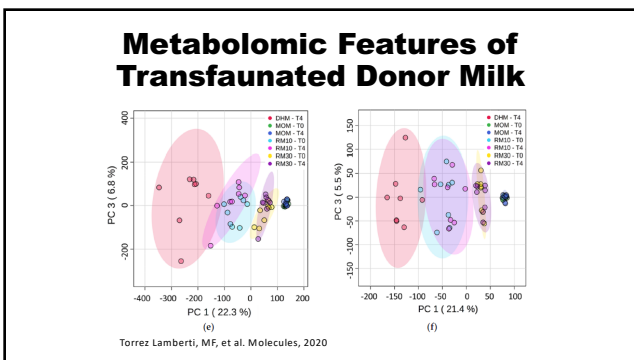
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**The Future: Questions**

- Should we be focusing on use of Fresh mother’s milk rather than banked donor milk?
- How can we promote mother’s own fresh milk use?

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**Is Donor Milk a Panacea?**

- No!
- There are many aspects of donor milk that are suboptimal for the preterm infant.
- Many of the active components including live microbial components that may provide benefits are lost in the processing of donor milk.
- Transfaunation techniques, stimulation of early lactation, and improvement of pasteurization techniques may be useful in increasing babies’ own mothers’ milk use or at least making donor milk more like the original.

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**Is Donor Milk a Panacea**

- Not much evidence exists on direct comparison of donor versus babies own mother milk is available.
- Studies comparing benefits of babies’ own mothers’ milk use over donor milk (with and without additives) are needed.
- Let’s keep working on the science.

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- Elizabeth De Groot (currently faculty at UF)
- Chuanming Guo (faculty)
- Sarah Egan
- Wang Jun (JG-CG)
- Doreen Wu (NIH) (PhD-GO-Orlando)
- Liqiang
- Jun-An Hwang (graduate student—microbiology and cell science)

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- Wei Yan (Beau Hospital, Shenzhen, China)
- Yanyan Ma (Shanghai University, Hong Kong)
- Yoon Jung (Japan, China)
- Wang Qing (Director of Pediatric ICU, Fudan University, Shanghai, China)
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