Exclusively Human Milk Diets for Preterm Infants: 3-year Outcomes

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Prematurity is associated with a variety of comorbidities related to hyperglycemia, oxidative stress, hypoxia/ischemia, the formation of glycation end products, micro- and macro vascular complications, and inflammation pathways. Researchers have sought to identify optimal nutrition for preterm infants to mitigate complications. Preterm formulas provide consistent delivery of nutrients and support postnatal growth, but are associated with pro-inflammatory effects, alterations in normal gut microbiome development, increased incidence of infections/sepsis, and longer durations of parenteral nutrition. Although human milk is the ideal diet for healthy full-term infants, human milk does not necessarily provide sufficient nutritional support for appropriate third-trimester growth and development. Consequently, ongoing research is needed to evaluate clinical outcomes with human milk in vulnerable preterm infants.

Use of Human Milk in the NICU

An increasing number of clinical trials and observational experience support benefits of a human milk–based diet for preterm infants who are very low birth weight (VLBW; ≤1,500 g) or extremely low birth weight (ELBW; ≤1,000 g), including shorter hospital stays, good growth, and lower rates of necrotizing enterocolitis (NEC). Several organizations now recommend the use of human milk (including donor milk, as necessary), including the American Academy of Pediatrics (AAP) Committee on Nutrition, the American Society for Parenteral and Enteral Nutrition (ASPEN), and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Committee on Nutrition, although some of these recommendations are based on weak evidence. A recent survey of level III and IV neonatal intensive care units (NICUs) in the United States found that human milk is increasingly being used, particularly in larger NICUs, with 59% of units now using donor human milk.[1] However, large variation exists among different centers in the criteria for the use of donor human milk (from <1,000 to <1,800 g and/or from gestational age <28 to <34 weeks).

Several studies and meta-analyses (although not all) published in the last few years have demonstrated a decrease in the incidence of Bell's stage ≥2 NEC associated with the use of an exclusively human milk diet **(Table 1)**, despite variation in the populations and protocols. Few prospective, randomized controlled trials have been conducted, and some centers that are already using human milk understandably lack equipoise to randomize some infants to formula.

Human Milk Use in the El Paso Children's Hospital NICU

The El Paso Children's Hospital includes a 50-bed, level III regional NICU that admits >1,000 infants, including 50 to 80 VLBW infants (<1,500 g) annually. In 2012, the rate of NEC among preterm infants was high (14.5%) compared with the national average (Vermont Oxford Network data, 3%-12% for VLBW infants). To decrease the incidence of NEC, the hospital administration was presented with a cost/benefit analysis for the adoption of exclusively human milk diets in ELBW infants; projections were derived from estimates based on the expected decline in NEC cases (per then-available literature), the number of "excess" NEC cases, and the costs per infant for medical and surgical NEC.

Table 1. Summary of reported NEC rates (Bell's stage ≥2).

Reference	Study type	Other (eg, formula, mixed)	HM only
Sanchez-Tamayo T, et al. *Ann Pediatr.* 2016. [Ahead of print]	Retrospective	7.7%	0.9%
Talavera MM, et al. *Pediatrics*. 2016;135:e20151119.	Retrospective	8%	3.1%
Colaizy TT, et al. *J Pediatr.* 2016;175:100-105.	Monte Carlo simulation	8.2% (mixed); 11.1% (formula)	1.3%
Hair AB, et al. *Breastfeed Med.* 2016;11:70-74.	Retrospective	16.7%	6.9%
Chowning R, et al. *J Perinatol.* 2016;36:221-224.	Retrospective	13.5%	3.4%
Spiegler J, et al. *J Pediatr*. 2016;169:76-80.	Prospective, cohort	2.2%	0.5%
Assad M, et al. *J Perinatol*. 2016;36:216-220.	Retrospective	10%	1.1%
Alshaikh B, et al. *Breastfeed Med.* 2015;10:355-361.	Retrospective	OR = 0.32 (95% CI, 0.11-0.93)	
Kimak KS, et al. *J Pediatr Gastroenterol Nutr.* 2015;61:445-450.	Case control	*P* = 0.007	
Johnson TJ, et al. *Neonatol.* 2015;107:271-276.	Retrospective	*P* = 0.02	
Abrams SA, et al. *Breastfeed Med.* 2014;9:281-285.	Prospective, randomized	17%	5%
Quigley M, McGuire *W. Cochrane Database Syst Rev.* 2014;(4):CD002971.	Meta-analysis	6.5%	2.3%
Hermann K, Carrol K. *Breastfeed Med.* 2014;9:184-190.	Observational	3.4%	1%
Christofalo EA, et al. *J Pediatr.* 2013;163:1592-1595.	Randomized, controlled	21%	3%
Sullivan S, et al. *J Pediatr.* 2010;156:562-567.	Randomized, controlled	All NEC: *P* = 0.02; surgical NEC: *P* = 0.007	
Meinzen-Derr J, et al. *J Perinatol.* 2009;29:57-62.	Randomized, controlled	HR = 0.85 (95% CI, 0.60-1.19)	
Sisk PM, et al. *J Perinatol.* 2007;27:428-433.	Prospective, cohort	10.6%	3.2%
Corpeleijn WE, et al. *JAMA Pediatr.* 2016;170:654-661.	Randomized, controlled	No difference	
Hein-Nielsen AL, et al. *Dan Med J.* 2015;62:A5091.	Retrospective	No difference	

Human milk diets were integrated in a 3-year (fiscal years 2013-2016), stepwise fashion, which facilitates examining staged improvements. During the first year of increased human milk use, the NICU started to provide Prolacta's Prolact+H²MF for infants ≤1,000 g birth weight. Review of several months of data indicated no new NEC cases in ELBW infants, but continued occurrence of NEC in other VLBW infants. In subsequent years, Prolact+H²MF and donor human milk diets were adopted for infants ≤1,250 g, and then for all infants ≤1,500 g.

Stepwise adoption of exclusively human milk diets for preterm infants resulted in marked decrease of NEC Bell's stage ≥2 during the past 2 years among VLBW infants **(Figure 1)**. An analysis of comorbidity rates of infants with exclusively human milk versus "mixed"

(human + bovine-based milk fortified) diets also showed declines in severe intraventricular hemorrhage and mortality **(Table 2)**. In contrast, the frequency of retinopathy of prematurity appeared to increase with an exclusively human milk diet, although more robust data are needed to ensure the data are not due to low patient numbers. Other outcomes seen after integration of exclusively human milk diets included elimination of deaths from NEC; decreases in length of stay, days on total parenteral nutrition, days with an indwelling central venous catheter, and days of antibiotic administration; less long-term morbidity; and lower NICU costs.

Figure 1. NEC (medical/surgical) rates in VLBW infants.

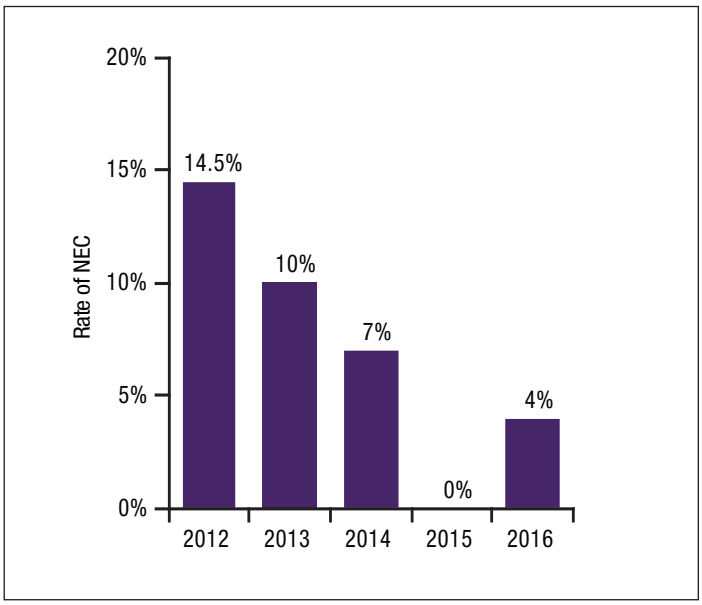

Table 2. Outcomes with exclusively human milk versus "mixed" diets in low birth weight infants.

Weight group:	500-749 g		750-999 g		1,000-1,250 g	
Diet:	Mixed	HM only	Mixed	HM only	Mixed	HM only
Chronic lung disease	50%	67%	64%	50%	18%	25%
Severe intraventricular hemorrhage	0	0	9%	0	9%	0
Periventricular leukomalacia	25%	17%	36%	27%	9%	25%
Severe retinopathy of prematurity	0	33%	9%	18%	0	0
Transfusions, n	7	6	4	3	1	1
NEC	40%	0	18%	0	0	0
Mortality	20%	0	0	0	0	0

Exclusively human milk diets are a practical, nutritional strategy to improve survival and health, and decrease hospital-related morbidities in VLBW and ELBW infants. In human milk, bioactive factors such as long-chain polyunsaturated DHA, choline, and lutein show marked variation among individuals and communities (1-2 orders of magnitude). Further investigations of clinical biomarker profiles, micronutrient intakes, and the impact of human milk components on longer-term outcomes are needed.

Reference

1. Hagadorn JI, et al. Variability of criteria for pasteurized donor human milk use: a survey of US neonatal intensive care unit medical directors. *J Parenter Enter Nutr.* 2016;40:326-333.