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Donor Human Milk for VLBWs: Patterns of Usage, Outcomes, and Unanswered Questions

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Abstract

Purpose of Review—Donor milk (DM) usage in the United States has increased substantially over the past ten years. Between 2007–2011, DM use in level 3 and 4 NICUs increased from 25% to 45%.

Recent Findings—Most centers have written protocols based on birthweight or gestational age, and give DM in an effort to prevent necrotizing enterocolitis (NEC). Evidence for protection against NEC using bovine fortified DM vs. formula is limited, although the exclusive human milk diet seems to offer protection compared to diets containing formula. Adequate growth can be achieved with DM fortified with either bovine or human milk-derived fortifiers, but use of additional fortification and protein supplementation may be required. Several randomized trials of donor milk vs. formula are ongoing in the VLBW population in North America that can answer important questions.

Summary—Further research is needed before donor milk, and the exclusive human milk diet, are considered standard of care.

Keywords

Donor Human Milk; necrotizing enterocolitis; exclusive human milk diet

Introduction

Maternal milk diets are the ideal for all infants, particularly for vulnerable populations including VLBW infants. Observational studies over the past 30 years in preterm infants have reported myriad benefits to maternal milk diets compared with contemporary formula options, including: better feeding tolerance, lower rates of sepsis^{1,2}, necrotizing enterocolitis NEC^{1–5}, and bronchopulmonary dysplasia^{2,6}, shorter length of hospital stay⁷, fewer re-hospitalizations⁶ and superior developmental outcomes at 2–8 years of age^{6,8,9}, with demonstration of a significant dose-response relationship^{6,9}.

With an increased understanding of the importance of human milk for VLBW infants, the use of pooled, pasteurized donor human milk (DM) has rapidly gained acceptance. Most

DM used in the United States is obtained from the member banks of the Human Milk Banking Association of North America, a non-profit organization. In 2003, 6 banks were dispensing milk; in late 2014 there are now 18 banks, with 10 more banks in various stages of development¹⁰. Between 2007 and 2011, total volume of DM dispensed by HMBANA banks doubled from 1.1 to 2.18 million ounces¹⁰.

Recent recommendations have been published from ESPGHAN¹¹, the AAP¹², and the WHO¹³ endorsing the use of human DM in preterm infants when maternal milk is unavailable. Despite these recommendations and wide-spread use, large scale studies of its use in VLBW infants during the era of routine human milk fortification are lacking. In 2011 the US Surgeon General called for further research to identify areas where the evidence regarding DM is inconclusive and to develop evidence-based clinical guidelines for its use¹⁴.

The use of DM in NICUs is well established, and data from the United States suggests an increasing acceptance of this product. Additionally, single center reports of short term nutritional and health outcomes of very low birthweight (VLBW) infants fed DM have been published that will inform future studies. The exclusive human milk diet, utilizing human milk fortifier derived from human DM rather than bovine sources also represents an emerging dietary option for VLBW infants which has been studied in limited populations.

Maternal and Donor Milk Use in US NICUs

Use of both maternal and donor human milk in US NICUs is common, and rates are increasing in recent years. An analysis of the Centers for Disease Control and Prevention's National Maternity Practices in Infant Nutrition and Care (MPINC) survey for the years 2007 to 2011 was conducted to determine patterns of human milk (maternal and/or donor) use in US NICUS. Responses were available for >80% of all facilities providing delivery services in the US during the years surveyed. Among level 2 and level 3–4 NICUS combined, the rates of low human milk usage (0–9% of infants fed human milk) declined from 8% in 2007 to 7.3% in 2011, and rates of high human milk usage (>90% of infants fed human milk) increased from 21.2% in 2007 to 30.8% in 2011. Use of human DM increased faster than use of all human milk combined, with 11.5% of units reporting use in 2007, and 22% reporting use in 2011. This increase in DM use was most pronounced in the level 3 and 4 centers, where use increased from 25.1% in 2007 to 45.2% in 2011¹⁵.

Building on this analysis, two groups have recently published reports of the prevalence of DM use, and the criteria for use in US NICUs. Parker and colleagues used purposive random sampling to conduct a mail survey of US level 3 NICU medical directors to assess patterns of DM use¹⁶. 60.3% (182/302) of directors surveyed responded, distributed equally across all US regions. 42% of directors reported use of DM in their NICU, with higher rates of use in the West (62%) and Midwest (47%), and lower use in the Northeast (23%) and South (36%). Among users of DM (76/182), 85% had been using the intervention for less than 5 years. Factors associated with DM use in multivariable analysis included 800 annual NICU admissions and Midwest or West location. Availability of surgical care for NEC or designation as a safety net hospital were not associated with DM use in this analysis.

Criteria used to initiate use were varied, but commonly included insufficient maternal milk supply, and infants below specified birthweight (83%) and gestational age (75%). At least 50% of respondents agreed that DM should be used in infants born at < 1500 g, and discontinued at 33–34 weeks postmenstrual age, and that it should be used after surgery for NEC. The majority of DM-using units had a specified guideline for use (73%), required signed parental consent for use (84%), and had high parental acceptance of DM (67% of units reported < 5% parental refusal)¹⁶.

Hagadorn and colleagues used an online survey design of medical directors of level 3 and 4 NICUS in the US to describe policy-driven use of DM¹⁷. 33% of medical directors (153/459) completed the survey, 59% of whom reported use of DM in their unit. Similar to the earlier survey of medical directors undertaken by Parker et al¹⁶, use of DM was associated with more NICU beds, higher annual admissions, and higher VLBW admissions. Additionally, as noted in MPINC, higher level NICUs were more likely to provide DM (74% of level 4 NICUs vs. 53% of level 3 NICUs). Directors were also queried regarding reasons for DM use, with many citing desire to reduce the incidence of NEC (58%) as the most important reason. Directors of centers that did not provide DM reported expense as the most common reason for non-use. 79% of directors reported use of a formal policy to guide DM use, and policies were varied, but typically included birthweight and/or gestational age criteria for both initiation and discontinuation of DM. 91% of directors reported that DM was used outside of the written criteria at physician discretion¹⁷.

From these three studies, it is clear that donor human milk use in US NICUS is prevalent and growing, particularly over the past 5–10 years. NICUs caring for the smallest and sickest infants in the greatest numbers use DM more frequently, and often do so in an effort to reduce the incidence of necrotizing enterocolitis (NEC).

Evidence regarding NEC and fortified DM

Although the desire to prevent NEC is often cited as a reason to use DM by neonatologists, evidence for this effect is limited. The most often cited references for reduced NEC with DM compared to formula diets are meta-analyses of trials that were conducted prior to the routine use of multi-component bovine milk-derived human milk fortifiers which are now standard of care for VLBW infants^{18,19}. These trials compared unfortified DM to contemporary formulas. The only randomized trial of bovine-fortified DM compared to preterm formula was published by Schanler and colleagues in 2005¹. Infants were randomized to receive preterm formula or fortified DM if maternal milk was insufficient. Infants receiving formula had higher incidence of NEC (11%) than those receiving either entirely fortified maternal milk (6%), or fortified DM (6%), but this difference was not statistically different ($p = 0.27$, formula vs. DM). Therefore, we have no clear evidence that use of DM with bovine-derived fortifier will result in decreased NEC. Rather, evidence is commonly extrapolated from data that bovine-fortified **maternal** milk is associated with lower rates of NEC than preterm formula^{1,7,20} but the effects of pooling and pasteurization on DM, including decreased levels of secretory IgA^{21–23}, lactoferrin, and lysozyme²³, make these extrapolations problematic.

Evidence regarding NEC and the exclusive human milk diet (EHM)

A recent published secondary analysis of the two previously published trials of the exclusive human milk diet (EHM) provide preliminary evidence that use of human milk-derived human milk fortifier (HHMF) in a human milk diet (maternal or donor) may offer protection against NEC when compared to preterm formula. The individual trials will be first reviewed as background. The first report of the EHM diet in VLBW infants published by Sullivan and colleagues in 2010²⁴ was an unblinded trial that randomized infants to receive either bovine fortifier for all maternal milk feedings and preterm formula if a supplement to maternal milk was required, or HHMF for all maternal milk feedings and HHMF fortified donor milk if a supplement to maternal milk was required. The bovine group experienced a higher incidence of NEC (11/69, 16 % vs. 8/138, 6% in the human group, $p=0.02$). Additionally, surgical NEC was more common in the bovine group, (7/69, 10 % vs. 2/138, 1.4% in the human group, $p = 0.007$)²⁴. The combined outcome of NEC and/or late onset sepsis occurred at similar rates between bovine (30%) and human (30%) groups. The same group of investigators then conducted a blinded randomized trial of EHM vs. preterm formula in infants whose mothers never provided milk²⁵. 53 infants were included, 24 received formula, and 29 EHM. Five infants in the formula group (21%) developed NEC, compared to 1 (3%) in the bovine group ($p = 0.08$), and surgical NEC occurred in only the bovine group (4/5 cases, $p = 0.04$)²⁵. Infants in the formula group in this trial experienced NEC at much higher rates than previously noted for exclusively formula fed infants (21% vs. an 11% incidence for infants exclusively fed formula in the NICHD “glutamine” trial²⁰), which should be noted when interpreting these results.

The investigators then performed a post-hoc analysis of the datasets combined²⁶. They found that NEC occurred more frequently in the groups receiving formula and/or bovine HMF (16/93, 17%) than those receiving EHM (9/167, 5%, $p=0.002$). Surgical NEC (11/93, 12%) and mortality (7/93, 8%) were also more common in the bovine groups than those receiving EHM (surgical NEC 2/167, 1%, $p = 0.0003$; mortality 3/167, 2%, $p = 0.04$)²⁶. Due to the small sample size of each trial, and the relatively high rates of NEC noted, these results should be interpreted with caution. However, taken together or separately they suggest that avoidance of **formula** results in lower incidence of NEC. There has not been a pure comparison of the use of HHMF and bovine HMF in diets that otherwise contain only maternal milk and/or donor milk, thus it is unknown if the EHM diet offers any benefit over a human milk diet fortified with bovine HMF with regards to NEC prevention.

Evidence regarding growth in VBLW infants fed DM

Since growth is closely linked to long term neurodevelopmental outcomes²⁷, any diet in widespread use in VLBWs needs to result in appropriate growth. Evidence for this is limited. However, there are two published trials of growth in VLBWs fed bovine fortified donor milk²⁸. In the initial randomized trial of DM as a supplement to maternal milk published by Schanler¹, growth was reported as a secondary outcome. A weight gain deficit of 3/g/kg was noted for infants fed maternal or donor milk compared to those fed formula, but no difference was noted between the donor and maternal groups, and length and head growth were similar across all three groups. Colaizy and colleagues specifically studied

growth in a cohort of VLBW infants fed varying proportions of maternal and donor milk²⁸. Infants receiving > 75% of the in-hospital diet as donor milk experienced a weight z-score change of -0.84 vs. -0.56 for infants receiving > 75% maternal milk ($p = 0.28$). Infants in this trial also received levels of protein fortification in excess of those produced with manufacturer-directed bovine HMF use, through additional bovine HMF use or as single component protein powders²⁸.

Hair and colleagues studied a similar cohort of VLBW infants fed the exclusive human milk diet, and report that with early use and rapid advancement of human HMF, weight gain of 24.8 g/kg/d was achieved, which exceeds most recommendations. Although 43% of their infants were SGA at discharge or 40 weeks PMA²⁹, the growth rates achieved with their protocol were better than those achieved in either of the initial EHM studies^{24,25}.

Therefore, it has been demonstrated that appropriate growth can be achieved with use of donor milk diets, when both bovine and human HMF products are used, but that fortification beyond the traditional first step (24 kcal/oz) may be required.

Ongoing donor milk research

As called for by the US Surgeon General¹⁴, there are several ongoing randomized trials of donor milk vs. preterm formula in VLBW infants in North America. O'Connor and colleagues recently published the protocol for the randomized, blinded DoMINO trial, which is currently completing follow-up³⁰. VLBW infants were randomized at birth to receive donor milk or preterm formula as a supplement if maternal milk was insufficient, or as the sole diet if the mother chose not to provide milk for 90 days or the duration of hospitalization. The primary outcome of the trial is the Cognitive Scale score of the Bayley Scales of Infant Development III (BSID III) at age 18–22 months, and the investigators hypothesize that infants randomized to donor milk will score 5 points higher than those randomized to formula. This trial also collected extensive in-hospital growth and outcome data³⁰. A similar trial is underway in Iowa, where Colaizy and colleagues also randomized VLBW infants at birth to donor milk or formula if maternal milk were insufficient or absent (clinicaltrials.gov NCT01232725), to assess the effect of DM on neurodevelopmental outcomes at 18–22 months. Finally, the NICHD Neonatal Research Network is also conducting a blinded, randomized trial of donor milk vs. preterm formula in VLBW infants whose mothers do not provide milk, or provide only small amounts in the first days after birth (clinicaltrials.gov NCT01534481), to assess the impact of donor milk on neurodevelopmental outcomes at age 22–26 months.

These three trials will be the first to investigate the neurodevelopmental outcomes of VLBW infants fed donor milk compared to those fed formula using blinded randomized trial designs in the era of routine milk fortification. A total of over 1100 infants will be included in the three trials combined, allowing for secondary investigation of the growth and neonatal morbidity outcomes associated with donor milk diets.

Conclusions

What do we know about donor milk? Its use is common, and increasing rapidly. Although commonly used to prevent NEC, its ability to do so is not well studied in the era of routine milk fortification. The exclusive human milk diet is associated with lower incidence of NEC compared to diets containing any preterm formula, but it has not been directly compared to diets containing human milk and bovine fortifier. Donor milk diets fortified with bovine or human milk derived fortifier can result in appropriate growth for VLBW infants, if care is taken to provide adequate protein and calorie intake.

What questions remain? Further research is needed in a variety of areas to fully understand the role of donor milk in the nutritional care of VLBW infants. Current ongoing studies will assess the 18–24 month neurodevelopmental outcomes of former VLBW infants fed donor milk compared to those fed preterm formula. Additionally, we need to investigate the effects of donor milk fortified with bovine HMF on incidence of NEC compared to maternal milk. Further studies of the exclusive human milk diet are required to determine if this diet offers any added benefit for protection against NEC over a human milk diet fortified with bovine HMF but lacking formula.

References

1. Schanler RJ, Lau C, Hurst NM, Smith EOB. Randomized Trial of Donor Human Milk Versus Preterm Formula as Substitutes for Mothers' Own Milk in the Feeding of Extremely Premature Infants. *Pediatrics*. 2005; 116(2):400–406. [PubMed: 16061595]
2. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics*. 1999; 103(6 Pt 1):1150–1157. [PubMed: 10353922]
3. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis.[see comment]. *Lancet*. 1990; 336(8730):1519–1523. [PubMed: 1979363]
4. Maayan-Metzger A, Avivi S, Schushan-Eisen I, Kuint J. Human Milk Versus Formula Feeding Among Preterm Infants: Short-Term Outcomes. *Am J Perinatol*. 2011
5. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol*. 2007; 27(7):428–433. [PubMed: 17443195]
6. Vohr BR, Poindexter BB, Dusick AM, et al. Beneficial Effects of Breast Milk in the Neonatal Intensive Care Unit on the Developmental Outcome of Extremely Low Birth Weight Infants at 18 Months of Age. *Pediatrics*. 2006; 118(1):e115–e123. [PubMed: 16818526]
7. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics*. 1999; 103(6 Pt 1):1150–1157. [PubMed: 10353922]
8. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics*. 2007; 120(4):e953–e959. [PubMed: 17908750]
9. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm.[see comment]. *Lancet*. 1992; 339(8788):261–264. [PubMed: 1346280]
10. America HMBaON. [Accessed 12/1/2014] HMBANA - Locations. 2014. <https://www.hmbana.org/locations#Developing>. 2014
11. Arslanoglu S, Corpeleijn W, Moro G, et al. Donor human milk for preterm infants: current evidence and research directions. *J Pediatr Gastroenterol Nutr*. 2013; 57(4):535–542. [PubMed: 24084373]

12. BREASTFEEDING SO. Breastfeeding and the Use of Human Milk. Pediatrics. 2012; 129(3):e827–e841. [PubMed: 22371471]
13. Organization WH. Guidelines on Optimal Feeding of Low Birthweight Infants in Low- and Middle-Income Countries. Geneva, Switzerland: World Health Organization; 2011.
14. Services UDoHaH. [Accessed 11/1/2014] The Surgeon General's call to action to support breastfeeding. 2011. <http://www.surgeongeneral.gov/library/calls/breastfeeding/>. 2014.
15. Perrine CG, Scanlon KS. Prevalence of Use of Human Milk in US Advanced Care Neonatal Units. Pediatrics. 2013; 131(6):1066–1071. [PubMed: 23669517] *Use of human milk, both maternal and donor, increased between 2007 and 2011 in the US. Use of donor milk and maternal milk rose fastest in Intensive Care NICUS, compared with lower levels of care.
16. Parker MGK, Barrero-Castillero A, Corwin BK, Kavanagh PL, Belfort MB, Wang CJ. Pasteurized Human Donor Milk Use among US Level 3 Neonatal Intensive Care Units. Journal of Human Lactation. 2013; 29(3):381–389. [PubMed: 23764482] *Survey of level 3 NICU medical directors reported 42% DM use. DM use was highest in the West US, in units with high admission rates.
17. Hagadorn JJ, Brownell EA, Lussier MM, Parker MGK, Herson VC. Variability of Criteria for Pasteurized Donor Human Milk Use: A Survey of U.S. Neonatal ICU Medical Directors. Journal of Parenteral and Enteral Nutrition. 2014 *Survey of level 3–4 NICU medical directors reported 59% DM use, 80% of units had a written policy, most based on gestational age and/or birthweight. Most used DM to prevent NEC, required written consent. Parental acceptance was high.
18. Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2007; 92(3):F169–F175. [PubMed: 16556615]
19. 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; (4):CD002971. [PubMed: 17943776]
20. Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol. 2009; 29(1):57–62. [PubMed: 18716628]
21. Braga LP, Palhares DB. Effect of evaporation and pasteurization in the biochemical and immunological composition of human milk. Jornal de pediatria. 2007; 83(1):59–63. [PubMed: 17279281]
22. Akinbi H, Meinzen-Derr J, Auer C, et al. Alterations in the host defense properties of human milk following prolonged storage or pasteurization. J Pediatr Gastroenterol Nutr. 2010; 51(3):347–352. [PubMed: 20639776]
23. Czank C, Prime DK, Hartmann B, Simmer K, Hartmann PE. Retention of the immunological proteins of pasteurized human milk in relation to pasteurizer design and practice. Pediatr Res. 2009; 66(4):374–379. [PubMed: 19581827]
24. Sullivan S, Schanler RJ, Kim JH, et al. 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. J Pediatr. 2010; 156(4):562–567. e561. [PubMed: 20036378]
25. Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized Trial of Exclusive Human Milk versus Preterm Formula Diets in Extremely Premature Infants. J Pediatr. 2013; 163(6):1592–1595. e1591. [PubMed: 23968744]
26. Abrams SA, Schanler RJ, Lee ML, Rechtman DJ. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. Breastfeed Med. 2014; 9(6):281–285. [PubMed: 24867268] *NEC was more common in VLBW infants fed diets containing preterm infant formula compared to the exclusive human milk diet, and mortality was also slightly higher.
27. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics. 2006; 117(4):1253–1261. [PubMed: 16585322]
28. Colaizy TT, Carlson S, Saftlas AF, Morriss FH Jr. Growth in VLBW infants fed predominantly fortified maternal and donor human milk diets: a retrospective cohort study. BMC pediatrics. 2012; 12:124. [PubMed: 22900590]

29. Hair AB, Hawthorne KM, Chetta KE, Abrams SA. Human milk feeding supports adequate growth in infants $\leq$ 1250 grams birth weight. BMC research notes. 2013; 6(1):459. [PubMed: 24220185] *VLBW infants fed the exclusive human milk diet in a setting of early and rapid advancement of fortification had adequate growth, but care is required to ensure good protein and calorie intake
30. Unger S, Gibbins S, Zupancic J, O'Connor DL. DoMINO: Donor milk for improved neurodevelopmental outcomes. BMC Pediatr. 2014; 14:123. [PubMed: 24884424] *The DoMINO trial randomized VLBW infants to receive preterm formula or donor milk when maternal milk was insufficient, with the hypothesis that donor milk use would result in superior neurodevelopmental outcomes at 18–22mo. The trial is ongoing.

Key Points

- Donor milk is commonly used to prevent NEC, but its ability to do so when fortified with bovine derived human milk fortifier is not well studied.
- The exclusive human milk diet is associated with lower incidence of NEC than diets containing formula, but it has not been compared to a diet containing human milk and bovine fortifier in the absence of preterm formula.
- Growth can be compromised with use of donor milk, but this can be overcome with careful attention to adequate protein and calorie fortification.
- Further research is needed before donor milk and the exclusive human milk diet become the gold standard for VLBW nutritional management.