Donor Human Milk Update: Evidence, Mechanisms, and Priorities for Research and Practice

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In the last decade, the use of pasteurized donor human milk (DHM) has become the standard of care for very low birthweight (VLBW; <1500 g) infants throughout the world when mothers' own milk (MOM) is not available.[1,2] DHM banks have been established even in countries that use limited MOM feedings in the neonatal intensive care unit (NICU).[3,4] Little research informs this rapid practice change. Multiple studies report that high-dose feedings of MOM during critical exposure periods in the NICU hospitalization reduce the incidence, severity, and risk of potentially preventable morbidities, including necrotizing enterocolitis (NEC); late onset sepsis; chronic lung disease; retinopathy of prematurity; rehospitalization after NICU discharge; and neurodevelopmental problems in infancy and childhood.[5-11] However, this same constellation of outcomes has not been attributed to DHM feedings.[12] Furthermore, when compared with MOM and formula-fed infants, primarily DHM-fed infants have demonstrated either slow weight gain or the need to "superfortify" DHM with exogenous bovine-based protein and other macronutrients.[12-14] Separately, research and quality improvement projects have begun to merge MOM and DHM into a common metric, human milk, despite the marked differences in the composition, efficacy, and associated costs of MOM and DHM. The blurring of MOM and DHM outcomes has significant implications for the targeting of resources that prioritize MOM feedings in the NICU. This article reviews the evidence about fundamental differences in MOM and DHM feedings for VLBW infants during the NICU hospitalization and provides recommendations for practice and research.

MOM and DHM: Compositional and Bioactive Differences that Impact Outcome

Previous comparisons addressing the composition and bioactivity of MOM and DHM have focused almost exclusively on the effects of pasteurization, with mixed findings for some components.[13,15,16] However, factors other than pasteurization impact DHM in clinically significant ways, including maturity of the mammary gland (preterm MOM vs term DHM), stage of lactation for which DHM replaces MOM (eg, mature DHM replacing MOM colostrum and transitional milk), and freeze-thaw cycles that are inherent in the storage and processing of DHM.

Furthermore, the addition of bovine fortifier has never been studied separately for DHM. For some MOM components, these factors are cumulative. Lactoferrin provides an excellent example.

Lactoferrin is a potent anti-infective, anti-inflammatory, immunomodulatory, and prebiotic substance in MOM that has been linked to the reduction of NEC and sepsis.[17-20] Lactoferrin concentrations are the highest in colostrum, and are higher in mothers who deliver preterm vs term.[21,22] Longitudinally, these concentrations decrease by ≥50% between days 0-5 and days 11-30 of lactation, and continue to decline through 2 months of lactation when they stabilize at approximately one-third of colostrum values (9 g/L vs 2-3 g/L).[21,22] Further reductions of 47%-55% occur with freezing.[23,24] This means that lactoferrin concentrations in DHM collected 2 months postbirth and frozen for 3 months may be as low as 1 g/L. Pasteurization further reduces baseline lactoferrin by up to 88%,[13] and fortification with a bovine-based fortifier containing iron further reduces remaining bioactivity.[25] Thus, even improved pasteurization processes cannot fully compensate for the sizeable differences in some MOM and DHM components.

The most profound misfit between MOM and DHM occurs when preterm MOM is replaced with DHM in the early postbirth period, a common clinical scenario because of lack of MOM or concerns about maternal medications and health status. Preclinical and human studies suggest that MOM produced as a function of mammary gland immaturity and early stage of lactation is mirrored by specific biology in the recipient infant during the early critical window postbirth. This potentiates immunomodulatory and nutritional programming as well as selective organ growth, including the immature brain.[19,26-35] In particular, the concentrations of high molecular weight bioactive proteins (including growth factors, secretory IgA, lactoferrin, interleukin 10, and soluble CD14) in preterm MOM are highest in colostrum but remain elevated through the first month of lactation.[36] The **Table** contrasts MOM and DHM as a function of mammary maturity and stage of lactation for MOM.

DHM	Donor human milk
VLBW	Very low birthweight
MOM	Mother's own milk
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit

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Table. Differences between MOM and DHM as a function of mammary gland maturity and stage of lactation

Components	Functions	Colostrum and transitional preterm MOM	Mature MOM	DHM
Bioactive proteins, including: • Immunoglobulins • Protective cytokines and chemokines • Milk fat globule membrane[17-26,32,37-39]	• Anti-inflammatory • Anti-infective • Gut barrier protection • Epigenetic • Immunomodulation • May have role in early immune programming	• High in MOM colostrum • Higher in preterm MOM colostrum • Highest in very preterm MOM colostrum • Decline slowest for least mature (earliest gestational age) mammary gland	• Become constant after 1 mo postbirth • Selective elevation in components following exposure to pathogens in infant environment (enteromammary pathway)	• Lower than mature MOM because of freezing, and pasteurization • Little or no bioactivity in some components
Growth factors, including: • Epidermal growth factor • Transforming growth factor • Vascular endothelial growth factor • Insulin-like growth factor-1 • Erythropoietin[33,34,40,41]	• Function synergistically to promote growth, maturation, and protection of gastrointestinal tract • May be especially important for very preterm infants who had less swallowing of amniotic fluid • Potential for absorption via open paracellular pathways in intestinal epithelium early postbirth • Speculated role in specific organ growth and protection	• High in MOM colostrum • Higher in preterm MOM colostrum • Highest in very preterm MOM colostrum • Decline slowest for least mature (earliest infant gestational age) mammary gland	• Reduced markedly after 1 mo post birth	• Further reduced with pasteurization • Bioactivity varies with growth factor
Macronutrients, including • Protein • Lactose • Lipid[26,36,39,42-44]	• Provide substrate for growth and development • Mature MOM lipids are the most variable and the most prone to iatrogenic deficiencies in the NICU setting	• Marked longitudinal changes because of tight junction closure in mammary epithelial cells • High total protein because of bioactive proteins, growth factors, MOM- borne hormones and other non-nutritional protein • High whey to casein ratio (little or no casein in colostrum) • Low lactose and lipid in colostrum, that increase in transitional MOM	• Lowest protein content in mammalian milk, but • Proteome is highly specific to human, targeting immunologic and neurologic protection • Lactose remains relatively constant, but is higher in foremilk than hindmilk • Lipid is highly variable and affected by NICU practices	• Multiple freeze-thaw cycles and container changes reduce lipid • All human milk-borne digestive enzymes are significantly reduced (amylases and proteases) are destroyed (lipases) with pasteurization, reducing bioavailability
Metabolic hormones, including: • Leptin • Adiponectin[45-51]	• Metabolic regulation • May have role in early nutrition programming	• Leptin and adiponectin highest in colostrum and decline thereafter	• Higher in hindmilk than composite or foremilk • Leptin stabilizes at 2 mo post-birth • Adiponectin declines over lactation	• Significant reductions with pasteurization that are additive to longitudinal decline
Milk microbiome • MOM-borne commensal bacteria that are not skin contaminants • Highly specific to individual mother[19,31,52]	• Thought important to early gut colonization • May be linked to individual MOM oligosaccharides for prebiotic substrate • May have role in early immune and nutritional programming • May have role in neuroprotection	• Present in colostrum • Present in preterm MOM as early as 24 wk of gestation • Highly variable among mothers	• Increase in number and type between colostrum and mature milk	• Destroyed with pasteurization
Oligosaccharides • Complex sugars without nutritional value • Third highest solute in MOM (higher than MOM protein) • > 200 identified in MOM • Marked individual variability in number and type[19,53-55]	• Prebiotic • Antimicrobial • Antiadhesive • Epithelial and immune cell modulation • Potential role in neurodevelopment	• Highest in colostrum and transitional MOM • Highly individual depending upon secretor status of mother	• Same pattern profile as in early lactation, but lower concentrations	• Largely preserved with storage and pasteurization • Different oligosaccharide pattern from infant's MOM
Soluble CD14 • Pattern recognition receptor[13,56,57]	• Facilitates bacterial-enterocyte crosstalk in the immature gut	• Higher in colostrum than mature human milk	• Lower than colostrum • 20× higher than maternal serum concentrations	• 88% reduction with pasteurization and freeze-thaw cycles

MOM and DHM: Impact on Potentially Preventable Morbidities and Growth

DHM and Morbidities

There is empirical evidence for the efficacy of DHM in reducing the risk, incidence, and severity of NEC when DHM replaces formula.[12,13,58-60] This consistent finding in randomized and nonrandomized studies is clinically and economically significant regardless of the lack of impact on other acquired morbidities. However, most DHM studies included some MOM feedings within a larger human milk metric, with no information about the relative proportions of MOM and DHM received before the onset of NEC. Because bovine-based formulas may negatively impact the integrity of the immature gut epithelial border in the early postbirth period as a function of increased intestinal permeability,[61] gut epithelial cell toxicity,[62] dysbiotic gut colonization,[63,64] and upregulation of inflammatory responses,[63] the primary benefit of DHM may be the avoidance of formula.[65] This knowledge has allowed clinicians to introduce enteral feedings of DHM earlier postbirth instead of waiting for MOM to become available. Thus, DHM may also contribute to reduction in NEC by enabling earlier enteral feeding and reducing the inflammatory impact of prolonged total parenteral nutrition.[66]

In contrast to MOM, studies about the use of DHM have not demonstrated a reduction in either sepsis or chronic lung disease or a positive impact on neurodevelopmental outcome in VLBW infants despite the reduction in NEC.[12-14,67] Numerous MOM components that are thought to contribute to reduced sepsis, chronic lung disease, and neurodevelopmental advantage are reduced or absent in DHM, and include myoinositol,[28,68] antioxidants,[69,70] lactadherin, and mucins,[37] growth factors such as insulin-like growth factor, transforming growth factor-β, and epidermal growth factor, soluble CD14, and adipokines.[34,40,45-49,56]

DHM and Slower Growth

Multiple studies reveal slower growth in DHM-fed vs MOM- and formula-fed VLBW infants.[7,12-14,59] To improve growth in DHM-fed infants, the most common solution is DHM fortification that may involve the earlier introduction and longer use of high concentrations of bovine protein.[12-14,71] This practice is based either on previous studies of MOM fortification or the need to "super-fortify" DHM to achieve growth targets,[13,14] rather than on separate long-term safety and efficacy studies of DHM fortification. Nonprotein factors may contribute to slower growth in DHM-fed infants and should inform the development and testing of alternative DHM enrichment strategies. For example, MOM adipokines, including leptin, adiponectin, and ghrelin, are linked to metabolic regulation in recipient infants, and are thought to have a role in early nutritional programming.[46,50] These MOM hormones, for which there are receptors in the fetal intestine, are present in preterm MOM, highly concentrated in colostrum and transitional MOM, and reduced with pasteurization.[45-49] DHM may also decrease growth because of the inconsistent delivery and utilization of MOM lipid.[36,42] Freeze-thaw cycles alter the structure of the fat globule membrane and its tightly regulated core and surface lipids,[43] and multiple transfers of DHM during storage and handling result in adherence of the nonhomogenized lipid to container surfaces.[36,42] Furthermore, bile salt stimulated lipase and lipoprotein lipase are completely inactivated and MOM amylases and proteases are reduced with pasteurization,[44] affecting macronutrient utilization even though baseline values may be preserved with processing.

Combining MOM and DHM into the Same Human Milk Feeding Group for Research and Quality Improvement

Most randomized studies comparing the effects of DHM and formula have included infants receiving some MOM in both groups because of the inability to assign feeding type ethically.[7,14,59,72] However, other studies have used the terminology, human milk-fed or breast milk-fed, to include both MOM and DHM feedings without any information detailing the relative proportions or the exposure periods for the 2 milks. Human milk-fed has been used to describe characteristics of study samples[73] and as an outcome variable in intervention studies.[60,74] Recent systematic reviews on the safety and efficacy of probiotics illustrate the limitations of using a common human milk feeding grouping when differences in MOM and DHM could impact outcome differently.[73,75-77] Only 1 review discussed the potential interaction between probiotics and type of feeding, but this comparison was between MOM- and formula-fed infants, not MOM- and DHM-fed infants.[77] In contrast to either formula or DHM, MOM contains an array of mother-specific probiotic bacteria (milk microbiome) along with highly complex and individual oligosaccharides that serve as prebiotics for these specific probiotic bacteria.[31,53] MOM-borne soluble CD14 and other bioactive MOM components enable bacterial-enterocyte crosstalk in the infant's immature intestine.[56] Pasteurization eradicates MOM probiotic bacteria and markedly reduces MOM-borne soluble CD14, which declines over lactation.[56,57] Thus, it is possible that DHM- and formula-fed infants would benefit from exogenous probiotics more than exclusively MOM-fed infants,[77] but available data do not inform this important issue. Furthermore, from a safety and efficacy perspective, it is unknown whether commercial probiotic strains compete with MOM probiotic bacteria for substrate (MOM oligosaccharides), potentially displacing or altering the impact of MOM probiotic bacteria on gut colonization.

Quality improvement initiatives focused on improving the use of human milk in the NICU have increasingly combined MOM and DHM into a common indicator, human milk feeding, even though this outcome was developed originally for MOM feedings only.[65,78] This limitation is clinically significant because quality improvement initiatives about human milk feeding are undertaken to reduce the prevalence of specific morbidities for which MOM is known to be protective without similar evidence for DHM. Thus, when high-dose

human milk feedings consisting mostly of DHM fail to reduce sepsis and are associated with slow growth, these findings are generalized to MOM as well. Furthermore, the processes involved in achieving high MOM feeding rates in the NICU are completely different from acquiring DHM, and raise issues as to how resources should be prioritized to achieve the quality initiative.

Impact of DHM Availability on Provision of MOM

One systematic review and 1 report of a large database of 22 California NICUs have suggested that the introduction of DHM programs does not reduce rates of provision of MOM for VLBW infants.[60,79] However, the measures used to evaluate the impact of DHM ranged from "any breastfeeding at NICU discharge," which was inconsistently defined among the studies, to actual measures of MOM dose for specific exposure periods pre- and postimplementation of a DHM program.[60,79] Esquerra-Zwiers et al[80] reported a decrease in the cumulative proportion of MOM received by VLBW infants at 14 and 28 days postbirth after the introduction of DHM into a NICU in which 98% of these infants had received some MOM prior to DHM availability. This decrease was concentrated primarily among low-income Black mothers who, in previous studies, changed the decision from formula to MOM following birth of a VLBW infant.[81] The study by Kantorowska et al[60] also revealed a racial difference in "any breastfeeding at NICU discharge" following the introduction of DHM programs, with Black mothers having lower odds of achieving this outcome.

Acceptability of DHM by NICU Families and Staff

Several studies have examined the acceptability of DHM by NICU families and staff in developing[82-84] and developed[85] countries. Concerns remain about the safety and quality of DHM in developing countries, especially those in which the prevalence of HIV is high.[82,84] Brownell et al[85] examined 5-year trends in nonconsent for DHM in a large US urban medical center, reporting that non-White race and increasing infant gestational age predicted refusal for DHM consent, although total refusals decreased for each of the 5 years following implementation of the DHM program. Other researchers have reported specific religious considerations related to the use of DHM.[86-88] Focusing on the timing and framing of the DHM consent process, Esquerra-Zwiers[89] found that mothers of VLBW infants objected to being approached for DHM consent before their own attempts to express MOM for their infants, and preferred a separate discussion about DHM that was not bundled as a part of other procedure-related NICU consents.

The Economics of MOM and DHM and Prioritization of Resources

DHM reduces the costs associated with NEC when substituted for formula,[90] but is significantly more costly than acquiring MOM,[91] which reduces multiple other morbidities and their associated costs in VLBW infants.[6,8,36] These comparisons raise the question as to how investments in human milk feeding should be targeted. Investing in DHM is often easier than addressing barriers to the provision of MOM in the NICU, but most lactation barriers in this population are modifiable when evidence-based practices and resources are prioritized.[92] The research literature is replete with strategies to acquire and feed MOM in the NICU, including assuring access to effective and efficient hospital-grade electric pumps, double collection kits, and customized breast shield sizing[93]; implementing breast pump use within 1 hour postbirth[94]; avoiding exclusive hand expression in the early days postbirth[95]; proactively monitoring pumped MOM volume during the critical first 2 weeks postbirth when breast-pump dependent mothers are at risk for long-lasting MOM volume problems[93]; integrating NICU-based breastfeeding peer counselors as direct lactation care providers[92,96]; and incorporating tested lactation technologies, such as milk analysis and test-weighing, to objectively manage growth on MOM feedings.[36]

Summary

Increasingly, the terminology human milk feeding is used to include both MOM and DHM for VLBW infants, implying that the multiple beneficial outcomes attributed only to MOM can be generalized to DHM. In particular, there is lack of fit between preterm MOM and DHM during the early critical postbirth window when nutritional and immunomodulatory programming and select organ growth via MOM components are thought to occur. Although DHM has been associated with reductions in NEC, MOM is more effective in the reduction of multiple morbidities and their costs, including NEC, and is less expensive to acquire than DHM. NICU care providers must frame the argument for the superiority of MOM over DHM with families, peers, and hospital administrators in a manner that results in high doses and longer exposure periods for MOM use in VLBW infants. ■

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References

1. Moro GE, Arslanoglu S, Bertino E, Corvaglia L, Montirosso R, Picaud JC, et al. XII. Human milk in feeding premature infants: consensus statement. J Pediatr Gastroenterol Nutr 2015;61:S16-9.
2. Perrine C, Scanlon K. Prevalence of use of human milk in US advanced care neonatal units. Pediatrics 2013;131:1066-71.
3. Liu X. The characteristics and operation of the first human milk bank. Paper presented at: the 3rd International Congress of the European Milk Bank Association; 2015 October 8-9; Lyon, France.
4. Namazova-Baranova L. The first human milk bank in Russia. What do Russians think about it? Preliminary results. Paper presented at: the 3rd International Congress of the European Milk Bank Association; 2015 October 8-9; Lyon, France.

5. Corpeleijn WE, Kouwenhoven SM, Pappa MC, van Vilet I, Scheerder I, Mulzer Y, et al. Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infants during the first 60 days of life. Neonatology 2012;102:276-81.
6. Patel A, Johnson T, Engstrom J, Fogg L, Jegier B, Bigger H, et al. Impact of early human milk on sepsis and health care costs in very low birthweight infants. J Perinatol 2013;33:514-9.
7. 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;116:400-6.
8. Johnson TJ, Patel AL, Bigger HR, Engstrom JL, Meier PP. Cost savings of human milk as a strategy to reduce the incidence of necrotizing enterocolitis in very low birth weight infants. Neonatology 2015;107:271-6.
9. Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, 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:e953-9.
10. Zhou J, Shukla VV, John D, Chen C. Human milk feeding as a protective factor for retinopathy of prematurity: a meta-analysis. Pediatrics 2015;136:e1576-86.
11. Spiegler J, Preuss M, Gebauer C, Bendiks M, Herting E, Gopel W, et al. Does breastmilk influence the development of bronchopulmonary dysplasia? J Pediatr 2016;169:76-80.
12. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2014;(4):CD002971. doi:10.1002/14651858.CD002971.pub3.
13. Underwood M, Scoble J. Human milk and the premature infant: focus on the use of pasteurized donor human milk in the NICU. In: Rajendra R, Preedy V, Patel V, eds. Diet and nutrition in critical care. New York (NY): Springer-Verlag; 2015. p. 795-806.
14. Colaizy TT. Donor human milk for very low birth weights: patterns of usage, outcomes, and unanswered questions. Curr Opin Pediatr 2015;27:172-6.
15. O'Connor DL, Ewaschuk JB, Unger S. Human milk pasteurization: benefits and risks. Curr Opin Clin Nutr Metab Care 2015;18:269-75.
16. Peila C, Coscia A, Bertino E, Cavaletto M, Spertino S, Icardi S, et al. Effects of Holder pasteurization on the protein profile of human milk. Ital J Pediatr 2016;42:36. doi:10.1186/s13052-016-0248-5.
17. Manzoni P. Clinical benefits of lactoferrin for infants and children. J Pediatr 2016;173:S43-52.
18. Sherman MP, Miller MM, Sherman J, Niklas V. Lactoferrin and necrotizing enterocolitis. Curr Opin Pediatr 2014;26:146-50.
19. Sherman MP, Zaghouani H, Niklas V. Gut microbiota, the immune system, and diet influence the neonatal gut-brain axis. Pediatr Res 2015;77:127-35.
20. Liao Y, Jiang R, Lonnerdal B. Biochemical and molecular impacts of lactoferrin on small intestinal growth and development during early life. Biochem Cell Biol 2012;90:476-84.
21. Ronayne de Ferrer PA, Baroni A, Sambucetti ME, Lopez NE, Ceriani Cernadas JM. Lactoferrin levels in term and preterm milk. J Am Coll Nutr 2000;19:370-3.
22. Rai D, Adelman AS, Zhuang W, Rai GP, Boettcher J, Lonnerdal B. Longitudinal changes in lactoferrin concentrations in human milk: a global systematic review. Crit Rev Food Sci Nutr 2014;54:1539-47.
23. Rollo DE, Radmacher PG, Turcu RM, Myers SR, Adamkin DH. Stability of lactoferrin in stored human milk. J Perinatol 2014;34:284-6.
24. Raoof NA, Adamkin DH, Radmacher PG, Telang S. Comparison of lactoferrin activity in fresh and stored human milk. J Perinatol 2016;36:207-9.
25. Bullen JJ. Iron-binding proteins in milk and resistance to *Escherichia coli* infection in infants. Postgrad Med J 1975;51:67-70.
26. Beck KL, Weber D, Phinney BS, Smilowitz JT, Hinde K, Lonnerdal B, et al. Comparative proteomics of human and macaque milk reveals species-specific nutrition during postnatal development. J Proteome Res 2015;14:2143-57.
27. Hassiotou F, Hartmann PE. At the dawn of a new discovery: the potential of breast milk stem cells. Adv Nutr 2014;5:770-8.
28. Pereira GR, Baker L, Egler J, Corcoran L, Chiavacci R. Serum myoinositol concentrations in premature infants fed human milk, formula for infants, and parenteral nutrition. Am J Clin Nutr 1990;51:589-93.
29. Twigger AJ, Hepworth AR, Lai CT, Chetwynd E, Stuebe AM, Blancafort P, et al. Gene expression in breastmilk cells is associated with maternal and infant characteristics. Sci Rep 2015;5:12933. doi:10.1038/srep12933.
30. Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of breast milk on intelligence quotient, brain size, and white matter development. Pediatr Res 2010;67:357-62.
31. Collado MC, Cernada M, Neu J, Perez-Martinez G, Gormaz M, Vento M. Factors influencing gastrointestinal tract and microbiota immune interaction in preterm infants. Pediatr Res 2015;77:726-31.
32. Collado MC, Santaella M, Mira-Pascual L, Martinez-Arias E, Khodayar-Pardo P, Ros G, et al. Longitudinal study of cytokine expression, lipid profile and neuronal growth factors in human breast milk from term and preterm deliveries. Nutrients 2015;7:8577-91.
33. Kidwell WR, Salomon DS. Growth factors in human milk: sources and potential physiological roles. In: Atkinson SA, Lonnerdal B, eds. Protein and non-protein nitrogen in human milk. Boca Raton (FL): CRC Press, Inc.; 1989. p. 77-91.
34. Dvorak B, Fituch CC, Williams CS, Hurst NM, Schanler RJ. Concentrations of epidermal growth factor and transforming growth factor-alpha in preterm milk. Adv Exp Med Biol 2004;554:407-9.
35. Dallas DC, Smink CJ, Robinson RC, Tian T, Guerrero A, Parker EA, et al. Endogenous human milk peptide release is greater after preterm birth than term birth. J Nutr 2015;145:425-33.
36. Meier PP, Patel AL, Bigger HR, Chen Y, Johnson TJ, Rossman B, et al. Human milk feedings in the neonatal intensive care unit. In: Rajendram R, Preedy VR, Patel VB, eds. Diet and nutrition in critical care. New York (NY): Springer-Verlag; 2015. p. 807-22.
37. Peterson JA, Hamosh M, Scallan CD, Ceriani RL, Henderson TR, Mehta NR, et al. Milk fat globule glycoproteins in human milk and in gastric aspirates of mother's milk-fed preterm infants. Pediatr Res 1998;44:499-506.
38. Lonnerdal B. Bioactive proteins in human milk: health, nutrition, and implications for infant formulas. J Pediatr 2016;173:S4-9.
39. Lonnerdal B. Bioactive proteins in human milk: mechanisms of action. J Pediatr 2010;156:S26-30.
40. Goelz R, Hihn E, Hamprecht K, Dietz K, Jahn G, Poets C, et al. Effects of different CMV-heat- inactivation-methods on growth factors in human breast milk. Pediatr Res 2009;65:458-61.
41. Rautava S, Nanthakumar NN, Dubert-Ferrandon A, Lu L, Rautava J, Walker WA. Breast milk- transforming growth factor-beta(2) specifically attenuates IL-1beta-induced inflammatory responses in the immature human intestine via an SMAD6- and ERK-dependent mechanism. Neonatology 2011;99:192-201.
42. Vieira AA, Soares FV, Pimenta HP, Abranches AD, Moreira ME. Analysis of the influence of pasteurization, freezing/thawing, and offer processes on human milk's macronutrient concentrations. Early Hum Dev 2011;87:577-80.
43. Keenan TW, Patton S. The structure of milk: implications for sampling and storage: a. The milk lipid globule membrane. In: Jensen RG, ed. Handbook of milk composition. San Diego (CA): Academic Press; 1995. p. 5-50.
44. Henderson TR, Fay TN, Hamosh M. Effect of pasteurization on long chain polyunsaturated fatty acid levels and enzyme activities of human milk. J Pediatr 1998;132:876-8.
45. Ilcol YO, Hizli ZB, Ozkan T. Leptin concentration in breast milk and its relationship to duration of lactation and hormonal status. Int Breastfeed J 2006;1:21. doi:10.1186/1746-4358-1-21.
46. Newburg DS, Woo JG, Morrow AL. Characteristics and potential functions of human milk adiponectin. J Pediatr 2010;156:S41-6.
47. Martin LJ, Woo JG, Geraghty SR, Altaye M, Davidson BS, Banach W, et al. Adiponectin is present in human milk and is associated with maternal factors. Am J Clin Nutr 2006;83:1106-11.

48. Yarandi SS, Hebbar G, Sauer CG, Cole CR, Ziegler TR. Diverse roles of leptin in the gastrointestinal tract: modulation of motility, absorption, growth, and inflammation. Nutrition 2011;27:269-75.
49. Ley SH, Hanley AJ, Stone D, O'Connor DL. Effects of pasteurization on adiponectin and insulin concentrations in donor human milk. Pediatr Res 2011;70:278-81.
50. Savino F, Liguori SA, Lupica MM. Adipokines in breast milk and preterm infants. Early Hum Dev 2010;86:77-80.
51. Resto M, O'Connor D, Leef K, Funanage V, Spear M, Locke R. Leptin levels in preterm human breast milk and infant formula. Pediatrics 2001;108: E15.
52. Khodayar-Pardo P, Mira-Pascual L, Collado MC, Martinez-Costa C. Impact of lactation stage, gestational age and mode of delivery on breast milk microbiota. J Perinatol 2014;34:599-605.
53. Underwood MA, Gaerlan S, De Leoz ML, Dimapasoc L, Kalanetra KM, Lemay DG, et al. Human milk oligosaccharides in premature infants: absorption, excretion, and influence on the intestinal microbiota. Pediatr Res 2015;78:670-7.
54. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology 2012;22:1147-62.
55. Marx C, Bridge R, Wolf AK, Rich W, Kim JH, Bode L. Human milk oligosaccharide composition differs between donor milk and mother's own milk in the NICU. J Hum Lact 2014;30:54-61.
56. Vidal K, Donnet-Hughes A. CD14: a soluble pattern recognition receptor in milk. Adv Exp Med Biol 2008;606:195-216.
57. Cossey V, Jeurissen A, Bossuyt X, Schuermans A. Effect of pasteurisation on the mannose- binding lectin activity and the concentration of soluble CD14 in human milk. J Hosp Infect 2009;73:96-7.
58. Cristofalo EA, Schanler RJ, Blanco CL, Sullivan S, Trawoeger R, Kiechl-Kohlendorfer U, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. J Pediatr 2013;163:1592-5.
59. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawoger R, Kiechl-Kohlendorfer U, 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;156:562-7.
60. Kantorowska A, Wei JC, Cohen RS, Lawrence RA, Gould JB, Lee HC. Impact of donor milk availability on breast milk use and necrotizing enterocolitis rates. Pediatrics 2016;137:1-8.
61. Taylor SN, Basile LA, Ebeling M, Wagner CL. Intestinal permeability in preterm infants by feeding type: mother's milk versus formula. Breastfeed Med 2009;4:11-5.
62. Penn A. Digested formula but not digested fresh human milk causes death of intestinal cells in vitro: implications for necrotizing enterocolitis. Pediatr Res 2012;72:560-7.
63. Chaud EC, Walker WA. Hypothesis: inappropriate colonization of the premature intestine can cause necrotizing enterocolitis. FASEB J 2001;15:1398-403.
64. Cilieborg MS, Boye M, Molbak L, Thymann T, Sangild PT. Preterm birth and necrotizing enterocolitis alter gut colonization in pigs. Pediatr Res 2011;69:10-6.
65. Meier PP, Engstrom JL, Patel AL, Jegier BJ, Bruns N. Improving the use of human milk during and after the NICU stay. Clin Perinatol 2010;37:217-45.
66. Siggers J, Sangild PT, Jensen TK, Siggers RH, Skovgaard K, Stoy AC, et al. Transition from parenteral to enteral nutrition induces immediate diet-dependent gut histological and immunological responses in preterm neonates. Am J Physiol Gastrointest Liver Physiol 2011;301:G435-45.
67. Unger SL, Gibbins S, Kiss A, O'Connor DL. Donor milk reduces necrotizing enterocolitis but does not improve neurodevelopment of very low birthweight (VLBW) infants at 18 months corrected age. Paper presented at: Pediatric Academic Society; 2016 April 30-May 3; Baltimore, MD.
68. de Segura AG, Escuder D, Montilla A, Bustos G, Pallas C, Fernandez L, et al. Heating-induced bacteriological and biochemical modifications in human donor milk after holder pasteurisation. J Pediatr Gastroenterol Nutr 2012;54:197-203.
69. Friel J, Diehl-Jones B, Cockell K, Chiu A, Rabanni R, Davies S, et al. Evidence of oxidative stress in relation to feeding type during early life in premature infants. Pediatr Res 2011;69:160-4.
70. Friel JK, Diehl-Jones WL, Suh M, Tsopmo A, Shirwadkar VP. Impact of iron and vitamin C- containing supplements on preterm human milk: in vitro. Free Radic Biol Med 2007;42:1591-8.
71. Cester EA, Bloomfield FH, Taylor J, Smith S, Cormack BE. Do recommended protein intakes improve neurodevelopment in extremely preterm babies? Arch Dis Child Fetal Neonatal Ed 2015;100:F243-7.
72. Unger S, Gibbins S, Zupancic J, O'Connor DL. DoMINO: donor milk for improved neurodevelopmental outcomes. BMC Pediatr 2014;14: 123.
73. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics 2010;125:921-30.
74. Marinelli KA, Lussier MM, Brownell E, Herson VC, Hagadorn JI. The effect of a donor milk policy on the diet of very low birth weight infants. J Hum Lact 2014;30:310-6.
75. Athalye-Jape G, Deshpande G, Rao S, Patole S. Benefits of probiotics on enteral nutrition in preterm neonates: a systematic review. Am J Clin Nutr 2014;100:1508-19.
76. Costeloe K, Hardy P, Juszczak E, Wilks M, Millar MR. Probiotics in preterm infants study collaborative group. *Bifidobacterium breve* BBG-001 in very preterm infants: a randomised controlled phase 3 trial. Lancet 2016;387:649-60.
77. Embleton ND, Zalewski S, Berrington JE. Probiotics for prevention of necrotizing enterocolitis and sepsis in preterm infants. Curr Opin Infect Dis 2016;29:256-61.
78. Bigger HR, Fogg LJ, Patel A, Johnson T, Engstrom JL, Meier PP. Quality indicators for human milk use in very low-birthweight infants: are we measuring what we should be measuring? J Perinatol 2014;34:287-91.
79. Williams T, Nair H, Simpson J, Embleton N. Use of donor human milk and maternal breastfeeding rates: a systematic review. J Hum Lact 2016;32:212-20.
80. Esquerra-Zwiers A, Wicks J, Rogers L, Engstrom JL, Meier PP, Patel AL. Impact of donor human milk in a high mother's own milk feeding neonatal intensive care unit. Poster presented at: 17th International Society for Research in Human Milk and Lactation Conference; 2014 October 24-27, Kiawah Island, SC.
81. Hoban R, Bigger H, Patel AL, Rossman B, Fogg LF, Meier P. Goals for human milk feeding in mothers of very low birth weight infants: how do goals change and are they achieved during the NICU hospitalization? Breastfeed Med 2015;10:305-11.
82. Coutsoudis I, Petrites A, Coutsoudis A. Acceptability of donated breast milk in a resource limited South African setting. Int Breastfeed J 2011;6:3.
83. Murray L, Anggrahini SM, Woda RR, Ayton JE, Beggs S. Exclusive breastfeeding and the acceptability of donor breast milk for sick, hospitalized infants in Kupang, Nusa Tenggara Timur, Indonesia: a mixed-methods study. J Hum Lact 2016;32:438-45.
84. Ighogboja IS, Olarewaju RS, Odumodu CU, Okuonghae HO. Mothers' attitudes towards donated breastmilk in Jos, Nigeria. J Hum Lact 1995;11:93-6.
85. Brownell EA, Smith KC, Cornell EL, Esposito PA, Wiley CC, Wang Z, et al. Five-year secular trends and predictors of nonconsent to receive donor milk in the neonatal intensive care unit. Breastfeed Med 2016;11: 281-5.
86. El-Khuffash A, Unger S. The concept of milk kinship in Islam: issues raised when offering preterm infants of Muslim families donor human milk. J Hum Lact 2012;28:125-7.
87. Khalil A, Buffin R, Sanlaville D, Picaud JC. Milk kinship is not an obstacle to using donor human milk to feed preterm infants in Muslim countries. Acta Paediatr 2016;105:462-7.
88. Kassierer MY, O'Connor DL, Rutherford E, Rolnitzky A, Unger S. Implications for observant Jewish families in the provision of mother's own and donor milk for their very low birth weight infant. J Hum Lact 2014;30:402-4.
89. Esquerra-Zwiers A, Rossman B, Meier P, Engstrom J, Janes J, Patel A. "It's somebody else's milk": unraveling the tension in mothers of preterm infants

who provide consent for pasteurized donor human milk. J Hum Lact 2016;32:95-102.
90. Ganapathy V, Hay JW, Kim JH. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. Breastfeed Med 2012;7:29-37.
91. Jegier BJ, Johnson TJ, Engstrom JL, Patel AL, Loera F, Meier P. The institutional cost of acquiring 100 ml of human milk for very low birth weight infants in the neonatal intensive care unit. J Hum Lact 2013;29:390-9.
92. Meier PP, Patel AL, Bigger HR, Rossman B, Engstrom JL. Supporting breastfeeding in the neonatal intensive care unit: Rush Mother's Milk Club as a case study of evidence-based care. Pediatr Clin North Am 2013;60:209-26.
93. Meier PP, Patel AL, Hoban R, Engstrom JL. Which breast pump for which mother: an evidence- based approach to individualizing breast pump technology. J Perinatol 2016;36:493-9.
94. Parker LA, Sullivan S, Krueger C, Mueller M. Association of timing of initiation of breastmilk expression on milk volume and timing of lactogenesis stage II among mothers of very low-birth- weight infants. Breastfeed Med 2015;10:84-9.
95. Lussier MM, Brownell EA, Proulx TA, Bielecki DM, Marinelli KA, Bellini SL, et al. Daily breastmilk volume in mothers of very low birth weight neonates: a repeated-measures randomized trial of hand expression versus electric breast pump expression. Breastfeed Med 2015;10:312-7.
96. Meier PP, Engstrom JL, Rossman B. Breastfeeding peer counselors as direct lactation care providers in the neonatal intensive care unit. J Hum Lact 2013;29:313-22.