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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; re-hospitalization 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 “super-fortify” 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

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for the targeting of resources that prioritize MOM feedings in the NICU. This paper 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 versus term DHM), stage of lactation for which DHM replaces MOM (e.g., mature DHM replacing MOM colostrum and transitional milk), 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 versus term.^{21,22} Longitudinally, these concentrations decrease by 50% between days 0–5 and days 11–30 of lactation, and continue to decline through two months of lactation when they stabilize at approximately one-third of colostrum values (9g/L versus 2–3 g/L).^{21,22} Further reductions of 47–55% occur with freezing.^{23,24} This means that lactoferrin concentrations in DHM collected two months post-birth and frozen for three 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 post-birth period, a common clinical scenario due to lack of MOM or concerns about maternal medications and health status. Pre-clinical 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 post-birth. 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.

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.^{12,13,37–39} This consistent finding in randomized and non-randomized 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 post-birth period as a function of increased intestinal permeability,⁴⁰ gut epithelial cell toxicity,⁴¹ dysbiotic gut colonization^{42,43} and upregulation of inflammatory responses;⁴² the primary benefit of DHM may be the avoidance of formula.⁴⁴ This knowledge has allowed clinicians to introduce enteral feedings of DHM earlier post-birth 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 TPN.⁴⁵

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.^{12–14,46} 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,^{28,47} antioxidants,^{48,49} lactadherin and mucins,⁵⁰ growth factors such as insulin-like growth factor, transforming growth factor- β and epidermal growth factor, soluble CD14 and adipokines.^{34,51–57}

DHM and Slower Growth

Multiple studies reveal slower growth in DHM-fed versus MOM- and formula-fed VLBW infants.^{7,12–14,38} 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.^{12–14,58} 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. Non-protein 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.^{52,59} 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.^{51–54,56} DHM may also decrease growth due to the inconsistent delivery and utilization of MOM lipid.^{36,60} Freeze-thaw cycles alter the structure of the fat globule membrane and its tightly regulated core and surface lipids,⁶¹ and multiple transfers of DHM during storage and handling result in adherence of the non-homogenized lipid to container surfaces.^{36,60} Furthermore, bile salt stimulated lipase and lipoprotein lipase are completely

inactivated and MOM amylases and proteases are reduced with pasteurization,⁶² 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 due to the inability to assign feeding type ethically.^{7,14,38,63} 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 two milks. *Human milk-fed* has been used to describe characteristics of study samples⁶⁴ and as an outcome variable in intervention studies.^{39,65} 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.^{64,66–68} Only one 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.⁶⁸ 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.^{31,69} MOM-borne soluble CD14 and other bioactive MOM components enable bacterial-enterocyte crosstalk in the infant's immature intestine.⁵⁵ Pasteurization eradicates MOM probiotic bacteria and markedly reduces MOM-borne soluble CD14, which declines over lactation.^{55,70} Thus, it is possible that DHM- and formula-fed infants would benefit from exogenous probiotics more than exclusively MOM-fed infants,⁶⁸ 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.^{44,71} 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 one 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.^{39,72} 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 post-implementation of a DHM program.^{39,72} Esquerra-Zwiers et al reported a decrease in the cumulative proportion of MOM received by VLBW infants at 14 and 28 days post-birth after the introduction of DHM into a NICU in which 98% of these infants had received some MOM prior to DHM availability.⁷³ This decrease was concentrated primarily among low-income mothers who, in previous studies, changed the decision from formula to MOM following birth of a VLBW infant.⁷⁴ The study by Kantorowska et al 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.³⁹

Acceptability of DHM by NICU Families and Staff

Several studies have examined the acceptability of DHM by NICU families and staff in developing^{75–77} and developed⁷⁸ countries. Concerns remain about the safety and quality of DHM in developing countries, especially those in which the prevalence of HIV is high.^{75,77} Brownell et al examined five-year trends in non-consent 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 five years following implementation of the DHM program.⁷⁸ Other researchers have reported specific religious considerations related to the use of DHM.^{79–81} Focusing on the timing and framing of the DHM consent process,⁸² Esquerra-Zwiers 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,⁸³ but is significantly more costly than acquiring MOM,⁸⁴ 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.⁸⁵ 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;⁸⁶ implementing breast pump use within 1 hour post-birth;⁸⁷ avoiding exclusive hand expression in the early days post-birth;⁸⁸ proactively monitoring pumped MOM volume during the critical first two-weeks post-birth when breast-pump dependent mothers are at risk for long-lasting MOM volume problems;⁸⁶ integrating NICU-based breastfeeding peer counselors as direct lactation care providers;^{85,89} 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 post-birth 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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Abbreviations

DHM	Donor human milk
VLBW	Very low birthweight
MOM	Mother's own milk
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

Component	Function	Colostrum and Transitional Preterm MOM	Mature MOM	DHM
<p>Bioactive Proteins, including:</p> <ul style="list-style-type: none"> Immunoglobulins Protective cytokines and chemokines Milk fat globule membrane <p>(17-26,32,50,90,91)</p>	<ul style="list-style-type: none"> Anti-inflammatory Anti-infective Gut barrier protection Epigenetic Immunomodulation May have role in early immune programming 	<ul style="list-style-type: none"> High in MOM colostrum Higher in preterm MOM colostrum Higher in very preterm MOM colostrum Decline slowest for least mature (earliest gestational age) mammary gland 	<ul style="list-style-type: none"> Become constant after 1 month post-birth Selective elevation in components following exposure to pathogens in infant environment (enteromammary pathway) 	<ul style="list-style-type: none"> Lower than mature MOM due to freezing, and pasteurization Little or no bioactivity in some components
<p>Growth Factors, including:</p> <ul style="list-style-type: none"> Epidermal growth factor Transforming growth factor Vascular endothelial growth factor Insulin-like growth factor-1 Erythropoietin <p>(33,34,57,92)</p>	<ul style="list-style-type: none"> Function synergistically to promote growth, maturation and protection of GI 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 post-birth Speculated role in specific organ growth and protection 	<ul style="list-style-type: none"> High in MOM colostrum Higher in preterm MOM colostrum Higher in very preterm MOM colostrum Decline slowest for least mature (earliest gestational age) mammary gland 	<ul style="list-style-type: none"> Reduced markedly after 1 month post-birth 	<ul style="list-style-type: none"> Further reduced with pasteurization Bioactivity varies with growth factor; some are eradicated, and some are preserved

Component	Function	Colostrum and Transitional Preterm MOM	Mature MOM	DHM
<p>Macronutrients, including</p> <ul style="list-style-type: none"> • Protein • Lactose • Lipid <p>(26,36,60–62,91)</p>	<ul style="list-style-type: none"> • Provide substrate for growth and development • Mature MOM lipids are the most variable and the most prone to iatrogenic deficiencies in the NICU setting 	<ul style="list-style-type: none"> • Marked longitudinal changes due to tight junction closure in mammary epithelial cells • High total protein due to 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Multiple freeze-thaw cycles and container changes reduce lipid • All HM-borne digestive enzymes are significantly reduced (amylases and proteases) are destroyed (lipases) with pasteurization, reducing bioavailability
<p>Metabolic Hormones, including:</p> <ul style="list-style-type: none"> • Leptin • Adiponectin <p>(51–54,56,59,93)</p>	<ul style="list-style-type: none"> • Metabolic regulation • May have role in early nutrition programming 	<ul style="list-style-type: none"> • Leptin and adiponectin highest in colostrum and decline thereafter 	<ul style="list-style-type: none"> • Higher in hindmilk than composite or foremilk • Leptin stabilizes at 2 months post-birth • Adiponectin declines over lactation 	<ul style="list-style-type: none"> • Significant reductions with pasteurization that are additive to longitudinal decline
<p>Milk Microbiome</p> <ul style="list-style-type: none"> • MOM-borne commensal bacteria that are not skin contaminants • Highly specific to individual mother 	<ul style="list-style-type: none"> • Thought important to early gut colonization • May be linked to individual MOM oligosaccharides for prebiotic substrate • May have role in early immune and 	<ul style="list-style-type: none"> • Present in colostrum • Present in preterm MOM as early as 24 weeks of gestation • Highly variable 	<ul style="list-style-type: none"> • Increase in number and type between colostrum and mature milk 	<ul style="list-style-type: none"> • Destroyed with pasteurization

Component	Function	Colostrum and Transitional Preterm MOM	Mature MOM	DHM
(19,31,94)	<ul style="list-style-type: none"> nutritional programming May have role in neuroprotection 	<ul style="list-style-type: none"> among mothers 		
Oligosaccharides <ul style="list-style-type: none"> • Complex sugars without nutritional value • 3rd highest solute in MOM (higher than MOM protein) • >200 identified in MOM • Marked individual variability in number and type (19,69,95,96)	<ul style="list-style-type: none"> • Prebiotic • Anti-microbial • Anti-adhesive • Epithelial and immune cell modulation • Potential role in neurodevelopment 	<ul style="list-style-type: none"> • Highest in colostrum and transitional MOM • Highly individual depending upon secretor status of mother 	<ul style="list-style-type: none"> • Same pattern profile as in early lactation, but lower concentrations 	<ul style="list-style-type: none"> • Largely preserved with storage and pasteurization • Different oligosaccharide pattern from infant's MOM
Soluble CD14 <ul style="list-style-type: none"> • Pattern recognition receptor (13,70,55)	<ul style="list-style-type: none"> • Facilitates bacterial-enterocyte cross-talk in the immature gut 	<ul style="list-style-type: none"> • Higher in colostrum than mature HM 	<ul style="list-style-type: none"> • Lower than colostrum • 20 X higher than maternal serum concentrations 	<ul style="list-style-type: none"> • 88% reduction with pasteurization and freeze-thaw cycles

Note: Numbers in parentheses of **component** column denote citations.