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