Human milk in the NICU: Dogma meets science

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Human milk either provided by the baby's own mother (MOM) or banked donor milk (DM) has become near standard of care for use in very low birthweight infants. In the United States, donor milk has supplanted the use of formula, especially since the published guidelines by the American Academy of Pediatrics (AAP) stating that only human milk should be fed to these infants [1]. Although the AAP guidelines have stimulated increased use of donor milk in the US, the number of human milk banks has been increasing worldwide for the past couple of decades. The beneficial effects of feeding premature infants MOM are based on sound aspects of human physiology and have been documented with a reasonable body of research. However, less is known about the effects of feeding these infants with pasteurised donor milk. Donated milk, when used for preterm infants, is usually pooled then pasteurised (62.5 C, 30 min) to remove possible infectious contaminants and distributed to various neonatal intensive care units (NICUs) through centralised milk banks. This process removes many immune and bioactive components, especially live cells including leukocytes and macrophages, potentially beneficial microbes, and enzymes. Thus, DM differs significantly from fresh MOM. It also differs significantly from formulas designed for preterm infants. Identifying the impact of pasteurisation and differences in these components on the clinical outcomes has been the focus of research studies over the past several decades. Nevertheless, in some cases dogma trumps the known scientific data when considering the use of donor milk in babies requiring neonatal intensive care. In this lecture, various aspects of providing banked donor milk to high risk preterm infants in the NICU will be addressed. The overarching objective is to objectively summarise the research literature on the nutritional practices in the NICU that pertain to the use of MOM, DM and formula. This will include an update of current understanding of the impact of pasteurisation on immune components of breast milk, with particular reference to those implicated in the prevention of necrotizing enterocolitis (NEC) and late onset sepsis (LOS). Furthermore, some of the benefits and drawbacks of donor human milk use will be discussed in terms of growth, mineralisation and impact on mother-infant interactions.

There are several questions that will be addressed:

a. What is the composition of donor human milk vs. MOM?
b. Human milk microbes: Are they pathogens, commensals, or just bystanders.
c. Does donor HM prevent NEC?
d. Are there differences in growth and development of preterm infants with DM vs. MOM vs. formula?

a. What is the composition of donor human milk vs. MOM?

MOM provided directly from the breast is the gold standard as all its biologically active components are preserved. Preterm infants require tube feeding and are either fed fresh expressed or frozen MOM, pasteurised DM or formulas. Milk storage and processing affects bioactive components of MOM and DM. These differences including cellular components, immune factors such as lactoferrin, IgA and IgG, macronutrients, micronutrients and enzymes will be summarised.

b. Human milk microbes: Are they pathogens, commensals, or just bystanders?

There has been a long term concern about feeding preterm infants with their underdeveloped immune systems human milk that may be colonised with microbes. In fact, it has been common practice to culture human milk samples and discard them if microbes were found in any quantities considered "significant". Commercial formulas are sterilised and do not contain microbes and donor human milk is pasteurised and should contain few if any microbes. Recently, it has become clear that human milk contains a wide variety of taxa of microbes (perhaps around 700), many of which do not originate from the skin of the mother or infant or the infant's mouth [2-4]. Instead, data suggests that many of these microbes originate from the mothers gastrointestinal tract [4]. This is especially relevant because alterations of the maternal microbiota by diet or microbial therapy could be used to promote a breast milk microbial ecology that is most conducive to infant health [5]. This is supported by elegant studies showing that genetically labelled microbes given to pregnant rodents can be found in the mothers' breast milk and subsequently in the infant[6]. The exact mechanism of transfer of maternal intestinal microbes to the mothers' breast remains poorly understood but it has been speculated that the intestinal tract during pregnancy is more permeable than during the non-pregnant state and that microbial translocation may occur readily through this highly permeable intestine. Another mechanism involves the transfer of microbes via dendritic cells which underlie the intestinal mucosa and can send their appendages into the lumen of the intestine and subsequently enter the bloodstream and present these cells to the mothers' breast [4]. The studies relating to these phenomena will be discussed.

The possibility that these found in human milk microbes actually play a role in development of the infant intestinal microbiome has been suggested [4]. Of interest is that temporally, the microbes from an individual mother's milk vary only slightly, but the microbes from an individual mother differ markedly from other mothers [2]. Whether this milk microbiome is specific for a certain mother infant dyad and that this specificity could confer benefits to the infant through an enteromammary system, which may offer dynamic immunologic responses from the mother to the newborn [7,8] will be discussed.

.Along the same thinking is the question of whether the technique of "kangaroo care" or "mother skin to skin care" may also offer benefits whereby the mother and infant are exposed to each other's microbes, and the mother acquires the infants' microbiota, which may offer specific benefits to the infant immune system.

It is common practice to add fortifiers to either preterm baby's own mother's milk or donor milk. The effect of these on the infant intestinal microbiome is poorly understood. Of interest is that there is some literature suggesting that fortifiers derived from human milk rather than bovine milk may be beneficial, [9] the relative effects of these on the developing neonatal intestinal microbiome have not been critically evaluated.

Another component of the breast milk that may serve to modulate the intestinal microbiome of the newborn are the human milk oligosaccharides. Several of these appear to perform a prebiotic function that includes promoting the growth of certain taxa of bacteria that may play beneficial roles in the infant gastrointestinal tract [10].

c. Does donor human milk prevent NEC and LOS?

NEC and LOS are major problems in NICU care and account for significant suffering as well as increased costs. Studies that relate to prevention of these diseases in human preterm infants have been hampered by lack of good definitions of these entities. NEC, for example, is a simple single pathophysiologic pathway disease and thus preventative strategies may not target the most common pathway. For example, when one considers using nutritional immune-related strategy for prevention of ischemic bowel disease (often termed “NEC”) seen in infants with certain congenital heart problems, this does not have biologic plausibility.

On the other hand, the more classical forms of “NEC” seen in human preterms do appear to have a major immune-inflammatory mechanism as a component of its pathophysiology. Human milk microbes as well as immune components are thus likely to play a biologically plausible role in prevention of the more classic forms of NEC.

Hence, several recent studies have reported that bioactive components of milk such as lactoferrin might be able to minimize LOS and also NEC [11]. The reported incidence of NEC and LOS inversely correlates to the gestational age [12,13], and enteral formula diets when coupled to parenteral nutrition appear to predispose to NEC, while progressive nutrition with colostrum and mother’s milk show a protective effect [14]. The putative protective effects of MOM over DM and formula against NEC and LOS have been the subject of several studies, but most have been underpowered and the individual studies have not shown a significant benefit of DM over formulas. Meta-analyses suggest that this may be the case [15], but these need to be taken in the context of when these studies were done and how NEC and sepsis have been defined [16]. Newer studies are ongoing and preliminary results suggest that DM may not have major benefits over formula in terms of NEC or LOS. These will be discussed.

d. Are there differences in growth and development of preterm infants with DM vs. MOM vs. formula?

There are major compositional differences in macro and micronutrients when comparing MOM, DM and preterm formulas. It is clear that the energy and protein content of human milk when provided to very low birthweight and extremely low birthweight infant do not meet their needs for growth and may in fact be detrimental from neurodevelopmental perspective unless they are fortified. Strategies have been developed for transitioning from parenteral nutrition to human milk, but these have often been met with at least transient deterioration in growth. Using fortifiers has been helpful, but specific strategies on when and how to most safely institute their incorporation are still being evaluated [17]. An update of these strategies will be presented.

Neurodevelopmental outcomes of preterm infants provided MOM, DM versus formulas have also been a focus of contention [18,19] and an overview of some of the available studies that provide comparisons of these outcomes will be discussed.

References

1. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827-41.
2. Hunt KM, Foster JA, Forney LJ, et al. Characterization of the diversity and temporal stability of bacterial communities in human milk. PLoS One 2011;6:e21313.
3. 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.
4. Jeurink PV, van Bergenhenegouwen J, Jimenez E, et al. Human milk: a source of more life than we imagine. Beneficial microbes 2013;4:17-30.
5. Thum C, Cookson AL, Otter DE, et al. Can nutritional modulation of maternal intestinal microbiota influence the development of the infant gastrointestinal tract? J Nutr 012;142:1921-8.
6. Perez PF, Dore J, Leclerc M, et al. Bacterial Imprinting of the Neonatal Immune System: Lessons From Maternal Cells? Pediatrics 2007;119:E724-32.
7. Kleinman RE, Walker WA. The enteromammary immune system: an important new concept in breast milk host defense. Dig Dis Sci 1979;24:876-82.
8. Riskin A, Almog M, Peri R, Halasz K, Srugo I, Kessel A. Changes in immunomodulatory constituents of human milk in response to active infection in the nursing infant. Pediatr Res 2012;71:220-5.
9. 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;156:562-7 e1.
10. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology 2012;22:1147-62.
11. Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, et al. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. JAMA 2009;302:1421-8.
12. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443-56.
13. Neu J, Walker WA. Necrotizing enterocolitis. N Engl J Med 2011;364:255-64.
14. Schanler RJ. The use of human milk for premature infants. Pediatr Clin North Am 2001;48:207-19.
15. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. The Cochrane database of systematic reviews 2014;4:CD002971.
16. Wynn JL, Wong HR, Shanley TP, Bizzarro MJ, Saiman L, Polin RA. Time for a neonatal-specific consensus definition for sepsis. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2014;15:523-8.
17. Roggero P, Gianni ML, Orsi A, et al. Implementation of nutritional strategies decreases postnatal growth restriction in preterm infants. PloS one 2012;7:e51166.
18. Unger S, Gibbins S, Zupancic J, O'Connor DL. DoMINO: Donor milk for improved neurodevelopmental outcomes. BMC pediatrics 2014;14:123.
19. Underwood MA. Human milk for the premature infant. Pediatr Clin North Am 2013;60:189-207.