Recommendations and guidelines for Perinatal practice

Donor human milk in preterm infant feeding: evidence and recommendations*

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Abstract

In preterm infants, feeding with human milk (HM) is a very effective intervention for the prevention of infections and necrotizing enterocolitis (NEC), and for potentially improved neurocognitive and cardiovascular outcomes in the long-term. Hospitals and physicians are advised to recommend HM for preterm and other high-risk infants either by direct breastfeeding and/or using the mother's own expressed milk. Donor HM is the preferred feeding when the mother's own milk is not available in sufficient quantity. While in some countries donor HM has been considered an effective tool in the delivery of health care to infants, skepticism regarding its nutritional and immunological quality has limited its distribution in other countries. The purpose of this paper is to summarize the clinical benefits of donor HM in preterm infants, and to discuss common concerns limiting its distribution as standard care. Clinically, the use of donor HM has been shown to prevent NEC, reduce feeding intolerance and improve long-term outcomes in premature infants. Common concerns, such as slow growth and loss of important biological components of donor HM due to storage and pasteurization, should not be a reason for denial of donor milk. Optimization of banking procedures and of HM fortification is available and should be applied. Banked donor milk should be promoted as standard component of health care for premature infants.

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Introduction

The feeding of human milk (HM) conveys substantial benefits to preterm infants. HM confers protection against sepsis and other infections [8, 13, 33, 35], protects against necrotizing enterocolitis (NEC) [19, 35, 39] and improves long-term neurocognitive development [7, 28, 42] and cardiovascular health outcomes [37, 38]. Recently, it has been shown that the feeding of HM substantially reduces the risk of death or NEC in a dose-dependent fashion [26]. That is why HM is the recommended feeding for all neonates including premature infants [1].

Mother's own milk is the first choice for feeding preterm infants. However, many mothers are not able to supply sufficient amounts of milk for their preterm infants during the neonatal period, when the feeding of HM is most important. Efforts to promote lactation and to define effective lactation strategies are likely to increase the milk supply. Donor HM is the feeding of choice when maternal milk is not available or is insufficient [1]. In many countries, the national policy to improve infant health outcomes considers banked HM as a reasonable and effective tool in the delivery of health care to infants and children [2], whereas skepticism about the nutritional and immunological quality of banked donor milk has limited its use in other countries.

We describe the clinical benefits of the use of donor HM for preterm infants, and discuss common concerns limiting its use in clinical practice.

Clinical benefits

Abundant information exists comparing the effects of HM with formula on clinical outcomes [7, 8, 13, 19, 26, 28, 33, 35, 37–39, 42] but until recently the evidence focusing specifically on pasteurized donor HM has been limited. Recent evidence documents clinical benefits in several important areas (Table 1).

A. Proven clinical benefits

Protection against necrotizing enterocolitis (NEC) Two recent systematic reviews [10, 32] addressed specifically the impact of donor HM vs. formula on clinical outcomes. Both

Table 1 Clinical benefits and common concerns deriving from the use of donor human milk in preterm infants.

Clinical benefits	Proven
	Protection against NEC
	Enhanced feeding tolerance
	Long-term health benefits
	Lower arterial blood pressure
	Lower ratios of LDL to HDL cholesterol
	and apoB to apoA-1
	Potential
	Enhanced immunity (short and long-term)
Common concerns	Slow growth of preterm infants
	Alterations in nutritional and biological quality of donor human milk

NEC = necrotizing enterocolitis, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

reviews have shown that donor milk has a protective effect against NEC in premature infants:

- A *Cochrane review* in 2007 [32] evaluated randomized controlled trials (RCTs) conducted in preterm and low birth weight infants. Meta-analysis from five trials demonstrated a significantly higher incidence of NEC in formula-fed infants. The observed effect sizes were similar across five studies, and there was no statistical evidence of heterogeneity. The pooled estimate suggests that one extra case of NEC will occur in every 33 infants who receive formula milk.
- The systematic review and meta-analysis of Boyd et al. in 2007 [10] evaluated RCTs and observational studies comparing the impact of donor human with formula on clinical outcomes. The combined evidence from these studies showed that donor milk as a sole diet reduces the risk of NEC by about 79%. An important finding deriving from this meta-analysis is that in settings where the risk of NEC in the formula group is about 5–20%, ~18.5 preterm infants would need to be given donor milk to prevent one case of NEC.

The paucity of data comparing formula milk with nutrient-fortified HM (only one study) limits both reviews and calls for new RCTs comparing the effect of fortified donor milk vs. formula.

Enhanced feeding tolerance   The systematic review of Boyd et al. [10] reported significantly fewer episodes of feeding intolerance (including NEC) and diarrhea in the donor HM group compared with the formula group. Infants in the donor milk group were found to tolerate full enteral feeds earlier and had significantly fewer withdrawals due to feeding intolerance.

Long-term health benefits   The RCTs conducted by Lucas et al. in the early 1980s and later follow-up provided solid experimental evidence for the long-term clinical benefits of donor HM feeding in preterm infants. In the early 1980s, HM banks were in common use and random assign-

ment of preterm infants to donor HM or formula was ethical because at that time the optimum diet for preterm infants was uncertain and the long-term outcomes of early feeding regimens were unknown [37].

The study started in 1982 and 926 preterm infants were randomly assigned in two parallel trials to receive (trial 1) donor HM or preterm formula, or (trial 2) standard term formula or preterm formula, as sole diet or as supplements to mother's milk. Long-term follow-up of this cohort was designed to test the hypothesis that early diet influences neurocognitive development and risk factors of cardiovascular disease [37, 38].

A representative subset (n = 216) was evaluated at age 13–16 years for key cardiovascular risk factors:

- Arterial blood pressure [37]: mean arterial blood pressure was lower in adolescents who had been randomized to donor milk than those given preterm formula. The proportion of enteral intake as HM in the neonatal period was inversely related to later mean arterial blood pressure.
- Lipoprotein profile [38]: Adolescents who had been randomized to donor milk had a lower ratio of low-density to high-density lipoprotein cholesterol (LDL to HDL) than those fed preterm formula. A greater proportion of HM intake was associated with lower ratios of LDL to HDL and apoB to apoA-1. This "dose-response" association, together with the experimental design of the study, supports a causal link between HM feeding and the lipoprotein profile later in life.

These data show the programming effect of early diet on clinical outcomes later in life and provide substantial evidence for the long-term beneficial effects of donor milk on cardiovascular health.

B. Potential clinical benefits

Enhanced immunity   The neonatal period is a critical window of opportunity for immunological adaptation. The immune system has to protect the host against pathogenic organisms, while ensuring tolerance to "self," to food and other environmental components, and to commensal bacteria. The education of the immune system in early life in a balanced way is critical not only for infection prevention, but also in minimizing the occurrence of immune-based disorders later in life [15]. HM plays an important role in the education of the immune system through its immune-active factors. Among these factors, human milk oligosaccharides (HMO) and long-chained polyunsaturated fatty acids (LCPUFA) are key immune-modulating components, and recently have been shown to maintain their quantity and pattern in donor HM after Holder pasteurization [6, 20]:

- HMO, after lactose and lipids, represent the third largest solid component in HM. They are multi-functional biomolecules having a high potential to promote health benefits, particularly to modulate immunity. Surviving intestinal digestion, HMO (i) exert prebiotic function, (ii) act as soluble analogs to epithelial receptors for specific

microbes, thus preventing their adhesion to the intestinal wall, (iii) have a trophic effect on intestinal mucosa through their fermentation products, and (iv) interact directly with cells of the immune system [9, 12, 23]. Thus, HMO are powerful candidates as key components of HM contributing to its protective effect against infections and NEC in preterm infants. Moreover, these immune-modulating biomolecules have a potential to prevent allergic diseases later in life.

- LCPUFA exert their immune-modulatory activities at different levels. The (n-3) LCPUFA metabolites induce eicosanoid production, alter gene expression, alter T-cell signaling; all contribute to immunological functional changes. Supplementation with (n-3) LCPUFA in infancy confirmed their influence on T-cell function and cytokine profile [15].

Briefly, feeding preterm infants with donor HM can be considered as a potential non-invasive intervention strategy to prevent the development of infection, NEC, allergy, and possibly other immune-related diseases.

Common concerns limiting the use of donor human milk

Slow growth

While HM-fed preterm infants derive non-nutritional benefits in terms of enhanced immunity, better neurocognitive development, and improved long-term clinical outcomes; nutritional concerns arise because HM may not meet the high nutrient requirements of the very low birth weight (VLBW) infant. Multicomponent fortification of HM is designed to maintain optimal nutritional intakes, but often falls short of this goal with regard to protein. This problem exists and probably is somewhat amplified with donor HM, which is most often provided by mothers of term infants and which is likely to have a lower protein content than mothers' milk of preterm babies [5, 24].

In fact, the above-mentioned two systematic reviews [10, 32] reported that preterm or low birth weight infants who received formula regained birth weight earlier and had higher short-term rates of weight gain, linear growth, and head growth than infants who received donor HM. However, in all trials except one [34], unfortified donor HM had been used. Furthermore, follow-up of the infants who participated in the two largest trials did not find a significant effect on long-term growth parameters or neurodevelopmental outcomes [27].

In recent years, it has become evident that preterm infants fed fortified HM (mother's own or donor HM) receive less protein than assumed [4] and continue to grow slower, in spite of fortification, than infants fed preterm formula [7, 11, 29, 30]. However, this should not be a reason to deny access to mother's own or donor HM. Rather, HM fortification should be optimized (individualized). Individualized fortification has been shown to be effective in improving protein

intakes, weight gain, and head circumference gain [3, 31]. There are two methods of individualization: ''adjustable fortification'' [3] and ''targeted fortification'' [31]. This topic has been discussed in detail in a recent review [5]. Another solution may be to increase the protein content of HM fortifiers, but this approach needs to be evaluated [4].

Alterations in nutritional and biological quality of donor human milk

Donor HM should be obtained from established HM banks which follow specific quality control guidelines, such as those from the Human Milk Banking Association of North America (HMBANA) (http://www.hmbana.org/) [21], United Kingdom Association of Human Milk Banking (UKAMB) (http://www.ukamb.org/) [16] and Italian Association of Human Milk Banks (AIBLUD) [25] (http://www.aiblud.org/). These guidelines recommend the Holder pasteurization method (62,5°, 30 min) to assure the microbiological safety of donor HM, and this is the widely performed practice.

It is known that processing of HM, particularly pasteurization, affects some of its nutritional and biological properties [14, 18, 22, 36, 40, 43]. A theoretical concern is that this may reduce the nutritional quality of HM and may attenuate its protective effects against infections and NEC, although clinically this has not been observed.

The Holder pasteurization process results in the loss of some biologically active milk components: sIgA, total IgA, lactoferrin, lysozyme, lymphocytes, lipase, alkaline phosphatase, cytokines, and some growth factors (IGFs) [14, 18, 22, 36, 40, 43]. Other key nutritional and biological components, however, such as oligosaccharides, vitamin A, D, E, lactose, LCPUFAs and epidermal growth factor (EGF) (important for intestinal maturation) are preserved [6, 14, 20, 40, 41].

Recently, an alternative pasteurization method, short time high-temperature (STHT) processing (72°C $\times$ 5–15 s) has been suggested to reduce the loss of important components

Table 2 Recommendations regarding the use of donor human milk in the feeding of preterm infants.

- Growing clinical evidence has placed human milk (HM) feeding as a basic right for preterm infants.
- Mother's own milk is the first choice in preterm infant feeding and strong efforts should be made to promote lactation.
- When mother's milk is not available, fortified donor human milk is the recommended alternative for this group of infants.
- Concerns regarding the nutritional and immunological quality of donor milk and slow growth of preterm infants fed HM should not be a barrier to its use.
- Optimization of donor HM processing (particularly pasteurization) and of fortification are required.
- Recent developments in pasteurization techniques appear to retain the bioactivity of human milk, and individualized fortification of HM provides improved protein intakes and growth. Thus, implementation of these techniques in human milk banks and utilization of individualized fortification are recommended.
- Donor milk banking should be protected, promoted, and supported as an extension of national breastfeeding policies.

of HM [17]. Evidence shows that this method preserves some of the biologically active key components (lactoferrin, sIgA, growth factors) and the antioxidant capacity of HM [14, 17, 36]. Research continues regarding the effect of STHT on other important HM components and protein quality, and the preliminary results seem promising.

Conclusions

Considering all the above-mentioned aspects related to the use of donor HM in preterm infant feeding, some recommendations can be given as listed in Table 2.

In conclusion, substantial clinical evidence has placed HM feeding and donor HM as a basic right for preterm infants. Novel HM fortification models and HM banking procedures are available and should be applied. Research on optimization of HM banking procedures and the composition of HM fortifiers are in progress, and it is very likely that the results of these studies will supplement the existing evidence regarding the benefits of donor HM for preterm infants. As a consequence, banked donor milk should be promoted as standard component of health care for premature infants.

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