

# Donor Human Milk for Preterm Infants: Current Evidence and Research Directions

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Society Commentary

**Abstract**   **Author Information**   **Article Outline**

**ABSTRACT** The Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition aims to document the existing evidence of the benefits and common concerns deriving from the use of donor human milk (DHM) in preterm infants. The comment also outlines gaps in knowledge and gives recommendations for practice and suggestions for future research directions. Protection against necrotizing enterocolitis is the major clinical benefit deriving from the use of DHM when compared with formula. Limited data also suggest unfortified DHM to be associated with improved feeding tolerance and with reduced cardiovascular risk factors during adolescence. Presence of a human milk bank (HMB) does not decrease breast-feeding rates at discharge, but decreases the use of formula during the first weeks of life. This commentary emphasizes that fresh own mother's milk (OMM) is the first choice in preterm infant feeding and strong efforts should be made to promote lactation. When OMM is not available, DHM is the recommended alternative. When neither OMM nor DHM is available, preterm formula should be used. DHM should be provided from an established HMB, which follows specific safety guidelines. Storage and processing of human milk reduces some biological components, which may diminish its health benefits. From a nutritional point of view, DHM, like HM, does not meet the requirements of preterm infants, necessitating a specific fortification regimen to optimize growth. Future research should focus on the improvement of milk processing in HMB, particularly of heat treatment; on the optimization of HM fortification; and on further evaluation of the potential clinical benefits of processed and fortified DHM.

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In a recent position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition, it was concluded that breast-feeding is the natural and advisable way of supporting the growth and development of healthy term infants <sup>(1)</sup>. Human milk (HM) also offers benefits to preterm infants <sup>(2-4)</sup>; however, in preterm infants, breast-feeding may not be possible, and own mother's milk (OMM) may not be available. In this situation, donor HM (DHM) and preterm infant formula are the alternatives.

Official bodies such as the World Health Organization <sup>(5)</sup> and the American Academy of Pediatrics <sup>(6)</sup> recommend the use of donated breast milk as the first alternative, when maternal milk is not available. American Academy of Pediatrics states that in such a situation, pasteurized DHM should be the first choice for preterm infants. To offer this opportunity to preterm infants, HM should be obtained from a HM bank (HMB). The number of HMBs is rapidly increasing worldwide. At present, in Europe, there are 186 HMBs, and new banks will be established with the support of the European Milk Bank Association ([www.europeanmilkbanking.com](http://www.europeanmilkbanking.com)); however, DHM is not available to all preterm infants.

In many countries, national policies to improve infant health outcomes consider DHM obtained from an HMB to be a reasonable and effective tool in the delivery of health care to infants and children <sup>(7)</sup>. Some countries have developed national guidelines that are published in English <sup>(8-11)</sup>.

This review aims to document the published evidence regarding the benefits deriving from the use of DHM for preterm infants, and to address the main concerns limiting its widespread adoption as a standard care. It also outlines the gaps in knowledge, and gives recommendations for practice and suggestions for future research.

## METHODS

The literature review included electronic searches of MEDLINE (1966–October 2011), EMBASE (1980–October 2011), CINAHL (1981–October 2011), the Cochrane Library, and conference proceedings. The electronic search used the following text words and MeSH terms: donor milk, human milk, breast milk, banked milk, milk bank, milk banking, (human milk OR breast milk) AND outcomes, (human milk OR breast milk) AND necrotizing enterocolitis, (human milk OR breast milk) AND infection, (human milk OR breast milk) AND neurodevelopment, (human milk OR breast milk) AND bronchopulmonary dysplasia, (human milk OR breast milk) AND (pasteurization OR heat).

Reference lists of the previous reviews and relevant studies were examined. Trials that had been reported only as abstracts were eligible for inclusion if sufficient information was available from the report.

## CLINICAL BENEFITS DERIVING FROM THE USE OF DHM

Randomized controlled trials (RCTs) focusing specifically on pasteurized DHM as a sole diet are sparse because it is no longer considered acceptable to randomize infants to any other diet if OMM is available. In most of the studies randomly assigning infants to HM or formula, the HM group includes both OMM and DHM.

### Necrotizing Enterocolitis (NEC)

Three systematic reviews <sup>(2,12,13)</sup> addressed specifically the effect of DHM versus formula on clinical outcomes. All of these reviews suggest that the use of DHM has a protective effect against NEC in premature infants.

The Cochrane review in 2007 <sup>(12)</sup> considered 5 RCTs conducted in preterm and low-birth-weight infants: Gross et al 1983, Lucas et al 1984 (trials 1 and 2), Schanler et al 2005, and Tyson et al 1983 <sup>(14–18)</sup>. In these studies, Gross et al <sup>(14)</sup> compared term formula with unfortified DHM, whereas Lucas et al <sup>(15,16)</sup> and Tyson et al <sup>(17)</sup> compared preterm formula (PF) with unfortified DHM. Lucas trial 1 provides NEC incidence comparing an exclusively DHM diet with PF in 159 infants, whereas Lucas trial 2 compares DHM with PF as a supplement to OMM <sup>(15,16)</sup>. The RCT conducted by Schanler et al <sup>(18)</sup> is the only one comparing PF with fortified DHM. DHM was pasteurized in all of the studies except the Tyson RCT <sup>(17)</sup>. A meta-analysis of data from 5 trials demonstrated a significantly higher incidence of NEC in formula-fed infants (typical relative risk 2.5, with 95% confidence interval [CI] 1.2–5.1). The observed effect sizes were similar across 5 studies, and there was no statistical evidence of heterogeneity. The pooled estimate suggests that 1 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 <sup>(2)</sup> and an earlier systematic review and meta-analysis by McGuire et al in 2003 <sup>(13)</sup> came to similar conclusions. The paucity of data on comparison of formula milk with nutrient-fortified HM (only 1 study) is the limitation in these reviews and highlights the need for new RCTs comparing the effect of fortified donor milk versus PF on NEC occurrence.

An intriguing point is the mechanism through which DHM may be offering protection against NEC. This protection may be through the supply of immunoprotective factors to the immature mucosa; however, the absence of harmful antigens may also be a contributing factor <sup>(19)</sup>. NEC may be caused by the detrimental effect of native cow's-milk protein on the developing human intestine. A recent multicenter RCT compared the outcomes of very-low-birth-weight (VLBW) infants fortified by 2 different kinds of HM fortifier (HMF) <sup>(20)</sup>. One group received HM-based HMF (HM concentrate with minerals and vitamins), whereas the other received bovine milk-based HMF and PF. The HM-based fortifier group had a significantly lower incidence of overall and surgical NEC than the other group.

## **Conclusion and Comments on NEC**

- Feeding preterm infants with DHM is associated with a decreased risk of NEC when compared with formula feeding.
- There are limited data on the comparison of feeding with fortified DHM versus PF. Because fortification of HM is the present practice for preterm and particularly for VLBW infants, future studies should compare the effect of feeding with fortified DHM versus formula on the NEC incidence.
- An exclusive HM diet (HM + HM-based fortifier) may reduce the NEC incidence even further, but this needs to be confirmed.

## **Feeding Tolerance**

Concerns regarding feeding intolerance and the perceived risk of NEC are the main obstacles for initiation and advancement of enteral feeds in VLBW infants. Three intervention trials <sup>(14,15,21,22)</sup> conducted in the 1980s and included in the recent 2 systematic reviews <sup>(2,13)</sup> reported significantly fewer episodes of feeding intolerance <sup>(14,15,21)</sup>, withdrawals because of intolerance <sup>(14)</sup>, and diarrhoea <sup>(22)</sup> in the unfortified DHM group compared with the formula group. In the large multicenter English trial <sup>(15,21)</sup>, infants fed exclusively unfortified DHM (trial 1) and as a supplement to OMM (trial 2) were found to establish full enteral feeds earlier and had fewer vomits and signs of gastric stasis compared with those who received infant formula; however, the data have not been published as a full article. All of the studies have been performed using native protein formula in contrast to hydrolyzed protein preterm infant formula, which has been shown to significantly improve feeding tolerance.

## Conclusion and Comments on Feeding Tolerance

- Limited available data from the 1980s support the hypothesis that unfortified DHM results in improved feeding tolerance compared with formula.
- Studies comparing the effect of fortified DHM versus formula on feeding tolerance are lacking.

## Bronchopulmonary Dysplasia

One RCT<sup>(18)</sup> designed to compare the incidence of infection-related events in extremely premature infants (<30 weeks of gestation) observed a reduction in the incidence of bronchopulmonary dysplasia (BPD) (oxygen need at postmenstrual age of 36 weeks) in the fortified DHM-fed infants compared with those fed PF (15% vs 28%;  $P = 0.048$ ).

## Conclusion and Comment on BPD

DHM may be protective against BPD. This needs to be determined by further RCTs.

## Long-Term Cardiovascular Risk Factors

Data on cardiovascular risk factors during adolescence are available from follow-up of a single randomized trial conducted in 5 neonatal units in the UK in the early 1980s. In 1 limb of the original study<sup>(15)</sup>, preterm infants were randomized to receive either unfortified DHM or a PF; randomization was stratified according to whether or not the mother provided her own milk. This is the only trial in which infants have been randomized to HM versus formula without confounding by the mother's decision to breast-feed<sup>(23)</sup>.

Adolescents (ages 13 to 16 years) who had been randomized to receive DHM, either as sole diet or as a supplement to maternal breast milk during the neonatal period, had significantly lower mean blood pressure (BP) (mean differences 4.1); however, follow-up was 26% only<sup>(24)</sup>. Adolescents who had been randomized to DHM also had a more favorable plasma lipid profile, with a lower ratio of low-density to high-density lipoprotein cholesterol than those fed PF<sup>(25)</sup>. Owing to the low percentage of follow-up (26%), the significance of these findings is uncertain.

## Conclusion and Comments on Cardiovascular Risk Factors

- DHM in early life may have beneficial effects on cardiovascular risk factors measured during adolescence; the significance of these findings for the development of cardiovascular disease is uncertain.
- A limitation in the evaluation of these findings is that the comparison was made between PF and unfortified DHM. This practice does not reflect the present feeding strategies in neonatal intensive care units (NICUs). If the underlying mechanism for these effects relates to slower early growth, it is important to consider whether these effects would persist if fortified DHM is used and early growth rates are faster.
- Further studies should compare the long-term outcomes between fortified DHM versus PF fed infants.

## Long-Term Neurodevelopment

The only RCT reporting impact of DHM on neurocognitive outcomes is the English 3-center study<sup>(26)</sup>. In this study, 502 preterm infants were assigned to receive either unfortified mature DHM or PF as sole enteral feeds or as supplements to OMM. PF was associated with an improved neurocognitive outcome at 1 year and no difference in neurocognitive outcomes (Bayley scores) was seen between the 2 diet groups at 18 months, but it must be noted that the DHM collected in the United Kingdom in the early 1980s had an energy content of 50 kcal/100 mL. The low energy content was the result of the fact that collected DHM was frequently drip milk

which had a lower fat content<sup>(26)</sup>. Despite the importance of this outcome parameter, no further follow-up results have been published by the authors with regard to long-term neurodevelopment, whereas other parameters such as cardiovascular biomarkers in adolescence have been published.

## Conclusion and Comments on Neurodevelopment

- No beneficial effect on neurocognitive outcome has been shown in the only available RCT.
- The comparison was made between PF and **unfortified DHM, which was frequently drip milk having low energy content**. This practice does not reflect the current feeding strategies in NICUs.
- Studies comparing fortified DHM and PF groups with regard to neurodevelopment are needed.

## Allergy

The neonatal period is a critical window of opportunity for immunological adaptation. HM plays an important role in the development of the immune system through its immunoactive factors. Among these factors, HM oligosaccharides and long-chain polyunsaturated fatty acids are well-known key immunomodulating components<sup>(27,28)</sup>. Recently, HM transforming growth factor- $\beta$  has been indicated as an immunoregulatory cytokine, particularly for allergy prevention<sup>(29,30)</sup>. The English multicenter trial evaluating the effect of feeding in the early postnatal period on allergic manifestations at 18 months after term found no difference in the incidence of allergic reactions between the DHM- and formula-fed groups<sup>(31)</sup>; however, in a subgroup of preterm infants with high risk for allergy, cow's-milk-based formula increased the risk of developing  $\geq 1$  allergic manifestations (particularly eczema) (odds ratio 3.6; 95% CI 1.4–9.1). High risk was defined as having a first-degree relative with a history of atopic disease (eczema, asthma, hay fever, drug reactions, or confirmed food allergy). No studies are available examining the influence of HM as compared with formula in infants with a high risk for developing allergy.

## Conclusion and Comment on Allergy

- The only available RCT shows that DHM does not have a protective effect against the development of allergy in preterm infants; however, the same RCT reports a protective effect of DHM against eczema in preterm infants at high risk for allergy.

# CONCERNS AND UNCERTAINTIES

## Safety

### Microbiological Safety

DHM should be obtained from established HMBs that follow specific guidelines for screening, storage, and handling procedures to optimize its composition while ensuring its safety for the recipient<sup>(32)</sup>. Many countries now have their own HMB guidelines<sup>(8–11,33)</sup>. The first HMB was established as early as 1909 in Vienna, Austria. Many banks have been established since then, and some closed following the early years of the HIV pandemic in the 1980s.

Pasteurization of the milk minimizes the risk of disease transmission via HM, inactivating most of the viral and bacterial contaminants. In addition, donors are screened in a similar way as for blood donation. No report has been published showing transfer of diseases through pasteurized DHM, although milk may contain microorganisms<sup>(34)</sup>. Nevertheless, HMBs, like blood banks, should be aware of the threat of emerging (milk transmissible) pathogens that are not included in contemporary screening protocols. There is concern that growth of *Bacillus* sp during the heating process may be increased<sup>(35)</sup>; however, although spore-forming

*Bacillus* sp may survive pasteurization, this is thought to be a rare contaminant of human breast milk in contrast to cow's milk<sup>(36)</sup>. Regardless, this type of contamination can be controlled by proper storage and handling after pasteurization, which should prevent any *Bacillus* sp from growing. HMBs should have policies for microbiological quality control.

## Chemical Pollutants, Including Drugs of Abuse

Environmental pollutants such as mercury, dioxins, and polychlorinated biphenyls (PCBs) are taken up via food and stored in fatty tissue. There are no specific studies conducted with DHM. Some of the pollutants can act as endocrine disruptors involving thyroid, hypothalamus, and gonads<sup>(37,38)</sup>. Prenatal exposure to an organochlorine compound has been reported to result in impaired neurodevelopment at 4 years<sup>(39)</sup>, whereas perinatal exposure to high PCB levels has been associated with neurotoxicity<sup>(40)</sup>, and perinatal dioxin exposure has been associated with persistent hematologic and immunologic disturbances<sup>(41)</sup>. Theoretically, these substances can be excreted in breast milk. The concentration of PCBs and dioxins in breast milk of European women has decreased during the last decade as a consequence of measures against environmental pollution. Furthermore, as suggested in the study, monitoring the effect of PCBs in colostrum milk on the visual function in infants<sup>(42)</sup>, HM may be offsetting potential deleterious effects of these pollutants through its various biofactors. Future studies should address the presence of these pollutants in DHM and their possible effects on infant health.

Besides environmental pollutants, other unwanted substances such as medication, alcohol, nicotine, and drugs of abuse are also excreted into the milk. Presently, no internationally accepted list of medicines that can safely be used by milk donors exists. HMBs are therefore expected to compile their own list based on available literature and pharmacological properties. Because DHM is generally intended for sick and premature infants, and infants are often exposed to milk from >1 donor, guidelines for medication use in HM donors should be more strict than those for women who are solely feeding their own healthy infants. The safety of DHM relies heavily on the accurate reporting of nicotine, alcohol, or drug abuse of potential donors because it is not feasible to routinely test all milk for a wide range of harmful substances. Special attention should also be paid to the use of herbal remedies and herbal teas because some contain harmful substances, for example, fennel tea can contain substantial amounts of estragole<sup>(43)</sup>.

## Conclusion and Comments on Safety

- DHM should be pasteurized.
- Donors should be screened in a similar way as for blood donation, and should be asked about their use of alcohol, nicotine, and drugs.
- Studies are needed to address the presence and possible health consequences of pollutants in DHM.

## Alterations in Nutritional and Biological Quality of DHM

Some significant concerns are related to the possible alterations in the nutritional and biological quality of DHM because of its handling and storage, but particularly because of the heat treatment. Holder pasteurization (62.5°C, 30 minutes) is the most commonly used method. It results in the loss of the quantity and/or activity of some biologically functional milk components to varying degrees:

1. Mild to moderate decrease in IgA and secretory IgA concentrations (~20%–30%, range 0%–60%) and activity (33%–39%)<sup>(44–53)</sup>.
2. Considerable loss in concentration/activity of lactoferrin (50%–75%)<sup>(46,47,49–51,54,55)</sup>, lysozyme (24%–74%)<sup>(44–48,50–52,54)</sup>, IgG (34%–76%)<sup>(45,47)</sup>, some cytokines (interleukin-10, tumor necrosis factor- $\alpha$ )<sup>(56,57)</sup>, growth factors, and hormones (insulin-like growth factor 1, adiponectin, insulin, and leptin)<sup>(58–60)</sup>, and antioxidant capacity of HM<sup>(61)</sup>.

3. Almost complete loss of lipase activity<sup>(44,49)</sup>, IgM (concentrations)<sup>(45,46)</sup>, and white blood cells<sup>(62,63)</sup>.

Other nutritional and biological components, such as oligosaccharides<sup>(64)</sup>, lactose, glucose<sup>(65,66)</sup>, long-chain polyunsaturated fatty acids, gangliosides<sup>(57,67,68)</sup>, vitamins A, D, E, B<sub>12</sub>, folic acid<sup>(44,69)</sup>, some cytokines (interleukin-2, -4, -5, -8, -13)<sup>(57)</sup>, and some growth factors (EGF and TGF-β<sub>1</sub>), are preserved<sup>(56,58)</sup>.

Holder pasteurization maintains the bactericidal activity of the milk against *Escherichia coli* better than high-temperature short-term pasteurization<sup>(70)</sup>. It has been also shown that despite the reduction in IgA concentrations, remaining molecules in the Holder-pasteurized HM effectively inhibit bacterial (enteropathogenic *E coli*) adhesion<sup>(71)</sup>. Similarly, in an earlier study, although Holder pasteurization decreased the activities of specific antibody to *E coli* and lactoferrin, pasteurized milk remained effective at inhibiting in vitro growth of *E coli*<sup>(54)</sup>.

New methods to improve the biological quality and safety of DHM are under investigation<sup>(72)</sup>. High-temperature short-term pasteurization (flash pasteurization, 72°C for 5–15 seconds)<sup>(44,49,55,58,70)</sup> and its homemade low-tech variant for developing countries (flash-heat treatment)<sup>(73–75)</sup>, thermoultrasonic treatment<sup>(50)</sup>, high-pressure processing<sup>(76,77)</sup>, and Ohmic heat treatment<sup>(72)</sup> are the alternative methods on which present studies are focused.

## Conclusion and Comments on Nutritional and Biological Quality of DHM

- Holder pasteurization, the most commonly used procedure, is safe but reduces the nutritional/biological quality of DHM.
- Pasteurization should be optimized to maintain microbiological safety while preserving the highest amount and activity of the bioactive milk components.

## Slow Growth

### Slow Growth Because of Inadequate Nutrient Content of DHM

HM does not meet the high nutrient requirements of the VLBW infant. Standard multicomponent fortification of HM designed to optimize nutritional intakes<sup>(78)</sup> often falls short of this goal with regard to protein<sup>(79,80)</sup>. This problem may be amplified with DHM, which is most often provided by the mothers of term infants beyond 1 month postpartum and which is likely to have lower protein content than preterm mothers' milk<sup>(66,81–83)</sup>. A recent observational study indicates that using standard fortification, weight gain is faster in preterm infants fed OMM than in those fed DHM, whereas there is no difference in terms of linear growth<sup>(84)</sup>.

The systematic reviews of Quigley<sup>(12)</sup> and Boyd<sup>(2)</sup> 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 DHM; however, of 8 trials included, only 1<sup>(18)</sup> compared fortified DHM with PF. In this trial, infants fed DHM had a slower rate of weight gain compared with PF (17.1 vs 20.1 g · kg<sup>-1</sup> · day<sup>-1</sup>; *P* = 0.001). Length and head circumference increments were similar in the 2 groups.

The fat and protein content of HM is extremely variable, and protein decreases with lactation duration. In recent years, it has become evident that preterm infants fed fortified HM (OMM or DHM) receive less protein than assumed<sup>(85)</sup> and continue to grow more slowly in the short term, even with standard HM fortification, compared with PF-fed infants. Although there is some uncertainty about the optimal growth, postnatal growth failure has not been solved with HM fortification in standard fashion<sup>(79)</sup>. Thus, HM fortification should be optimized to achieve better short-term growth, which is associated with improved neurocognitive outcome. Individualized fortification has been shown to be effective in improving protein intake, weight gain, and head circumference gain<sup>(86,87)</sup>. There are 2 ways to individualize HM fortification: “adjustable fortification” (individualization based on blood urea nitrogen measurements)<sup>(86)</sup> and “targeted fortification” (individualization based on milk analysis)

(87). Improvement of the quality of HMF is a further issue, and HM-based fortifier may offer benefits compared with cow's-milk-based fortifiers as shown in the multicentric study using Prolact + H<sup>2</sup>MF (HM concentrate with minerals and vitamins) (20). Earlier studies showed that infants fed exclusively HM proteins (HM + HM protein supplement) have plasma amino acid concentrations that differ significantly from those fed either whey-predominant or casein-predominant formulas at similar protein intakes. The amino acid pattern of low-birth-weight infants fed exclusively HM proteins is similar to the pattern found in growing breast-fed term infants (88,89).

## Potential Slow Growth Because of Alterations in the Nutritional Quality of DHM

As mentioned before, lipase activity is almost completely lost following Holder pasteurization. It has also been shown that heat induces alterations of the milk fat globule surface removing the glycoprotein filaments (90). These heat-induced changes can explain the reduced milk fat absorption reported in pasteurized HM-fed preterm infants (91,92). Optimizing the heat processing and determining the best method of pasteurization for maintaining the nutritional and biological quality of DHM are essential.

### Conclusion and Comments on Growth

- HM- and DHM-fed preterm infants have slower early growth than PF-fed infants.
- Inadequacy of standard HM fortification, particularly with regard to protein, and decreased fat absorption owing to the loss of lipase activity following pasteurization and loss of fat during handling are the main factors explaining the slower growth seen in infants who receive DHM.
- Individualized fortification (adjustable or targeted) may help to ensure adequate nutrient intakes.
- Studies on the quality of fortifiers and different heat treatment strategies are needed.

## Does the Presence of an HMB Compete With Breast-feeding?

The purpose of HM banking is to provide a HM supply for infants (mainly preterm). Promotion of breast-feeding and use of OMM come first. When OMM is not available or is insufficient, DHM is used along with the ongoing efforts to promote lactation. In fact, the European Milk Bank Association, in its constitution, states the first 3 objectives of the Association as follows:

1. To promote breast-feeding
2. To promote the donation of HM to HMBs
3. To promote the use of DHM for premature infants and other infants with specific needs who do not have access to OMM

Some concerns have been raised that the presence of an HMB and the use of DHM may attenuate the efforts to promote lactation resulting in decreased breast-feeding rates.

No RCT could be identified addressing this concern, but recently some reports showed the opposite: A report from Australia (93) cites the breast-feeding rates in the 3 years following the establishment of an HMB. Despite a marked increase in DHM use in the NICU, opening an HMB did not reduce the rate of milk expression, and breast-feeding rates at discharge increased.

In an attempt to improve HM availability for preterm infants, health care providers of a NICU in UT designed an integrated approach: “Breast Milk Early Saves Trouble Program” (94). This program consisted of using exclusively HM (OMM and/or DHM) in the NICU. Its implementation for 12 months increased HM and DHM use in NICU, and breast-feeding rates at discharge tended to increase compared with the situation before the implementation period (53% vs 44%;  $P = 0.09$ )

A Spanish study conducted in Madrid <sup>(95)</sup> directly addressed this concern and evaluated the effect of opening an HMB in a NICU on the rates of exclusive breast-feeding at discharge and formula use in the NICU. The researchers concluded that presence of an HMB in a neonatal unit did not reduce the rate of exclusive breast-feeding at discharge, but did reduce the use of infant formula during the first 4 weeks of life (37% vs 60%;  $P = 0.01$ ). The availability of having DHM also enabled earlier initiation of enteral feeding.

## **Conclusion and Comment on the Relation of HMBs and Rates of Breast-feeding**

The existing data show that the presence of an HMB and use of DHM in the NICU do not decrease the breast-feeding rates at discharge, but decrease formula use during the first weeks of life.

# CONCLUSIONS, RECOMMENDATIONS, FUTURE RESEARCH DIRECTIONS

## Conclusions

Based on the evidence presented in this commentary, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition concludes the following:

1. DHM is associated with reduced NEC rates compared with cow's-milk–based formula.
2. Unfortified DHM, like HM, is associated with slower neonatal growth when compared with PF.
3. Appropriately handled and pasteurized DHM is microbiologically safe.
4. Presence of an HMB does not decrease the breast-feeding rates at discharge, but may decrease formula use during the first weeks of life.

## Recommendations

1. OMM is the first choice in preterm infant feeding, and strong efforts should be made to promote lactation.
2. When mother's milk is not available, DHM is the preferred choice. When mother's milk and DHM are not available, PF should be used.
3. No DHM should be provided outside the organization of an established HMB.
4. Adequate screening of donors and pasteurization of the donor milk should be performed.
5. DHM should be fortified to meet early nutrient requirements and achieve better short-term growth, which is associated with improved neurocognitive outcome. Individualized fortification is advised.

## Research Directions

1. Randomized clinical trials comparing
  1. The impact of feeding with PF versus fortified DHM on short-term clinical outcomes: growth, NEC, sepsis and other infections, retinopathy of prematurity, BPD, feeding tolerance, and mortality
  2. The impact of feeding with PF versus fortified DHM on long-term clinical outcomes: allergy, neurodevelopmental outcomes, obesity, metabolic syndrome, and other cardiovascular risk factors
  3. The impact of feeding with DHM with bovine fortifier versus HM diet (OMM/DHM + HM-based fortifier) on short-term and long-term clinical outcomes
2. Development and evaluation of different pasteurization techniques to optimize microbiological safety, and to maintain the biological and nutritional quality of HM
3. Development of systems to ensure the lowest possible level of toxic products and pollutants in the donor HM

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