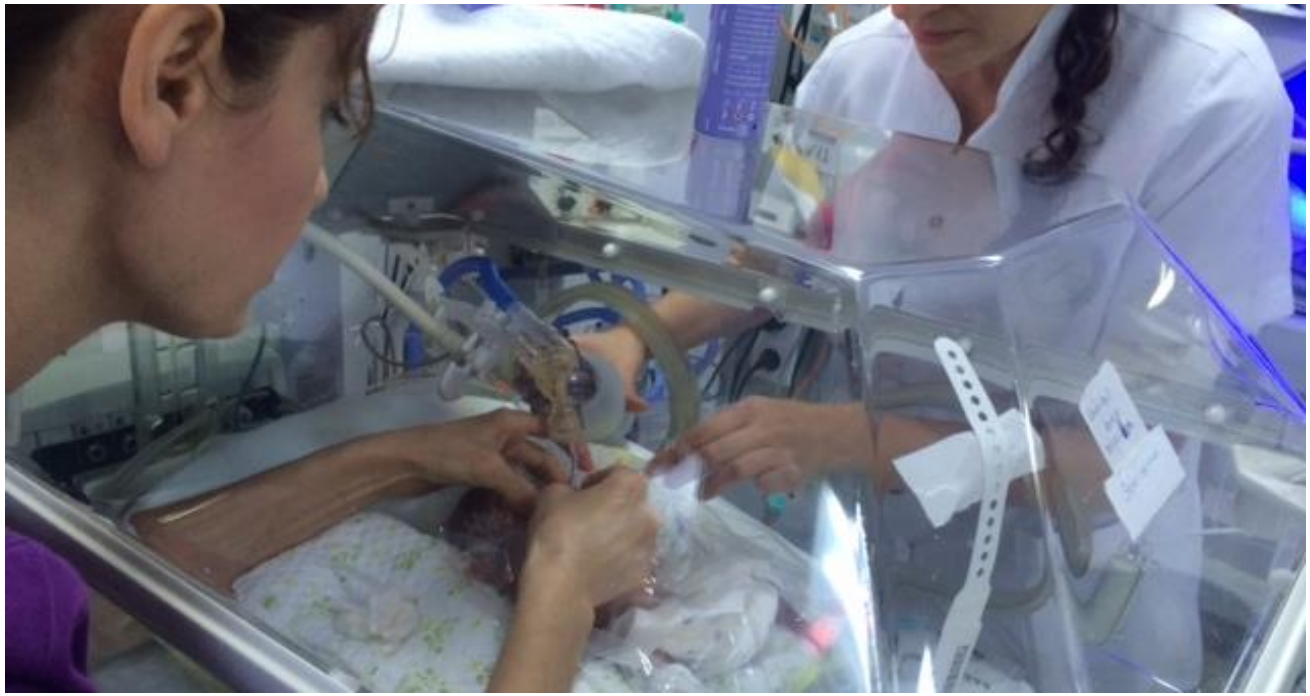
İSTANBUL MEDENİYET ÜNİVERSİTESİ

BENEFITS OF DONOR HUMAN MILK

emba
EUROPEAN MILK BANK ASSOCIATION



Prof. Dr. Sertaç Arslanoğlu

Director, Division of Neonatology
Administrative Director, Department of Pediatrics, İstanbul Medeniyet University

Vice President, European Milk Bank Association (EMBA)

Nutrition-
High Level of Responsibility

Nutritional Goals

- Ensure a growth similar to the IU growth rate
- Ensure a body composition similar to that of the fetus of the same gestational age
- Prevent postnatal growth failure
- Minimize the risk of NEC
- Ensure a satisfactory functional development
- Improve the health outcomes at the short- and long-term

Nutritional Goals

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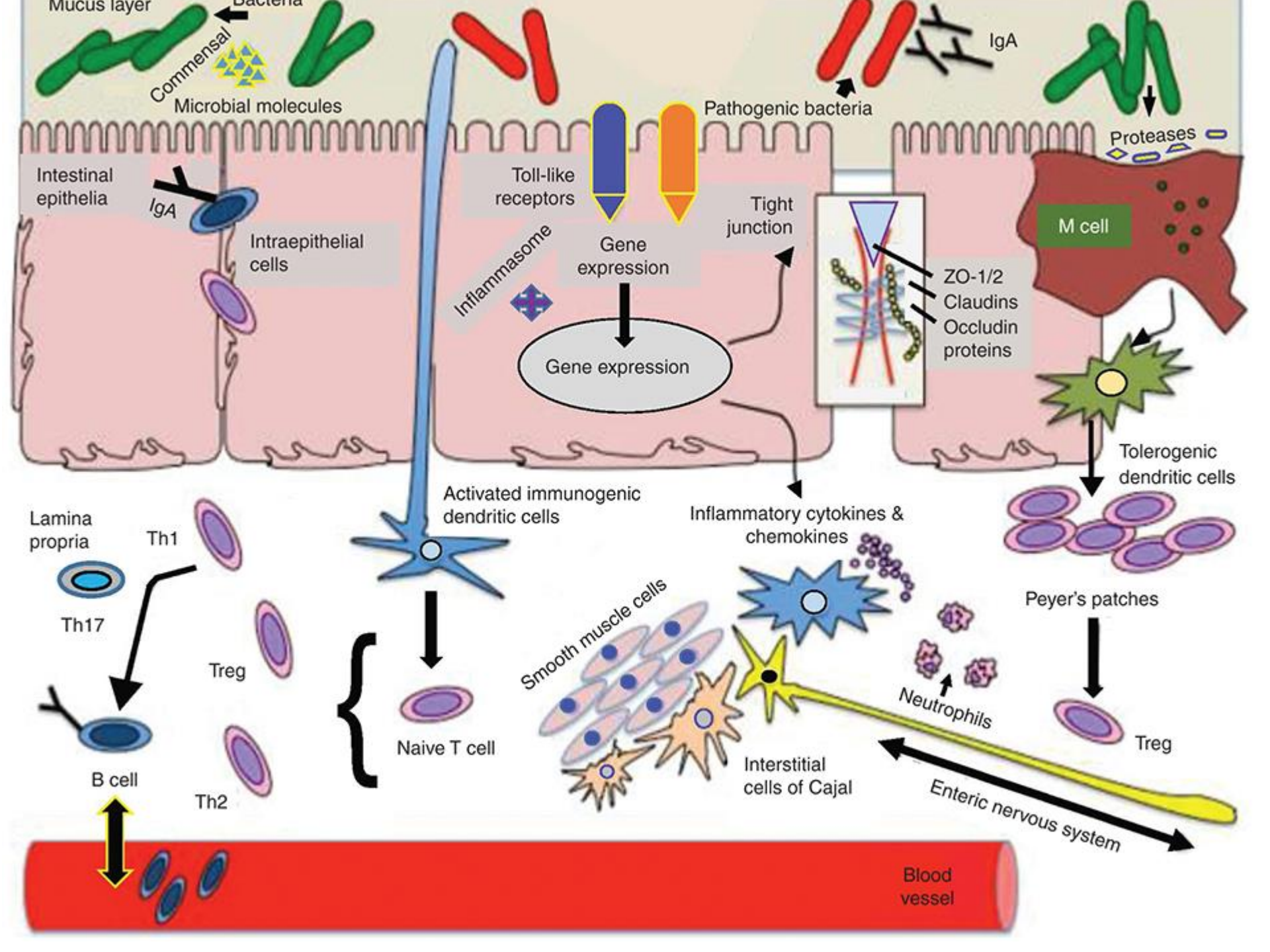
- Ensure a body composition similar to that of the fetus of the same gestational age
- Prevent postnatal growth failure
- Minimize the risk of NEC
- Ensure a satisfactory functional development
- Improve the health outcomes at the short- and long-term
- Develop a beneficial intestinal microbiota


Mucus layer
Bacteria
Commensal
Microbial molecules
IgA
Pathogenic bacteria
Proteases
Intestinal epithelia
IgA
Intraepithelial cells
Toll-like receptors
Inflammasome
Gene expression
Gene expression
Tight junction
ZO-1/2
Claudins
Occludin proteins
M cell
Tolerogenic dendritic cells
Activated immunogenic dendritic cells
Inflammatory cytokines & chemokines
Lamina propria
Th1
Th17
Treg
Th2
B cell
Naive T cell
Smooth muscle cells
Neutrophils
Interstitial cells of Cajal
Peyer's patches
Treg
Enteric nervous system
Blood vessel

REALITY IN OUR NICUs

1. Extrauterine growth retardation is still a problem at discharge
2. Also the body composition at discharge is abnormal (decreased lean body mass, increased visceral and total adiposity)
3. These are due to inappropriate nutrition with potential negative effect on brain development and late obesity, insulin resistance

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---disbiotic intestinal environment

Recipe=HM

- Dual action
  - Source of nutrients
  - A myriad of bioactive components
- The most potent immunonutrient
- A synbiotic
- Chronobiotic

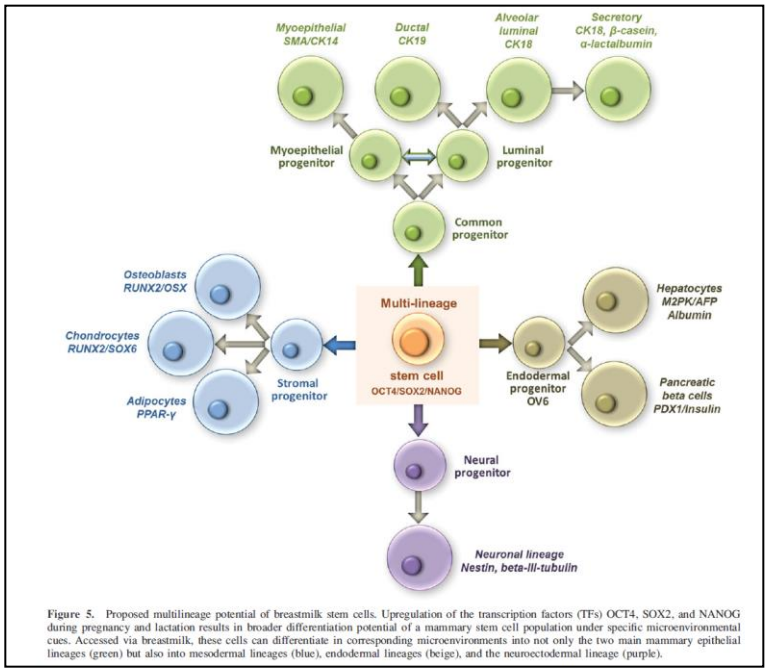
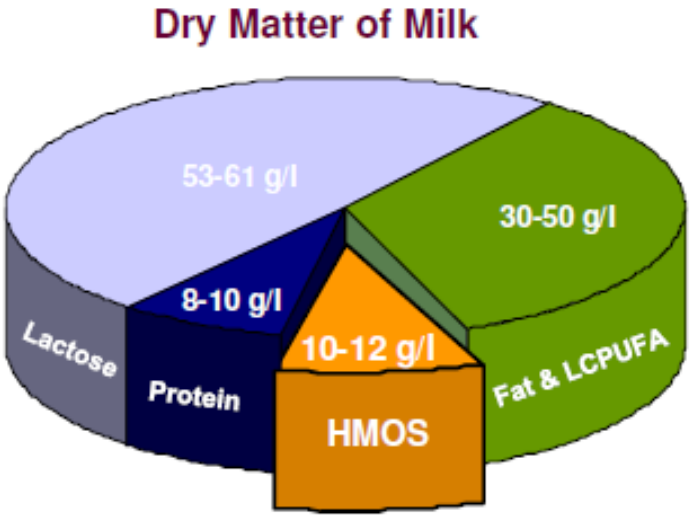
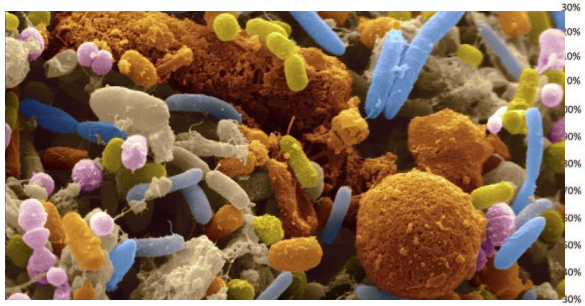
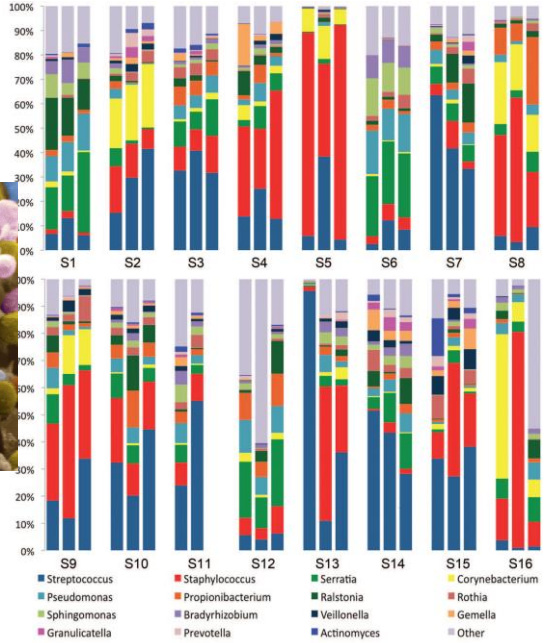


Figure 5. Proposed multilineage potential of breastmilk stem cells. Upregulation of the transcription factors (TFs) OCT4, SOX2, and NANOG during pregnancy and lactation results in broader differentiation potential of a mammary stem cell population under specific microenvironmental cues. Accessed via breastmilk, these cells can differentiate in corresponding microenvironments into not only the two main mammary epithelial lineages (green) but also into mesodermal lineages (blue), endodermal lineages (beige), and the neuroectodermal lineage (purple).







BENEFICIAL EFFECTS OF HUMAN MILK

Evidence show that preterm infants fed HM

- Lower rates of infection (sepsis, UTI)
- Lower rates of NEC
- Lower rates of ROP
- Lower rates of BPD
- Imroved feeding tolerance
- Lower MORTALITY

MOM- Persistent Beneficial Effects

- Fewer hospitalizations for respiratory illness up to 3-7 y of age
- Overall re-admission rate for infectious disorders decreased by 5% for every 10mL/kg/day of human milk received during the NICU stay

Vohr BR, PoindexterBB, DusickAM,etal. Persistent beneficial effects of breastmilk ingested in the neonatal intensive care unit on outcomes of extremely low birthweight infants at 30 months of age. Pediatrics. 2007;120(4):e953–e959.

MOM- Persistent Beneficial Effects

- Improved neurocognitive outcomes outcomes
- Lower rates of arterial HT, insulin resistance, better lipid profiles at adolescence

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

Pediatrics 2012;129:e827–e841

POLICY STATEMENT

Breastfeeding and the Use of Human Milk

SECTION ON BREASTFEEDING

KEY WORDS
breastfeeding, complementary foods, infant nutrition, lactation, human milk, nursing

ABBREVIATIONS
AAP—American Academy of Pediatrics
AHRQ—Agency for Healthcare Research and Quality
CDC—Centers for Disease Control and Prevention
CI—confidence interval
CMV—cytomegalovirus
DHA—docosahexaenoic acid
NEC—necrotizing enterocolitis
OR—odds ratio
SIDS—sudden infant death syndrome
WHO—World Health Organization

abstract

FREE

Breastfeeding and human milk are the normative standards for infant feeding and nutrition. Given the documented short- and long-term medical and neurodevelopmental advantages of breastfeeding, infant nutrition should be considered a public health issue and not only a lifestyle choice. The American Academy of Pediatrics reaffirms its

Human milk is the preferred milk for all neonates including preterm infants

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

*†Sertac Arslanoglu, ‡Willemijn Corpeleijn, *Guido Moro, §Christian Braegger, ||Cristina Campoy, ¶Virginie Colomb, #Tamas Decsi, **Magnus Domellöf, ††Mary Fewtrell, ‡‡Iva Hojsak, §§Walter Mihatsch, ||||Christian Mølgaard, ¶¶Raanan Shamir, ##Dominique Turck, and ‡Johannes van Goudoever, ESPGHAN Committee on Nutrition

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 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.

Key Words: donor milk, human milk, human milk banking, pasteurization, preterm infant

(*JPGN* 2013;57: 535–542)

Breastfeeding: a smart investment in people and in economies

Ian Hooton/Science Photo Library

See Editorial page 404
See Series pages 475 and 491

If breastfeeding did not already exist, someone who invented it today would deserve a dual Nobel Prize in medicine and economics. For while "breast is best" for lifelong health, it is also excellent economics. Breastfeeding is a child's first inoculation against death, disease, and poverty, but also their most enduring investment in physical, cognitive, and social capacity.

When we nourish a child, we drive future economic growth.[1,2] The *Lancet* Breastfeeding Series[3,4] shows why breastfeeding is one of the highest impact interventions providing benefits for children, women, and society. Breastfeeding reduces infant morbidity and mortality, increases Intelligence Quotient (IQ) score, improves school achievement, and boosts adult earnings[3,4]—all essential for reducing poverty. It also contributes to equity by giving all children a nutritional head start for success in life.

For the first time in history, less than 10% of the world's population lives in extreme poverty.[5] Strong economic growth in developing countries coupled with smart investments in human development have driven this change. But progress must accelerate if we are to achieve the World Bank's goals—and the new global Sustainable Development Goals—to end extreme poverty and boost shared prosperity by 2030.[5]

In this context, never has the breastfeeding agenda been more timely. For many people living in poverty, malnutrition remains a prime contributor to stunted development, and this *Lancet* Series documents how breastfeeding can make a lasting difference.[3,4]

But knowing isn't the same as doing. The challenge now is to scale up breastfeeding. Paradoxically, breastfeeding is one of the few positive health behaviours that is more common among the poor than among the richer countries.[3] Data on poverty from the World Bank suggest that rising inequality and social exclusion seem to accompany rising prosperity in many countries.[5]

This Series suggests that alongside other factors, breastfeeding could have an important role in addressing inequality by providing equal opportunity to all children to grow and contribute to national economies, and countries such as Bangladesh and Brazil show that it is possible to increase breastfeeding with comprehensive strategies.[4]

The World Bank Group is committed to support the expansion of breastfeeding. We are enhancing our own investments in breastfeeding through health, social protection, agriculture, gender, labour and jobs programmes as reflected in our current portfolio. We are sharing global knowledge on delivering these interventions effectively. We are making the economic case to ministers of health, finance, and planning, as well as to political leaders. And we are emphasising the importance of an enabling policy environment—such as labour laws and maternity leave—while bringing to bear the latest knowledge from behavioural economics to change mental models and social norms around breastfeeding.[6]

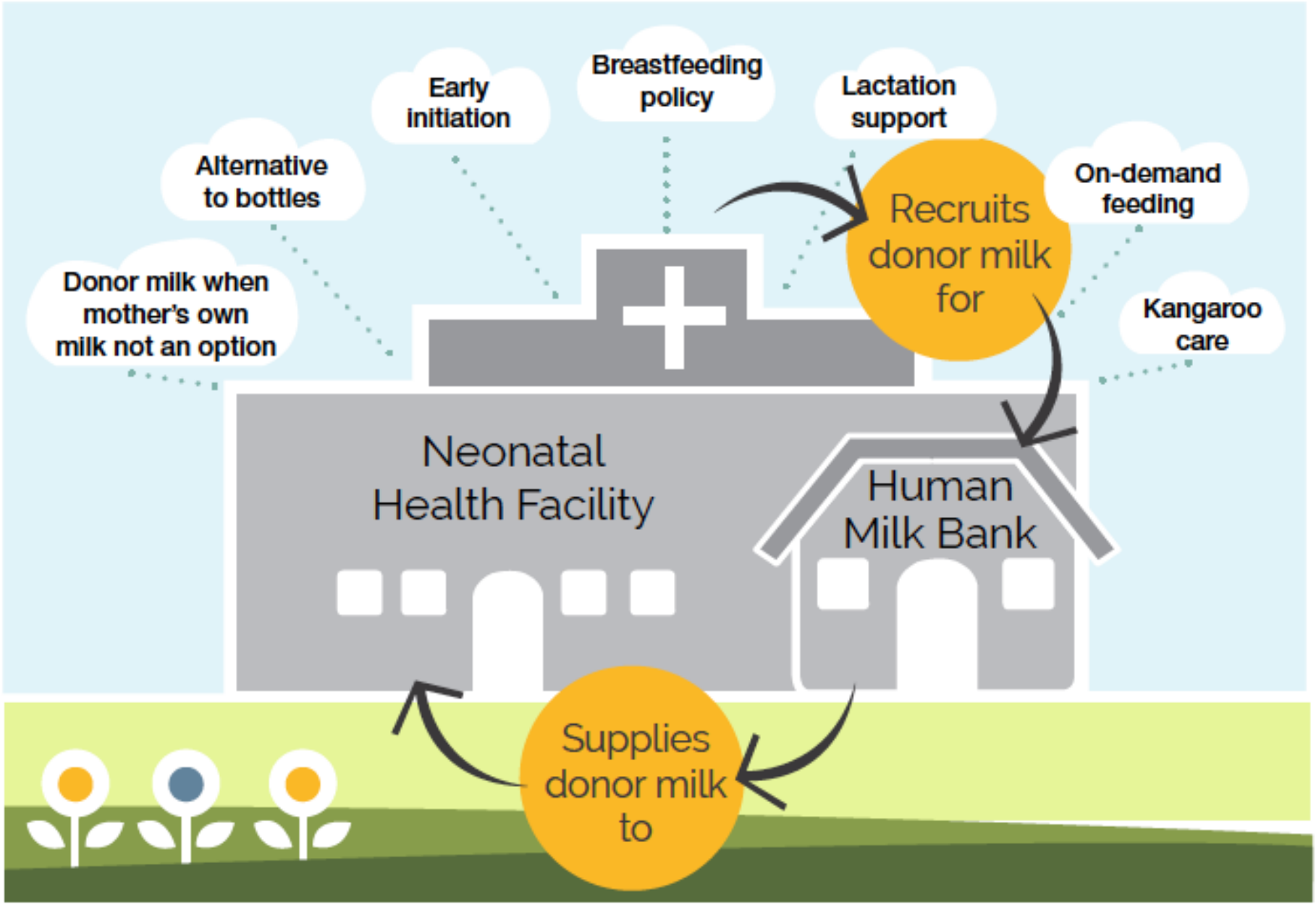
The evidence on breastfeeding leaves no doubt that it is a smart and cost-effective investment in a more prosperous future. Let's ensure that every child—and every nation—can reap the benefits of breastfeeding.

Keith Hansen
The World Bank, Washington, DC 20433, USA
khansen@worldbank.org

I am Vice President for Human Development, World Bank Group. I declare no competing interests.

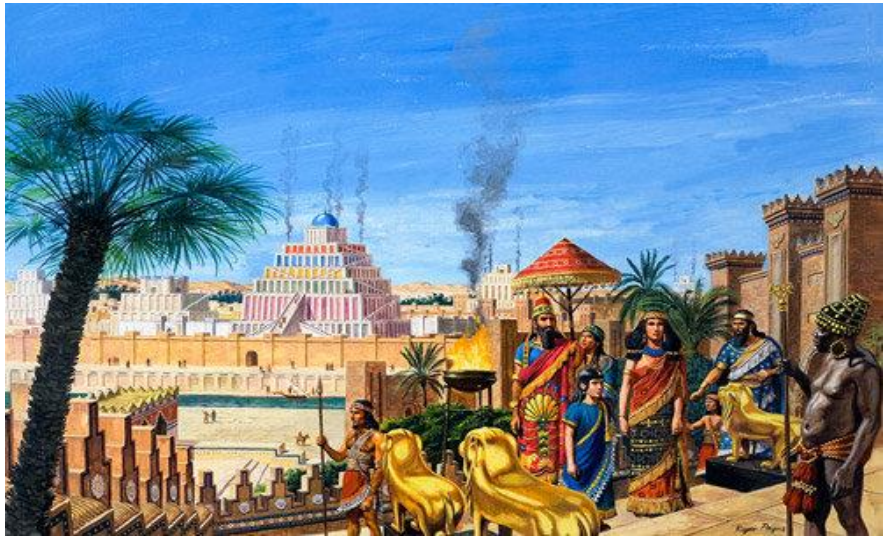
1 Hoddinott JH, Alderman H, Behrman JR, Haddad H, Horton S. The economic rationale for investing in stunting reduction. Matern Child Nutr 2013; 9 (suppl 2): 69–82.
2 World Bank. Repositioning nutrition as central to development: a strategy for large-scale action. Washington, DC: World Bank, 2006.
3 Victora CG, Bahl R, Barros AJD, et al, for *The Lancet* Breastfeeding Series Group. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; 387: 475–90.
4 Rollins NC, Bhandari N, Hajeebhoy N, et al, on behalf of *The Lancet* Breastfeeding Series Group. Why invest, and what it will take to improve breastfeeding practices? *Lancet* 2016; 387: 491–504.
5 World Bank Group. Global monitoring report 2015/2016: development goals in an era of demographic change. Washington, DC: World Bank, 2016.
6 World Bank. World development report 2015: mind, behavior and society. Washington, DC: World Bank, 2015.

Mother-Baby Friendly Initiative: Integrating human milk banks



MILK BANKING

Babylonia 1780 BC



Evidence of the support for "wet nursing" is already present in the Code of Hammurabi.

The First Human Milk Bank
Vienna 1909

- University of Vienna
  St. Anna Childrens Hospital
- Intestinal flora of he neonates fed breastmilk is different.
- Breastmilk is life saving.

«Imperial Institute for Maternal and Infant Care»
« The first HMB»

Theodor Escherisch (1857-1911)


214
ctive Milk Banks
17 Planned Milk Banks
Austria
Belgium
Bulgaria
Croatia
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Italy
Netherlands
Norway
Poland
Portugal
Romania
Russia
Serbia
Slovakia
Slovenia
Spain
Sweden
Switzerland
Turkey
UK
17 Finland
12 Norway
28 Sweden
1 Estonia
1 Scotland
1 N. Ireland
2 Denmark
14 England
1 Lithuania
1 Netherlands
4 Belgium
3 15 Germany
5 4 Poland
Russia 1
4 Czech Republic
6 Slovakia
1 Ukraine
36 France
6 Switzerland
2 Austria
8 Hungary
1 Slovenia
1 Romania
1 1 Portugal
Croatia 1
3 Serbia
1 Bulgaria
8 Spain
33 Italy
Turkey 2
1 2 Greece
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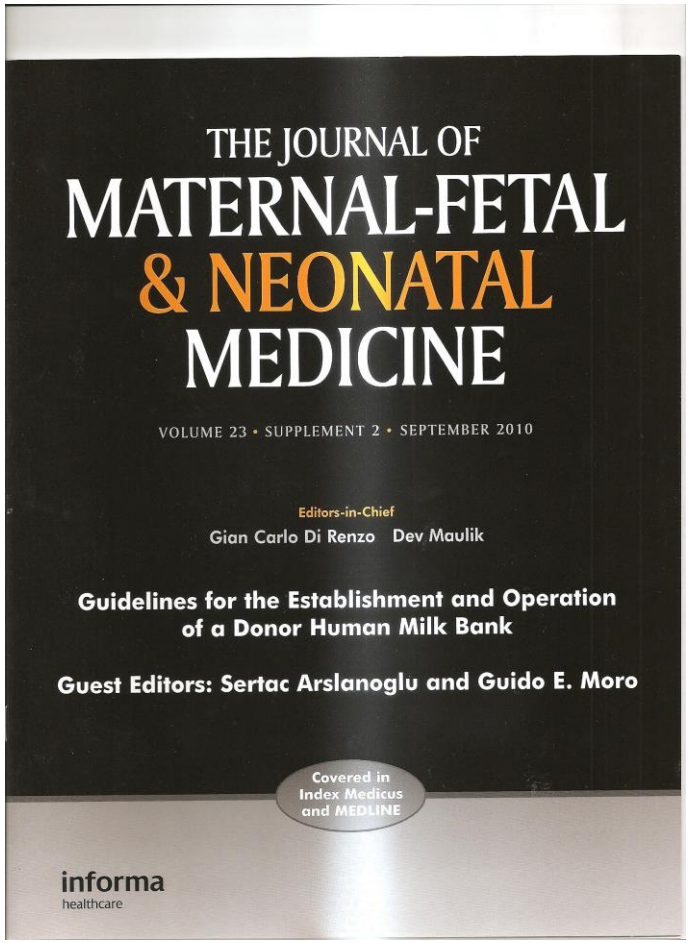
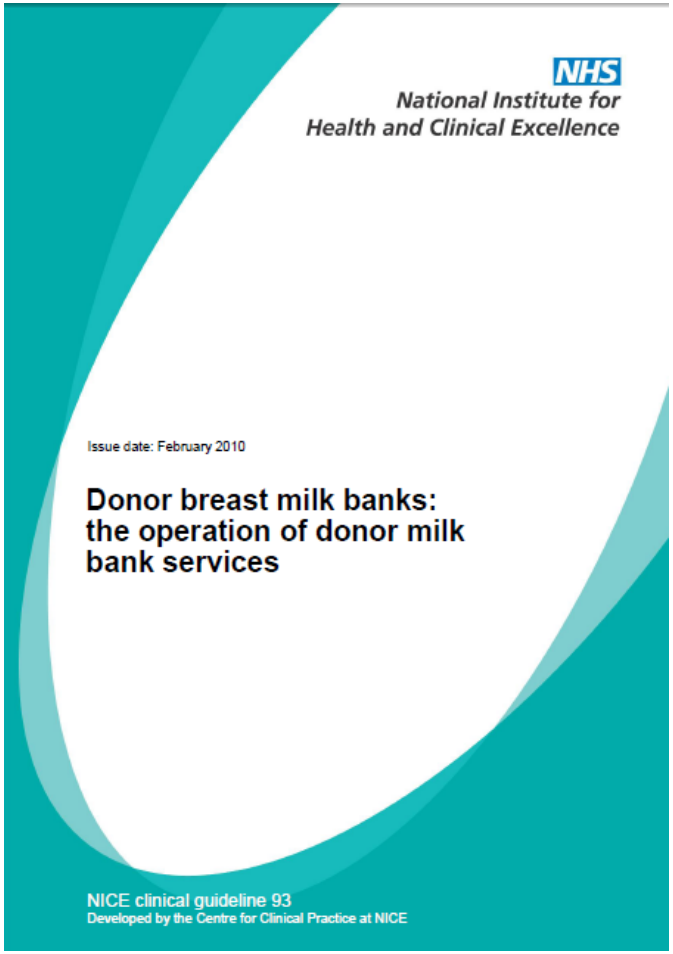
EUROPEAN MILK BANK ASSOCIATION





- Donor human milk is not the same as MOM
- Donor human milk is not the alternative to MOM
- Donor human milk is alternative to formula

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

*†Sertac Arslanoglu, ‡Willemijn Corpeleijn, *Guido Moro, §Christian Braegger, ||Cristina Campoy, ¶Virginie Colomb, #Tamas Decsi, **Magnus Domellöf, ††Mary Fewtrell, ‡‡Iva Hojsak, §§Walter Mihatsch, ||||Christian Mølgaard, ¶¶Raanan Shamir, ##Dominique Turck, and ‡Johannes van Goudoever, ESPGHAN Committee on Nutrition

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Key Words: donor milk, human milk, human milk banking, pasteurization, preterm infant

(*JPGN* 2013;57: 535–542)

This review aimed

1. to document the published evidence regarding the benefits deriving from the use of DHM for preterm infants
2. to address the main concerns limiting its widespread adoption as a standard care
3. to outline the gaps in knowledge, and
4. to give recommendations for practice and suggestions for future research.

CLINICAL OUTCOMES- RCTs with DHM

- Necrotizing enterocolitis (NEC)
- Feeding intolerance
- Bronchopulmonary dysplasia (BPD)
- Long-term cardiovascular risk factors
- Allergy
- Long-term neurocognitive outcome

1. NEC

Necrotizing Enterocolitis

Three systematic reviews (2,12,13) 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:

Systematic Reviews

SYSTEMATIC REVIEW

Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review

W McGuire, M Y Anthony

Arch Dis Child Fetal Neonatal Ed 2003;**88**:F11–F14

Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis

Catherine A Boyd, Maria A Quigley, Peter Brocklehurst

Arch Dis Child Fetal Neonatal Ed 2007;**92**:F169–F175. doi: 10.1136/adc.2005.089490

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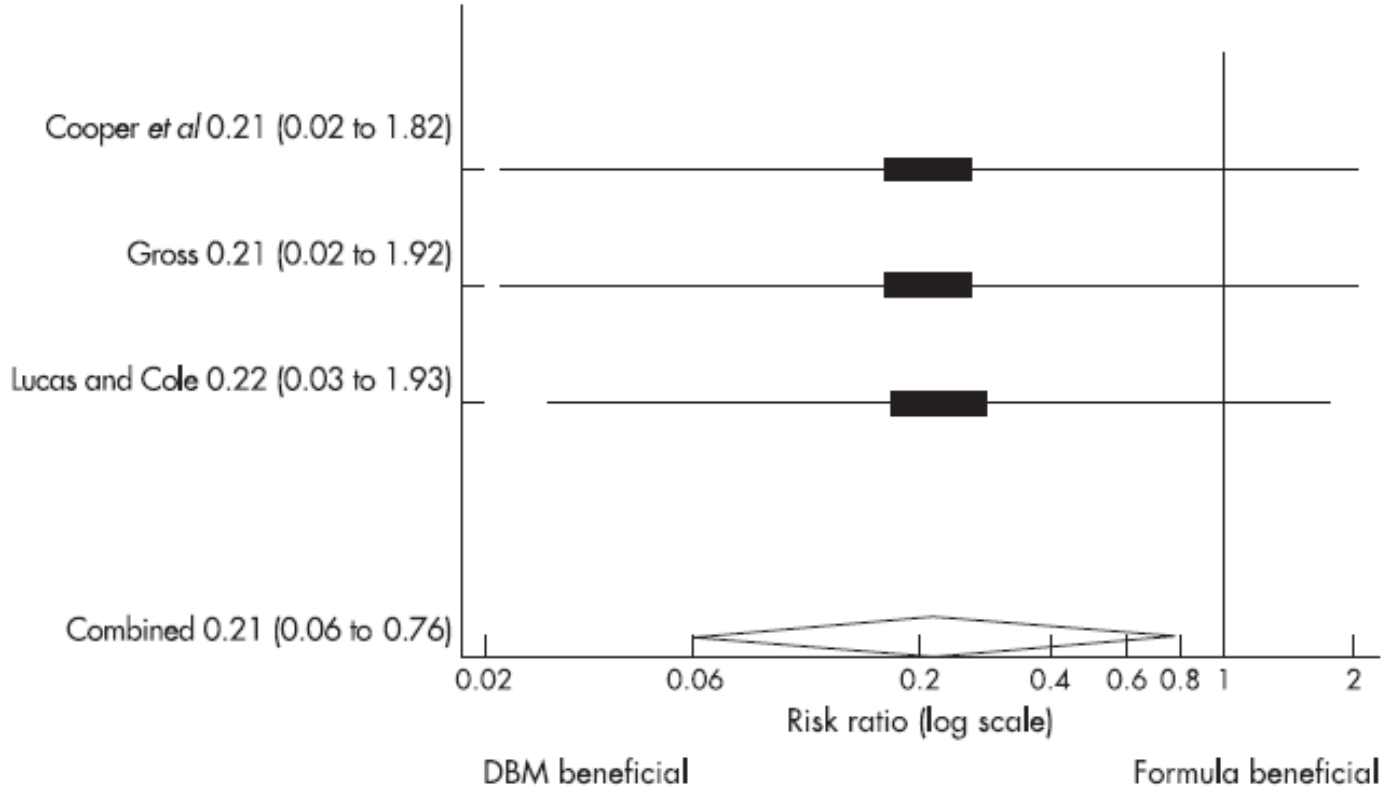


Donor milk decreases the risk of NEC 79 % (95% CI 24% to 94%).

Formula milk versus donor breast milk for feeding preterm or low birth weight infants (Review)

Quigley MA, Henderson G, Anthony MY, McGuire W

THE COCHRANE COLLABORATION®

This version first published online: 17 October 2007 in Issue 4, 2007.
Date of most recent substantive amendment: 18 June 2007

Formula milk versus donor breast milk for feeding preterm low birth weight infants (Review)

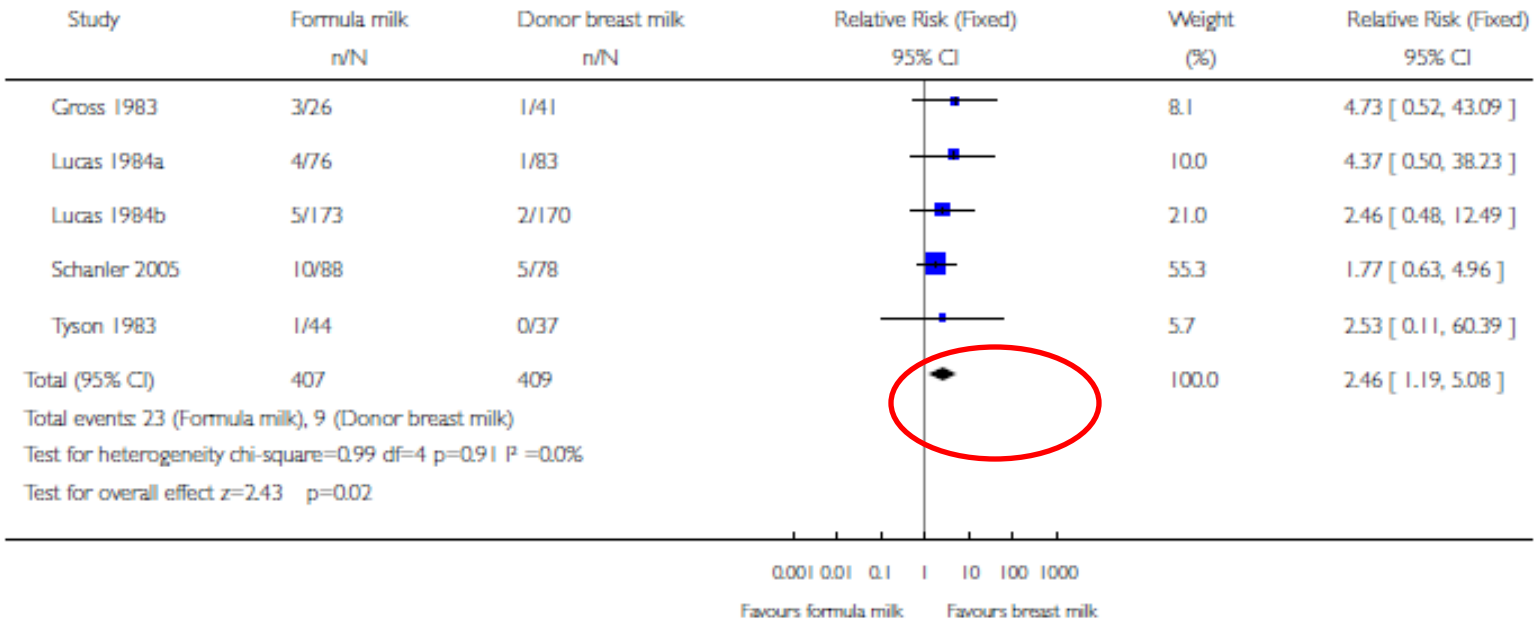
THE COCHRANE COLLABORATION®

- Mataanalysis shows feeding with formula compared with donor milk increases the risk of developing NEC.

This version first published online: 17 October 2007 in Issue 4, 2007.
Date of most recent substantive amendment: 18 June 2007

Comparison: 01 Formula milk versus donor breast milk

Outcome: 20 Necrotising enterocolitis



NEC

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

Conclusion and Comments on Feeding Tolerance

- Limited available data from the1980s 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.

3. Bronchopulmonary Dysplasia

Conclusion and Comment on BPD

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

4. Long-term Cardiovascular Risk Factors

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 vs. PF fed infants.

6. 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
- Alterations in Nutritional/Biological Quality
- Growth
- Does the presence of a human milk bank compete with breastfeeding at discharge?

1. SAFETY

Conclusion and Comment 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.

2. ALTERATIONS IN NUTRITIONAL/BIOLOGICAL QUALITY

1. Mild-moderate decrease in IgA and secretory IgA concentrations (~20%–30%, range: 0%–60%) and activity (33%–39%) (44–53).
2. Considerable loss in concentration/activity of lactoferrin (50%–75%) (46,47,49–51,54,55), lysozyme (24%–74%) (44–48,50–52,54), IgG (34%–76%) (45,47), some cytokines (interleukin-10, tumor necrosis factor-alpha) (56,57), growth factors, and hormones (insulin-like growth factor 1, adinopectin, insulin, and leptin) (58–60), and antioxidant capacity of HM (61).
3. Almost complete loss of lipase activity (44,49), IgM (concentrations) (45,46), and white blood cells (62,63).

2. ALTERATIONS IN NUTRITIONAL/BIOLOGICAL QUALITY

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.

3. SLOW GROWTH

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 towing 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.

4. DOES THE PRESENCE OF A HUMAN MILK BANK COMPETE WITH BF?

Evidence

Location		Endpoints
Australia Perth King Edward Memorial Hospital	Review/Service Description Opening of a HMB	BF rates at discharge In 3 y after the opening of HMB
US Utah	BEST (Breast milk saves trouble) implementation	BF rates at discharge HM use in NICU
Spain Madrid	Opening of a HMB	BF rates at discharge Formula use in NICU

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

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

DE GRUYTER DOI 10.1515/jpm-2012-0196 — J. Perinat. Med. 2013; 41(2): 129–131

Recommendation and Guidelines for Perinatal Practice

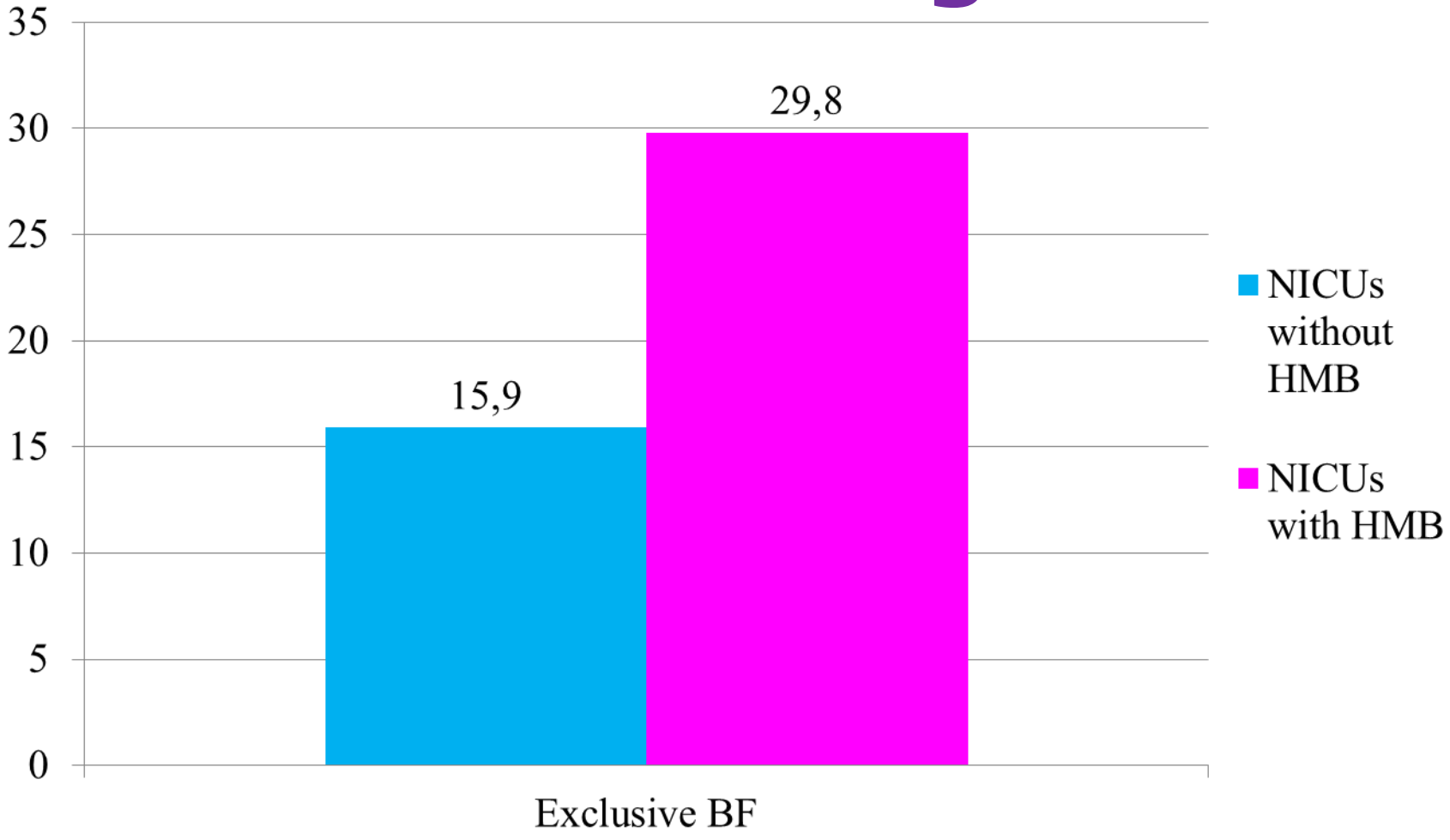
Sertac Arslanoglu[a], Guido E. Moro[a,*], Roberto Bellù, Daniela Turoli, Giuseppe De Nisi, Paola Tonetto and Enrico Bertino

Presence of human milk bank is associated with elevated rate of exclusive breastfeeding in VLBW infants

ITALIAN NEONATAL NETWORK-VON 2010 Data

- **Data from 83 NICUs participating to VON**
- **Subjects: 4277 VLBW infants**
- **Breastfeeding at discharge**
  - **Any**
  - **Exclusive**
- **Centers without HMB: 64**
  3333 infants
- **Centers with HMB: 19**
  944 infants

Exclusive breastfeeding at discharge



Italian Neonatal Network- VON 2010

ESPGHAN 2013

CONCLUSIONS, RECOMMENDATIONS, FUTURE RESEARCH DIRECTIONS

Conclusions

Based on the evidence presented in this Comment, the European Society for Paediatric 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.

Cochrane Library

Cochrane Database of Systematic Reviews

Formula versus donor breast milk for feeding preterm or low birth weight infants (Review)

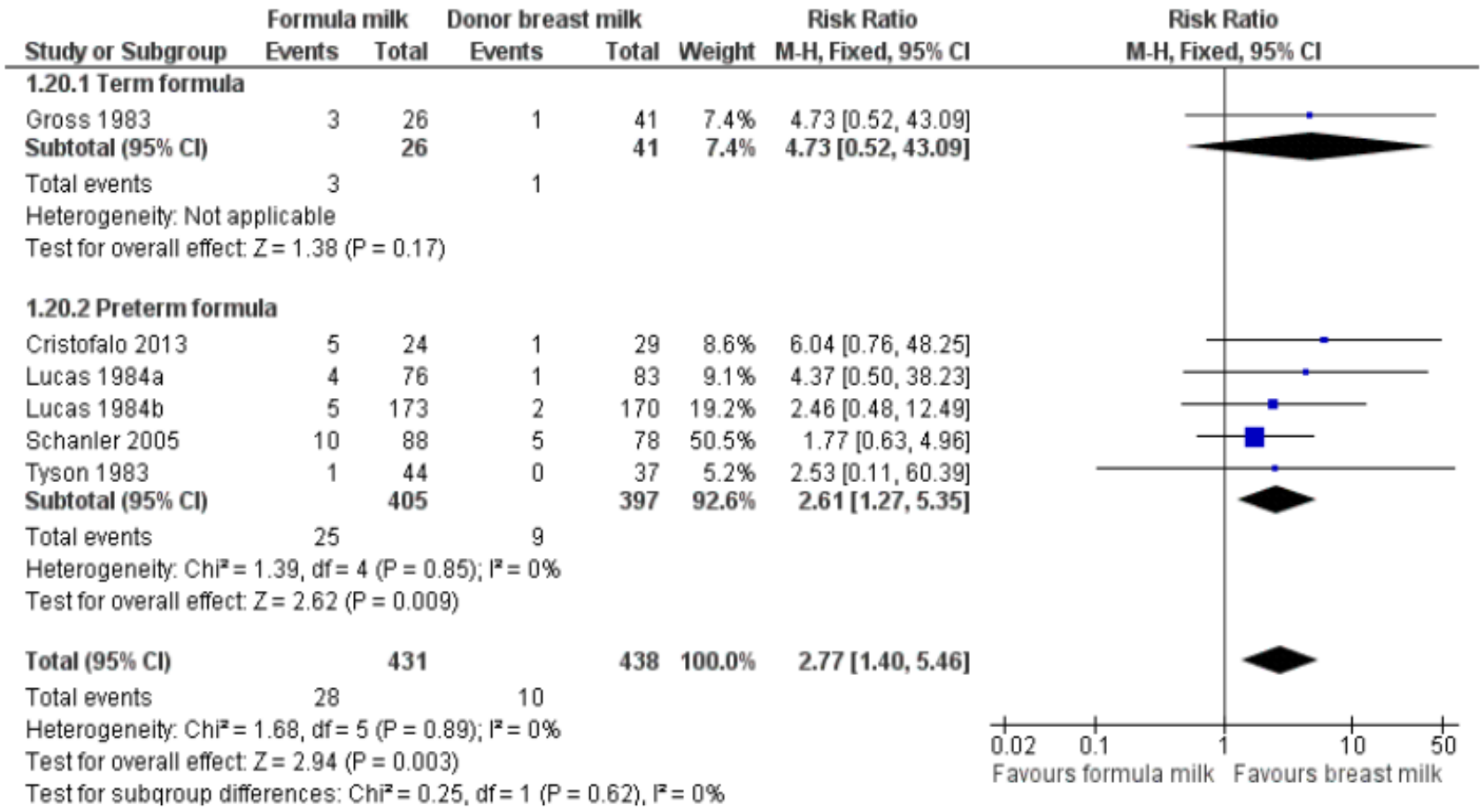
Quigley M, McGuire W

Quigley M, McGuire W.
Formula versus donor breast milk for feeding preterm or low birth weight infants.
Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD002971.
DOI: 10.1002/14651858.CD002971.pub3.

www.cochranelibrary.com

WILEY

Figure 6. Forest plot of comparison: 1 Formula (term or preterm) versus donor breast milk, outcome: 1.20 Necrotising enterocolitis.



Pediatrics 2016

Impact of Donor Milk Availability on Breast Milk Use and Necrotizing Enterocolitis Rates

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abstract

OBJECTIVES: To examine the availability of donor human milk (DHM) in a population-based cohort and assess whether the availability of DHM was associated with rates of breast milk feeding at NICU discharge and rates of necrotizing enterocolitis (NEC).

METHODS: Individual patient clinical data for very low birth weight infants from the California Perinatal Quality Care Collaborative were linked to hospital-level data on DHM availability from the Mothers' Milk Bank of San José for 2007 to 2013. Trends of DHM availability were examined by level of NICU care. Hospitals that transitioned from not having DHM to having DHM availability during the study period were examined to assess changes in rates of breast milk feeding at NICU discharge and NEC.

RESULTS: The availability of DHM increased from 27 to 55 hospitals during the study period. The availability increased for all levels of care including regional, community, and

- In a multicenter investigation, the use of DHM was associated with a 10 % increase in the rate of MOM utilization and a 2.6 % decrease in the rate of NEC.

Necrotizing Enterocolitis and Growth in Preterm Infants Fed Predominantly Maternal Milk, Pasteurized Donor Milk, or Preterm Formula: A Retrospective Study

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In Infants With Necrotizing Enterocolitis, Gut Dysbiosis Precedes Disease

Julie A. Jacob, MA

When Edward McCabe, MD, PhD, was a pediatric resident in the mid-1970s, he often treated preterm infants with necrotizing enterocolitis (NEC). "It's a horrible disease," he said. Forty years later, when he retired from clinical practice in 2012, few strides had been made in prevention, treatment, or mortality. The lack of significant advances to prevent or treat NEC in fragile preterm infants is frustrating to clinicians who care for them, McCabe said.

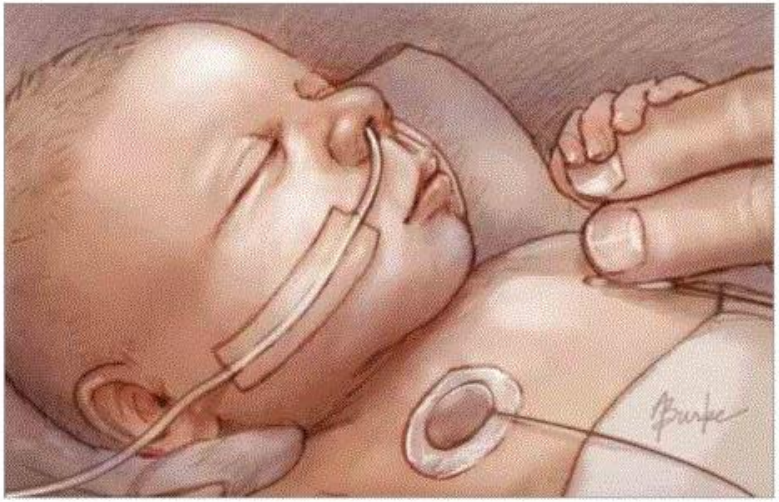
"There have been lots of studies on [causes and treatments] with essentially no change in mortality," said McCabe, the senior vice president and chief medical officer for the March of Dimes. Currently, about 12% of preterm infants weighing less than 1500 g develop NEC, and about one-third die from sepsis or other complications (Gephart SM et al. *Adv Neonatal Care*. 2012;12[2]:77-87; http://1.usa.gov/21IRhiH).

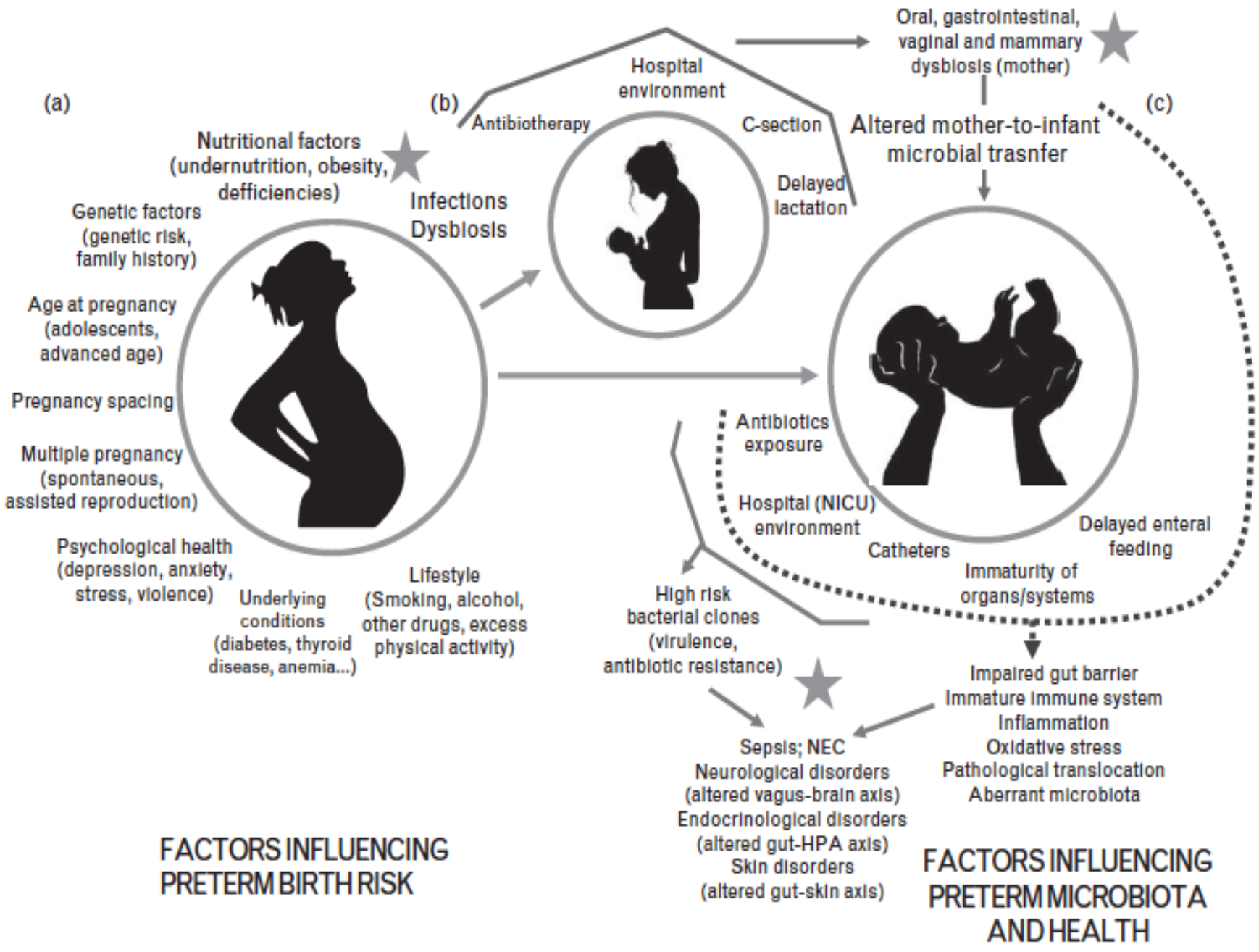
However, a new prospective case-control study by researchers at Washington University School of Medicine in St Louis provides a preliminary road map for additional investigation into causes and potential treatments (Warner BB et al. *Lancet*. doi: 10.1016/S0140-6736(16)00081-7 [published online March 8, 2016]). The research team sequenced DNA extracted from 3586 stool samples retrieved from 166 preterm infants who were hospitalized in neonatal intensive care units at 3 hospitals: St Louis (Missouri) Children's Hospital; Kosair Children's Hospital in Louisville, Kentucky; and Children's Hospital at Oklahoma University in Oklahoma City. All babies weighing less than 1500 g without congenital heart disease or intestinal perforations who were expected to survive more than 1 week were eligible for the study. The babies' stool samples were analyzed from neonatal admission to 60 days of age or until a NEC diagnosis, whichever occurred first.

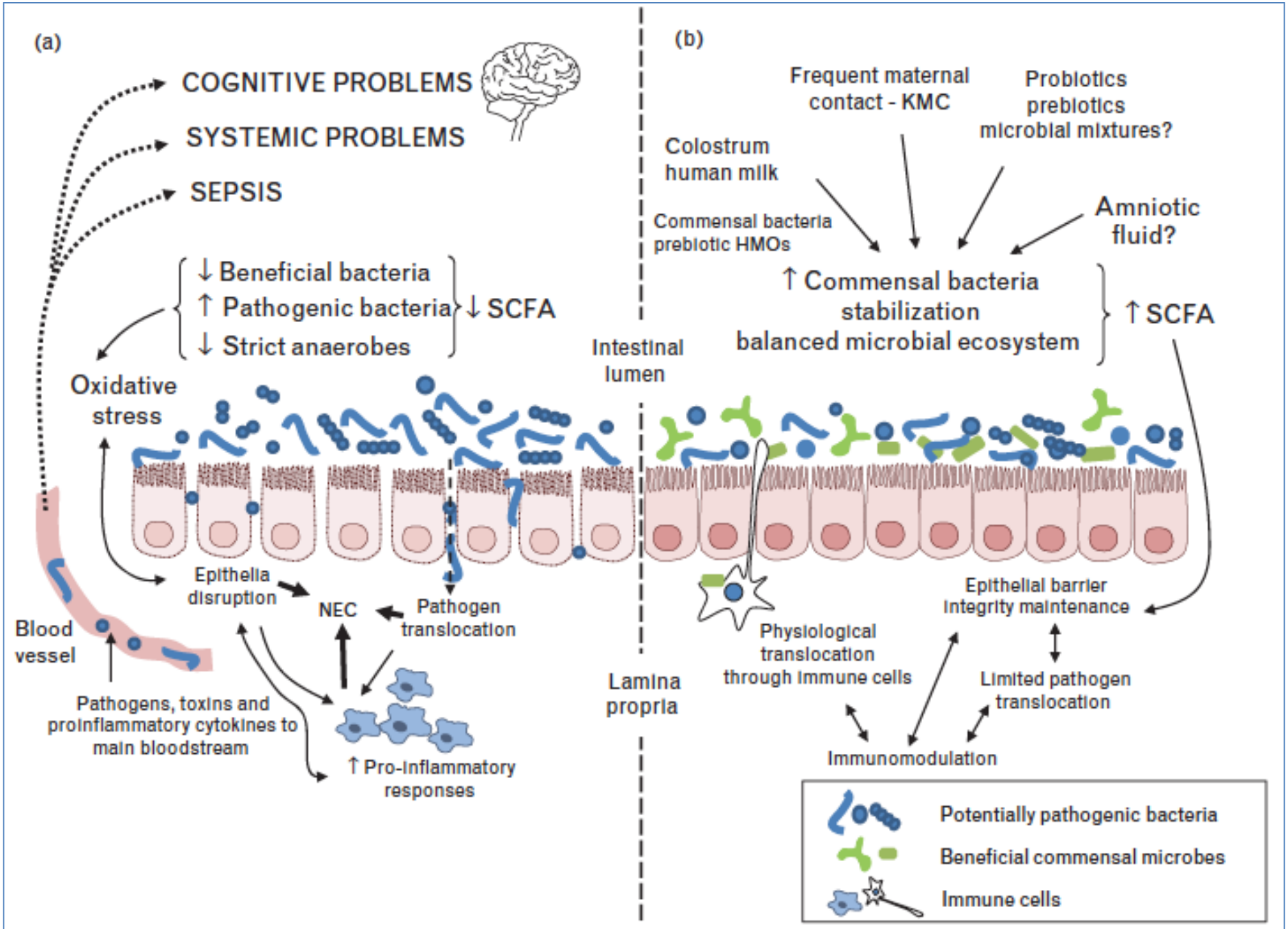
Investigators discovered that the gastrointestinal bacterial microbiome of 46 preterm babies who developed NEC contained significantly more gram-negative gammaproteobacteria, such as *Escherichia coli*, and less anaerobic bacteria, particularly *Negativicutes*, compared with preterm babies who did not develop the disease.

"Neonatologists have long believed that gut bacteria could have a bearing on developing or being protected from necrotizing enterocolitis," said Phillip I. Tarr, MD, the study's senior author and a professor of pediatrics and microbiology at the Washington University School of Medicine in St Louis. That hypothesis, he explained, is based on several factors, including the association between greater antibiotic use and NEC and the protective factor of breastfeeding. "However, the identity of the risk-conferring microbes had not been clarified," Tarr added.

It was the study's scope and methodology, however, that enabled the researchers to demonstrate that the gut microbiome transition occurs before infants develop NEC, noted Scott Lorch, MD, a neonatologist and director of the Neonatal-Perinatal Medicine Fellowship at the Children's Hospital of Philadelphia, who was not involved in the study. Because thousands of stool samples were sequenced from the time the infants were admitted to neonatal intensive care—before any were diagnosed with NEC—researchers were able to study how the infants' gut microbiomes evolved over several




(a)
Nutritional factors (undernutrition, obesity, defficiencies)
Infections Dysbiosis
Genetic factors (genetic risk, family history)
Age at pregnancy (adolescents, advanced age)
Pregnancy spacing
Multiple pregnancy (spontaneous, assisted reproduction)
Psychological health (depression, anxiety, stress, violence)
Underlying conditions (diabetes, thyroid disease, anemia...)
Lifestyle (Smoking, alcohol, other drugs, excess physical activity)
(b)
Hospital environment
Antibiotherapy
C-section
Delayed lactation
Oral, gastrointestinal, vaginal and mammary dysbiosis (mother)
(c)
Altered mother-to-infant microbial trasnfer
Antibiotics exposure
Hospital (NICU) environment
Catheters
Delayed enteral feeding
Immaturity of organs/systems
High risk bacterial clones (virulence, antibiotic resistance)
Impaired gut barrier
Immature immune system
Inflammation
Oxidative stress
Pathological translocation
Aberrant microbiota
Sepsis; NEC
Neurological disorders (altered vagus-brain axis)
Endocrinological disorders (altered gut-HPA axis)
Skin disorders (altered gut-skin axis)
FACTORS INFLUENCING PRETERM BIRTH RISK
FACTORS INFLUENCING PRETERM MICROBIOTA AND HEALTH


(a)
COGNITIVE PROBLEMS
SYSTEMIC PROBLEMS
SEPSIS
↓ Beneficial bacteria
↑ Pathogenic bacteria
↓ Strict anaerobes
↓ SCFA
Oxidative stress
Epithelia disruption
NEC
Pathogen translocation
Blood vessel
Pathogens, toxins and proinflammatory cytokines to main bloodstream
↑ Pro-inflammatory responses
(b)
Frequent maternal contact - KMC
Probiotics prebiotics microbial mixtures?
Colostrum human milk
Commensal bacteria prebiotic HMOs
Amniotic fluid?
↑ Commensal bacteria stabilization balanced microbial ecosystem
↑ SCFA
Intestinal lumen
Lamina propria
Epithelial barrier integrity maintenance
Physiological translocation through immune cells
Limited pathogen translocation
Immunomodulation
Potentially pathogenic bacteria
Beneficial commensal microbes
Immune cells

Gut 2017

Human milk oligosaccharide composition predicts risk of necrotising enterocolitis in preterm infants

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Abstract

Objective Necrotising enterocolitis (NEC) is one of the most common and often fatal intestinal disorders in preterm infants. Markers to identify at-risk infants as well as therapies to prevent and treat NEC are limited and urgently needed. NEC incidence is significantly lower in breast-fed compared with formula-fed infants. Infant formula lacks human milk oligosaccharides (HMO), such as disialyllacto-N-tetraose (DSLNT), which prevents NEC in neonatal rats. However, it is unknown if DSLNT also protects human preterm infants.

Design We conducted a multicentre clinical cohort study and recruited 200 mothers and their very low birthweight infants that were predominantly human milk-fed. We analysed HMO composition in breast milk fed to infants over the first 28 days post partum, matched each NEC case with five controls and used logistic regression and generalised estimating equation to test the hypothesis that infants who develop NEC receive milk with less DSLNT than infants who do not develop NEC.

Results Eight infants in the cohort developed NEC (Bell stage 2 or 3). DSLNT concentrations were significantly lower in almost all milk samples in NEC cases compared with controls, and its abundance could identify NEC cases prior to onset. Aggregate assessment of DSLNT over multiple days enhanced the separation of NEC cases and control subjects.

Conclusions DSLNT content in breast milk is a potential non-invasive marker to identify infants at risk of developing NEC, and

Review

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Use of Donor Human Milk and Maternal Breastfeeding Rates: A Systematic Review

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Abstract

The number of human milk banks is growing worldwide. The introduction of donor human milk (DHM) to neonatal units has been advocated as a strategy to promote maternal breastfeeding. However, concern has been raised that the introduction of DHM may actually lead to a decrease in maternal breastfeeding. To address this question, we conducted a systematic literature review of studies that assessed maternal breastfeeding rates before and after the introduction of DHM. We searched 7 electronic databases, carried out citation tracking, and contacted experts in the field. Where data for breastfeeding rates before and after the introduction of DHM were directly comparable, a relative risk was calculated. Our search identified 286 studies, of which 10 met the inclusion criteria. Definitions of patient populations and study outcomes varied, limiting meaningful comparison. Where possible, relative risks (RR) were calculated on aggregated data. The introduction of DHM had a significant positive impact on any breastfeeding on discharge (RR, 1.19; 95% confidence interval [CI], 1.06-1.35; $P = .005$) but none on exclusive maternal breastfeeding on discharge (RR, 1.12; 95% CI, 0.91-1.40; $P = .27$) or on exclusive administration of own mother's milk (OMM) days 1 to 28 of life (RR, 1.08; 95% CI, 0.78-1.49; $P = .65$). A single-center study demonstrated a significant decrease in the percentage of feeds that were OMM after the introduction of DHM. In conclusion, the available data demonstrate some evidence of positive and negative effects on measures of maternal breastfeeding when DHM is introduced to a neonatal unit.

Keywords

breastfeeding, donor human milk, milk banks

JAMA | Original Investigation

Effect of Supplemental Donor Human Milk Compared With Preterm Formula on Neurode of Very Low-Birth-Weight Infants at 18 Month: A Randomized Clinical Trial

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IMPORTANCE For many very low-birth-weight (VLBW) infants, there is insufficient mother's milk, and a supplement of pasteurized donor human milk or preterm formula is required. Awareness of the benefits of mother's milk has led to an increase in use of donor milk, despite limited data evaluating its efficacy.

OBJECTIVE To determine if nutrient-enriched donor milk compared with formula, as a supplement to mother's milk, reduces neonatal morbidity, supports growth, and improves neurodevelopment in VLBW infants.

DESIGN, SETTING, AND PARTICIPANTS In this pragmatic, double-blind, randomized trial, VLBW infants were recruited from 4 neonatal units in Ontario, Canada, within 96 hours of birth between October 2010 and December 2012. Follow-up was completed in July 2015.

INTERVENTIONS Infants were fed either donor milk or formula for 90 days or to discharge when mother's milk was unavailable.

MAIN OUTCOMES AND MEASURES The primary outcome was the cognitive composite score on

CONCLUSIONS AND RELEVANCE Among VLBW infants, use of supplemental donor milk compared with formula did not improve neurodevelopment at 18 months' corrected age. If donor milk is used in settings with high provision of mother's milk, this outcome should not be considered a treatment goal.

Decreased NEC

Table 4. In-Hospital Mortality and Major Morbidities[a]

	No./Total No. (%)			
	Donor Milk (n = 181)	Preterm Formula (n = 182)	Risk Difference, % (95% CI)[b]	*P* Value
Mortality and morbidity index[c]	78/181 (43.1)	73/182 (40.1)	5.0 (−2.7 to 12.7)	.20
Death	17/181 (9.4)	20/182 (11.0)	−1.0 (−9.7 to 7.6)	.82
Late-onset sepsis	44/181 (24.3)	35/182 (19.2)	3.8 (−2.6 to 10.2)	.24
Necrotizing enterocolitis				
All stages	7/181 (3.9)	20/182 (11.0)	−7.1 (−12.5 to −1.8)	.01
Stage ≥II	3/181 (1.7)	12/182 (6.6)	−4.9 (−9.0 to −0.9)	.02
Oxygen support at 36 wk postconception	44/175 (25.1)	37/179 (20.7)	4.2 (−4.9 to 13.4)	.36
Severe retinopathy of prematurity	7/181 (3.9)	8/182 (4.4)	−0.5 (−4.6 to 3.6)	.80
Severe brain injury	38/181 (21.0)	37/182 (20.3)	4.5 (−3.7 to 12.8)	.28

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Beyond Necrotizing Enterocolitis Prevention: Improving Outcomes with an Exclusive Human Milk–Based Diet

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- Texas, Illinois, Florida, California, multicentric
- <1250 g, <28 wks 1587infants
- BOV vs HUM

	BOV (n = *125*)	*HUM* (n = *56*)	p-*Value*
Medical NEC (%)	6.1	2.1	0.00005
Surgical NEC (%)	10.6	4.8	0.00002

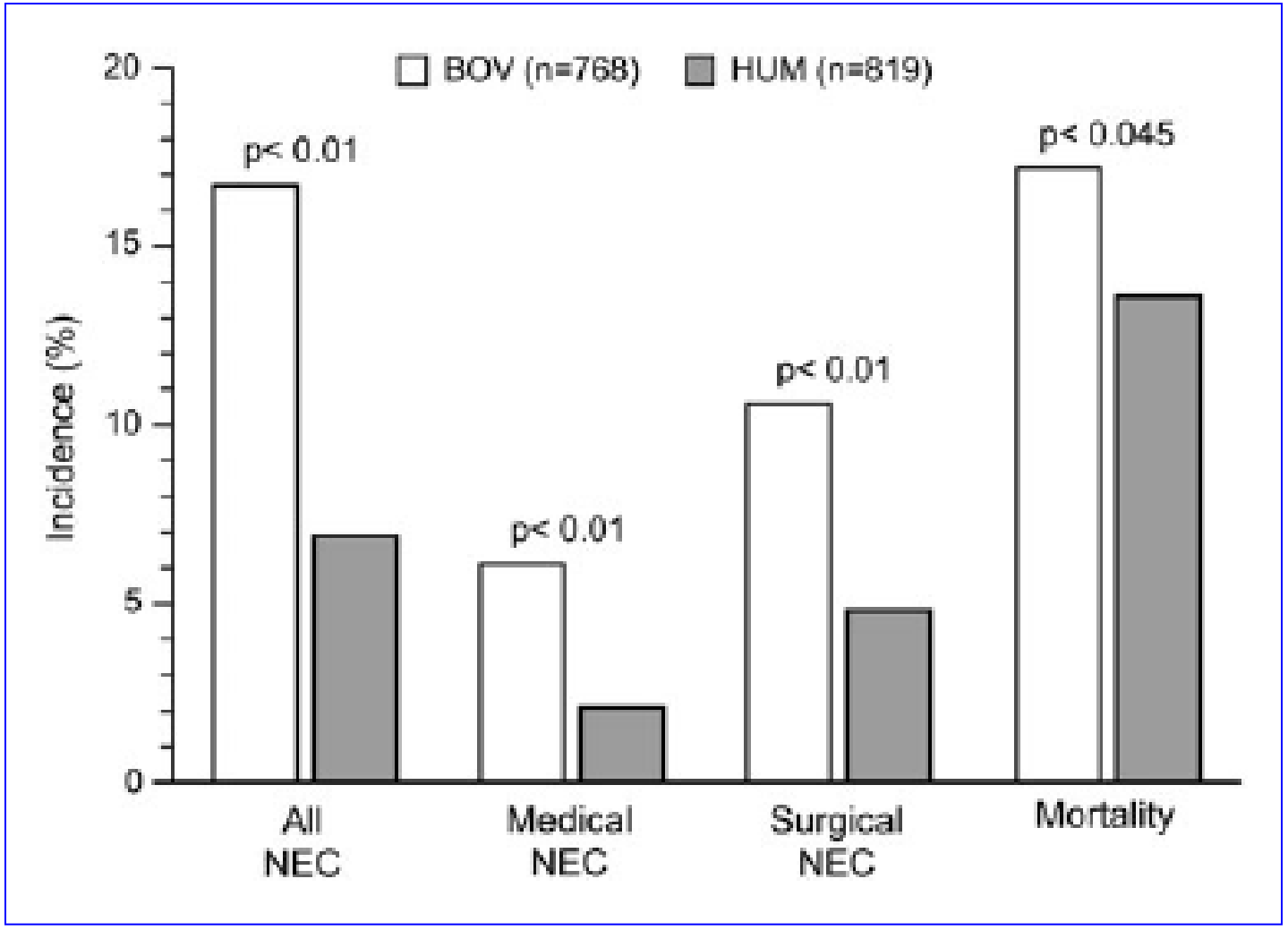

TABLE 4. SECONDARY OUTCOMES

	BOV (n = *768*)	*HUM* (n = *819*)	p-*Value*
Late-onset infection (%)	30.3	19.0	<0.00001
IVH: Grade 3 or 4 (%)	16.8	14.5	0.22
Ventilator (days)	32.2 ± 44.9	29.3 ± 44.2	0.003
Length of stay (days)	94.7 ± 62.1	92.4 ± 54.4	0.44
Postmenstrual age at discharge (weeks)	40.1 ± 8.8	39.4 ± 7.5	0.10
Retinopathy of prematurity (%)	9.0	5.2	0.003
Patent ductus arteriosus (%)	64.7	55.1	0.0001
Bronchopulmonary dysplasia (%)	56.3	47.7	0.0015

IVH, intraventricular hemorrhage.

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Human Milk
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Human Milk in Feeding Premature Infants: From Tradition to Bioengineering

Proceedings of a Consensus Development Conference–EXPO 2015, Milan, Italy, May 15–16

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POLICY STATEMENT

Breastfeeding and the Use of Human Milk

SECTION ON BREASTFEEDING

KEY WORDS
breastfeeding, complementary foods, infant nutrition, lactation, human milk, nursing

ABBREVIATIONS
AAP—American Academy of Pediatrics
AHRQ—Agency for Healthcare Research and Quality
CDC—Centers for Disease Control and Prevention
CI—confidence interval
CMV—cytomegalovirus
DHA—docosahexaenoic acid
NEC—necrotizing enterocolitis
OR—odds ratio
SIDS—sudden infant death syndrome
WHO—World Health Organization

abstract

FREE

Breastfeeding and human milk are the normative standards for infant feeding and nutrition. Given the documented short- and long-term medical and neurodevelopmental advantages of breastfeeding, infant nutrition should be considered a public health issue and not only a lifestyle choice. The American Academy of Pediatrics reaffirms its recommendation of exclusive breastfeeding for about 6 months, followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant. Medical contraindications to breastfeeding are rare. Infant growth should be monitored with the World Health Organization (WHO) Growth Curve Standards to avoid mislabeling infants as underweight or failing to thrive. Hospital routines to encourage and support the initiation and sustaining of exclusive breastfeeding should be based on the American Academy of Pediatrics-endorsed WHO/UNICEF "Ten Steps to Successful Breastfeeding." National strategies supported by the US Surgeon General's Call to Action, the Centers for Disease Control and Prevention, and The

SOCIETY COMMENTARY

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

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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 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.

Key Words: donor milk, human milk, human milk banking, pasteurization, preterm infant

(*JPGN* 2013;57: 535–542)

- All preterm infants should be fed human milk.
- When breast milk is unavailable donor milk should be used.
- Human milk should be fortified for the infants < 1800 g.

ESPGHAN 2013

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 towing 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.

CONCLUSIONS

1. Human milk is the best food for all neonates and has vital importance for sick and preterm infants in NICU
2. Absence of human milk is associated with NEC, infection, ROP, BPD, mortality, and neurocognitive deficits
3. OMM is the gold standard, every effort should be done to promote lactation
4. When OMM is not available, DHM is the recommended choice.
5. DHM has to be obtained from HM Banks following specific guidelines

CONCLUSIONS II

5. DHM is recommended to be fortified for preterm infants weighing less than 1800 g

6. Individualized fortification is recommended

7. Human milk derived fortifiers would increase the quality

8. DHM is pasteurized to ensure microbiological and viral safety

9. At the moment Holder pasteurization is the best compromise to ensure safety and attain milk quality

10. Pasteurization methods must be optimized. New methods are under investigation. Some are promising (ex:Flash)

CONCLUSIONS III

11. Cultural, religious beliefs are not barriers to milk banking, alternative models are available


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