Innovations That Are Reducing the Gap Between Breast Milk and Infant Formula

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Disclosures

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Learning Objectives

- Summarize what is known about the bioactive components found in human milk
- Recognize how cognitive development is impacted by docosahexaenoic acid (DHA) and milk fat globule membrane (MFGM)
- Examine how bioactive components are closing the nutritional gap between infant formula and human milk

The Importance of Human Breast Milk

- Human milk is the *gold standard*
- Breast feeding provides optimal support for physiological growth and development of term infants
- Proper infancy and early childhood nutrition supports
  - Cognitive development
  - Immune development
  - Optimal growth

Demmelmair H, et al. *Nutrients.* 2017;9(8).

Benefits of Breast Milk vs Formula

- Contains milk fat globule membrane (MFGM)
  - Important source of bioactive components
  - Supports cognitive development
- Lactoferrin, a glycoprotein, supports gut health through intestinal development
  - Provides antimicrobial activity and stimulates immune defense
- Human milk oligosaccharides (HMOs) are prebiotics that fuel a healthy gut microbiome

Hernell O, et al. *J Pediatr.* 2016;173 Suppl:S60-5. Lönnerdal B. *Am J Clin Nutr.* 2014;99:712S-7S.

Breastfed vs Formula-Fed Infants

- Different growth patterns
- **Fewer AOM, gastrointestinal, and possibly other infections**
- Reduced risk for obesity
- Reduced risk for type 1 diabetes
- Lower blood pressure?
- Lower total and LDL cholesterol?
- **Better cognitive achievements**

AOM, acute otitis media.

Dutch State Institute for Nutrition and Health. Van Rossum CMT, et al. 2005; US AHRQ. *Evid Rep Technol Assess*. 2007; ESPGHAN Committee on Nutrition. Agostoni C, et al. *J Pediatr Gastroenterol Nutr*. 2009; EFSA: Opinion on complementary feeding of infants. 2009.

IQ of Breastfed vs Formula-Fed Infants

- Meta-analysis
  (17 studies)
- Breastfed related to improved performance of intelligence tests
  (3.44 points)
- Adjusting for mother's IQ
  (fewer studies)
  (2.62; 1.25–3.98)

Horta BL, et al. *Acta Paediatr.* 2015.

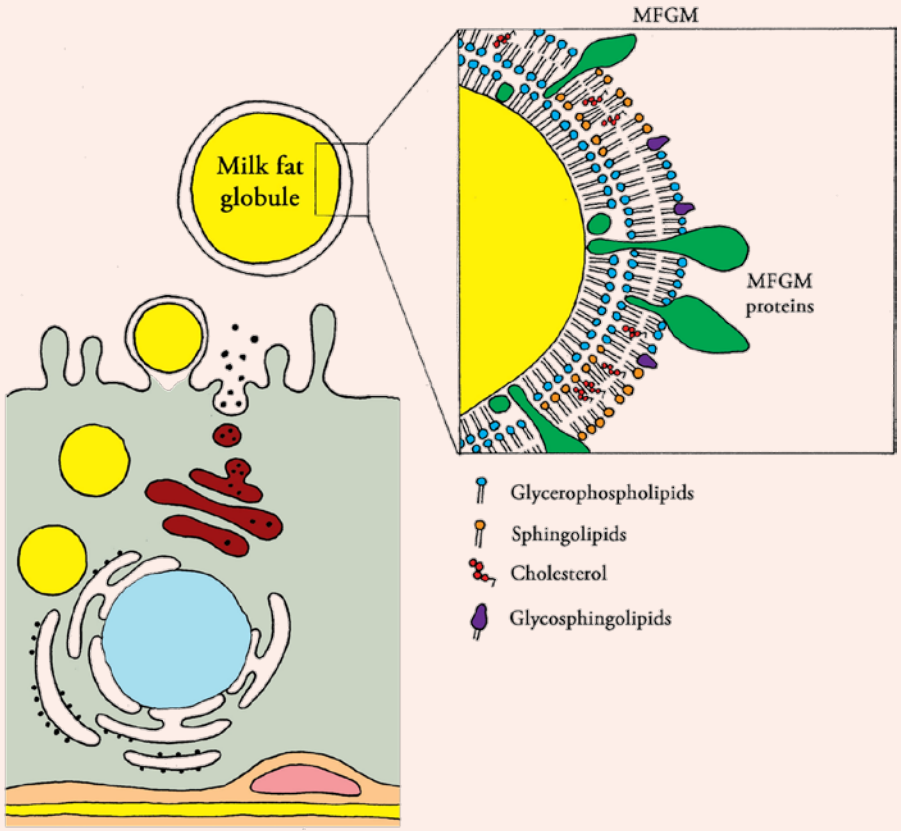
Effects of Breastfeeding on Childhood Otitis Media

- Introduction of formula before 6 months of age increases the risk of OM.
- Breastfeeding seems to be associated with an average 30–40% risk reduction of OM.
- The protective effect of breastfeeding has not been proven to exist beyond 6 years of age.

OM, otitis media.

Kørvel-Hanquist A, et al. *Curr Allergy Asthma Rep.* 2017.

Could Milk Fat Be Part of the Explanation?



Schematic of the release of the milk fat globule and composition of the MFGM.

The milk fat, including the MFGM-fraction, has traditionally been discarded from bovine milk and replaced with vegetable oils when infant formulas were produced.

While the TG fatty acid composition and TG structure have been made similar to human milk, the MFGM remained missing.

TG, triacylglycerol.

Hernell O, et al. *J Pediatr.* 2016;173 Suppl:S60-5.

MFGM Components and Impact

Brain Function

- Choline
- Sphingomyelin
- Gangliosides
- Cholesterol
- Sialic acid
- Inositol
- Cerebrosides

Immune Defense

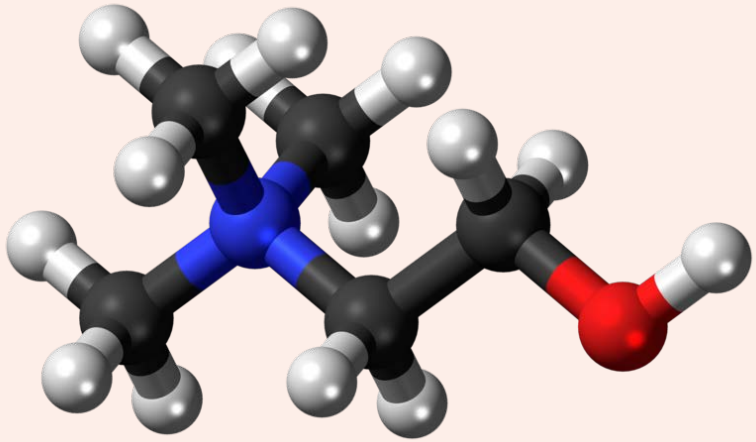
- Mucins
- Butyrophilin
- Lactadherin
- CD14
- TLR1
- TLR4
- Xanthine oxidase

CD14, cluster of differentiation 14; TLR, toll-like receptor.

Choline/Phosphatidylcholine

- Facilitates memory and learning skills in rodents[1]

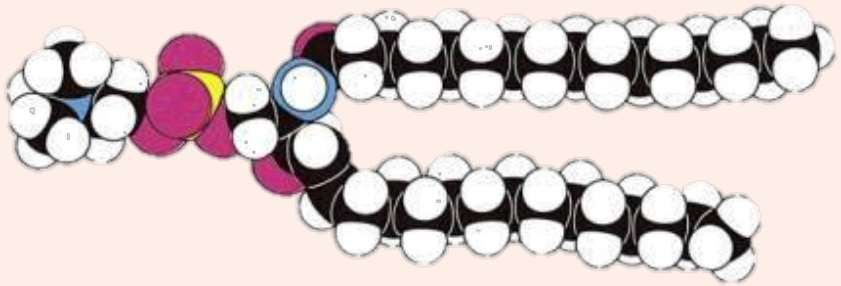
- Early second trimester maternal plasma choline and betaine concentrations related to measures of cognitive development in term infants at 18 months[2]



1. Zeisel SH. *J Pediatr.* 2006. 2. Wu BT, et al. *PloS One.* 2012.

Sphingomyelin

- Supplementation to rats accelerated myelination of cortex[1]
- When supplemented to breast milk (milk with or without added SM), neuro-behavioral development at 18 months improved in very low-birthweight infants (n=24)[2]

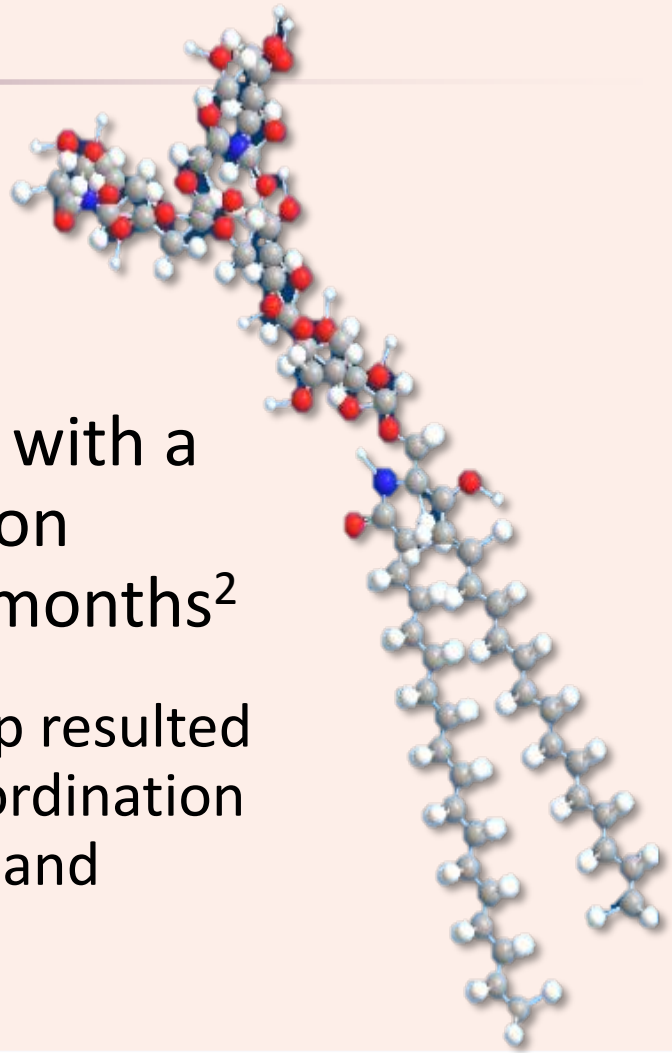


Sphingophospholipides (sphingomyelin)—
Space-filling model of molecule

SM, sphingomyelin.

1. Oshida K et al. *Pediatr Res.* 2003; 2. Tanaka K, et al. *Brain Dev.* 2013.

Sialic Acid/Gangliosides



- Sialic acid supplementation improves learning and memory in piglets[1]
- Supplementation of infant formula with a ganglioside-enriched milk fat fraction improved neurodevelopment at 6 months[2]
- Using the Griffith Scales, treatment group resulted in increased scores for hand-and-eye coordination IQ ($P<0.006$), performance IQ ($P<0.001$), and general IQ ($P=0.041$)[2]

1. Wang B, et al. *Am J Clin Nutr.* 2007; 2. Gurnida DA, et al. *Early Hum Dev.* 2012.

Why Infections Are Affected

Many factors in human milk provide expected or proven antimicrobial effects

Some are components of the MFGM (e.g., butyrophilin, MUC1, lactadherin, CD14, toll-like receptor 1 and 4, xanthine oxidase, gangliosides, oligosaccharides)

Examples:

- MFGM in formula fed to rat pups promoted development of the intestinal epithelium and gut integrity, impacted the microbiota development, and was protective against *C Difficile* toxin-induced inflammation[1]
- In a DBPCRT in healthy adults, a concentrate rich in natural bioactive phospholipids and sphingolipids reduced symptoms when challenged with a diarrheagenic E. coli[2]

DBPCRT, double-blind, placebo-controlled randomized trials.

1. Bhinder G, et al. *Sci Rep.* 2017; 2. Ten Bruggencate SJ, et al. *J Nutr.* 2016.

How Human Milk Bioactive Proteins Work

- Proteins present in high concentration
  - Source of amino acids
  - Exert biological function(s) in recipient infant
- Proteins present in low concentration
  - Unimportant as amino acid source
  - Exert biological function(s) in recipient infant
- Function(s) can be exerted by:
  - Intact protein (resistant to proteolysis)
  - Peptides formed during digestion
  - Complex molecules, such as glycolipids and glycoproteins

Bioactive Components

- Contribute to optimal neurodevelopment, including cognitive development
- Improve nutrient absorption
- Protect against pathogens
- Enhance immune system development

Demmelmair H, et al. *Nutrients.* 2017;9. pii: E817.

Functional/Bioactive Compounds in Human Milk

Lipids

- Gangliosides
- Sphingomeylin
- Oligosaccharides

Proteins

- Growth factors
- Enzymes
- Enzyme inhibitors
- Hormones
- Cytokines, chemokines
- Binding proteins
- Immunoglobulins

LCPUFAs Are Also Bioactives

- Inner MFGM layer contains phospholipids rich in
  - Long-chain polyunsaturated fatty acids (LCPUFAs)
    - Docosahexaenoic acid (DHA)
    - Arachidonic acid (ARA)
- Linked to myelination and synaptic transmission
- Present in high concentration in the brain
- Linked to brain development
- DHA and ARA were added to infant formulas some time ago, with positive effects

Colombo J, et al. *Am J Clin Nutr.* 2013; 98: 403–412. Demmelmair H, et al. *Nutrients.* 2017;9. pii: E817.

Measuring Cognitive Development

- Good nutrition in the first year of life is essential for optimal cognitive development.

- Studies that measure the effects of dietary intake on executive cognitive function during early childhood need to be targeted to the age of the infant or child.

Colombo J, et al. *Am Clin Nutr.* 2013;98:403–12.

Common Development Assessment Tools

Bayley Scales of Infant Development, version 2 (BSID-2): A global test of development used from birth to 3 years of age

MacArthur-Bates Communicative Development Inventory (MBCDI): Measures child's productive (expressive) vocabulary; number of words reported by parent; appropriate for use 8 to 30 months

Delayed Response (DR): Assesses spatial memory, given at 24, 30, and 36 months

Bear/Dragon: Game to assess children's ability to follow commands, given at 36, 42, and 48 months

Stroop: Children asked to inhibit a learned response (eg, signal day for night; red for yellow), given at 36, 42, 48, and 60 months

Colombo J, et al. *Am Clin Nutr.* 2013;98:403–12.

Common Development Assessment Tools, *cont.*

Dimensional Change Card Sort (DCCS): Measures discrimination learning, provides data on rule learning and the ability to inhibit use of an old rule when a new one is introduced; given at 36, 42, 48, and 60 months

Tower of Hanoi: Puzzle used as a neuropsychological and developmental assessment of rule learning and maintenance, goal-directed behavior, planning, and error correction; given at 48, 60, and 72 months

Peabody Picture Vocabulary Test, 3rd edition (PPVT-III): Measures vocabulary in individuals from 2.5 to 90 years of age; indicant of verbal IQ (given at 60 months)

Weschler Preschool Primary Intelligence Scale, 3rd edition (WPPSI-III): Most widely used and best-standardized tests of early intelligence; given at 72 months

Colombo J, et al. *Am Clin Nutr.* 2013;98:403–12.

Why MFGM Is Important for Brain Development

- Essential to optimal brain development during early life
- Involved in neuronal growth and brain development
  - Migration
  - Maturation
  - Neuritogenesis
  - Synaptogenesis
  - Myelination
  - Neonatal retinal maturation and development
- Dietary sphingomyelins and gangliosides can modify tissue composition of these lipids

Palmano K, et al. *Nutrients.* 2015;7:3891-913. Hernell O, et al. *J Pediatr.* 2016;173 Suppl:S60-5.

Advantages of MFGM Supplementation

- Recent supplementation of MFGM in infant formula provides additional advantages over and above DHA and ARA alone [see trial data][1]
- Evidence suggests components of MFGM contribute to cognition [Timby et al study; Gurnida et al study][1,2]
- Contributes to gut health and immunity
- Reduces risk of infections[3]

1. Timby N, et al. *Am J Clin Nutr.* 2014;99:860-8. 2. Gurnida DA, *Early Hum Dev.* 2012;88:595-601.
3. Timby N, et al. *J Pediatr Gastroenterol Nutr.* 2015;60:384-9.

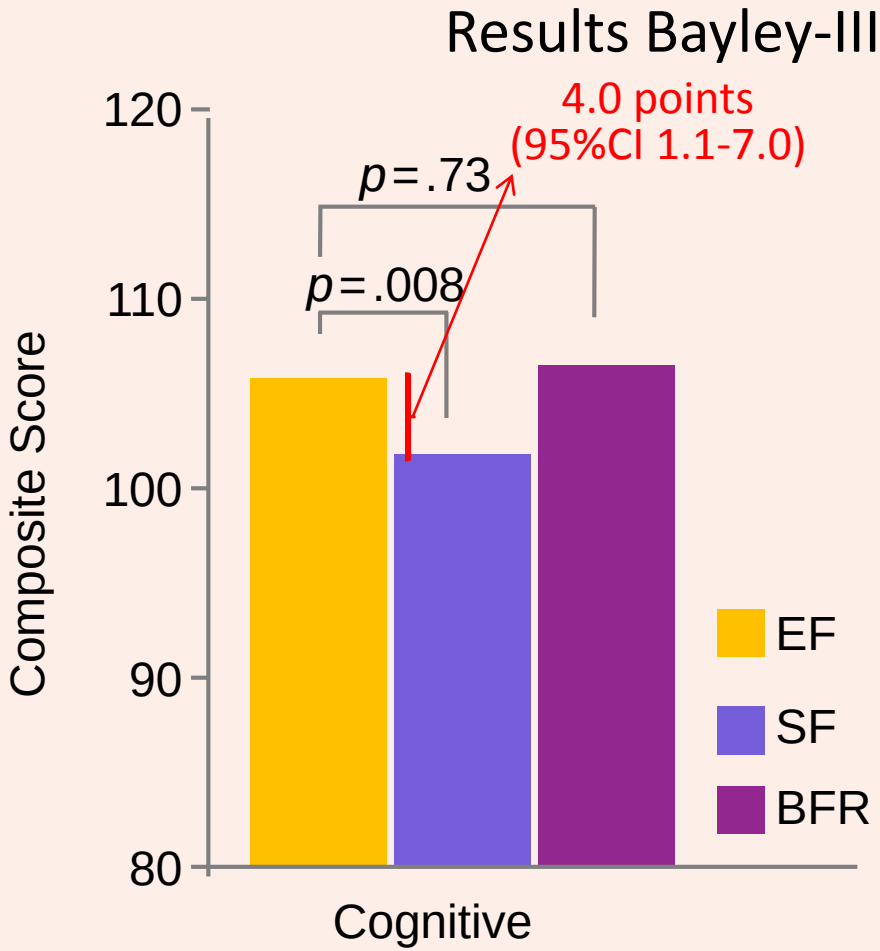
Clinical Trials of MFGM

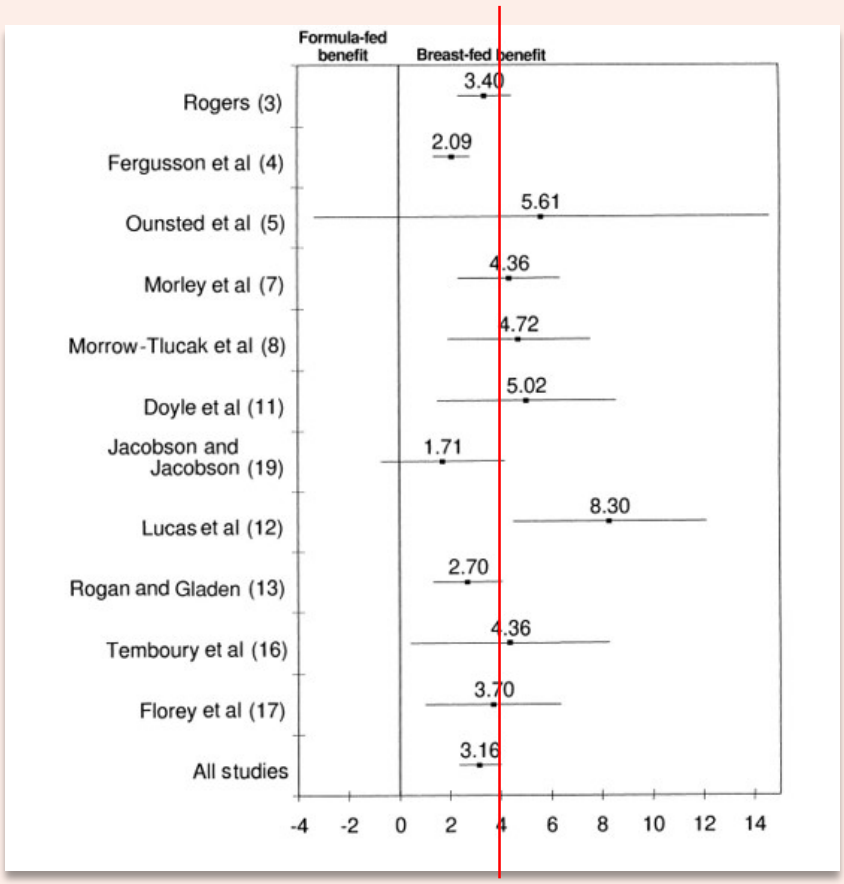
Sweden—Timby et al study: n=160; <2 to 6 mos

- Randomized to a low-energy, low-protein supplemented infant formula with bovine MFGM or a standard formula until 6 months of age. breastfed infants as reference group.
- At 12 months, MFGM-supplemented group obtained significantly higher cognitive scores on Bayley-III compared to standard formula group (105.8 ± 9.2 vs 101.8 ± 8.0, M ± SD)
- Scores of the MGFM group did not differ from the breastfed group (106.4 ± 9.5)
- Decreased incidence of otitis media in infants <6 months
- Did not find an increased risk of skin reactions in MFGM-supplemented group

Timby N, et al. *J Pediatr Gastroenterol Nutr.* 2015;60:384-9. Timby N, et al. *Clin Med Insights Pediatr.* 2015;9:63–64. Timby N, et al. *PLOS One.* 2017;12(1):e0169831.

Cognitive Performance of Infants Fed Formula With MFGM Similar to Breast Milk

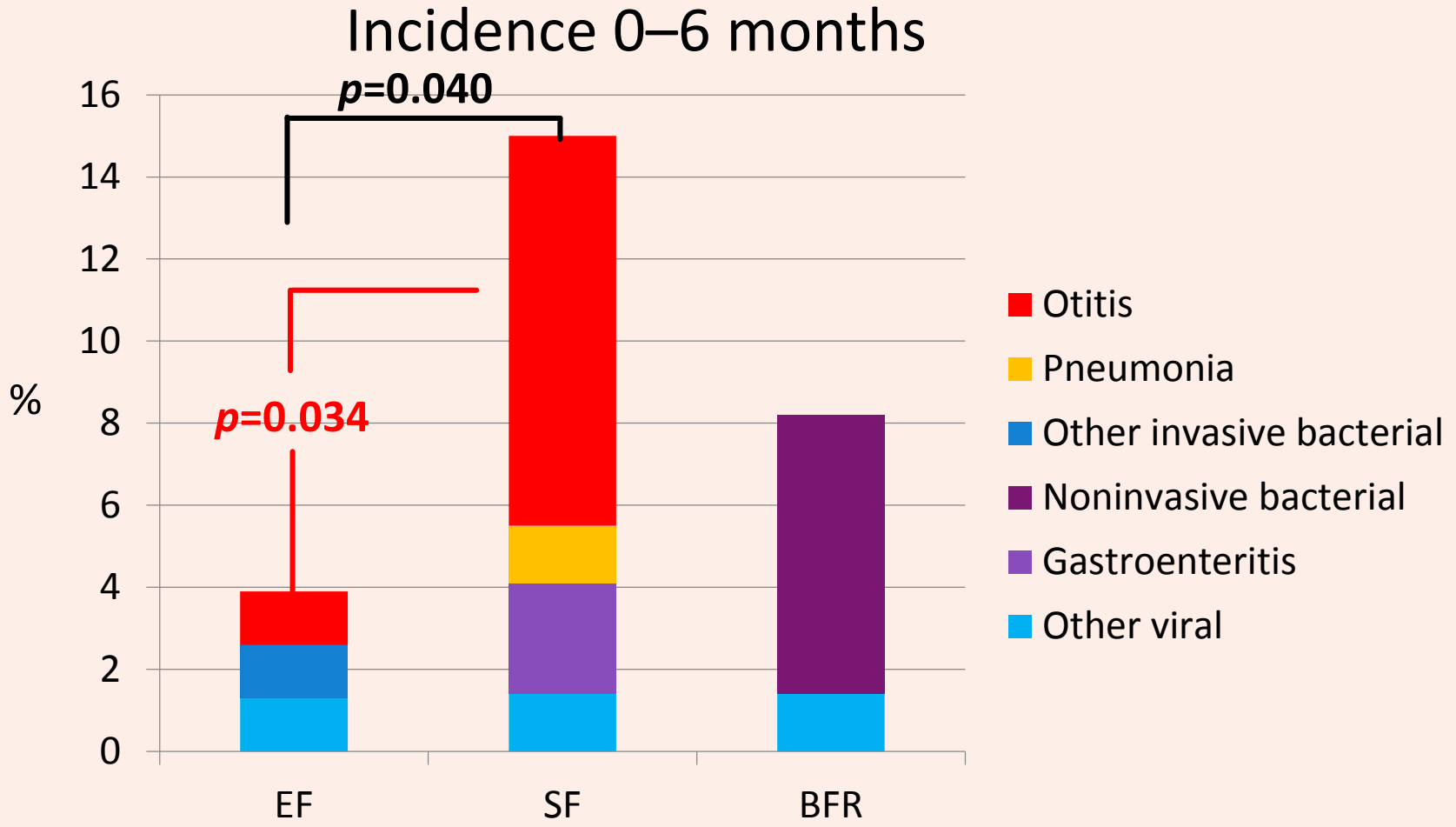




Note: Both EF and SF contained supplemental DHA.
BFR, breastfed reference; EF, experimental formula; SF, standard formula.

Timby N, et al. *Am J Clin Nutr.* 2014.
Anderson JW, et al. *Am J Clin Nutr.* 1999;70:525-535. Used with permission by The American Society for Nutrition.

Infections Treated With Antibiotics or Hospitalization



Note: Both EF and SF contained supplemental DHA.
BFR, breastfed reference; EF, experimental formula; SF, standard formula.

Timby N, et al. *J Pediatr Gastroenterol Nutr.* 2015;60:384-9.

Clinical Trials of MFGM, *cont.*

Indonesia—Gurnida et al study: n=70; randomized to supplement or control

- Studied 2–24 weeks of age; control group (n=30) received standard infant formula; treatment group (n=29) received same formula supplemented with complex milk lipid to increase the ganglioside content to approximately 11–12 µg/ml
- Evaluated impact on **cognitive function**
  - Primary outcome Griffiths Mental Developmental Scale at 24 weeks of age
- Serum ganglioside concentrations significantly higher in supplemented infants
- Scored better in hand-eye coordination IQ and performance IQ

Gurnida DA, et al. *Early Hum Dev.* 2012;88:595-601.

Clinical Trials of MFGM, *cont.*

Peru—Zavaleta et al study: n=499

- Study 6–11 months old
- Received daily for 6 months a complementary food (40 g/day) with protein source of either the MFGM-protein fraction or skim-milk proteins (control)
- Global prevalence of diarrhea was 3.84% and 4.37% in the MFGM group and control group, respectively ($P<0.05$)
- **Particularly reduced episodes of bloody diarrhea:** adjusted OR of 0.54 (95% CI 0.31–0.93, $P=0.025$)

OR, odds ratio.

Zavaleta N, et al. *J Pediatr Gastroenterol Nutr.* 2011;53(5):561-8.

Clinical Trials of MFGM, *cont.*

Belgium—Veereman-Wauters et al study: n=182; preschool aged 2.5–6 years (97 girls and 85 boys)

- Evaluated effect of daily milk-based supplement with MFGM phospholipids
- Outcomes were days with fever, diarrhea, constipation, coughing, doctor visit, medication, or school missed during the intervention
- **Achenbach System of Empirically Based Assessment** by parents and teachers at end of intervention
- Intervention group had fewer days with fever and lower parental scoring of behavioral problems. Not confirmed by teachers (105/169)

Veereman-Wauters G, et al. *Nutrition.* 2012;28(7-8):749-52.

Clinical Trials With MFGM Components

France & Italy—Billeaud et al study: n=119

- Infants age ≤14 days were randomized to standard infant formula (control), standard formula enriched with a lipid-rich MFGM fraction (MFGM-L), or standard formula enriched with a protein-rich MFGM fraction (MFGM-P)
- **Primary outcome:** Mean weight gain and safety of infant formulas enriched with bovine milk MFGM fractions, protein-enriched or phospholipid-enriched
- Higher incidence of eczema (not clear how diagnosed or at what age) in group receiving high-protein MFGM preparation; however, in Timby et al, same protein-enriched MFGM preparation did not observe sign of increased incidence of skin reactions

Billeaud C, et al. *Clin Med Insights Pediatr.* 2014;8:51-60. Timby N, et al. *Clin Med Insights Pediatr.* 2015.

Clinical Trials of MFGM, *cont.*

India—Poppitt et al study: n=450; infants 8–24 months

- Daily dose of milk powder supplemented with 2 g of a spray-dried ganglioside concentrate for 12 weeks
- Assessed diarrheal morbidity
- No difference in primary outcome of rotavirus diarrhea, or in secondary outcomes, including all-cause diarrhea
- High-ganglioside CML was acceptable for long-term consumption in infants ages 8 to 24 months
- More RCTs needed

CML, complex milk lipid; RCT, randomized controlled trials.

Poppitt SD, et al. *J Pediatr Gastroenterol Nutr.* 2014;59:167–171.

MFGM Clinical Trials Summary

Study	Age	Supplementation	Results from MFGM Group
Timby et al 2015	<2 to 6 mo	MFGM	Higher cognitive score. Lower incidence of otitis media.
Gurnida et al 2012	2–8 to 24 wks	Complex milk lipids	Higher hand and eye coordination IQ, performance IQ and general IQ.
Zavaleta et al 2011	6 to 11 mos	MFGM	Lower longitudinal prevalence of diarrhea and incidence of bloody diarrhea.
Veereman-Wauters et al 2012	2.5 to 6 yrs, during 4 mos	MFGM	Fewer fever days; lower parental score of internal, external and total behavioral problems.
Billeaud et al 2014	14 days to 4 mo	Compared lipid-rich and protein-rich MFGM fractions	Noninferior weight gain or adverse effects. Higher rate of eczema in protein-rich MFGM group.
Poppitt et al 2014	8–24 mo, during 12 wks	Complex milk lipids	Diarrhea (rotavirus) prevention. No difference between groups.

Study Limitations

- Different MFGM fractions used
- Different age groups
- Different outcomes
- Studies not comparable

Future Studies:

- More needed with identical MFGM fractions, longer follow-up times (a year or longer) through early childhood, and larger cohorts
- Include additional cognitive-function markers and clearly defined and established diagnosis of eczema

Why DHA Levels Are Important

- Significant LCPUFA lipid in the brain
- Found in the central nervous system, at synaptic terminals, mitochondria, and endoplasmic reticulum
- Early brain development is affected by DHA and ARA intake

Carlson S, et al. *Am Clin Nutr.* 2013;98:403–12. Weiser MJ, et al. *Nutrients.* 2016;8:99.

Clinical Trials of LCPUFA Supplementation on Infant/Toddler Cognitive Outcomes

DIAMOND study [Dallas cohort]: n=141

- Double-masked, randomized, controlled 12-month feeding trial, with 18-month cognitive assessment
- Infants 1–9 days of age assigned randomly to receive 1 of 4 term infant formulas with 1 of 4 levels of DHA:
  - Control (0% DHA), n=46
  - 0.32% DHA, n=45
  - 0.64% DHA, n=44
  - or 0.96% DHA, n=46
- All DHA-supplemented formulas contained 0.64% ARA

Drover JR, et al. *Early Hum Dev.* 2011;87:223-30.

DIAMOND Study [Dallas cohort], *cont.*

- Formulas were well tolerated; no adverse events
- All DHA-supplemented infants showed a significantly higher MSID MDI score at 18 months compared to the control group (104.1 vs 98.4; p=0.02)
- **Conclusion**: Dietary supplementation of DHA during first year of life leads to enhanced cognitive development at 18 months

MSID, Minnesota Studies in International Development; MDI, Mental Development Index.

Drover JR, et al. *Early Hum Dev.* 2011;87:223-30. Weiser MJ, et al. *Nutrients.* 2016;8:99.

Clinical Trials of DHA: Long-term Effects of LCPUFA Supplementation on Childhood Cognitive Outcomes

DIAMOND study [Kansas City cohort]: n=81

- Double-blind, RCT of LCPUFA supplementation
- Infants re-enrolled at 18 mo, tested every 6 mo until 6 years, on age-appropriate standardized and specific cognitive tests
- Significant, positive effects observed
  - Rule-learning and inhibition tasks from 3 to 5 years
  - Peabody Picture Vocabulary Test at 5 years
  - Weschler Primary Preschool Scales of Intelligence at 6 y
- Effects of LCPUFAs not found on tasks of spatial memory, simple inhibition, or advanced problem solving

Colombo J, et al. *Am Clin Nutr.* 2013;98:403–12. (Clinical Trial NCT00266825)

DIAMOND Study [KC cohort], *cont.*

- LCPUFA intake seen through
  - Early measures of **attention**
  - Preschool measures of **rule learning** and **implementation** (Stroop and DCCS)
  - Later measures of verbal ability (PPVT and WPPSI)
- There were also positive effects of LCPUFAs on first-year attention
- Higher cognitive scores in childhood demonstrate the benefits of early LCPUFA are prolonged long after LCPUFA supplementation ends

DCCS, Dimensional Change Card Sort; PPVT, Peabody Picture Vocabulary Test; WPPSI, Weschler Preschool Primary Intelligence Scale.

Colombo J, et al. *Am Clin Nutr.* 2013;98:403–12. (Clinical Trial NCT00266825)

DHA Significance in Infant Formula

- Evidence shows DHA supplementation is important in the diet of infants for first 24 months
- Significant role of DHA in the body (ie, nerve cells, myelination, and neurotransmission)
- Trials show DHA levels are safe and well tolerated

Weiser MJ, et al. *Nutrients.* 2016;8:99. Delgado-Noguera MF, et al. *Cochrane Database Syst Rev.* 2015;7.

Myelination Effects

How do DHA and MFGM support synaptic transmission and myelination?

- Adequate dietary lipid intake is crucial in the myelination process
- DHA protects neurons and helps conduct signals more efficiently
- As components of MFGM, sphingomyelin and gangliosides promote myelination and synaptic transmissions
- DHA stabilizes neurons, helping to transmit information faster

Weiser MJ, et al. *Nutrients.* 2016;8:99.

Long-term Impact of Infant Nutrition on Cognition

- Attention
- Memory (working and long-term)
- Perception
- Language
- Problem solving
- Comprehension
- Reasoning
- Computation
- Reading and speech

Behavioral Regulation Benefits in Young Children

- MFGM and DHA supplementation provide additional benefits for immune function
- Continued studies are needed to examine evidence for safety and tolerance
- LCPUFA plays a vital role in health, cognition, and visual development, allergic and respiratory diseases

Technological Advances in Infant Formula

- Technology now allows the addition of bovine MFGM to infant formula

- Double-blind RCTs provide evidence:
  - Inclusion of MFGM & DHA in formula is safe
  - Inclusion of MFGM & DHA enhances neurodevelopment and improves defense against infections

Hernell O, et al. *J Pediatr.* 2016;173 Suppl:S60-5.

How Bioactives Are Reducing the Nutritional Gap

- MFGM and DHA enrichments in infant formula have shown cognitive outcomes similar to breast milk [see DIAMOND trial & Timby et al 2015 study].
- Although more are needed, studies show MFGM and DHA supplements can provide essential nutrients to diets of infants.
- Although more are needed, studies show promising results regarding both neurodevelopment and defense against infections.

Hernell O, et al. *J Pediatr.* 2016;173 Suppl:S60-5.

DHA and MFGM Combined Benefits

- DHA and MFGM are found in breast milk
- Advances in dairy technology allow MFGM and DHA to be supplemented at levels similar to breast milk
- Bovine MFGM similar to human MFGM[1,2]
- DHA plus MFGM supplemented at clinically effective levels have demonstrated improved cognition similar to breast milk

1. Lönnerdal B. *Am J Clin Nutr.* 2014;99:712S-7S. 2. Timby N, et al. *J Pediatr Gastroenterol Nutr.* 2015;60:384-9.

Infant Nutrition Summary

- Breast milk is the best source of nutrition for nearly all infants
- Optimal nutrition is essential for
  - Cognitive development
  - Postnatal intestinal function and immunity
  - Better health outcomes later in life
- Understanding composition of human milk has led to advances of infant formula
- Studies of infants fed formula with MFGM and DHA show cognitive performance similar to breastfed infants

ANY
QUESTIONS?

Thank You

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