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**NLC**  
NUTRICIA LEARNING CENTER

Thank you for joining!  
We'll begin shortly

**What's Under the Lid of  
Your Hydrolyzed Formula?  
Looking Beyond Macro- and  
Micronutrients**

Jessica M Lowe, DCN, MPH, RDN  
Medical Science Liaison  
May 23, 2023



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**WHAT'S UNDER THE LID OF YOUR HYDROLYZED FORMULA?  
LOOKING BEYOND MACRO- AND MICRONUTRIENTS**

Jessica M Lowe, DCN, MPH, RDN | Medical Science Liaison



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**DISCLOSURES**

Jessica Lowe, DCN, MPH, RDN is employed as a Medical Science  
Liason by Nutricia North America



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**OBJECTIVES**

- 1 List beneficial bioactive components in human milk
- 2 Review clinical relevance of prebiotics, nucleotides, and whey in formula
- 3 Describe the importance of lactose in infant formula and benefits to the gut microbiota
- 4 Summarize the benefits of these components in formula for infants with food allergies

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**Nutricia North America  
supports the use of  
human milk wherever possible.**

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**ALPHABET SOUP**



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**ALPHABET SOUP**



**Breast Milk/Human Milk**  
Milk produced by the human mammary glands to feed infants and young children

**Breastfeeding**  
The practice of feeding an infant or young child breastmilk directly from the breast

CDC. Infant and Young Children Feeding in Emergencies Toolkit: Glossary. <https://www.cdc.gov/emergencies/glossary/index.html>. Updated September 13, 2022. Accessed May 1, 2023.

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**BENEFITS OF BREASTFEEDING AND HUMAN MILK**

Victoria CG, et al. Breastfeeding in the 21<sup>st</sup> century: epidemiology, mechanism, and lifelong effect. *The Lancet*. 2016;387(10017):475-490.

**Risk Reduction**

- Sudden infant death: 36%
- Necrotizing enterocolitis: 58%
- Otitis media: 43%
- Asthma: 9%
- Malocclusions: 68%
- Overweight/Obesity: 26%
- Type 2 Diabetes: 35%

**Higher Performance:**

- Intelligence tests: 3.4 IQ

Victoria, et al. *The Lancet*. 2016.

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**STAGES OF HUMAN MILK COMPOSITION**




**Colostrum**  
Days <1-4

- Rich in protein, fat-soluble vitamins, minerals, and immunoglobulins
- Passive immunity



**Transitional Milk**  
Days 5-20

- Rich in fat, lactose, water-soluble vitamins
- Higher in kcals than colostrum



**Mature Milk**  
Days 20+

- Fore milk: start of feed
- Hind milk: as breast empties

[1] Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr*. 2014;14:216. [2] Italianer MF, et al. Circadian variation in human milk composition, a systematic review. *Nutrients*. 2020;12(8):2328.

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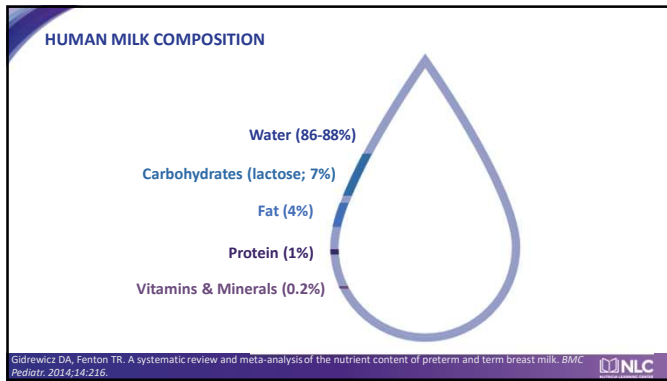
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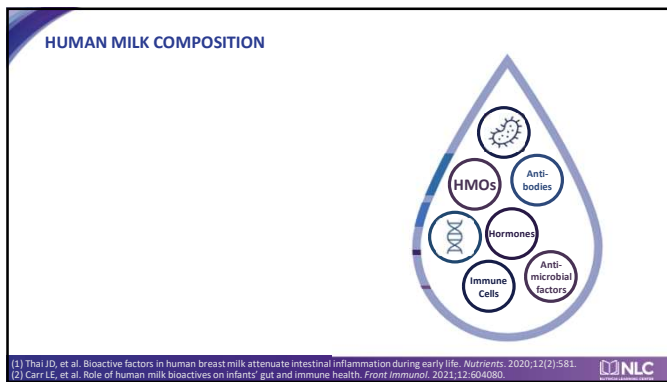
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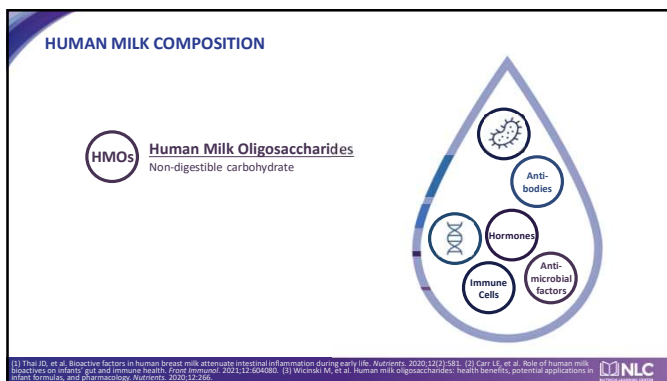
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**HUMAN MILK COMPOSITION**

**HMOs Human Milk Oligosaccharides**  
Non-digestible carbohydrate

**Volume Decreases over Lactation**

- Colostrum: 20-25 g/L
- Mature milk: 5-15 g/L

**Benefits**

- Prebiotic effect
- Antiadhesive antimicrobials
- Immune modulators
- Modulators of intestinal cell response
- Neurodevelopment and cognition

Legend:

- Glucose
- Galactose
- N-Acetylglucosamine
- Fucose
- Sialic acid

(1) Møller S, et al. Infant complementary feeding of prebiotics for the microbiome and immunity. *Nutrients*. 2020;11:364. (2) Thiel S, et al. Systematic review of the concentrations of oligosaccharides in human milk. *Nutr Rev*. 2017;11:920-933. (3) Wicinski M, et al. Human milk oligosaccharides: health benefits, potential applications in infant formulas, and pharmacology. *Nutrients*. 2020;12:798.

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**HUMAN MILK COMPOSITION**

**HMOs Human Milk Oligosaccharides**  
Non-digestible carbohydrate

**Nucleotides**  
Non-protein nitrogen

**Antibodies**

**Hormones**

**Immune Cells**

**Antimicrobial factors**

(1) Thai JD, et al. Bioactive factors in human breast milk attenuate intestinal inflammation during early life. *Nutrients*. 2020;12(2):581. (2) Carr LE, et al. Role of human milk bioactives on infants' gut and immune health. *Front Immunol*. 2021;12:604080.

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**HUMAN MILK COMPOSITION**

**Nucleotides**  
Non-protein nitrogen

**Provide 2-5% of NPN**

**Biological Effects**

- Intestinal growth and differentiation
- Intestinal repair
- Somatic growth
- Iron absorption
- Intestinal flora
- Lipid metabolism
- Immune function

Phosphate Group

Pentose Sugar

Nitrogenous Base

Hodgkinson A, et al. Nucleotides: an updated review of their concentration in breastmilk. *Nutr Res*. 2022;99:13-24.

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**KEEP IN MIND:**  
The majority of infants will  
receive some formula in the  
first 6 months of life.

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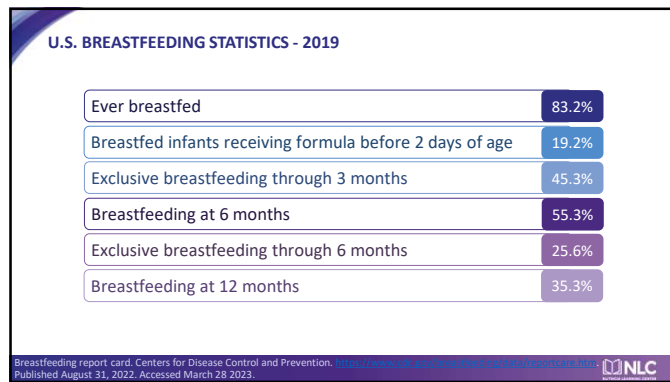
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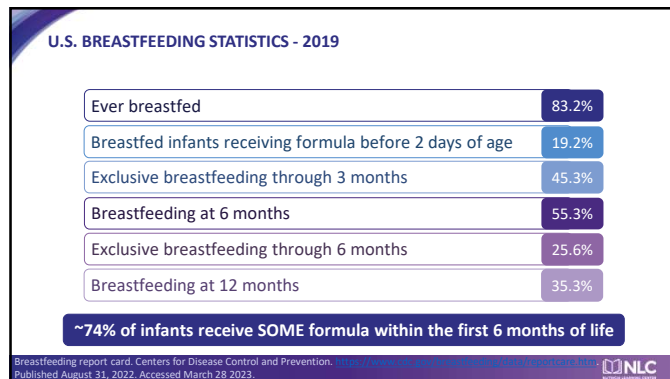
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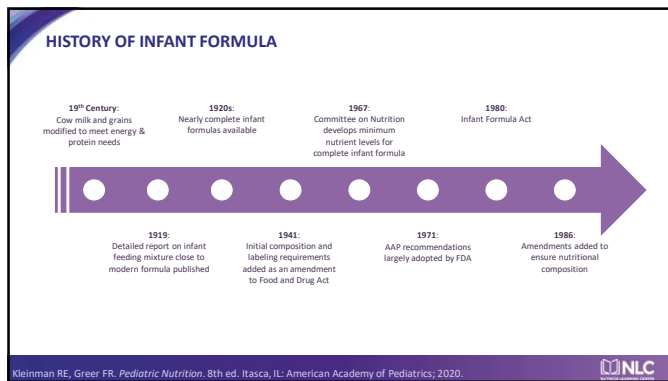
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### INFANT FORMULA ACT OF 1980

**Amended the Federal Food, Drug & Cosmetic Act**  
Permits the Secretary of Health and Human Services to revise such requirements, establish quality control procedures, and establish requirements respecting the retention of records of required procedures.

- Establishes minimum nutrient requirements
- Defines adulteration
- Establishes nutrient and quality control procedures
- Prescribes recall procedures
- Specifies inspection requirements

Newberry RE. The Infant Formula Act of 1980. *J Assoc Off Anal Chem*. 1982;65(6):1472-1473.

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### FORMULA INGREDIENTS

GRAS or FDA-approved safe food additives

"Label claim" of an ingredient is the minimum among present at the end of shelf life

Structure function label claims for infant formula ingredients

- "Truthful and not misleading"
- "Competent and reliable scientific evidence"

**Examples:**

- Taurine
- DHA/ARA
- Prebiotics/Probiotics
- Lutein/Lycopene
- Lactoferrin

GRAS = generally recognized as safe; FDA = Food and Drug Administration.  
Kleinman RE, Greer FR. *Pediatric Nutrition*. 8th ed. 2020. 89-90.

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Infant formula is intended  
as an effective substitute for  
infant feeding.

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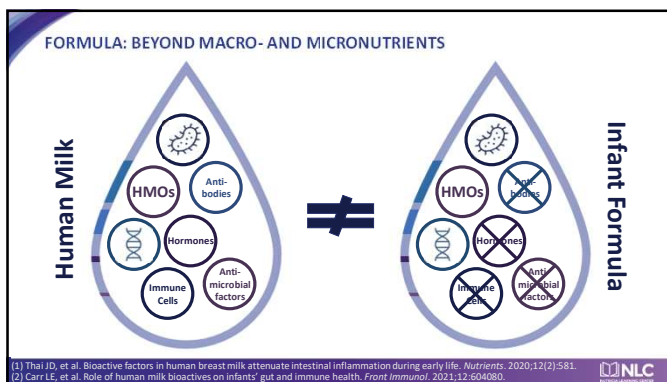
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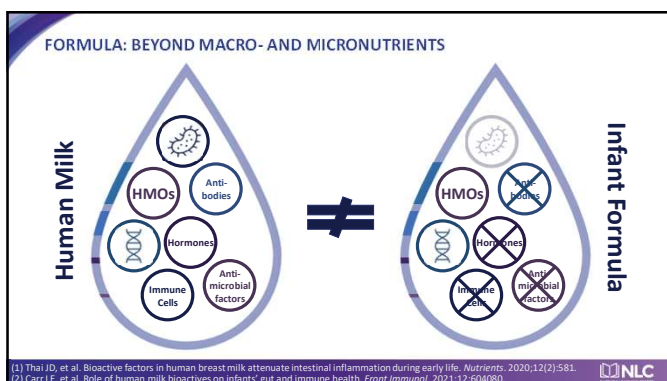
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**FORMULA: BEYOND MACRO- AND MICRONUTRIENTS**

**HMOs** Human Milk Oligosaccharides act as a **PREBIOTIC** found naturally in human milk.

(1) McKen S, et al. Infant complementary feeding of prebiotics for the microbiome and immunity. *Nutrients*. 2019;11:364. (2) Wicinski M, et al. Human milk oligosaccharides: health benefits, potential applications in infant formulas, and pharmacology. *Nutrients*. 2020;12:246.

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**FORMULA: PREBIOTICS**

**International Scientific Association for Probiotics & Prebiotics (ISAPP)**

A prebiotic is 'a substrate that is selectively utilized by host microorganisms conferring a health benefit'

Gibson GR, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;13(4):491-502.

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**FORMULA: PREBIOTICS**

**Galacto-oligosaccharides (GOSs)**

**Fructo-oligosaccharides (FOSs)**

**Inulin**

(1) McKen S, et al. Infant complementary feeding of prebiotics for the microbiome and immunity. *Nutrients*. 2019;11:364. (2) Gibson GR, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;13(4):491-502. (3) Gibson GR, et al. International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;13(4):491-502. (4) Gibson GR, et al. International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;13(4):491-502. (5) Gibson GR, et al. International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;13(4):491-502.

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**FORMULA: PREBIOTICS**

Veererman-Waauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *JPGN*. 2011;52(6):763-771.

Randomized, Double-Blinded, 2-Center Clinical Trial

Intervention Groups	<ul style="list-style-type: none"> <li>• SYN1 at 0.4 g/dL: n=21</li> <li>• SYN1 at 0.8 g/dL: n=20</li> <li>• GOS/FOS (90:10) 0.8g/dL: n=19</li> </ul>
Control Groups	<ul style="list-style-type: none"> <li>• Standard infant formula (without prebiotics): n=21</li> <li>• Breastfed infants: n=29</li> </ul>

Veererman-Waauters, et al. *JPGN*. 2011.

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**FORMULA: PREBIOTICS**

Veererman-Waauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *JPGN*. 2011;52(6):763-771.

<u>Enrollment</u>	<u>Day 14</u>	<u>Day 28</u>
<ul style="list-style-type: none"> <li>• DOB</li> <li>• Sex</li> <li>• Gestational age</li> <li>• APGAR scores (1-10 minutes)</li> <li>• Mother antibiotic intake</li> <li>• Perinatal data</li> <li>• Mode of delivery</li> <li>• Anthropometrics at birth</li> <li>• Fecal microbiota (day 3)</li> </ul>	<ul style="list-style-type: none"> <li>• Anthropometrics</li> <li>• Fecal microbiota</li> <li>• Parental records</li> <li>• Formula intake</li> <li>• Stool characteristics</li> <li>• Crying behavior</li> <li>• Occurrence of regurgitation</li> <li>• Occurrence of vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Anthropometrics</li> <li>• Fecal microbiota</li> <li>• Parental records</li> <li>• Formula intake</li> <li>• Stool characteristics</li> <li>• Crying behavior</li> <li>• Occurrence of regurgitation</li> <li>• Occurrence of vomiting</li> </ul>

Veererman-Waauters, et al. *JPGN*. 2011.

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**FORMULA: PREBIOTICS**

Veererman-Waauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *JPGN*. 2011;52(6):763-771.

<b>Enrollment</b>	 <p>N=110 n=47   n=63</p>	 <p>Gestational Age 39 ± 1 week</p>	 <p>Maternal Abx n=9 (8.2%)</p>
	 <p>Weight at Birth 3.5 ± 1.7 kg</p>	 <p>Length at Birth 50.5 ± 1.7 cm</p>	 <p>Head Circumference at Birth 34.7 ± 1.2 cm</p>

Veererman-Waauters, et al. *JPGN*. 2011.

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FORMULA: PREBIOTICS

Veererman-Waauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *JPGN.* 2011;52(6):763-771.

Anthropometrics	No influence on growth during study period
Food Intake	No difference between groups
Regurgitation & Vomiting	Little to no difference between groups
Stool Frequency	No difference between groups Stool frequency decreased with time
Stool Consistency	Breastfed infants had the softest stools; control group had the hardest All infants on prebiotics had softer stools than the control group

Day 28

Veererman-Waauters, et al. *JPGN.* 2011.

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FORMULA: PREBIOTICS

Veererman-Waauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *JPGN.* 2011;52(6):763-771.

Differences in Bifidobacterium Counts among Feeding Groups

Group	Day 3	Day 14	Day 28
Control	~8.2	~8.5	~9.0
BF	~8.5	~8.8	~9.2
GOS/FOS	~8.6	~8.9	~9.3
SYN1 0.8	~8.7	~9.0	~9.4
SYN1 0.4	~8.8	~9.1	~9.5

\*Significant difference from Day 3 AND control group.

Veererman-Waauters, et al. *JPGN.* 2011.

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FORMULA: BEYOND MACRO- AND MICRONUTRIENTS

**Nucleotides:** first added to infant formula in the 1960's, and became common by the 1980's

HMOs  
Nucleotides  
Antibiotics

Kleinman RE, Greer FR. *Pediatric Nutrition.* 8th ed. Itasca, IL: American Academy of Pediatrics; 2020.

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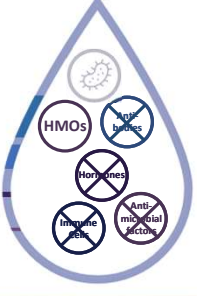
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**FORMULA: BEYOND MACRO- AND MICRONUTRIENTS**

The FDA does not set recommended levels of nucleotides for infant formula.



Abrams S, Bergner EM. Is it time to revise the current nutrient requirements for infant formulas principally established in 1980? *Adv Nutr*. 2023. NLC

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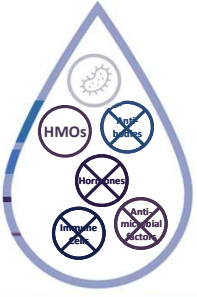
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**FORMULA: BEYOND MACRO- AND MICRONUTRIENTS**

The FDA does not set recommended levels of nucleotides for infant formula.

Nucleotides are not essential. HOWEVER, during periods of rapid growth or disease, nucleotide synthesis may not be able to keep up with demand.



(1) Abrams S, Bergner EM. Is it time to revise the current nutrient requirements for infant formulas principally established in 1980? *Adv Nutr*. 2023. (2) Hodgkinson A, et al. Nucleotides: an updated review of their concentration in breastmilk. *Nutr Rev*. 2022;99:13-24. NLC

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**FORMULA: NUCLEOTIDES**

Gutierrez-Castrellon P, et al. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Br J Nutr*. 2007;98(Suppl1):S64-S67.

**Databases**

- PubMed, Embase, LILACS, ARTEMISA, Cochrane Controlled Trial Register, Bandolier, and DARE

**Inclusion Criteria**

- RCT comparing infant formula containing ribonucleotides with formulae without nucleotides or breastmilk
- Healthy children under 2 years of age

**Publication Quality**

- Jadad and CONSORT guidelines

Gutierrez-Castrellon, et al. *Br J Nutr*. 2007. NLC

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**FORMULA: NUCLEOTIDES**

Gutierrez-Castrellon P, et al. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Br J Nutr.* 2007;98(Supp1):S64-S67.

**9 Studies**

Outcomes of Interest

- 1 Antibody titers
- 2 Episodes of diarrhea
- 3 Acute respiratory infections

Gutierrez-Castrellon, et al. *Br J Nutr.* 2007.

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**FORMULA: NUCLEOTIDES**

Gutierrez-Castrellon P, et al. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Br J Nutr.* 2007;98(Supp1):S64-S67.

**9 Studies**

<u>Outcomes of Interest</u>	<u>Findings</u>
1 Antibody titers	Better antibody response to immunizations
2 Episodes of diarrhea	Fewer episodes of diarrhea
3 Acute respiratory infections	No difference in risk for URI

URI = upper respiratory infection  
Gutierrez-Castrellon, et al. *Br J Nutr.* 2007.

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**FORMULA: NUCLEOTIDES**

Gutierrez-Castrellon P, et al. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Br J Nutr.* 2007;98(Supp1):S64-S67.

**9 Studies**

<u>Outcomes of Interest</u>	<u>Findings</u>
1 Antibody titers	Better antibody response to immunizations
2 Episodes of diarrhea	Fewer episodes of diarrhea
3 Acute respiratory infections	No difference in risk for URI

Benefits begin at 1.9 mg/100 kcal and are maintained/increased with 10.8 mg/100 kcal

URI = upper respiratory infection  
Gutierrez-Castrellon, et al. *Br J Nutr.* 2007.

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**FORMULA: NUCLEOTIDES**

Wang L, et al. Effects of dietary nucleotide supplementation on growth in infants: a meta-analysis of randomized controlled trials. *Eur J Nutr.* 2019;58(3):1213-1221.

- Databases**
  - PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure Database
- Inclusion Criteria**
  - RCT focusing on effect of nucleotide supplementation on growth
  - Healthy infants; no congenital or hereditary conditions
  - Nucleotide supplementation was initiated within 1-month post-birth
- Publication Quality**
  - PRISMA Guidelines
  - Cochrane Collaboration Risk of Bias Tool

Wang, et al. *Eur J Nutr.* 2019. 

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**FORMULA: NUCLEOTIDES**

Wang L, et al. Effects of dietary nucleotide supplementation on growth in infants: a meta-analysis of randomized controlled trials. *Eur J Nutr.* 2019;58(3):1213-1221.

**Outcomes of Interest**

**8 Studies**

- 1 Weight & z-score
- 2 Rate of weight gain
- 3 Length & z-score
- 4 Rate of linear growth
- 5 Head circumference & z-score
- 6 Rate of head circumference gain

Wang, et al. *Eur J Nutr.* 2019. 

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**FORMULA: NUCLEOTIDES**


Wang L, et al. Effects of dietary nucleotide supplementation on growth in infants: a meta-analysis of randomized controlled trials. *Eur J Nutr.* 2019;58(3):1213-1221.

**Outcomes of Interest**      **Findings**

**8 Studies**

- 1 Weight & z-score → No effect of nucleotide supplementation
- 2 Rate of weight gain → Sig. increased rate [0.26 (95%CI: 0.06-0.47)]
- 3 Length & z-score → No effect of nucleotide supplementation
- 4 Rate of linear growth → Only 1 article identified
- 5 Head circumference & z-score → Sig. differences at 7-8 weeks [0.30 (95%CI: 0.10-0.50)]\*
- 6 Rate of head circumference gain → Sig. increased rate [0.34 (95%CI: 0.09-0.58)]

\*No effect on head circumference at week 16 and 20-28

Wang, et al. *Eur J Nutr.* 2019. 

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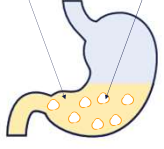
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**FORMULA: MACRONUTRIENT COMPOSITION - PROTEIN**

**Whey vs. Casein**

**Whey:Casein Ratio**

- Human Milk 60:40
- Cow Milk 20:80



Donovan SM. Human milk proteins: composition and physiological significance. Nestle Nutr Inst Workshop Series. 2019;90:93-101. NLC

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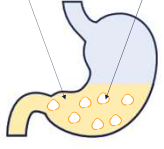
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**FORMULA: MACRONUTRIENT COMPOSITION - PROTEIN**

**Whey vs. Casein**

**Whey:Casein Ratio**

- Human Milk 60:40
- Cow Milk 20:80



**Meyer, et al.**  
*BMC Gastroenterol.* 2015

↓ Gastroesophageal Reflux  
↑ Gastric Emptying

[1] Donovan SM. Human milk proteins: composition and physiological significance. Nestle Nutr Inst Workshop Series. 2019;90:93-101. [2] Meyer, et al. Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children. BMC Gastroenterol. 2015;15:137. NLC

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**FORMULA: MACRONUTRIENT COMPOSITION - CARBOHYDRATE**

**Lactose**

- Human milk contains ~7% carbohydrates
- Primary carbohydrate in breastmilk
- Lactose is a disaccharide



Heyman MB. Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. Pediatrics. 2006;111(3):1279-1286. NLC

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**FORMULA: LACTOSE**

What about lactose intolerance?

<b>Developmental Lactase Deficiency</b> Observed in premature infants (<34 weeks gestation) 	<b>Congenital Lactase Deficiency</b> Rare and severe autosomal recessive disorder presenting in newborns 
<b>Lactase Non-Persistence</b> Physiological gradual decline of lactase activity 	<b>Secondary Lactose Intolerance</b> May occur secondary to small bowel injury 

Heine RG, et al. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children – common misconceptions revisited. *World Allergy Organ J*. 2017;10(1):41.

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National Lactose Intolerance Center

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**FORMULA: LACTOSE**

What about lactose intolerance?

<b>Developmental Lactase Deficiency</b> Observed in premature infants (<34 weeks gestation) 	<b>Congenital Lactase Deficiency</b> Rare and severe autosomal recessive disorder presenting in newborns 
<b>Lactase Non-Persistence</b> Physiological gradual decline of lactase activity 	<b>Secondary Lactose Intolerance</b> May occur secondary to small bowel injury 

**Strzalkowski and Young. *Clin Exp Allergy*. 2021.**  
 Medically necessitated lactose-reduced formula: 7.5%  
 Lactose-reduced formula consumption: 55%

(1) Heine RG, et al. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children – common misconceptions revisited. *World Allergy Organ J*. 2017;10(1):41. (2) Strzalkowski, et al. Protein and carbohydrate content of infant formula purchased in the United States. *Clin Exp Allergy*. 2022;52(11):1304-1305.

**NLC**  
National Lactose Intolerance Center

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


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**Lactose Intolerance ≠ Cow Milk Allergy**  
 Lactose intolerance mediator: carbohydrate  
 Cow milk allergy mediator: protein

(1) Heine RG, et al. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children – common misconceptions revisited. *World Allergy Organ J*. 2017;10(1):41. (2) Strzalkowski, et al. Protein and carbohydrate content of infant formula purchased in the United States. *Clin Exp Allergy*. 2022;52(11):1304-1305.

**NLC**  
National Lactose Intolerance Center

48

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# FORMULA: LACTOSE

Francavilla, et al. Effect of lactose on gut microbiota and metabolome of infants with cow milk allergy. *Pediatr Allergy Immunol.* 2012;23(5):420-427.

## Prospective Clinical Trial

### Study Groups

- Control (n=12): healthy infants
- Intervention (n=16): infants with CMA

### Intervention

- Phase 1: 2 eHF without lactose for 2 months
- Phase 2: eHF with lactose for 2 months

Francavilla, et al. *Pediatr Allergy Immunol.* 2012.



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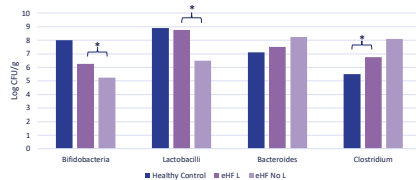
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# FORMULA: LACTOSE

Francavilla, et al. Effect of lactose on gut microbiota and metabolome of infants with cow milk allergy. *Pediatr Allergy Immunol.* 2012;23(5):420-427.

Median values of main microbial groups in fecal samples



Francavilla, et al. *Pediatr Allergy Immunol.* 2012.



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How might these components  
in formula benefit infants with  
food allergies?

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**PALATABILITY AND ACCEPTANCE OF FORMULA IN CMA**

Sensory experiences that infants experience in the first months of life may correlate with food preferences in both childhood and adulthood

- 1 Health professionals often observe selective/picky eating behaviors in children with a history of cow milk allergy
- 2 Hydrosylates and amino acid-based formulas are less palatable due to the hydrolysis process

Warren CM, et al. The US population-level burden of cow's milk allergy. *World Allergy Organ J.* 2022;15(4):100644. 

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**PALATABILITY AND ACCEPTANCE OF EHF**


Maslin, et al. Palatability of hypoallergenic formula for cow milk allergy and healthcare professional recommendation. *Pediatr Allergy Immunol.* 2018;29(8):857-862.

Randomized, Block Design



4 Sample Formulas:

- EHF W1 & EHF W2: Whey + Lactose
- EHF C1 & EHF C2: Casein without Lactose

Maslin, et al. *Pediatr Allergy Immunol.* 2018. 

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**Palatability Questionnaire**

- Increase the chance of non-rejection
- Results in more content families
- Decreases wastage & healthcare costs
- Increases compliance
- Decreases switch to other formula
- Results in more content infants

Maslin, et al. *Pediatr Allergy Immunol.* 2018. 

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- Decreases wastage & healthcare costs
- Increases compliance
- Decreases switch to other formula
- Results in more content infants

**Top 2 Palatability Rankings**

Rank	EHF W1	EHF W2	EHF C1	EHF C2
Most Liked	77%	19%	1%	1%
2nd Most Liked	19%	56%	21%	1%

Maslin, et al. *Pediatr Allergy Immunol.* 2018. **NLC**

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**PREBIOTIC FIBERS AND BIFIDOGENIC GUT COLONIZATION**

WE KNOW Supplementing Term Formula with GOS:FOS...

- 1 Stimulates the growth of bifidobacterial and lactobacilli in the intestine
- 2 Results in stool characteristics close to those found in human milk-fed infants

Veereman-Wauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infants formulae. *JPGN.* 2011;52(6):763-771. **NLC**

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Arslanoglu, et al. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr.* 2007;137(11):2420-2424.

[1] Veereman-Wauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infants formulae. *JPGN.* 2011;52(6):763-771. [2] Arslanoglu, et al. *J Nutr.* 2007. **NLC**

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### GOS/FOS: DEVELOPING INFECTIONS AND ALLERGIES

Arslanoglu, et al. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr.* 2007;137(11):2420-2424.

#### Randomized, Double-Blinded, Controlled Study

- Inclusion Criteria**
- Healthy, term infants
  - Parental history of atopic eczema, allergic rhinitis, or asthma
- Study Groups**
- Control (n=104): 0.0 g/100 mL GOS/FOS
  - Intervention (n=102): 0.8 g/100 mL GOS/FOS

Arslanoglu, et al. *J Nutr.* 2007.



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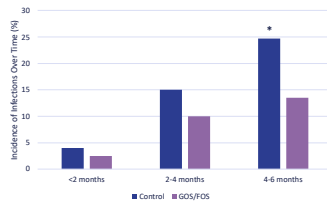
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### GOS/FOS ↓ THE INCIDENCE OF INFECTIONS

Arslanoglu, et al. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr.* 2007;137(11):2420-2424.



Arslanoglu, et al. *J Nutr.* 2007.



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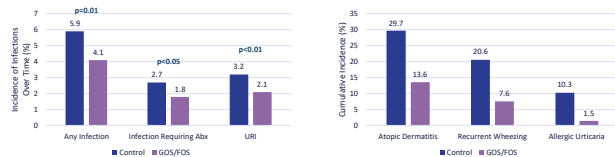
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### GOS/FOS ↓ THE INCIDENCE OF INFECTIONS & ALLERGIC MANIFESTATIONS

Arslanoglu, et al. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr.* 2008;138(6):1091-1095.

Control (n=68): 0.0 g/100 mL GOS/FOS  
Intervention (n=66): 0.8 g/100 mL GOS/FOS



Arslanoglu, et al. *J Nutr.* 2008.



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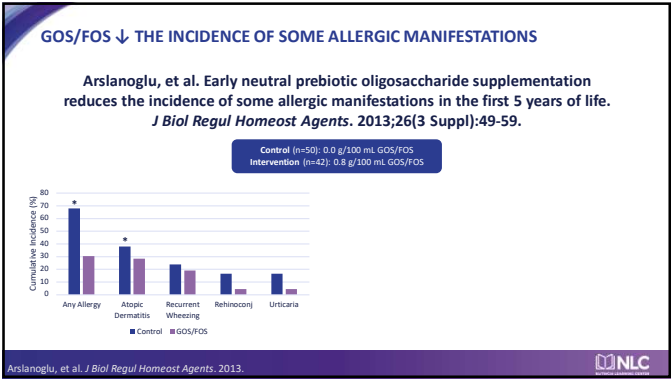
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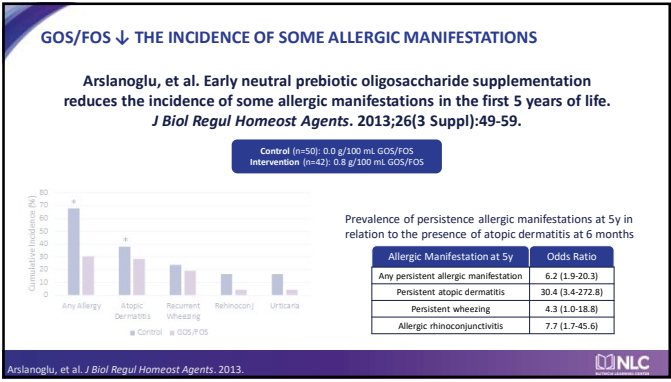
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**IN SUMMARY**

Human milk provides infants with and without disease ideal nutrition and support growth and development.

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IN SUMMARY

Human milk provides infants with and without disease ideal nutrition and support growth and development.

Infant formulas are incorporating key elements of human milk - lactose, prebiotics, nucleotides, DHA/ARA – shown to support gut health and the immune system.



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IN SUMMARY

Human milk provides infants with and without disease ideal nutrition and support growth and development.

Infant formulas are incorporating key elements of human milk - lactose, prebiotics, nucleotides, DHA/ARA – shown to support gut health and the immune system.

Supporting infants with cow milk allergy:

- Incorporating whey and lactose into eHF may improve palatability
- Efforts to support the gut microbiome by consuming prebiotics appear to be beneficial



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REFERENCES

1) CDC. Infant and Young Children Feeding in Emergencies Toolkit: Glossary. <https://www.cdc.gov/nutrition/emergencies-infant-feeding/glossary.html> Updated September 13, 2022. Accessed May 1, 2023.

2) Victora CG, et al. Breastfeeding in the 21<sup>st</sup> century: epidemiology, mechanism, and lifelong effect. *The Lancet*. 2016;387(10017):475-490.

3) Gidycz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. *BMC Pediatr*. 2014;14:216.

4) Italianer MF, et al. Circadian variation in human milk composition, a systematic review. *Nutrients*. 2020;12(8):2328.

5) Thai JD, et al. Bioactive factors in human breast milk attenuate intestinal inflammation during early life. *Nutrients*. 2020;12(2):581.

6) Carr LE, et al. Role of human milk bioactives on infants' gut and immune health. *Front Immunol*. 2021;12:604080.

7) Wicinski M, et al. Human milk oligosaccharides: health benefits, potential applications in infant formulas, and pharmacology. *Nutrients*. 2020;12:266.

8) McKeen S, et al. Infant complementary feeding of prebiotics for the microbiome and immunity. *Nutrients*. 2019;11:364.

9) Thuri S, et al. Systematic review of the concentrations of oligosaccharides in human milk. *Nutr Rev*. 2017;11:920-933.

10) Hodgkinson A, et al. Nucleotides: an updated review of their concentration in breastmilk. *Nutr Res*. 2022;99:13-24.

11) Breastfeeding report card. Centers for Disease Control and Prevention. <https://www.cdc.gov/breastfeeding/data/reportcard.htm>. Published August 31, 2022. Accessed March 28 2023.

12) Kleinman RE, Greer FR. *Pediatric Nutrition*. 8th ed. Itasca, IL: American Academy of Pediatrics; 2020.

13) Newberry RE. The Infant Formula Act of 1980. *J Assoc Off Anal Chem*. 1982;65(6):1472-1473.

14) Gibson GR, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;14(8):491-501.

15) Del Fabro S, et al. Microbiota-independent immunological effects of non-digestible oligosaccharides in the context of inflammatory bowel disease. *Proc Nutr Soc*. 2020;1-11.

16) Espinosa RM, et al. Efforts to emulate human milk oligosaccharides. *Br J Nutr*. 2007;98(5):574-579.

17) Verreman-Wauters, et al. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *JPGN*. 2011;52(6):763-771.



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REFERENCES

18) Abrams S, Berger EM. Is it time to revise the current nutrient requirements for infant formulas principally established in 1980? *Adv Nutr*. 2023; 15(5):567-577.

19) Gutierrez-Castrellon P, et al. Immune response to nucleotide-supplemented infant formulae: systematic review and meta-analysis. *Br J Nutr*. 2007;98(Suppl):S64-S67.

20) Wang L, et al. Effects of dietary nucleotide supplementation on growth in infants: a meta-analysis of randomized controlled trials. *Eur J Nutr*. 2019;58(3):1213-1221.

21) Donovan SM. Human milk proteins: composition and physiological significance. *Nestle Nutr Inst Workshop Series*. 2019;90:93-101.

22) Meyer, et al. Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children. *BMC Gastroenterol*. 2015;15:137.

23) Heyman MB, Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. *Pediatrics*. 2006;118(3):1279-1286.

24) Heine RG, et al. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children – common misconceptions revisited. *World Allergy Organ J*. 2017;10(1):41.

25) Szallowski, et al. Protein and carbohydrate content of infant formula purchased in the United States. *Clin Exp Allergy*. 2022;52(11):1291-1301.

26) Francavilla, et al. Effect of lactose on gut microbiota and metabolome of infants with cow milk allergy. *Pediatr Allergy Immunol*. 2012;23(5):420-427.


27) Warren CM, et al. The US population-level burden of cow's milk allergy. *World Allergy Organ J*. 2021;15(4):100644.

28) Maslin, et al. Reliability of hypoallergenic formula for cow milk allergy and healthcare professional recommendation. *Pediatr Allergy Immunol*. 2018;29(8):857-862.

29) Arslanoglu, et al. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr*. 2007;137(11):2430-2434.

30) Arslanoglu, et al. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr*. 2008;138(6):1091-1095.

31) Arslanoglu, et al. Early neutral prebiotic oligosaccharide supplementation reduces the incidence of some allergic manifestations in the first 5 years of life. *J Biol Regul Homeost Agents*. 2013;26(3 Suppl):49-59.



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