Early Life Feeding Choices and the Allergic March

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Presented by
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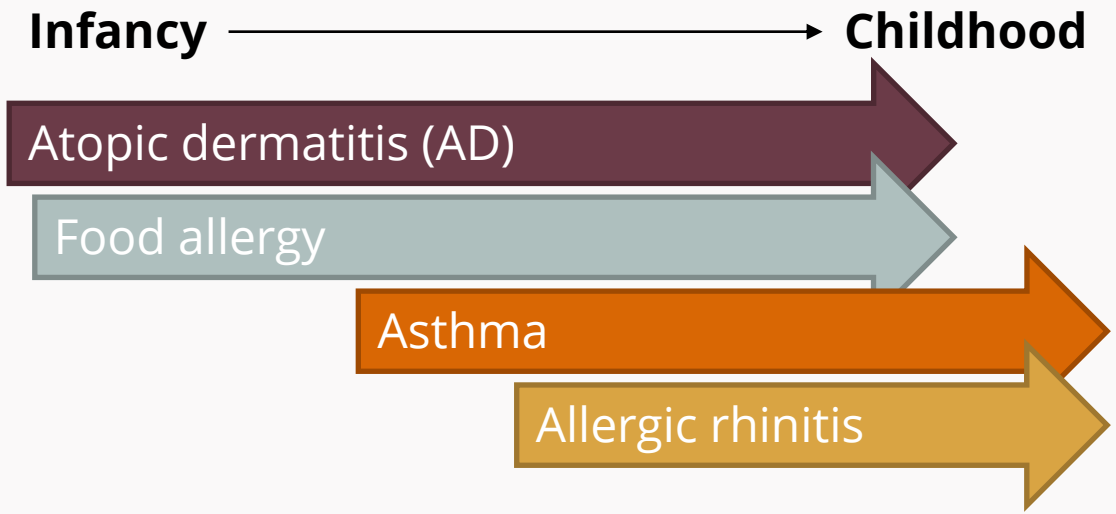
Learning Objectives

- Describe the recent evidence on strategies for allergy risk reduction, management, and tolerance induction
- Outline the long-term impacts to food allergy, highlighting the psychological, psychosocial, and financial disease burden for patients and their families
- Differentiate the appropriate application of various feeding options, including a variety of infant formulas and probiotics, to reduce the risk of allergic development and/or manage existing allergies

Overview of the Atopic March

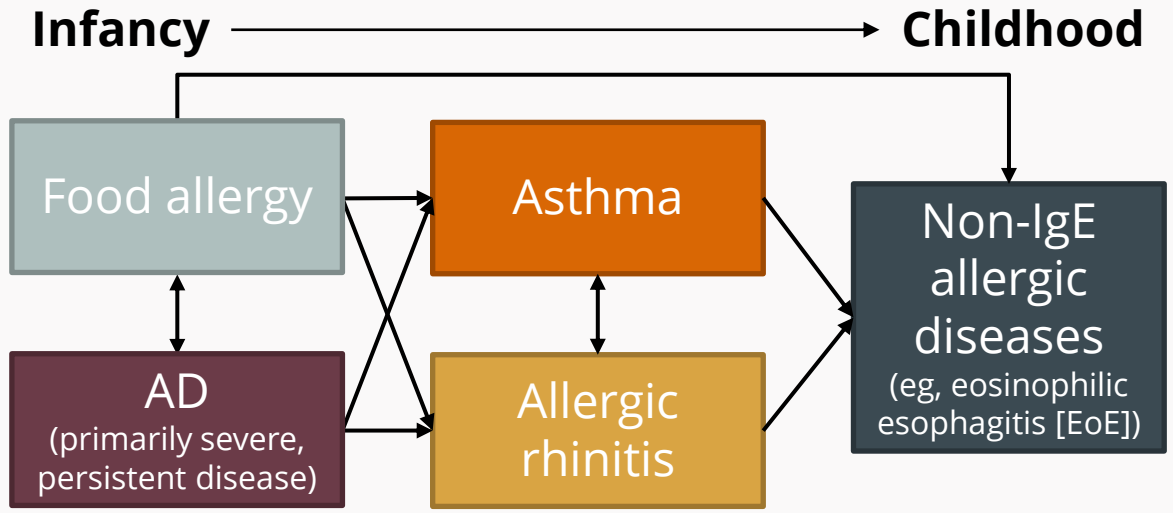
Epidemiology of the Allergic March[1]

Conventional Definition of Allergic March



AD as an "entry point" to allergic disease, followed by development of gastrointestinal and then respiratory allergic comorbidities

Current Concept of Allergic March

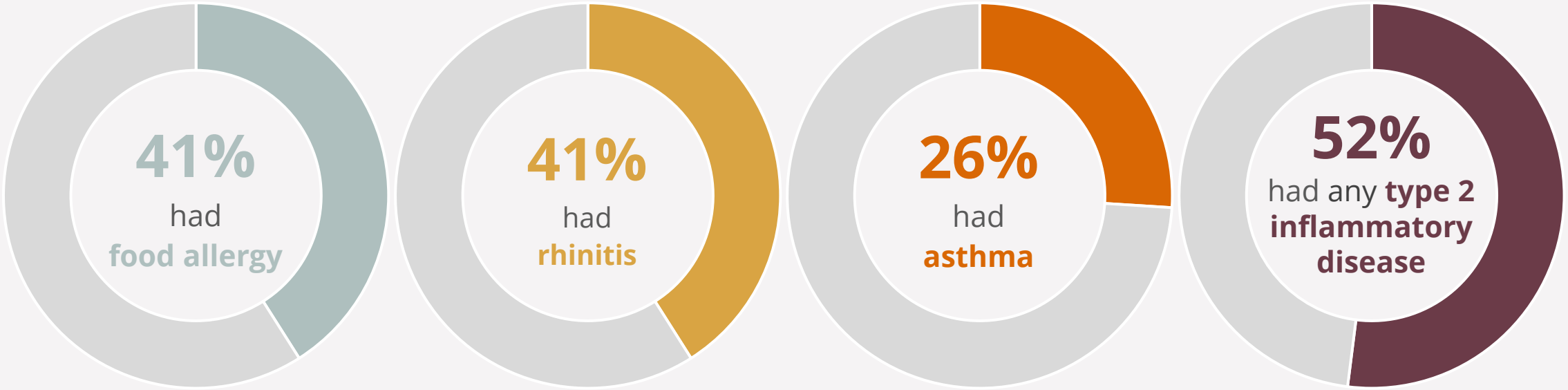


Early occurrence of AD with subsequent development of allergen-induced type 2 inflammatory conditions

1. Paller AS et al. *J Allergy Clin Immunol*. 2019;143(1):46-55.

Epidemiologic Data Supporting the Atopic March

In systematic reviews and meta-analyses of people with AD...[1-4]



1. Christensen MO et al. *J Eur Acad Dermatol Venereol.* 2023;37(5):984-1003. **2.** Ravnborg N et al. *J Am Acad Dermatol.* 2021;84(2):471-478.
3. Knudgaard MH et al. *Ann Allergy Asthma Immunol.* 2021;127(1):49-56.e1. **4.** Paller AS et al. *J Am Acad Dermatol.* 2022;86(4):758-765.

EoE as a Late Allergic March Manifestation

AD and IgE-mediated food allergy are strongly associated with risk for EoE diagnosis.[1]

Risk for Subsequent Diagnosis Following Primary Atopic Diagnosis

	Secondary diagnosis				
Primary diagnosis	**AD**	**IgE-mediated FA**	**Asthma**	**EoE**	**AR**
AD	-	2.5	1.5	3.2	1.9
IgE-mediated FA	-	-	1.5	9.1	1.7
Asthma	-	-	-	1.9	1.7
EoE	-	-	-	-	2.5
AR	-	-	-	2.8	-

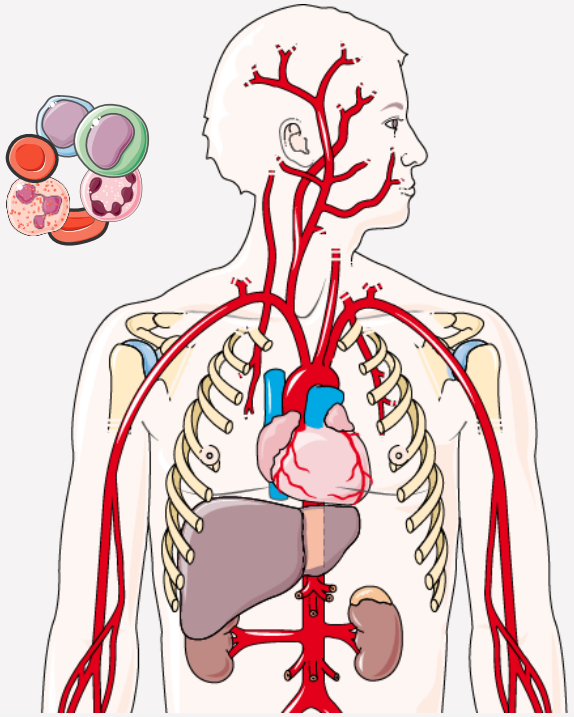
AR, allergic rhinitis; FA, food allergy

1. Hill DA et al. *J Allergy Clin Immunol Pract.* 2018;6(5):1528-1533.

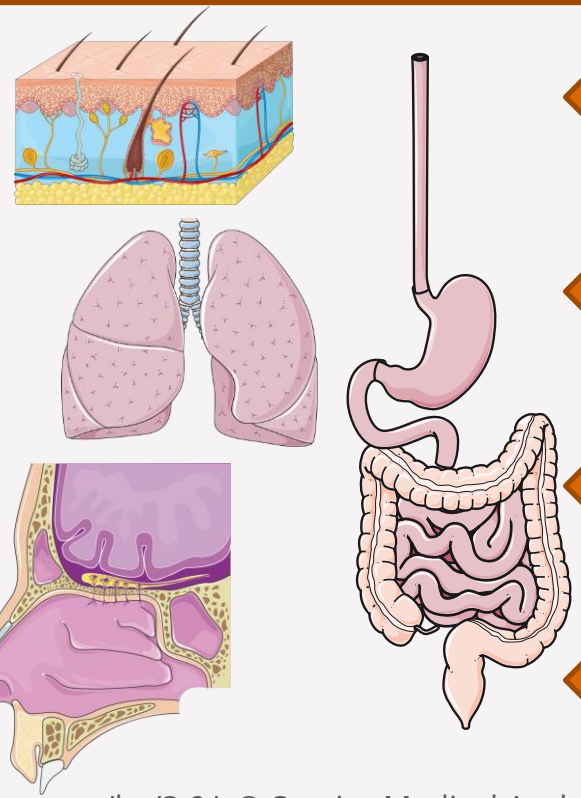
Allergic March Contributing Factors[1]

Systemic factors

- Genomics
- Epigenetics
- Type 2 inflammation



Tissue-specific factors



- Local immune response
- Barrier dysfunction
- Dysbiosis
- Environmental stressors

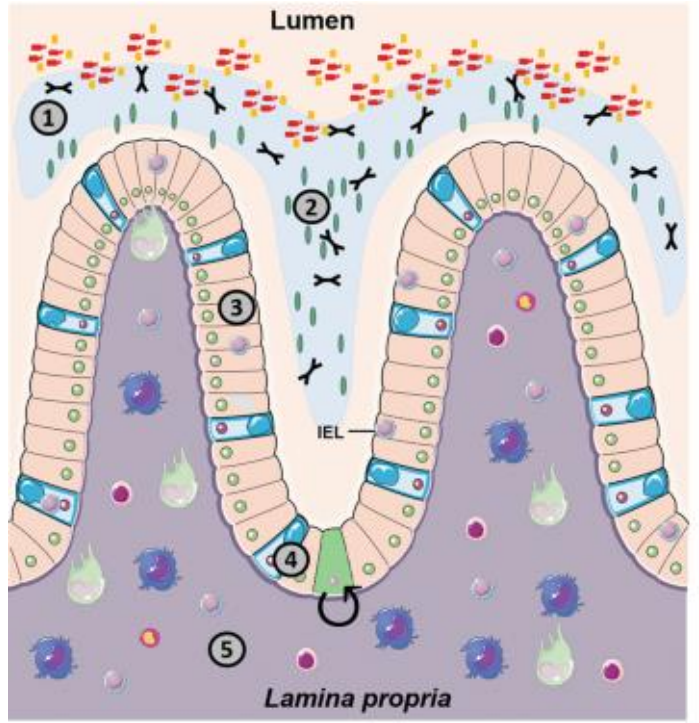
1. Paller AS et al. *J Allergy Clin Immunol*. 2019;143(1):46-55.

The GI System and the Gut Microbiome

- Semipermeable barrier that allows absorption of nutrients and protects against pathogens and antigens[1]
- Functions dependent on healthy cellular and microbial architecture[1]
- Microbiome disruption (ie, dysbiosis) can…[1,2]
  - Trigger inflammation
  - Loosen epithelial tight junctions

Components of the GI Barrier[2]

1. Mucus and commensal microbiota
2. Biochemical
3. Cellular
4. IESCs
5. Immune cells



IEC, intestinal epithelial cell; IESC, intestinal epithelial stem cell
Image used under Creative Commons license (CC BY 4.0). https://creativecommons.org/licenses/by/4.0/. Thoo L et al. *Cell Death Dis*. 2019;10(11):849. https://www.nature.com/articles/s41419-019-2086-z.

1. Farré R et al. *Nutrients*. 2020;12(4):1185. **2.** Thoo L et al. *Cell Death Dis*. 2019;10(11):849.

Interaction Between the Gut Microbiome, Immune Signaling, and Allergic March

~70% Proportion of immune cells located within the GI mucosa.[1]

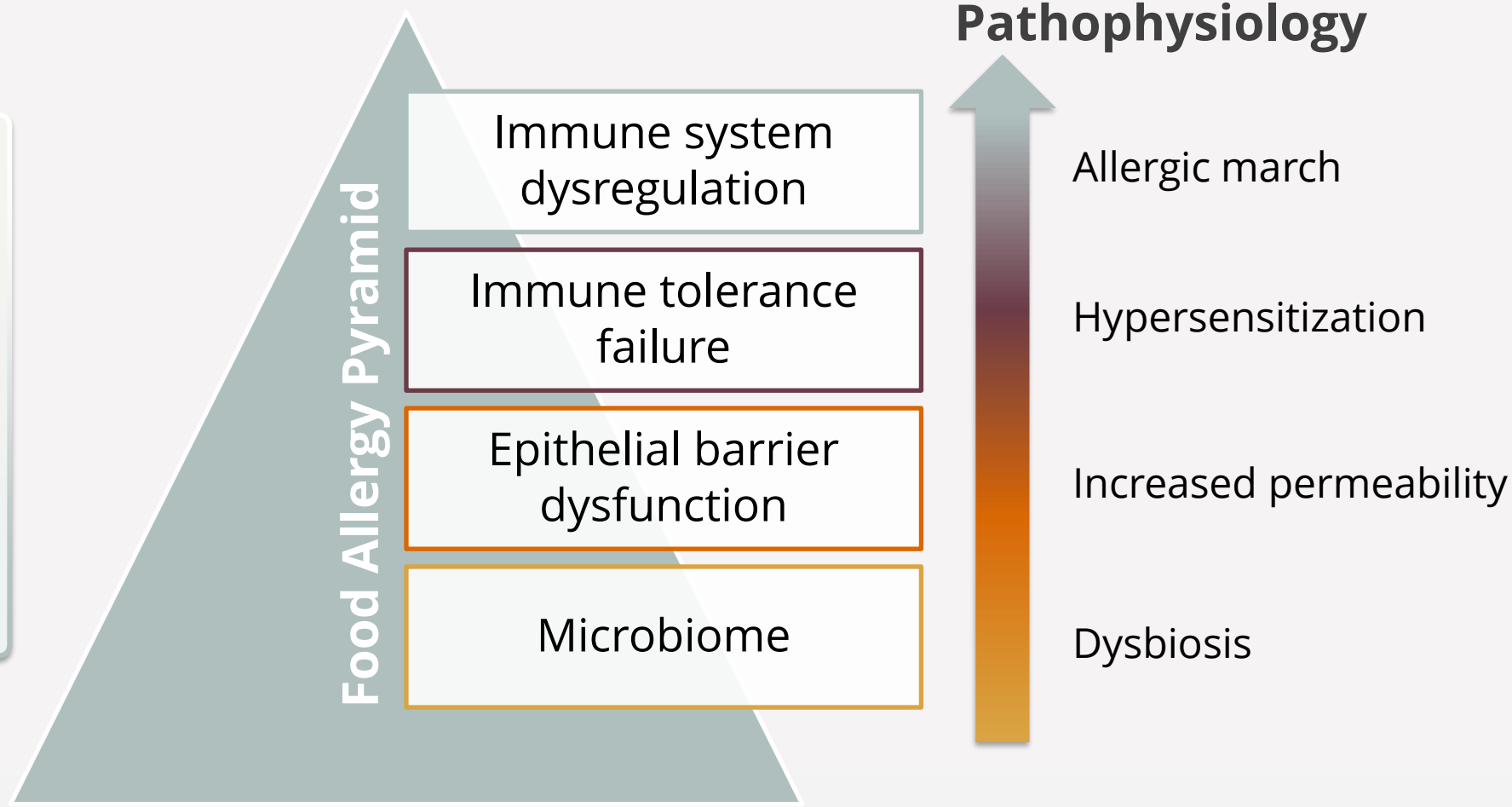
The gut microbiome and immune system have complex and interwoven signaling pathways, with the microbiome playing a role in…[2,3]

- Protection from pathogenic infections
- Tolerance **or** sensitization to potential autoimmune and allergic signals
- Production of biochemical products that can influence immune response
- Maintenance of tight epithelial junctions

1. Wiertsema SP et al. *Nutrients*. 2021;13(3):886. **2.** Farré R et al. *Nutrients*. 2020;12(4):1185. **3.** Thoo L et al. *Cell Death Dis*. 2019;10(11):849.

The Microbiome and the Allergic March[1]

Gut dysbiosis has been identified as a potentially modifiable foundational event in the development of food allergy.



1. Berni Canani R et al. *Front Immunol.* 2019;10:191.

Long-Term Effects of Food Allergy

Prevalence of Food Allergy in US Children

5.8%

prevalence of **diagnosed** food allergy in US children[1]

7.6%

prevalence of **parent-reported** food allergy in US children[2]

- Diagnosed food allergy prevalence increases with older age in children and declines in adulthood:[1,3]
  - **4.4%** of 0- to 5-year-olds
  - **5.8%** of 6- to 11-year-olds
  - **7.1%** of 12- to 17-year-olds
  - **6.2%** of adults
- Among children with a parent-reported food allergy:[2]
  - **42%** are considered severe
  - **40%** are allergic to multiple foods

1. Zablotsky B et al. *NCHS Data Brief*. 2023;(459):1-8. **2.** Gupta RS et al. *Pediatrics*. 2018;142(6):e20181235. **3.** Ng AE, Boersma P. *NCHS Data Brief*. 2023;(460):1-8.

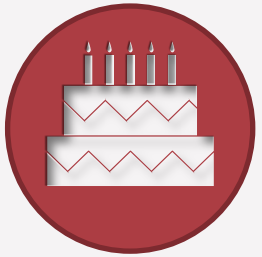
Burden of Food Allergy Among Patients and Families

Health effects: FA-related emergency department visits[1]

- 1 in 5 children in the last year
- 2 in 5 children over their lifetimes

Emotional effects: parental thoughts about FA[2]

- 4 in 5 parents report it's always in the back of their minds
- 3 in 4 parents report fear or anxiety



Social effects: challenges for parents navigating social events[2]

- Eating out (74%)
- Birthday parties (69%)
- Entertainment activities (59%)

1. Gupta RS et al. *Pediatrics*. 2018;142(6):e20181235. **2.** Asthma and Allergy Foundation of America (AAFA). My life with food allergy parent survey report. 2019. https://www.aafa.org/wp-content/uploads/2022/08/aafa-my-life-with-food-allergy-parent-survey-report.pdf.

Financial Burden of Food Allergy[1]

~$3300 Annual out-of-pocket expenses for families of children with food allergies.

- **Out-of-pocket expenses** have been attributed to:
  - Specialized diet ($2823)
  - Epinephrine ($255)
  - Antihistamines ($191)

- **1 in 5** parents and caregivers report indirect financial effects (eg, need for additional childcare, ability to work outside the home)

1. Bilaver L et al. *J Allergy Clin Immunol.* 2023;151(2):AB186.

The Allergic March and Food Allergy: Key Takeaways

- The gut microbiome interacts with the immune system, playing a role in the development of immune tolerance.
- Gut dysbiosis can lead to dysregulation of the immune system, promoting immune hypersensitivity and the development of type 2 inflammation.
- Food allergy is an early component of the atopic march with a considerable public health burden.

Nutrition-Related Strategies for Preventing Food Allergy

Breast Milk & Formula

Potential Protective Factors Against the Progression of the Allergic March[1]

Gut Barrier	Skin Barrier	Respiratory Tract Barrier
• Breastfeeding • Microbial exposure • Special formulas • Probiotics • Healthy diet • Avoidance of antibiotics and antiseptics	• Breastfeeding • Microbial exposure • Probiotics • Emollients • Avoidance of environmental allergens	• Breastfeeding • Microbial exposure • Probiotics • Avoidance of pollution and cigarette smoke

Potential nutritional factors that may help to mitigate the allergic march

1. Carucci L et al. *Front Pediatr*. 2020;8:440.

Human Breast Milk and Atopic Disease Risk

Although breast milk indisputably provides **optimal nutrition** through the first 6 months of life, its role in **allergy prevention is unclear**.[1]

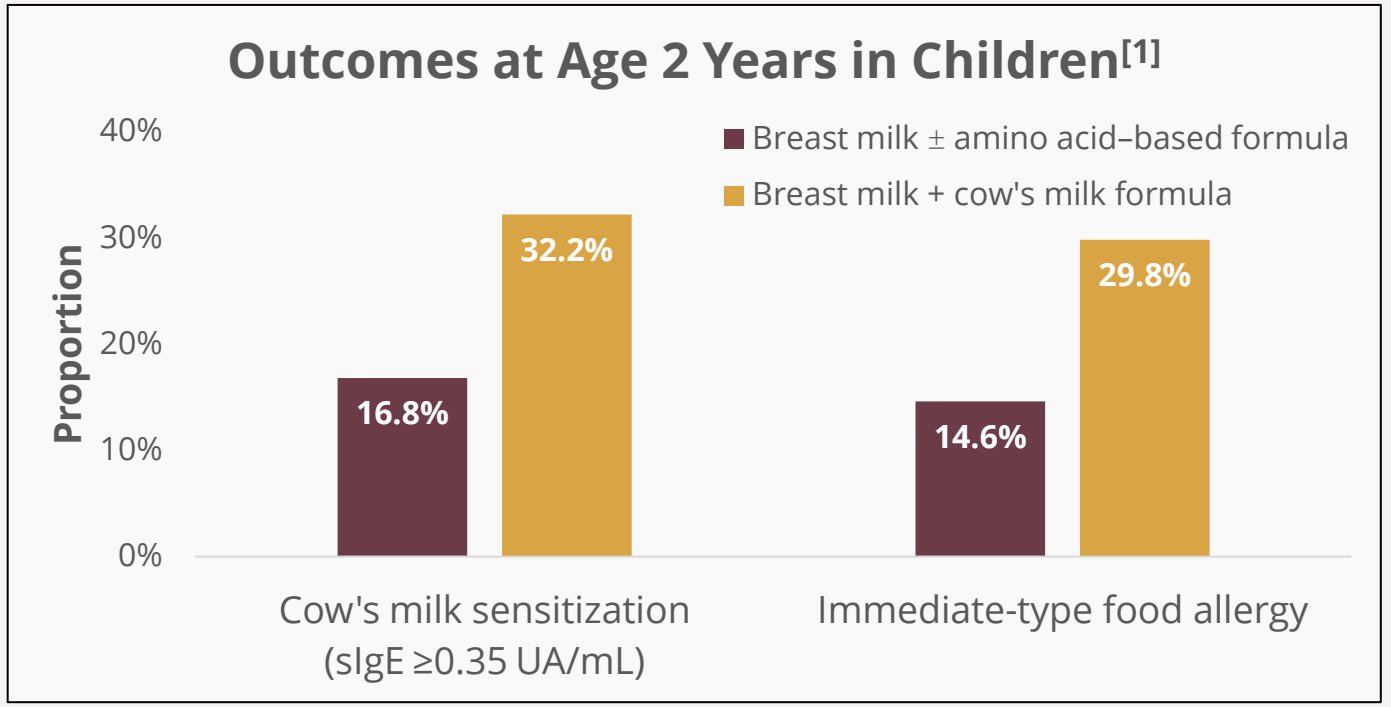
- Benefits of breast milk include lower risk of **infection**, **obesity**, and certain **autoimmune disorders**[1]
- Available data show **variable** effect of breast milk on allergic disease:[1,2]
  - Exclusive early breastfeeding **reduces** atopic dermatitis risk
  - Longer duration may **reduce** early childhood wheezing/asthma
  - **Inconclusive association** with risk for IgE-mediated food allergy

1. Nuzzi G et al. *Children (Basel).* 2021;8(5):330. **2.** Patel R et al. *Int J Epidemiol.* 2014;43(3):679-690.

Cow's Milk Formula Exposure and Risk for Cow's Milk Allergy: Timing

ABC Randomized Controlled Trial[1]

- Compared breastfeeding with or without amino acid–based formula (n = 156) to breastfeeding with cow's milk formula (n = 156) in the **first 3 days** of life
- Primary endpoint of sensitization to cow's milk at age 2 years



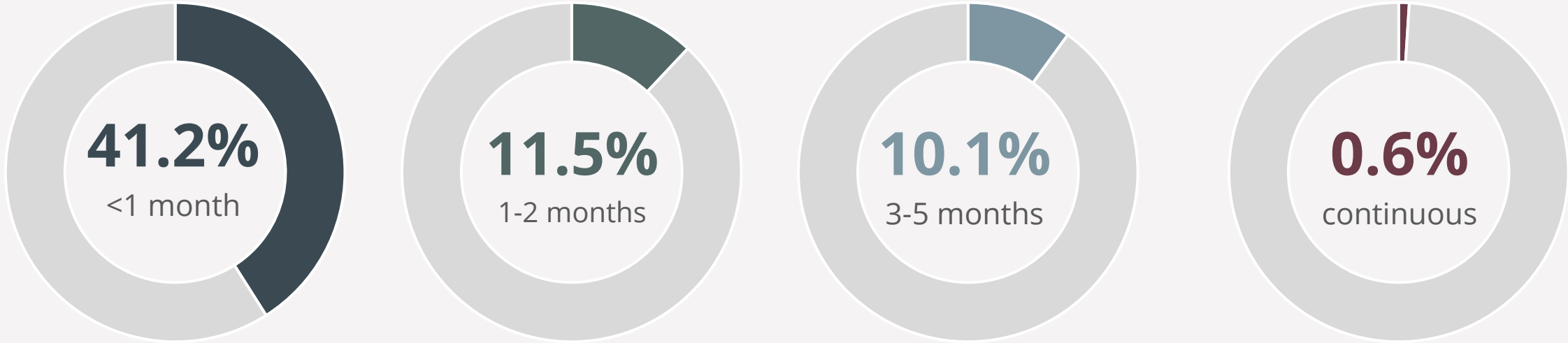
In addition to increasing sensitization, cow's milk formula in the first 3 days of life also increased the risk of asthma or recurrent wheeze (17.9% vs 9.9%).[2]

1. Urashima M et al. *JAMA Pediatr.* 2019;173(12):1137-1145. **2.** Tachimoto H et al. *JAMA Netw Open.* 2020;3(10):e2018534.

Cow's Milk Formula Exposure and Risk for Cow's Milk Allergy: Continuity[a],[1]

In a cohort of 431 infants who received cow's milk formula in the first 3 days of life, early discontinuation increased the risk of cow's milk allergy at 6 months.

Discontinuation of cow's milk formula at <1 to 5 months



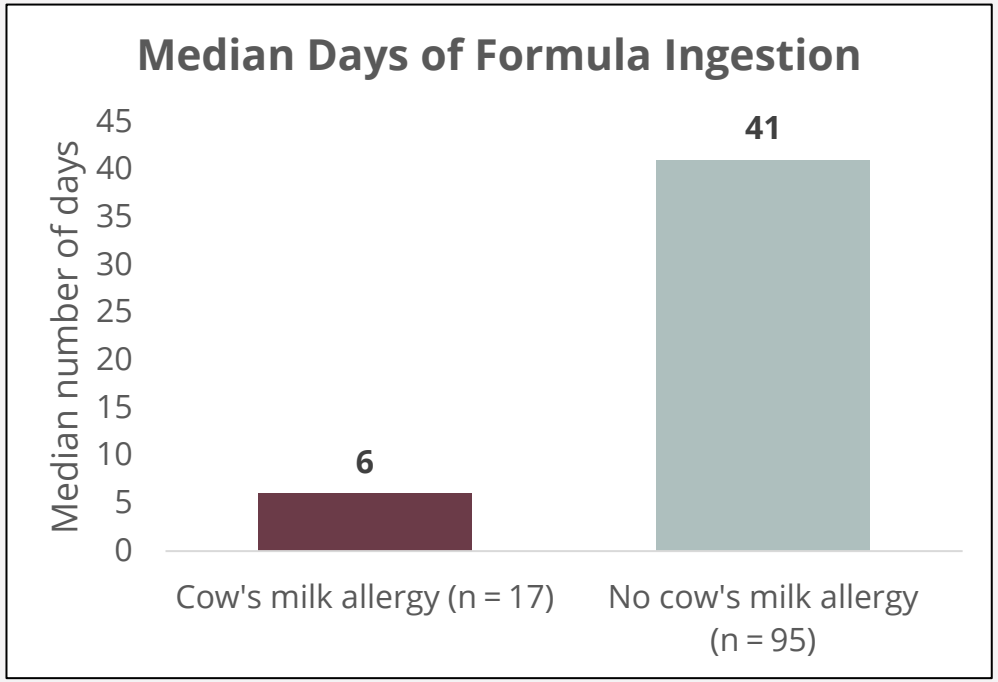
Continuous feeding

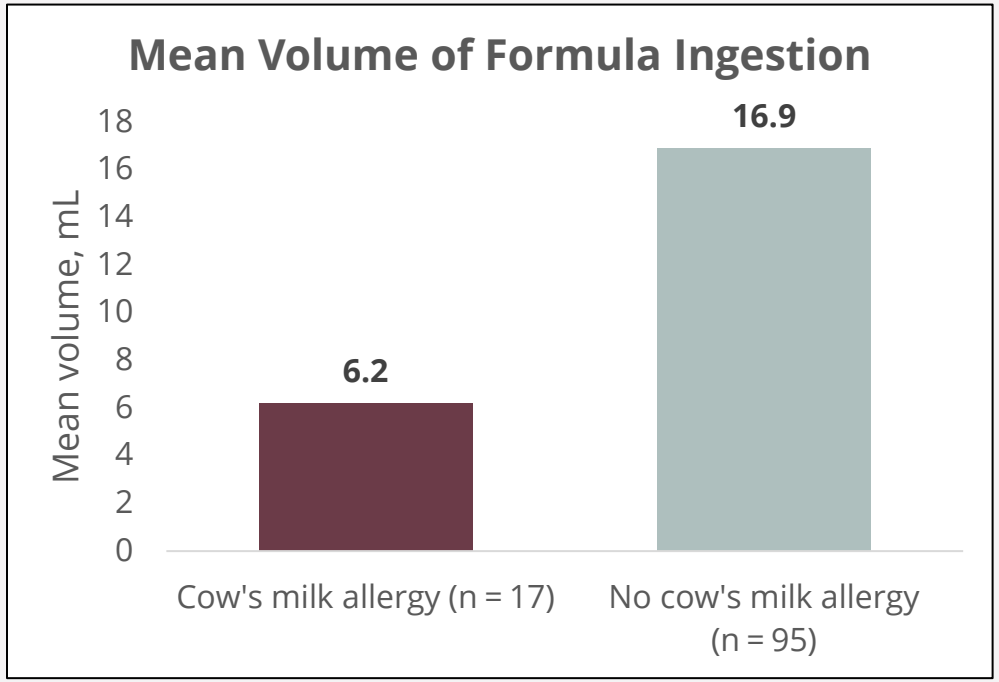
a. Data are from infants enrolled in the SPADE study, who were randomized to receive breast milk and cow's milk formula (≥10 mL/d) from 1 to 3 months of age (n = 243) or breast milk with or without soy formula from 1 to 3 months of age (n = 249). From 3 to 6 months of age, infants received breast milk with or without cow's milk formula.[2]

1. Sakihara T et al. *J Allergy Clin Immunol Pract.* 2022;10(1):172-179. **2.** Sakihara T et al. *J Allergy Clin Immunol.* 2021;147(1):224-232.e8

Cow's Milk Formula Exposure and Risk for Cow's Milk Allergy: Frequency and Quantity[1]

In a cohort of 112 infants who discontinued cow's milk formula after the first 3 days of life, frequency and quantity of formula feeds were associated with risk for cow's milk allergy.





1. Sakihara T et al. *J Allergy Clin Immunol Pract.* 2022;10(1):172-179.

Summary of Evidence for Timing and Continuity of Cow's Milk Formula in Infants[1]

Odds of Cow's Milk Allergy According to Formula Feeding in First Days of Life and Age at Formula Introduction

		Age at Introduction		
		<2 weeks (n = 416)	**2 weeks to <6 months** (n = 494)	**≥6 months** (n = 388)
Formula given in hospital after delivery	**Yes**	1.0 (reference)	4.0×	4.3×
	No	5.1×	2.6×	5.0×

Regardless of timing of formula introduction, emphasis should be placed on the supplementary role of formula compared with breast milk.

1. Switkowski KM et al. *J Allergy Clin Immunol Pract.* 2022;10(10):2713-2721.e2.

Clinical Decision Making for Formula Choice

In healthy infants, there is no clear role for specialized formula for the prevention of food allergy.[1-3]

- **Standard cow's milk formula** is the preferred choice for most healthy infants[1-3]

- Experts recommend **against** the use of the following formulas for allergy prevention:[1,2]
  - Soy formula
  - Goat's milk formula
  - Formula made from other mammalian milk

1. Kopp MV et al. *Allergol Select.* 2022;6:61-97. **2.** Halken S et al. *Pediatr Allergy Immunol*. 2021;32(5):843-858. **3.** Greer FR et al. *Pediatrics*. 2019;143(4):e20190281.

Nutrition-Related Strategies for Preventing Food Allergy

Microbiome Support

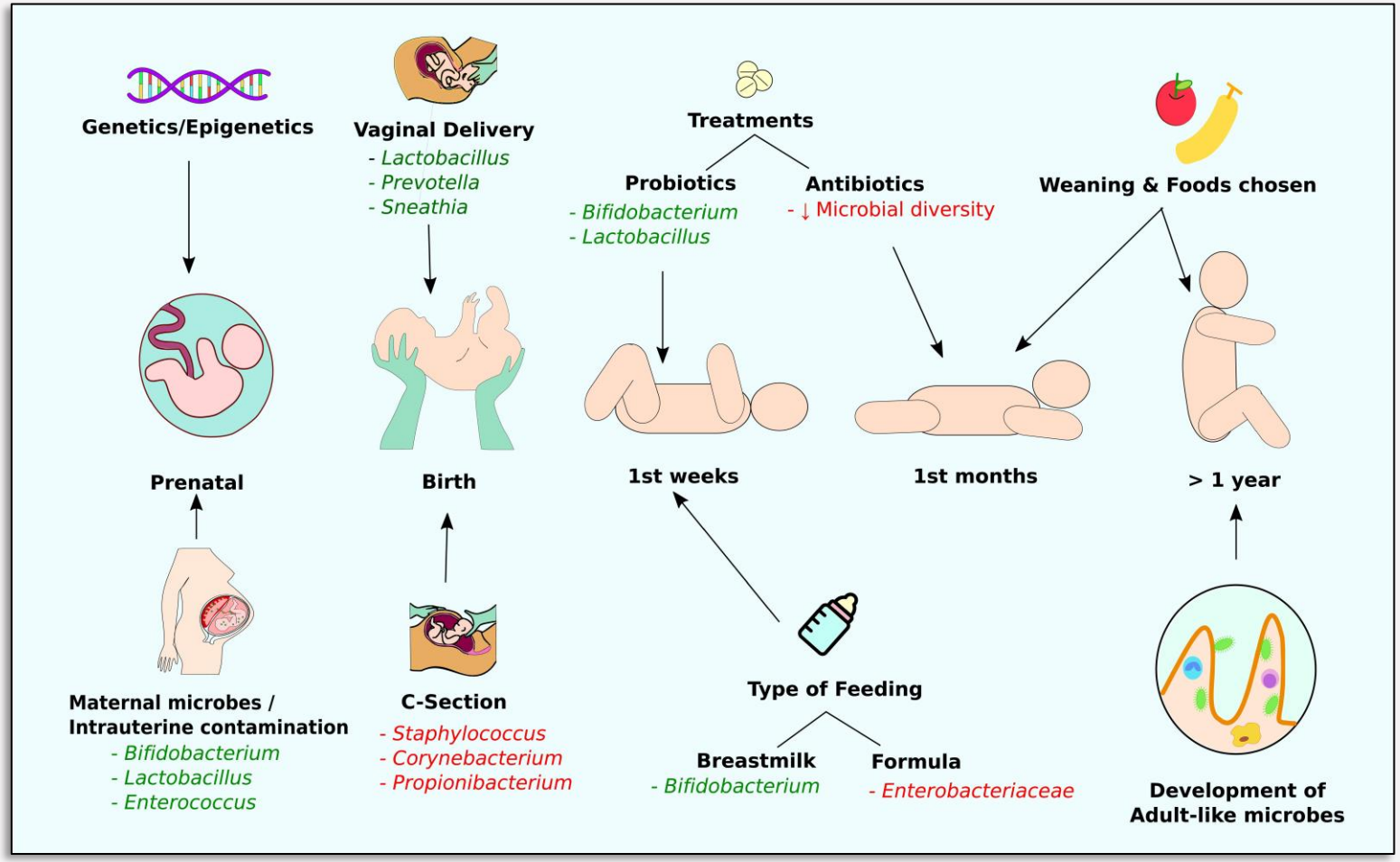
Window of Opportunity for Microbiome Modification[1]

- The **first 1000 days of life** are associated with rapid development and maturation of metabolic, endocrine, neural, and immune pathways
  - Represent a “window of opportunity” for microbiome development

- During this period, the microbiome can be affected by several factors:
  - **Prenatal:** maternal microbiome (GI and vaginal)
  - **Perinatal:** mode of delivery
  - **Postnatal:** antibiotic use, diet, environmental exposures, types and timing of complementary foods, probiotic use

1. Robertson RC et al. *Trends Microbiol.* 2019;27(2):131-147.

External Factors and Development of the Microbiome[1]

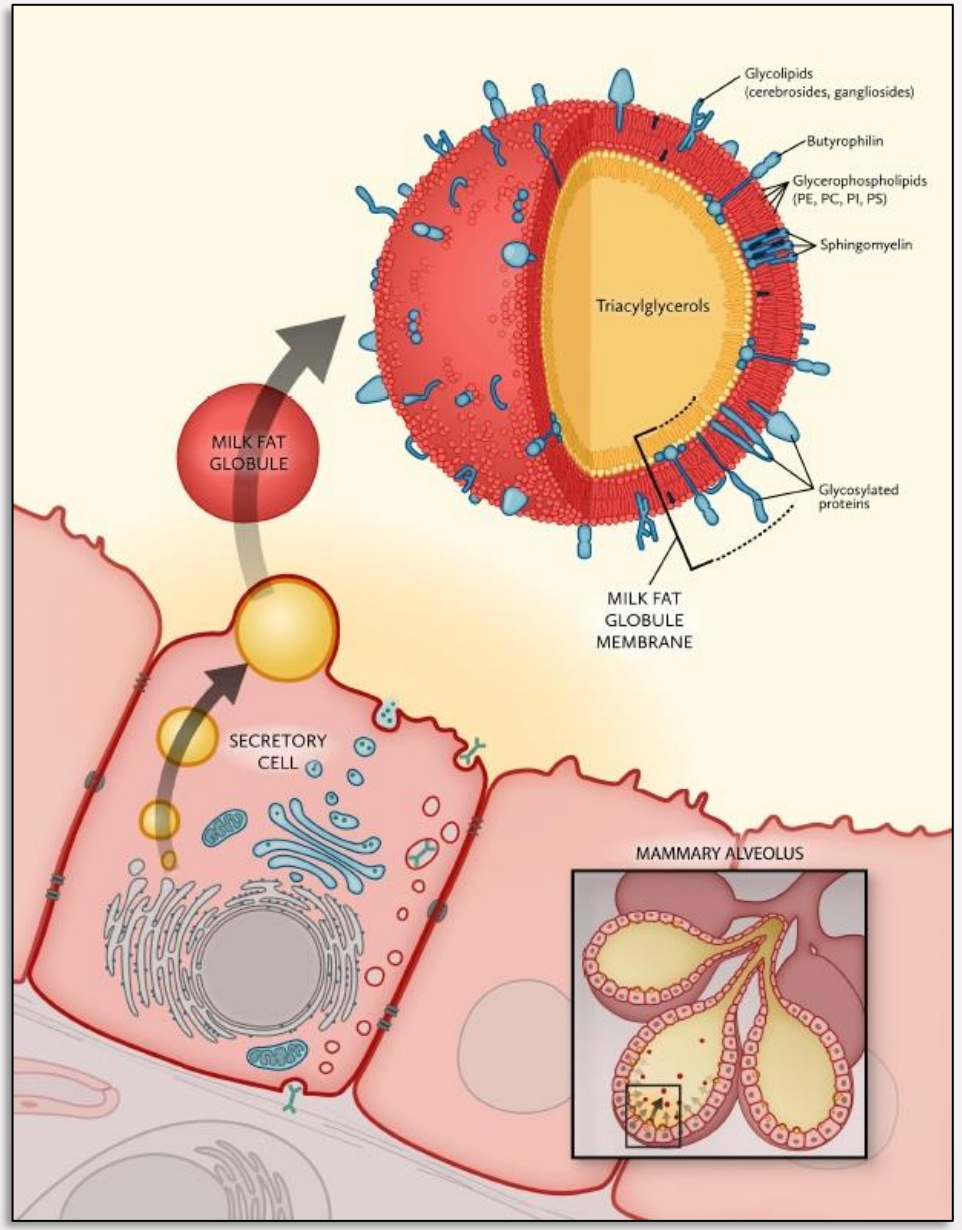


As the microbiome matures, *Bifidobacteria* and *Lactobacilli* are replaced by a more diverse adult-like microbiome, which facilitates digestion of complementary foods.

1. Eshraghi RS et al. *Front Cell Neurosci.* 2018;12:256.

Milk Fat Globule Membranes[1]

- Milk fat globule membranes (MFGMs) are lipoprotein structures that surround fat globules in milk
  - Important for GI, immune, and cognitive developmental health
- MFGMs interact with and adhere to *Lactobacilli* and other infant microbiota
  - Codelivery of MFGMs with *Lactobacilli* may serve to protect probiotics during transit through the harsh GI environment



1. Kosmerl E et al. *Microorganisms*. 2021;9(2):341.

Potential Impact of MFGM Supplementation on the Brain-Immune-Gut Axis and the Microbiome[1]

Brain

- Improved cognitive scores
- Improved developmental and attention scores
- Improved social and emotional behavior scores
- Improved short-term memory
- Fewer behavioral and affective disorders

Immune

- Reduced risk of otitis media
- Fewer upper respiratory infection, cough, and diarrhea cases
- Lower levels of IL-2 and IL-17A
- Cytokine profile more similar to breastfed infants

Gut

- Fewer incidences of diarrhea
- Fewer incidences of bloody diarrhea

Microbiome

- Improved gut microbial activity and function
- Lower prevalence of otitis media–related bacteria

1. Mohamed HJJ et al. *JGH Open*. 2022;6(7):454-461.

Nutrition-Related Strategies for Preventing Food Allergy

Complementary Foods

Changes to the Microbiome After Introduction of Complementary Foods[1]

- Once complementary foods are introduced, the infant microbiome undergoes **rapid structural** and **functional** changes
  - Increases in diversity
  - Matures into more adult-like microbiome

- The microbiome becomes better equipped to extract energy from a diet containing complementary foods
  - Compared with infant diets, adult diets are **richer in carbohydrates such as fiber**
  - Bacterial species capable of degrading glycans, mucin, and complex carbohydrates

1. Homann CM et al. *Nutrients*. 2021;13(8):2639.

Early Allergen Exposure Through Complementary Foods

Based on the results of the LEAP and EAT studies, guidelines encourage early introduction of allergenic foods when developmentally ready, between 4 and 6 months.[1-3]

- **2017 NIAID guidelines** for peanut introduction vary based on risk for food allergy[2]
  - For most infants (no or mild AD and no egg allergy), peanut protein should be introduced when developmentally ready and according to cultural practices
- **2021 North American consensus guidelines** recommend introduction of peanut around 4-6 months and egg around 6 months as part of a diverse diet[3]
  - Introduction of other potentially allergenic foods should not be delayed

NIAID, National Institute of Allergy and Infectious Diseases

1. Du Toit G et al. *N Engl J Med*. 2015;372(9):803-813. **2.** Togias A et al. *J Allergy Clin Immunol.* 2017;139(1):29-44. **3.** Fleischer DM et al. *J Allergy Clin Immunol Pract.* 2021;9(1):22-43.e4.

Increasing Evidence for Earlier Introduction of Multiple Potentially Allergenic Foods

In the LEAP and EAT intention-to-treat analyses, the strongest evidence for early introduction was for peanut foods.[1]

Per-protocol analyses of the EAT study indicate potential benefits for other allergenic foods.[2]

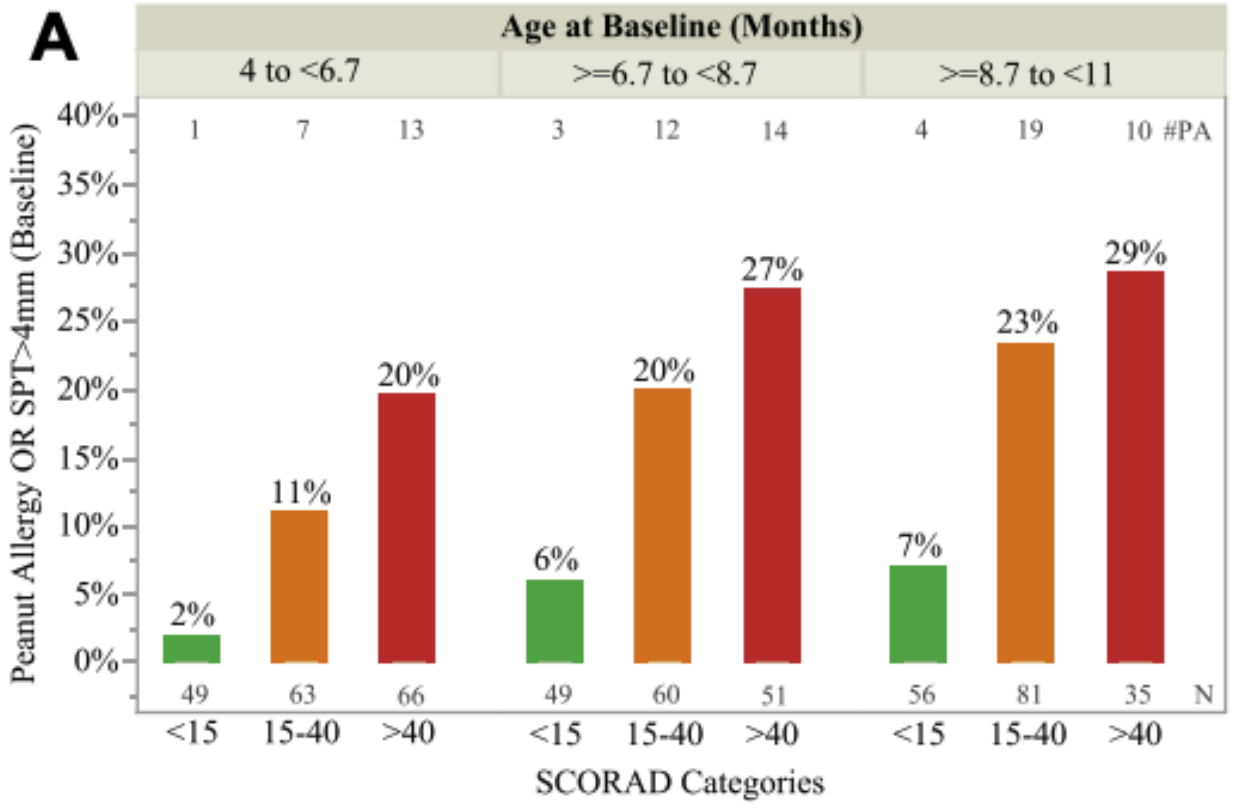
Meta-Analysis of Earlier vs Later Introduction of Allergenic Foods[3]

Complementary food	Number of studies	Number of individuals	Effect on allergy risk	Certainty of evidence
Multiple allergenic foods	4	3295	↓51%	Moderate
Egg	9	4811	↓40%	High
Peanut	4	3796	↓69%	High
Cow's milk	6	3900	↓16%	Very low

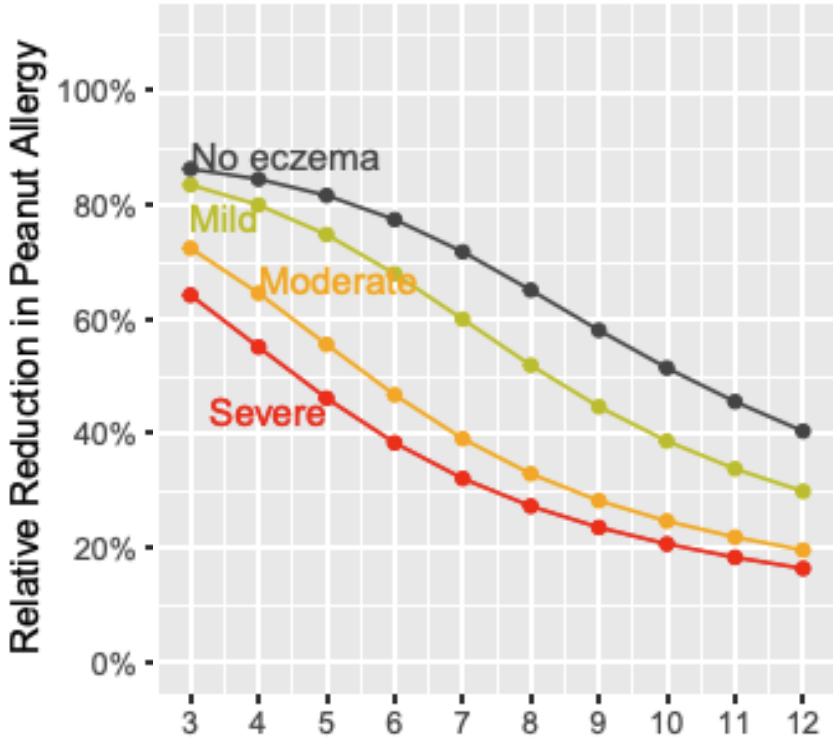
1. Du Toit G et al. *N Engl J Med*. 2015;372(9):803-813. **2.** Perkin MR et al. *N Engl J Med*. 2016;374(18):1733-1743. **3.** Scarpone R et al. *JAMA Pediatr.* 2023;177(5):489-497.

LEAP and EAT Modeling Study: Potential "Window of Opportunity" for Allergy Prevention[1]

Increasing Likelihood of Baseline Peanut Sensitization With Older Age and More Severe AD



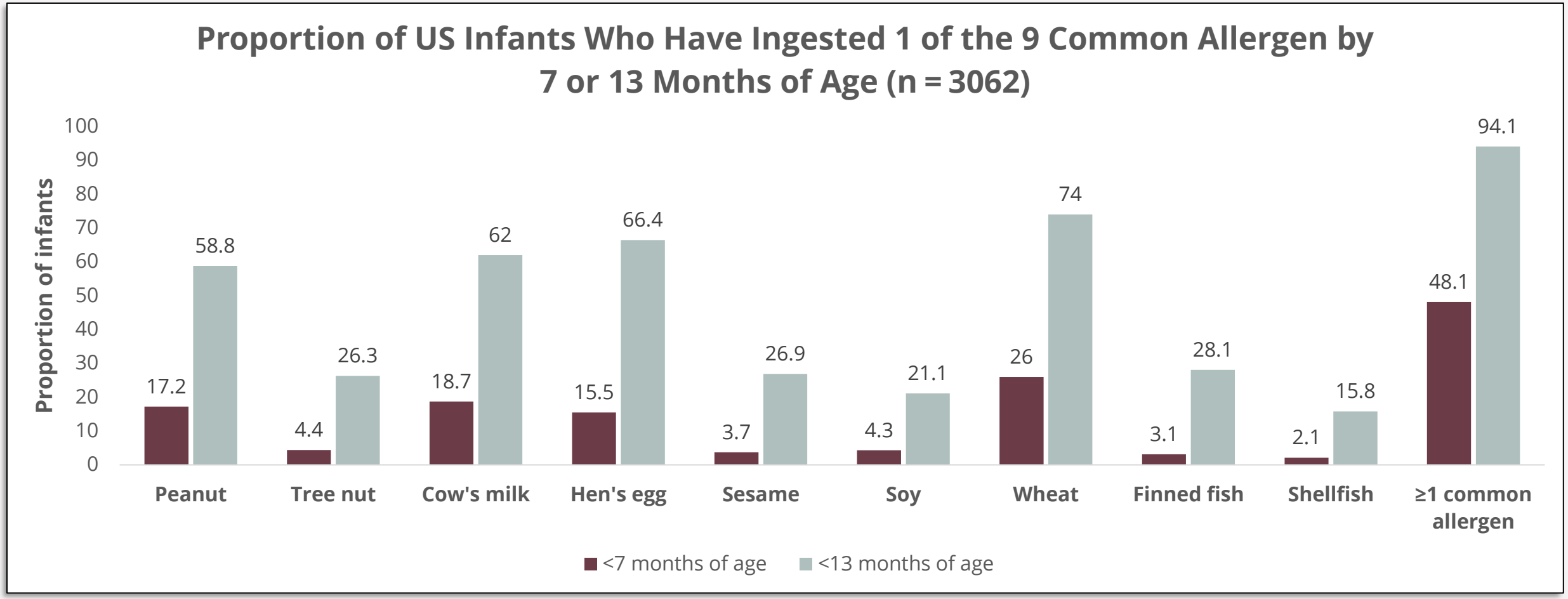
Relatively Narrow Window of Opportunity for Early Peanut Introduction by AD Severity



SCORAD, SCORing Atopic Dermatitis; SPT, skin prick test

1. Roberts G et al. *J Allergy Clin Immunol.* 2023;151(5):1329-1336. Figure 1a and 3c used under terms of a Creative Commons licence (http://creativecommons.org/licenses/by/4.0)

Low Rate of Uptake of Early Allergen Introduction in the United States (2021 Survey)[1]



1. Venter C et al. *Pediatr Allergy Immunol.* 2022;33(12):e13896.

Challenges of Early Allergen Introduction Among Clinicians

- In a survey of 1781 pediatricians, only **28.9%** of respondents reported full implementation of NIAID guidelines[1]

- Several barriers to early allergen introduction have been identified by pediatricians:[1]
  - Trouble understanding or correctly applying guidelines (33%)
  - Conducting supervised peanut feeding (32%)
  - Lack of clinic time (29%)
  - Conducting specific IgE antibody testing (15%)
  - Concerns about allergy reactions (14%)

In a survey of primary care providers (PCPs), **40% of respondents** believed that the youngest age for peanut introduction was 1 year.[2]

1. Gupta RS et al. *JAMA Netw Open.* 2020;3(7):e2010511. **2.** Alvarez A et al. *Allergy Asthma Proc.* 2020;41(3):167-171.

Addressing Myths and Misperceptions Among Parents

Parental concerns are commonly cited as barriers to early introduction of allergens and should be addressed by clinicians beginning at 2- and 4-month well-child visits.[1]

Key counseling points:

- Early introduction of allergenic foods as part of a diverse diet should begin at 4 to 6 months of age
  - » Begin with peanut protein and add other potential allergens once peanut is tolerated
- Severe allergic reactions are rare with the first ingestion of a food
- Not all patients with positive IgE tests will have an allergic reaction to foods—prompt referral to an allergist is recommended

1. Anagnostou A. *Children (Basel).* 2021;8(6):497.

Key Takeaways

- Nutrition-related strategies for the prevention of food allergy should begin prior to 6 months of age.
- Early and continuous feeding of cow's milk formula may reduce the risk of cow's milk allergy (but should not replace breastfeeding).
- MFGMs and *Lactobacillus* GG probiotics may promote brain, immune, and gut health early in infancy.

Food Allergy Management: Evidence-Based Strategies

Allergen Avoidance and Preparedness for Emergency Treatment[1]

- Primary approach for food allergy management involves **allergen avoidance** and **emergency treatment**
  - All patients should receive (and carry) a prescription for an epinephrine autoinjector

- Best practices for elimination diets
  - Limit food combinations with allergenic potential
  - Ensure adequate and optimal nutrition without deficiencies in macro- or micronutrients
  - Counsel on food label literacy
  - Consider dietitian referral, particularly for patients with multiple food allergies
  - Avoid unnecessary elimination diets

1. Fleischer DM et al. *J Allergy Clin Immunol Pract.* 2021;9(1):22-43.e4.

Hypoallergenic Formulas for Cow's Milk Allergy[1],[2]

Increasing hydrolysis level is associated with decreasing allergenicity

Intact cow's milk protein

Partial hydrolysis

Extensive hydrolysis

Amino acids

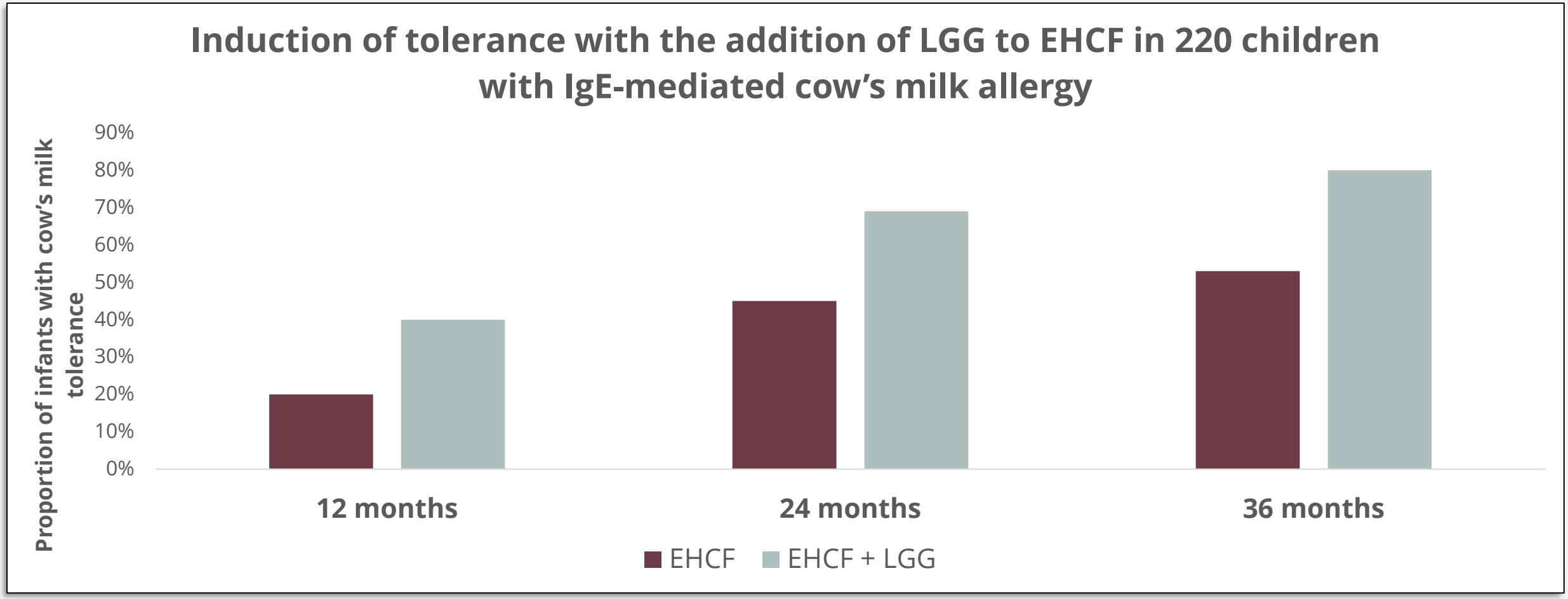
▲ Devoid of large allergens but contain small, potentially beneficial peptides that may increase tolerance

▼ Hypoallergenic; unlikely to increase tolerance acquisition

Decreasing allergenicity

1. Asthma and Allergy Foundation of America. Formula Options for Kids with Food Allergies. September 2020. https://kidswithfoodallergies.org/recipes-diet/nutrition-and-health/formula-options-for-kids-with-food-allergies/. **2.** Australasian Society of Clinical Immunology and Allergy (ASCIA). Guide for milk substitutes in cow's milk allergy. 2023. https://www.allergy.org.au/hp/papers/guide-for-milk-substitutes-cows-milk-allergy.

Addition of LGG to Extensively Hydrolyzed Formula for Tolerance Induction[1]



LGG, *Lactobacillus rhamnosus* GG; EHCF, extensively hydrolyzed casein formula

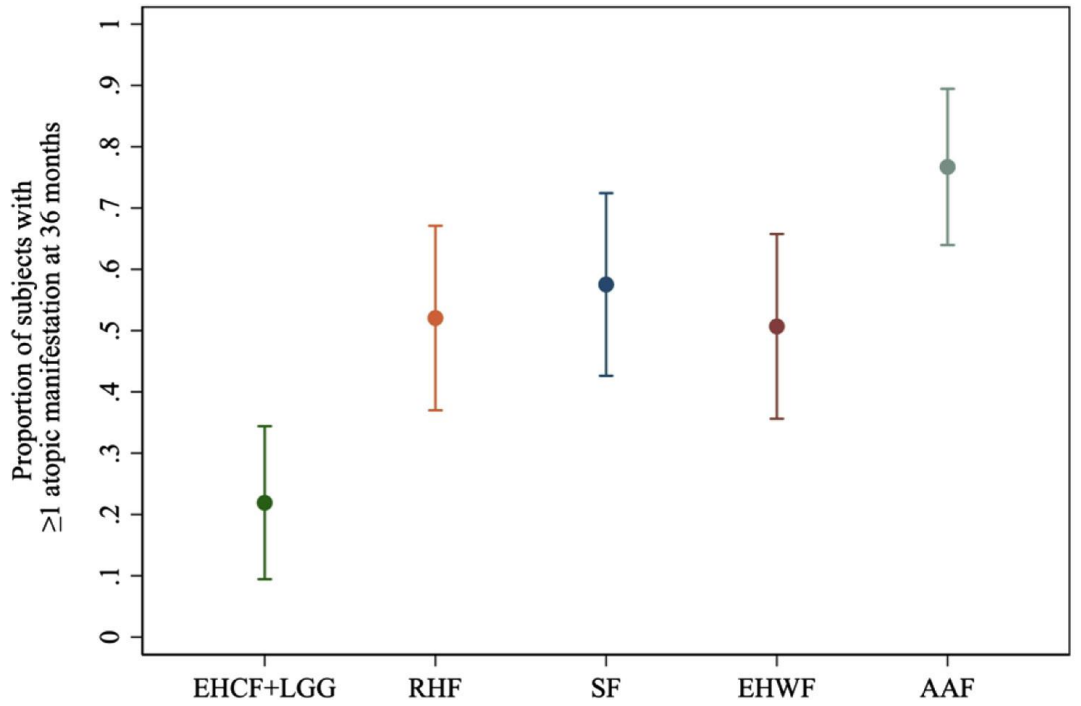
1. Berni Canani R et al. *J Allergy Clin Immunol.* 2017;139(6):1906-1913.e4.

Hypoallergenic Formulas With or Without LGG for Cow's Milk Allergy[1]

Atopic March Cohort Study

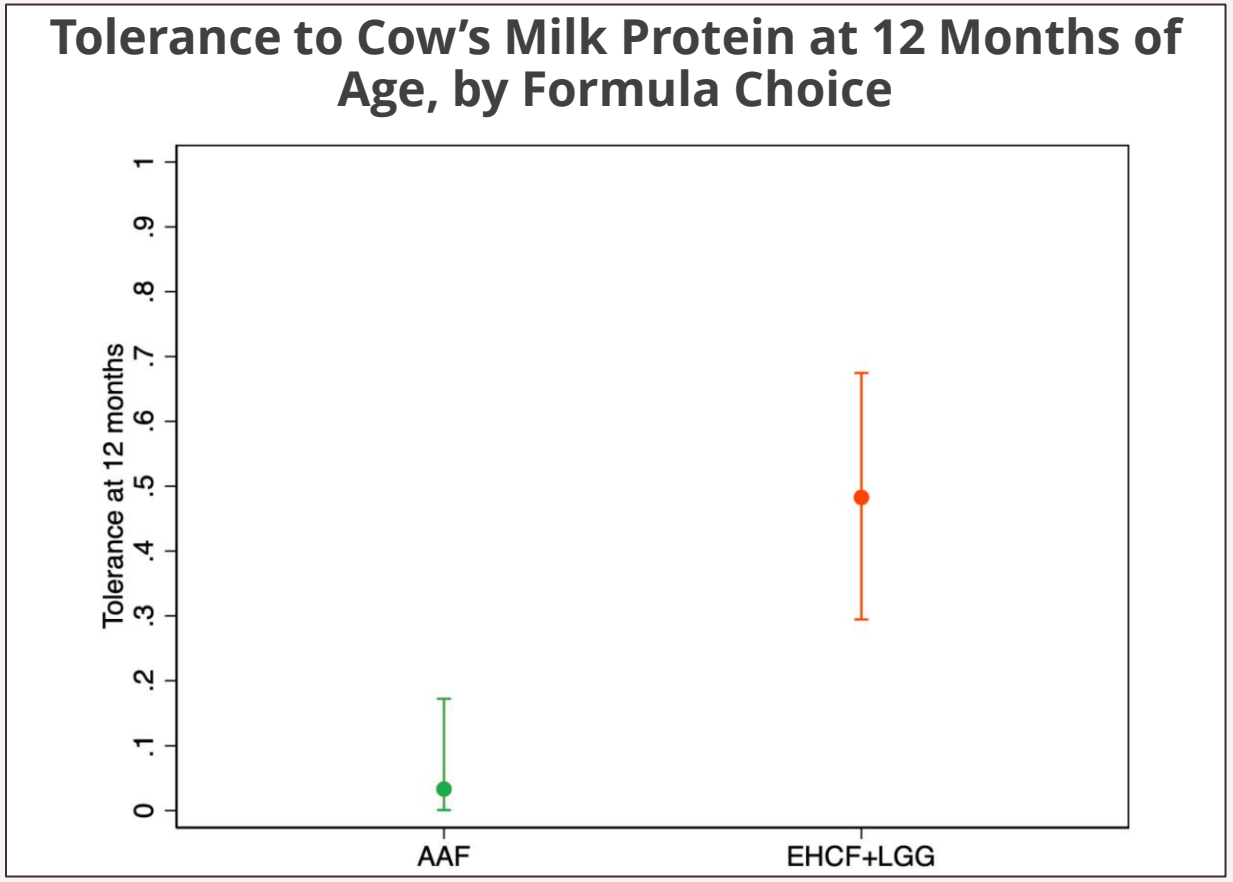
- Enrolled 365 infants with cow's milk allergy to different formula cohorts:
  - Extensively hydrolyzed casein formula + *L rhamnosus* GG (EHCF + LGG)
  - Rice hydrolyzed formula (RHF)
  - Soy formula (SF)
  - Extensively hydrolyzed whey formula (EHWF)
  - Amino acid–based formula (AAF)
- Relative to other formula types, EHCF + LGG was associated with more rapid and durable tolerance

Risk of Any Allergic Manifestation at 3 Years in Patients With Cow's Milk Allergy, by Formula Choice



1. Nocerino R et al. *J Pediatr.* 2021;232:183-191.e3.

Step-Down Approach RCT: Switching From AAF to EHCF + LGG Formula[1]



SDACMA Trial

- Enrolled 60 infants with IgE-mediated cow's milk allergy managed with AAF for at least 4 weeks who tolerated EHCF in a food challenge
- Randomized to continued AAF or switch to EHCF
- Showed that the switch was well tolerated and associated with more rapid tolerance acquisition

1. Nocerino R et al. *Allergy*. 2023;10.1111/all.15750.

Reintroduction With "Food Ladders" to Induce Allergen Tolerance[1]

Food ladders are home-based strategies for dietary advancement that slowly increases allergen exposure.[1]

- Begins with introduction of heavily heat-treated foods and progresses to less-processed products[1]
  - For example, cow's milk allergen ladders may begin with baked muffins, followed by baked hard cheeses, followed by soft cheeses
- Intended to help with the development of natural tolerance[1]
- Largely safe in appropriately selected patients with non-IgE–mediated food allergies[1]
  - Effectiveness decreases as allergen-specific IgE levels increase[2]

1. Chua GT et al. *Allergy Asthma Clin Immunol.* 2022;18(1):51. **2.** Hayden J et al. *J Allergy Clin Immunol.* 2023;151(2 suppl):AB4.

Allergen Immunotherapy for IgE-mediated Food Allergies

- Allergen immunotherapy cannot “cure” food allergies in the traditional sense[1]

- The goal of allergen immunotherapy is to **reduce** sensitization and **increase** tolerance to allow controlled consumption of small amounts of allergens[1]
  - Requires ongoing treatment to maintain tolerance

- Oral immunotherapy effectiveness varies by type of allergen:[2]
  - Peanut: 9.9-fold increase
  - Hen’s egg: 8.9-fold increase
  - Cow’s milk: 5.7-fold increase

1. Brozek JL et al. *World Allergy Organ J.* 2022;15(4):100646. **2.** de Silva D et al. *Allergy*. 2022;77(6):1852-1862.

Key Takeaways

- Along with AD, food allergy is one of the first manifestations in the allergic march.
- Food allergy is associated with considerable health, financial, and psychosocial burdens among families and patients.
- Gut microbiome modulation may reduce the risk of allergy development and increase tolerance acquisition.
- Early introduction of potentially allergenic complementary foods during the 4- to 6-month “window of opportunity” can significantly reduce the risk of food allergy.