Confronting the Allergic March

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Presented by
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This activity is supported by an educational grant from
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Alessio Fasano, MD

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Learning Objectives

- Understand the allergic march and the role of gut microbiome dysbiosis as a critical factor underlying food allergy
- Describe the prevalence, risk factors, clinical presentation, and diagnostic approach for cow's milk protein allergy (CMPA)
- Apply novel strategies for management of CMPA, including new techniques to accelerate milk allergen tolerance

Overview of the Allergic March

Introduction to the Allergic March

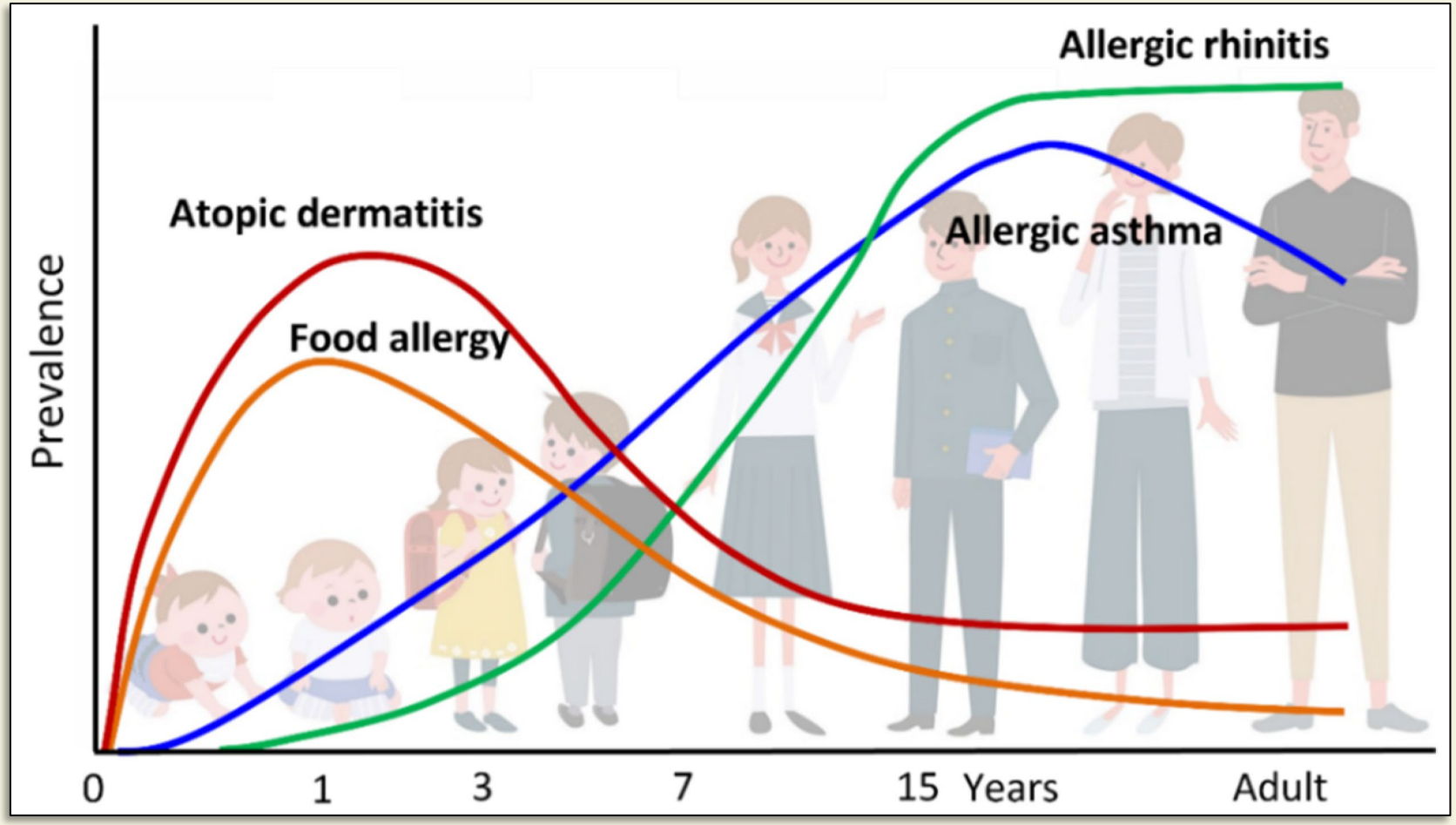
The **allergic (or atopic) march** is the term for the natural history and progression of allergic diseases[1]

- Typical sequence of appearance of allergic diseases[2]

  Atopic dermatitis (AD) → food allergy → allergic asthma → allergic rhinitis
- Follows the developmental evolution of the skin, gastrointestinal (GI) tract, and respiratory tract[2]
- Provides a conceptual framework for research into the mechanisms, prevention, and treatment of allergic diseases[2]

1. Asthma and Allergy Foundation of America (AAFA). The allergic or atopic march. June 2022. https://aafa.org/allergies/living-with-allergies/allergic-march/. **2.** Yang L et al. *Front Immunol*. 2020;11:1907.

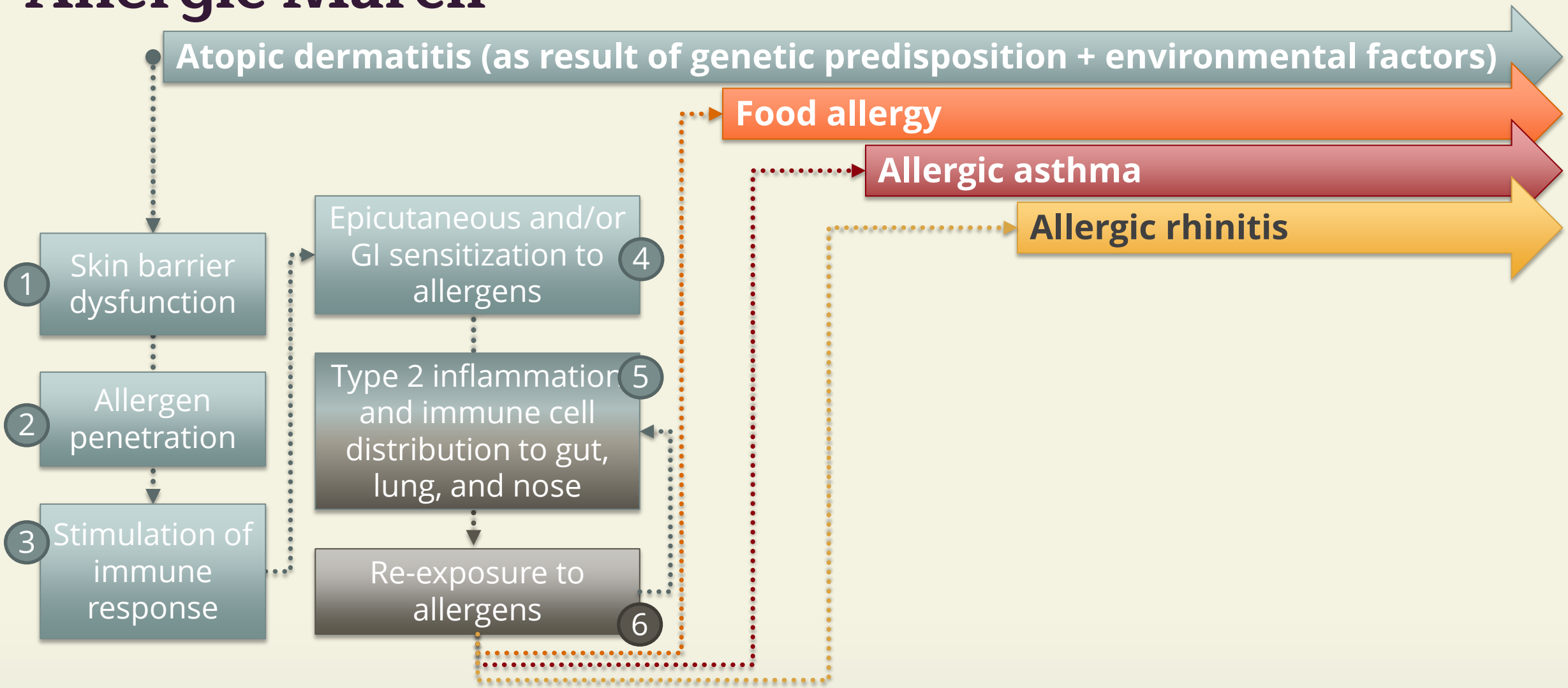
Progression of the Allergic March



Some allergic diseases can remit in childhood, while others persist into adulthood.[1]

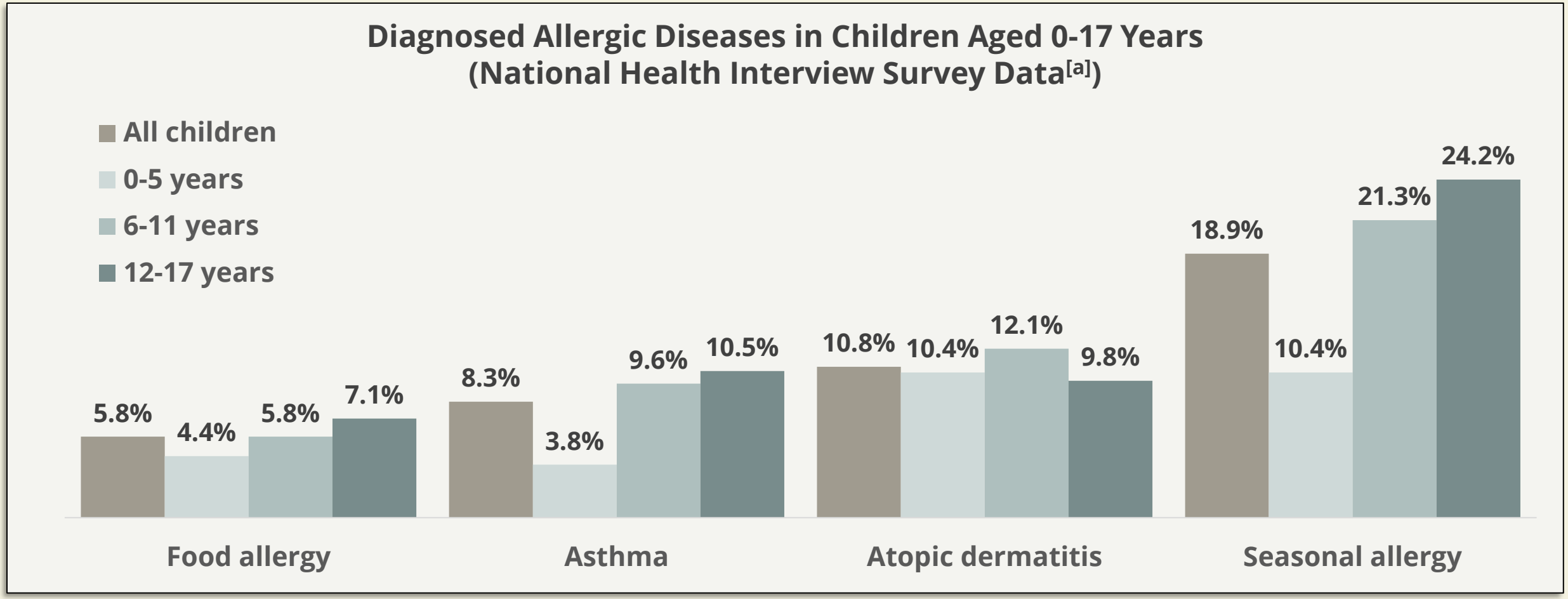
1. Tsuge M et al. *Children (Basel).* 2021;8(11):1067.

Proposed Sequence of Events Influencing the Allergic March[1,2]



1. Tsuge M et al. *Children (Basel).* 2021;8(11):1067. **2.** Gabryszewski SJ et al. *Ann Allergy Asthma Immunol*. 2021;127(3):293-300.

US Data for Allergic Diseases in Children[1,2]



a. 2016 data for asthma and 2021 data for other allergic conditions

1. Zablotsky B et al. NCHS Data Brief. 2023;(459):1-8. **2.** Zahran HS et al. *MMWR Morb Mortal Wkly Rep*. 2018;67(5):149-155.

What Is the Etiology of the Allergic March?

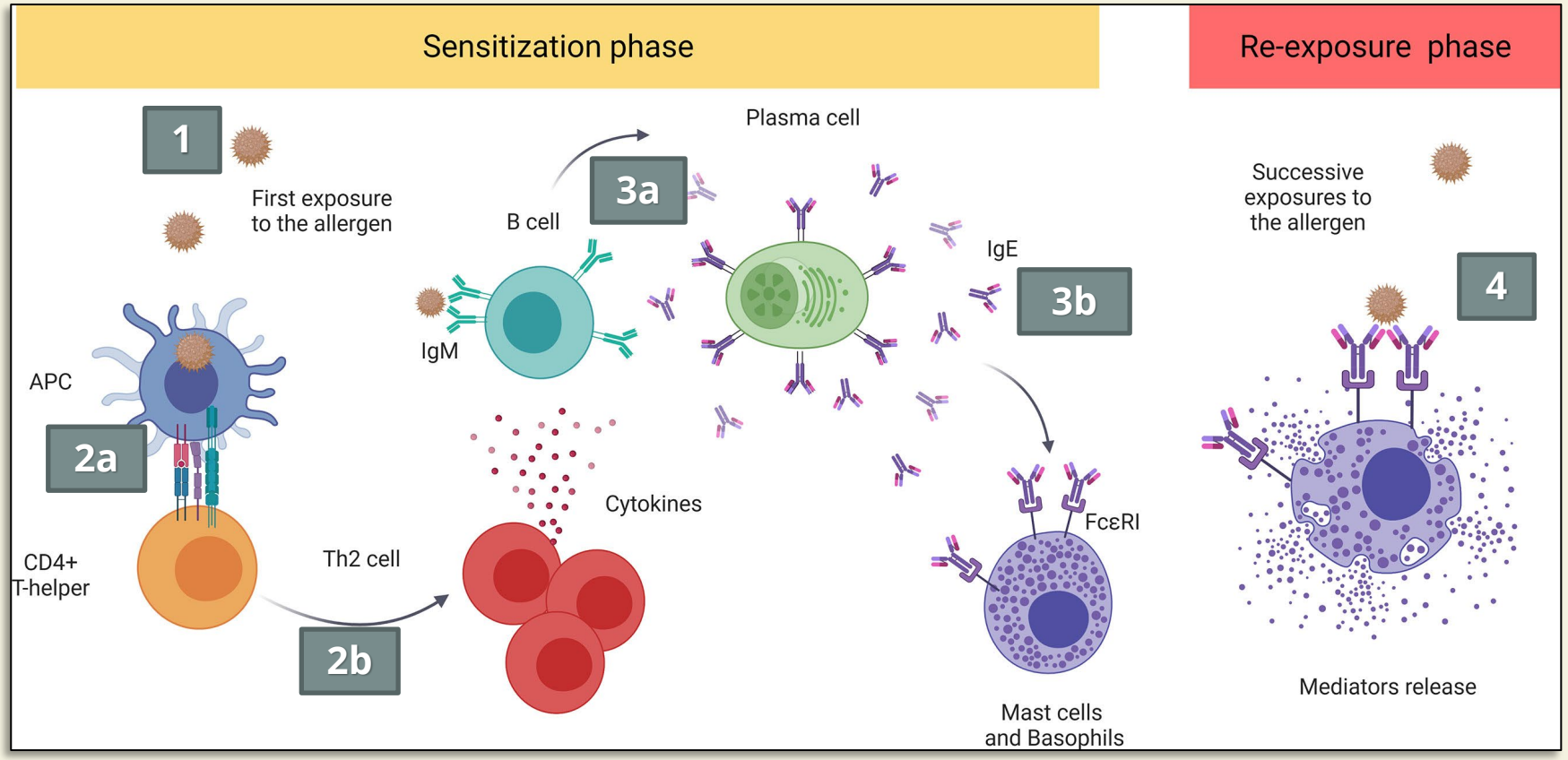
Physiology of the Immune Response & Allergy

Broadly, **allergens** are defined as molecules that can bind to **IgE antibodies**.[1]

- **IgE** antibodies are immunoglobulin proteins that form complexes with antigens and trigger allergic responses[2]
- **Sensitizing allergens** are those that can induce allergen-specific IgE antibodies[1]
- Allergens typically enter the body via mucosal surfaces of either the **airways** or the **GI tract**[1]
  - **Skin penetration** is increasingly believed to play a role in the development of hypersensitivity to allergens

1. Matricardi PM et al. *Pediatr Allergy Immunol.* 2016;27 Suppl 23:1-250. **2.** Godwin L et al. Biochemistry, immunoglobulin E. September 24, 2022. https://www.ncbi.nlm.nih.gov/books/NBK541058/.

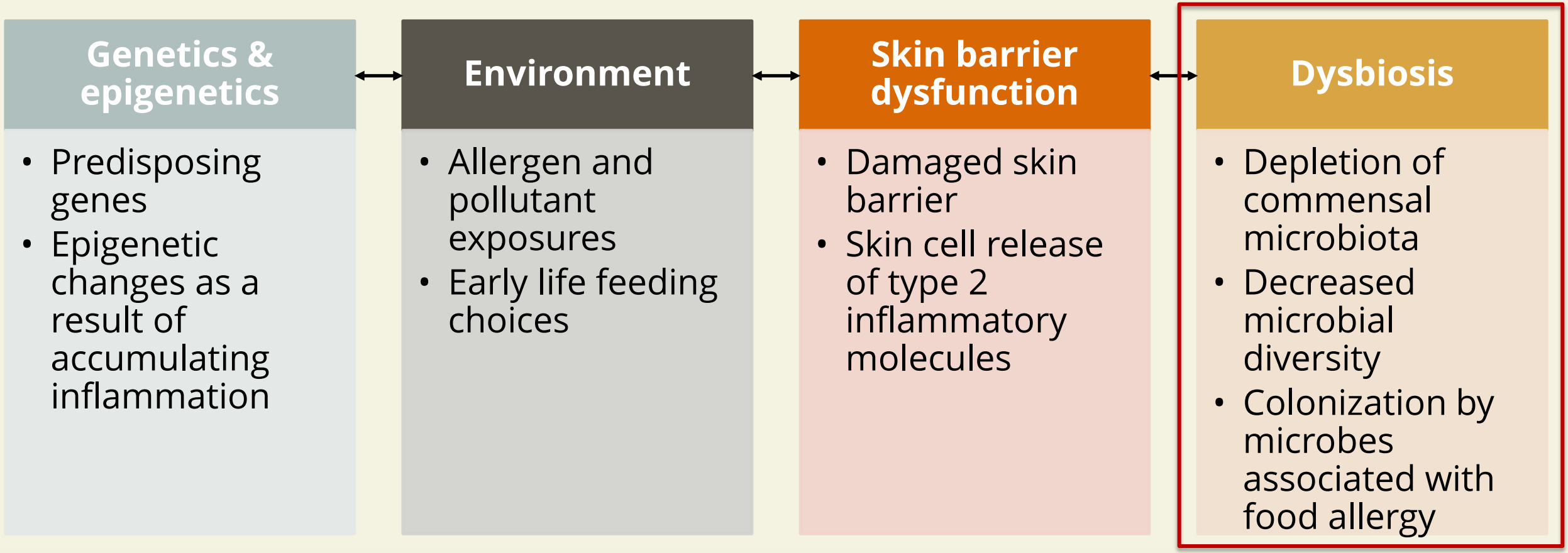
The Process of IgE-Mediated Allergen Sensitization[1]



1. First exposure to allergen
2. APCs capture and present processed allergen to CD4+ T cells, which become Th2 cells
3. Th2 cells stimulate B cells, which release allergen-specific IgE
4. Re-exposure leads to activation of IgE complexes, inducing degranulation of mast cells and basophils

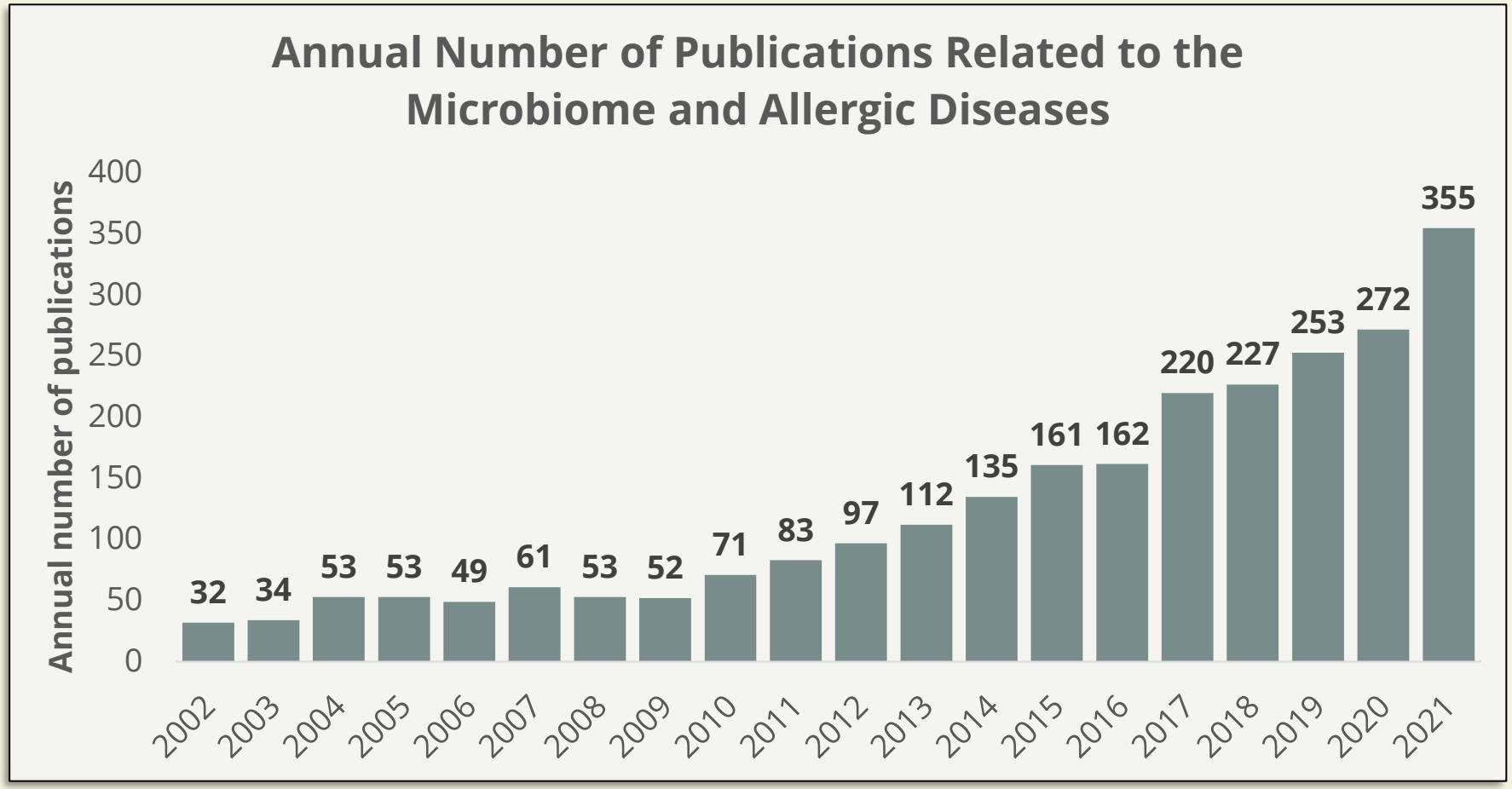
1. Nuñez-Borque E et al. *Front Immunol.* 2022;13:836222.

Proposed Etiologic Drivers of the Allergic March[1-3]



1. Tsuge M et al. *Children (Basel).* 2021;8(11):1067. **2.** Maiello N et al. *Children (Basel).* 2022;9(4):450. **3.** Wang J et al. *Signal Transduct Target Ther.* 2023;8(1):138. **4.** Gu S et al. *Food Sci Hum Wellness.* 2023;12(3):681-690.

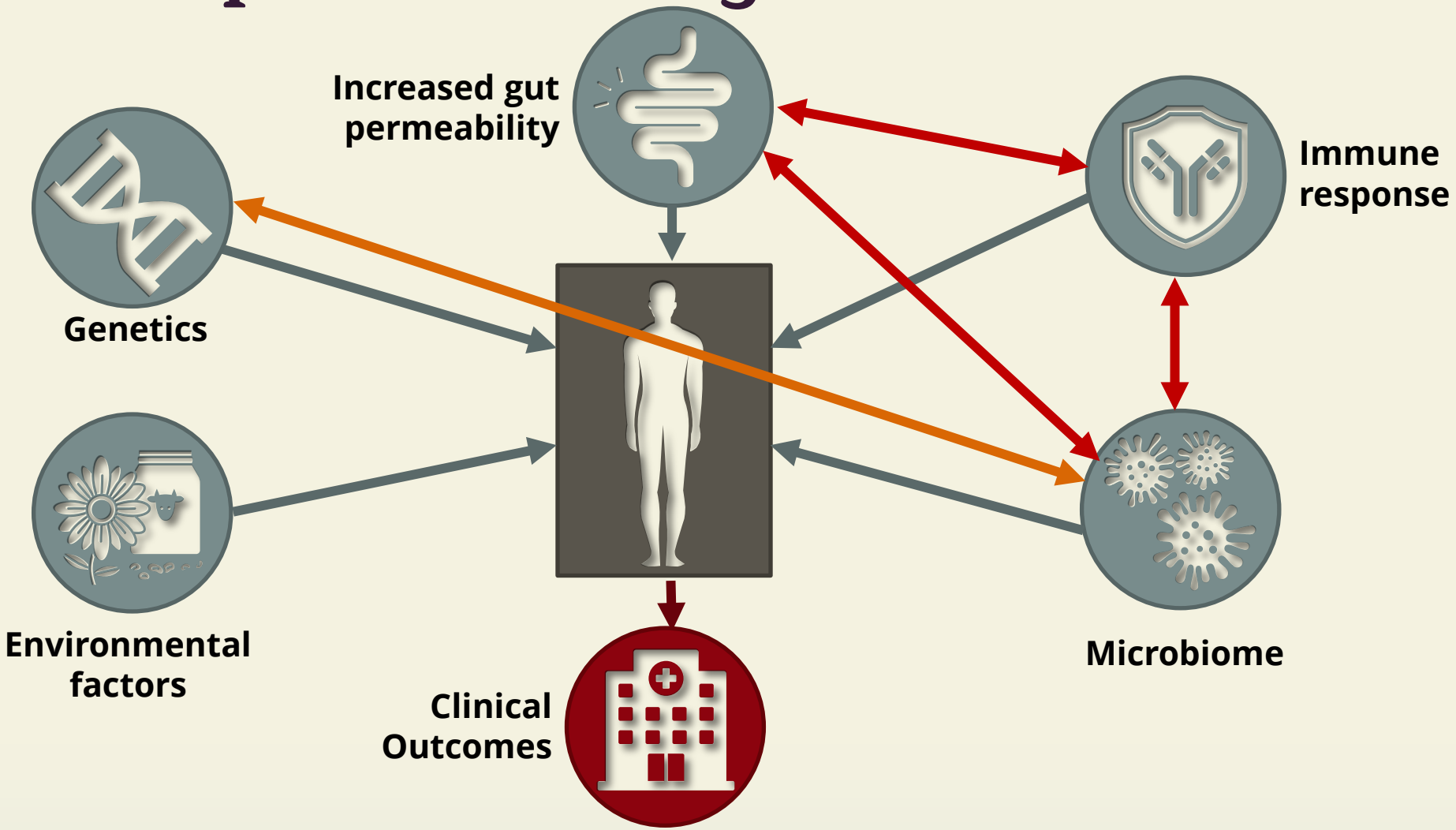
Rapid Expansion of Gut Microbiome–Allergy Research[1]



The number of publications related to the microbiome and allergy has rapidly increased over the last 2 decades

1. Lv H et al. *Front Immunol.* 2022;13:1045795.

The Yin and Yang Between Tolerance and Immune Response Leading to Immune Disorders[1]



1. Fasano A. *Clin Rev Allergy Immunol.* 2012;42(1):71-78.

Role of the Healthy Gut Microbiome in Protecting Against Allergic Diseases

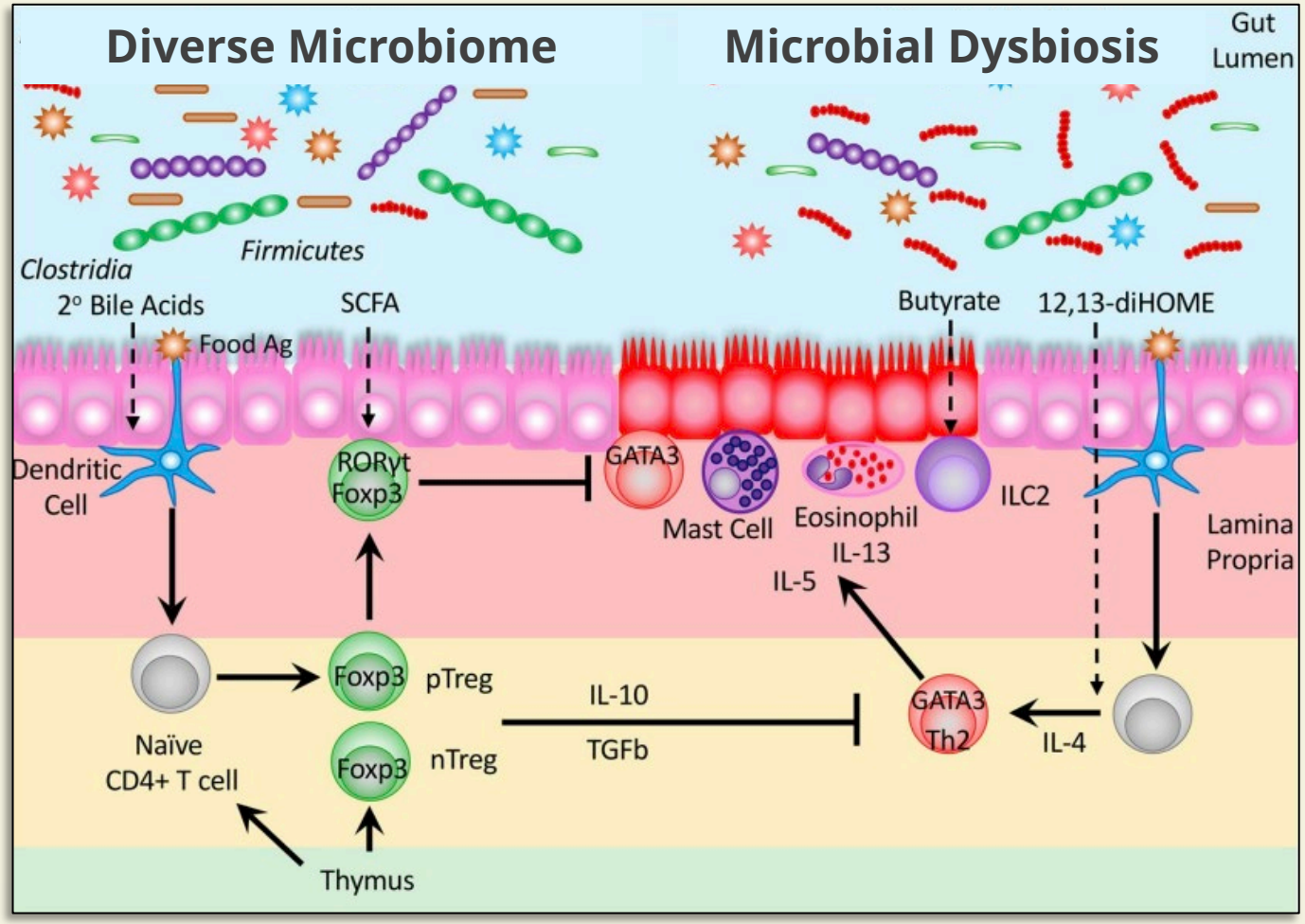
Symbiotic microbes have coevolved with humans to perform **essential physiologic functions.**[1]

Physiologic functions of a healthy gut microbiome:

- Metabolism of prebiotic fiber to short-chain fatty acids (SCFAs)[1]
- Protection against colonization by pathogens[1]
- Facilitation of antigen-experienced regulatory T cells (Tregs), which are important for suppression of type 2 inflammation[2]

1. Nance CL et al. *Children (Basel).* 2020;7(6):50. **2.** Bunyavanich S, Berin MC. *J Allergy Clin Immunol.* 2019;144(6):1468-1477.

Role of Dysbiosis in the Development of Allergic Diseases[1]



- Loss of protective SCFAs and dampening effects of Tregs
- Release of inflammatory molecules that promote Th2 cell activation
- Recruitment of immune cells, including mast cells and eosinophils

1. Augustine T, Kumar M et al. *Clin Rev Allergy Immunol.* 2022;10.1007/s12016-022-08939-9.

Factors Influencing the Development of the Infant Gut Microbiome

Prenatal[1]

- Maternal microbiota
- Maternal diet
- Maternal stress
- Genetics

Perinatal[1,2]

- Mode of delivery (vaginal vs Cesarean)
- Gestational age

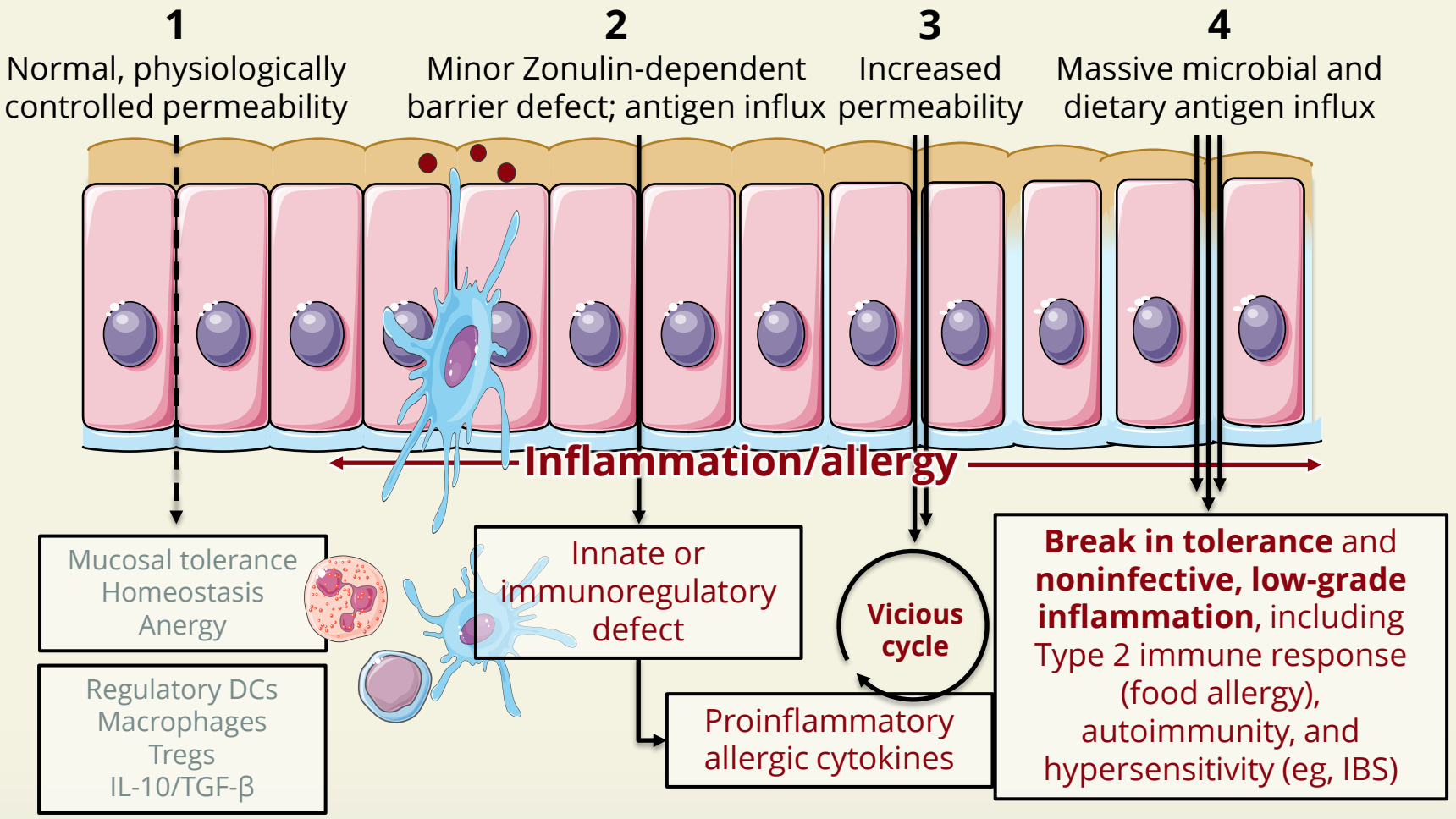
Postnatal[1,2]

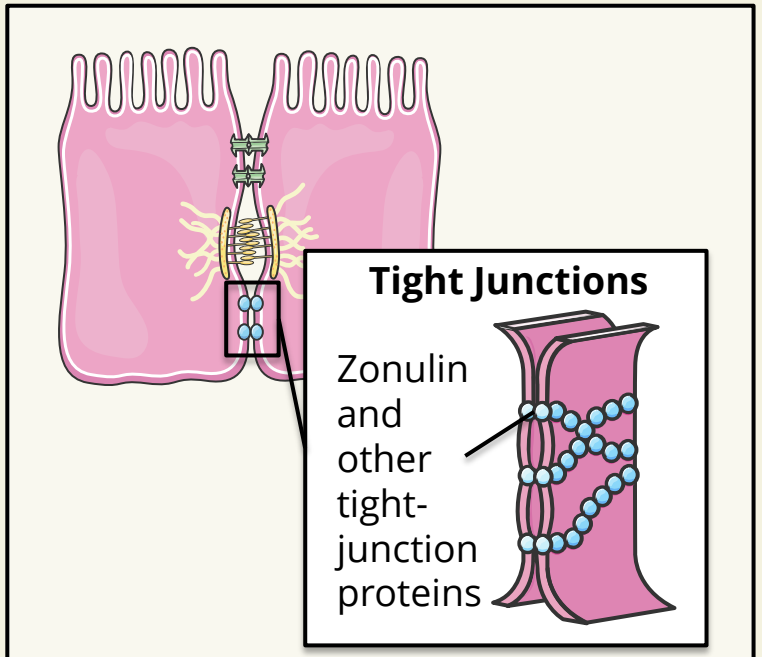
- Feeding mode (breast milk vs formula)
- Geographic region
- Household and family environment
- Maternal diet
- Timing and types of complementary food
- Antibiotic exposure

1. Yao Y et al. *Front Immunol.* 2021;12:708472. **2.** Milani C et al. *Microbiol Mol Biol Rev*. 2017;81(4):e00036-17.

Excessive and Inappropriate Inflammatory Process Associated to a Dysfunction of Intestinal Barrier:

Loss of Mucosal Immune Homeostasis[1]

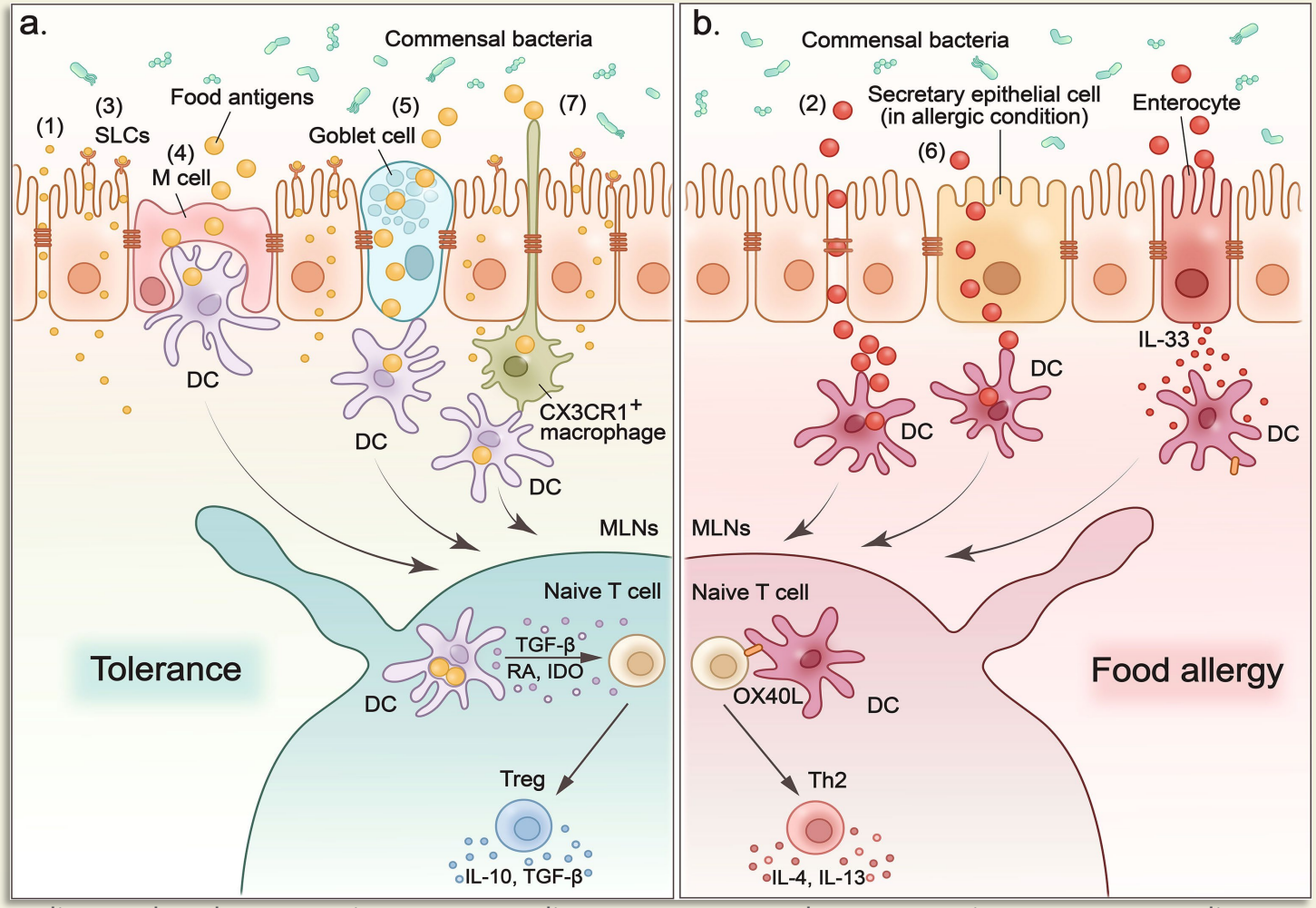




Tight junctions are a "dark horse" implicated in several disease states, from acute injury to chronic inflammation and autoimmunity.

1. Sturgeon C, Fasano A. *Tissue Barriers.* 2016;4(4):e1251384.

Intestinal Permeability & Food Allergy[1]

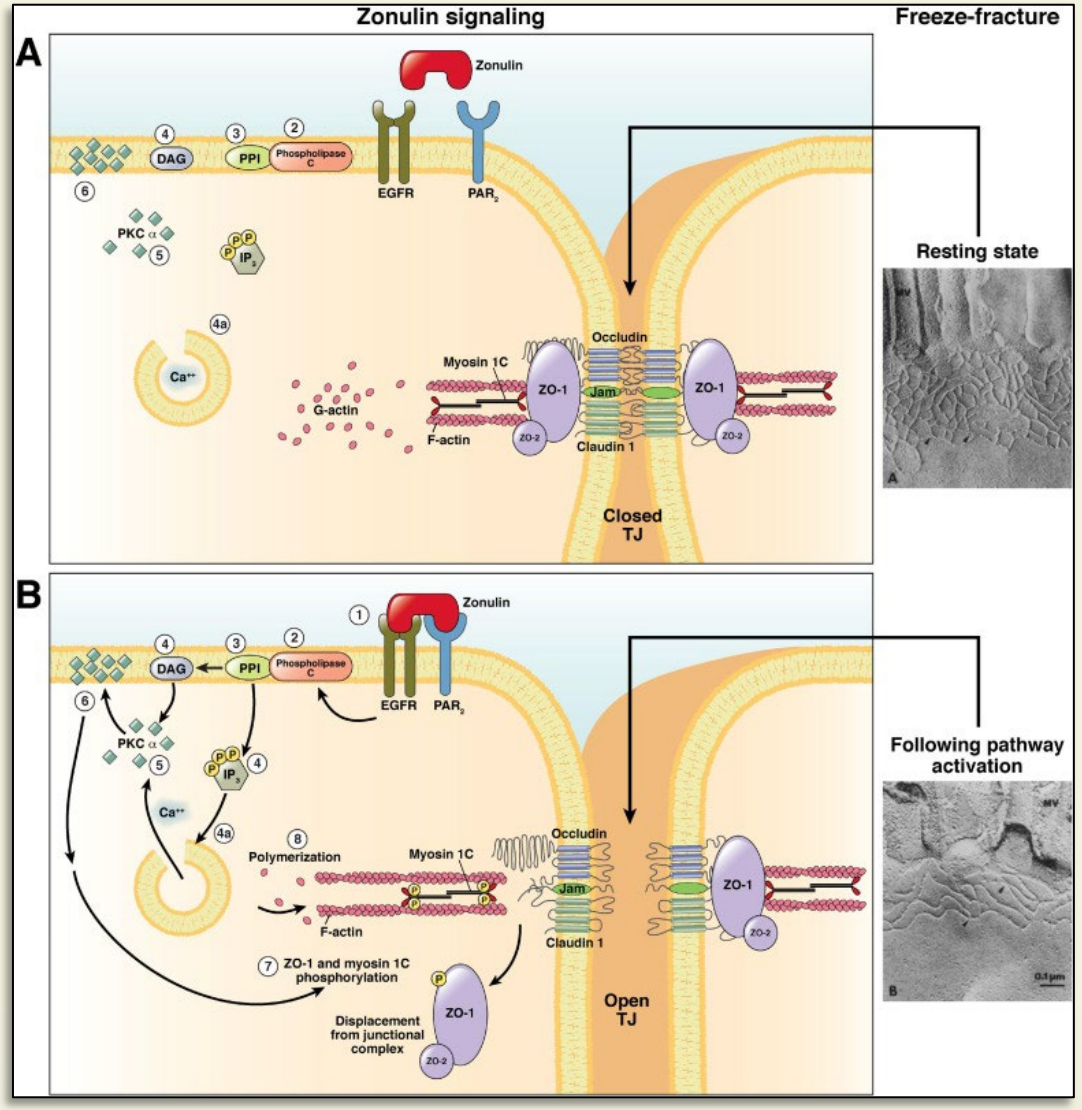


Degradation of tight junctions increases the permeability of the intestinal barrier, leading to uncontrolled entry of antigens and contributing to the development of food allergy.

1. Xiong Y et al. *Front Immunol*. 2022;13:906122.

Literature Report on Zonulin and Chronic Inflammatory Diseases[1,2]

Disease	Model	Reference (PMID)	Disease	Model	Reference (PMID)
ADHD	Human	36786182	**Irritable bowel syndrome**	Human	31210949
Aging	Human	29896420	**HIV**	Human	29762690
Ankylosing spondylitis	Human	28069576	**Long COVID**	Human	1182544
Asthma	Human	34465387	**MIS-C**	Human	34032635
Autism	Human	36447452	**ME/CFS**	Human	35946099
Bipolar disorders	Human	37098666	**Multiple sclerosis**	Mouse	25184418
Celiac ddisease	Human	32162764	**Multiple sclerosis**	Human	31317818
Colitis/IBD (Crohn disease)	Human	34979917	**Necrotizing enterocolitis (NEC)**	Human	35279661
Colitis	Mouse	28423466	**Nonalcoholic fatty liver disease**	Human	32255299
Depressive disorders	Human	34320451	**Non-Celiac gluten Sensitivity**	Human	32060130
Food allergies	Human	36297068	**Obesity/insulin resistance**	Human	35666025
Gestational diabetes	Human	35994108	**Sepsis**	Human	23457771
Glioma	Human	19701495	**Type 1 diabetes**	Human	16644703
Glioma	Cells	23637756	**Type 2 diabetes**	Human	24347174



1. Fasano A. *Clin Gastroenterol Hepatol.* 2012;10(10):1096-1100. **2.** Sturgeon C, Fasano A. *Tissue Barriers.* 2016;4(4):e1251384.

Overview of Cow's Milk Protein Allergy

Types of Cow's Milk Protein Allergy[1]

The **World Allergy Organization (WAO)** uses the following definitions for cow's milk hypersensitivities:

- **Cow's milk protein allergy (CMPA)** is a hypersensitivity reaction caused by immune signaling
- **IgE-mediated CMPA** is a hypersensitivity reaction to cow's milk protein (CMP) mediated by IgE binding to Fcε receptors on mast cells and basophils, leading to the rapid release of histamine and other inflammatory mediators
- **Non-IgE-mediated CMPA** is a hypersensitivity reaction to proteins in cow's milk that is caused by cell-mediated and other non-IgE mechanisms, leading to delayed-onset reactions
- **Cow's milk intolerance** is a nonallergic hypersensitivity

1. Fiocchi A et al. *World Allergy Organ J.* 2022;15(1):100609.

Comparison of IgE-mediated CMPA, Non-IgE–mediated CMPA, and Intolerance[1,2]

	IgE-mediated CMPA	Non-IgE-mediated CMPA	CMP intolerance
Mechanism of disease	Allergic hypersensitivity mediated by IgE	Allergic hypersensitivity mediated by immune cells	Nonallergic hypersensitivity
Organ system specificity	Broad, including oral, respiratory, cardiovascular, cutaneous, and gastrointestinal	Usually specific to GI system	Usually specific to GI system
Timing of symptoms	Rapid (usually within minutes)	Delayed (hours or days)	Delayed (hours or days)
Examples	N/A	Food protein-induced allergic proctocolitis (FPIAP), food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPIE)	Lactose intolerance

1. Jensen SA et al. *World Allergy Organ J.* 2022;15(9):100668. **2.** Fiocchi A et al. *World Allergy Organ J.* 2022;15(1):100609.

Symptoms of Mild-to-Moderate CMPA

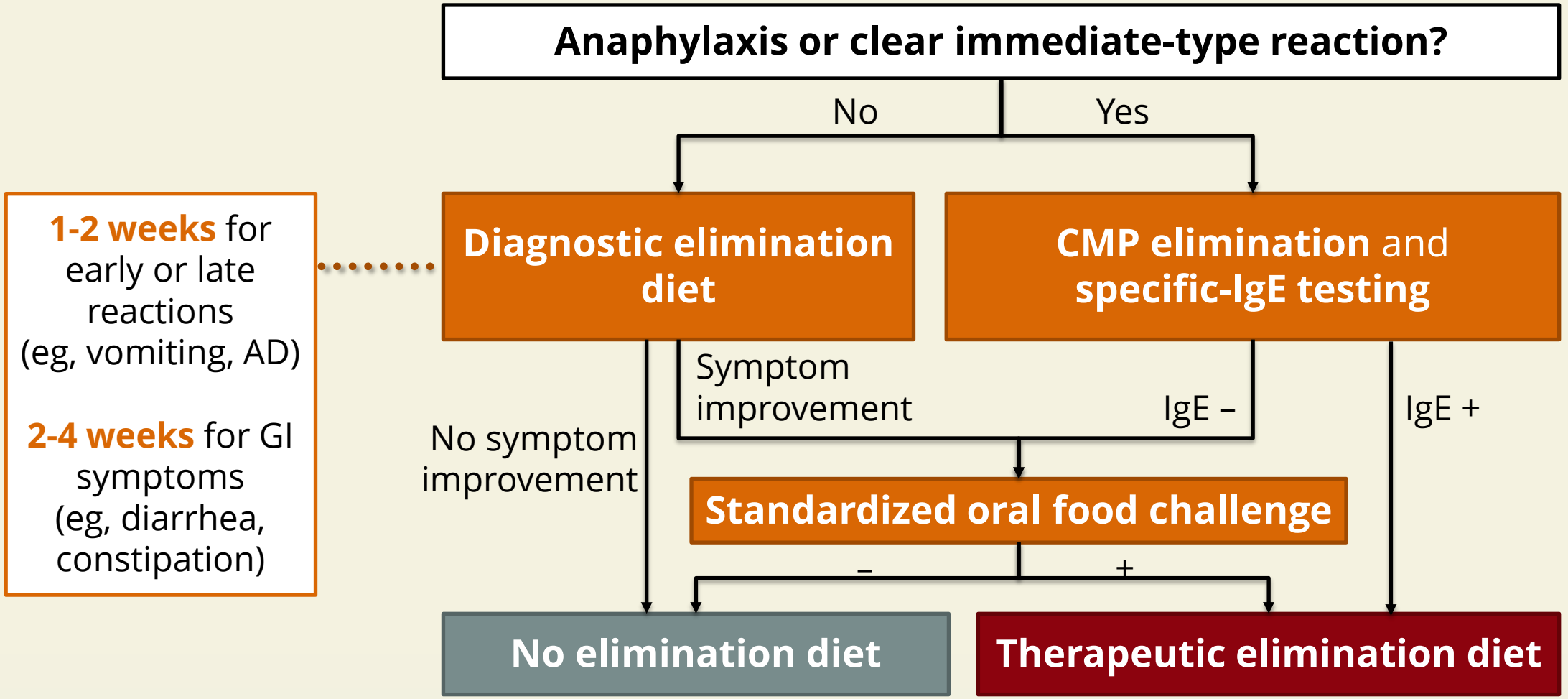
Symptoms of IgE-Mediated CMPA[1]
Skin (≥1 almost always present)
• Pruritus • Erythema • Urticaria • Angioedema • Acute “flare” of AD
Gastrointestinal
• Vomiting • Diarrhea • Abdominal pain or colic
Respiratory (rarely occur in the absence of other symptoms)
• Acute rhinitis • Acute conjunctivitis

Symptoms of Non-IgE-Mediated CMPA[1]
Gastrointestinal (most common)
• Persistent irritability • Vomiting or reflux • Food refusal or aversion • Diarrhea or constipation • Abdominal pain • Blood or mucus in stools in otherwise well infant
Skin
• Pruritus • Erythema • Nonspecific rash • Moderate, persistent AD

Note: These symptoms are exceedingly common in infants without CMPA, underscoring the importance of structured diagnostic evaluation[1,2]

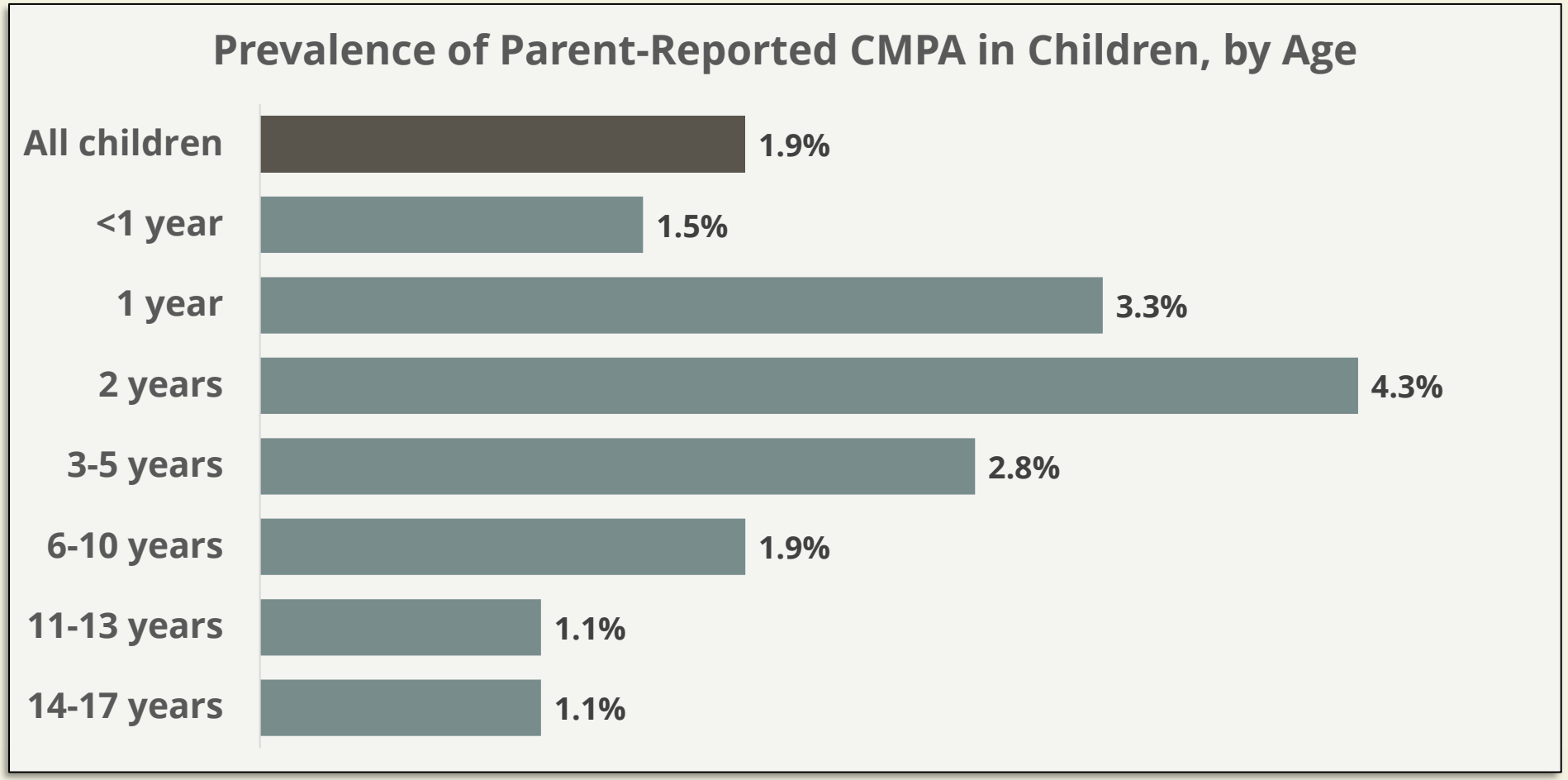
1. Fox A et al. *Clin Transl Allergy*. 2019;9:40. **2.** Vincent R et al. *Clin Exp Allergy*. 2022;52(1):82-93.

Algorithm for Diagnosing CMPA in Infants[1]



1. Koletzko S et al. *J Pediatr Gastroenterol Nutr.* 2012;55(2):221-229.

Epidemiology of CMPA Among Infants & Children[1]



CMPA is most common in infants and toddlers and often remits as children age.

1. Gupta RS et al. *Pediatrics*. 2018;142(6):e20181235.

Risk Factors for CMPA

Several early risk factors for CMPA have been identified:

- Family history for allergy[1]
- Breastfeeding extent and duration[1]
- Antibiotic exposure during pregnancy[2]
- Exposure to complementary foods before age 4 months[2]
- Presence of atopic dermatitis (higher risk for more severe disease)[3]

1. Sardecka I et al. *Allergy Asthma Proc*. 2018;39(6):e44-e54. **2.** Zhang JY et al. *Zhongguo Dang Dai Er Ke Za Zhi.* 2020;22(1):42-46.
3. Kawada S. *PLoS One.* 2020;15(10):e0240980.

What About Breastfeeding and Allergies?

- Breastfeeding may be one of the most relevant factors affecting development of the newborn immune system[1,2]
  - **Bioactive compounds in human milk** are immunomodulating (eg, TGF-β, HGF, cytokines)
  - **The GI tracts of breastfed infants are colonized with favorable microbes** that positively influence immune system development[3]

While the undisputed gold standard in infant nutrition, the role of breastfeeding in improving allergy outcomes is unclear.[1]

Recent studies suggest the effects of breastfeeding may be modified by the interaction with other genetic, environmental, dietary, and immunologic factors.[4]

TGF-β: transforming growth factor β; HGF: hepatocyte growth factor

1. Munblit D et al. *Nutrients.* 2017;9(6):532. **2.** Nuzzi G et al. *Children (Basel).* 2021;8(5):330. **3.** Selma-Royo M et al. *Semin Perinatol*. 2021;45(6):151450. **4.** Danielewicz H. *Nutrients*. 2022;14(15):3011.

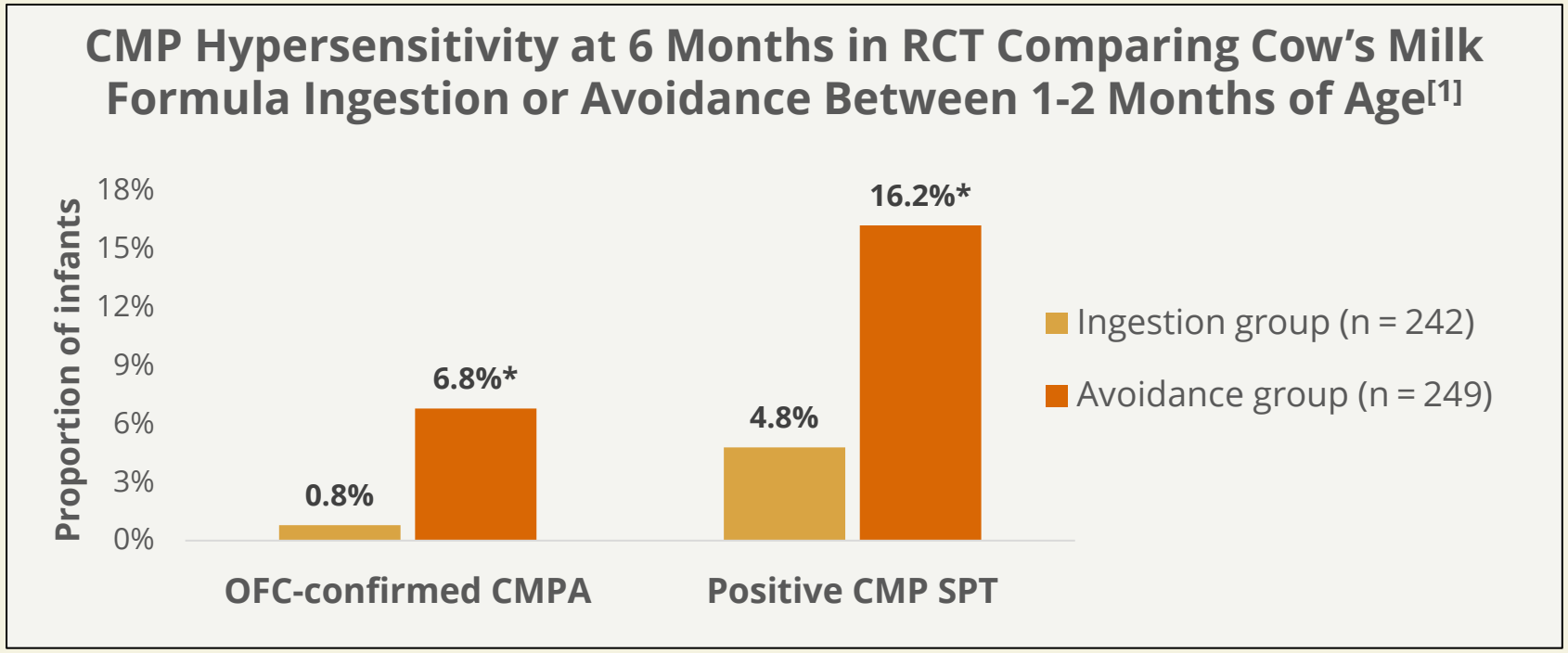
Breastfeeding and Prevention of CMPA: Data Remain Inconclusive

Although exclusive breastfeeding provides **optimal infant nutrition** and **should be encouraged** through 4-6 months of age, breastfeeding has not consistently been linked to the prevention of CMPA.[1-3]

- Despite inconsistent benefit for CMPA prevention, breastfeeding appears to be protective for atopic dermatitis[1,3]
  - May also reduce the risk for wheeze and asthma[3]
- Breastfeeding remains a key component of optimizing the health of the immune system and gut microbiome in the developing infant[3]

1. Greer FR et al. *Pediatrics.* 2019;143(4):e20190281. **2.** Meek JY et al. *Pediatrics*. 2022;150(1):e2022057988. **3.** Nuzzi G et al. *Children (Basel)*. 2021;8(5):330.

Early Complementary Cow's Milk Formula Feeding for CMPA Prevention



In contrast with continuous CMF exposure, intermittent CMF exposure or discontinuation of CMF after early exposure **increases** the risk for CMPA.[2,3]

Early and continued cow's milk formula ingestion reduces the risk of CMPA **without** interfering with breastfeeding.[1-3]

*$P < .001$

1. Sakihara T et al. *J Allergy Clin Immunol.* 2021;147(1):224-232.e8. **2.** Lachover-Roth I et al. *Ann Allergy Asthma Immunol.* 2023;130(2):233-239.e4. **3.** Sakihara T et al. *J Allergy Clin Immunol Pract.* 2022;10(1):172-179.

Impact of Formula Type on CMPA

- Soy formulas and formulas made from other mammals (eg, goat) are **not** recommended for allergy prevention[1,2]
- Data regarding hydrolysate formulas for allergy prevention are **mixed**[2-4]
  - Differences across individual formulas preclude broad recommendations by formula type
  - For infants at high risk for allergic diseases, hydrolyzed formulas may be considered on a per-product basis

Most healthy infants can be fed intact-protein cow's milk formula without impacting allergy risk.

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. **4.** Dias JA et al. *Nutrients*. 2022;14(19):4016.

CMPA Prevention Summary

- One of the major risk factors for CMPA is **dysbiosis**, which can be mediated by **mode of delivery**, **feeding choices**, and other **environmental** and **genetic factors**
- Although breastfeeding provides **optimal infant nutrition**, data are **inconclusive** for a relationship between breastfeeding and the prevention of CMPA
- Early and ongoing cow's milk formula feeding can reduce the risk of CMP hypersensitivity without interfering with breastfeeding
- Data regarding the effects of hydrolysate formula on CMPA risk are mixed
  - Most healthy infants can be fed intact-protein cow's milk formula without affecting allergy risk

Novel Strategies for CMPA Management & Induction of Tolerance

CMPA Management: Dietary Avoidance

Dietary avoidance is the conventional management approach for CMPA.[1-4]

- Continued breastfeeding should be encouraged
- For infants receiving formula, intact cow's milk protein formula should be avoided
  - Extensively hydrolyzed formulas are recommended
- For those eating complementary foods, special attention to adequate calcium intake is recommended

Maternal elimination diets are not generally necessary; for **99%** of infants, breast milk of a woman consuming cow's milk does not contain sufficient milk allergens to trigger allergy.[5]

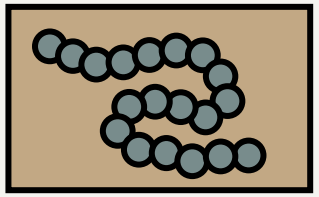
1. Nowak-Wegrzyn A et al. *Pediatr Allergy Immunol*. 2023;34 Suppl 28:162-167. **2.** Luyt D et al. *Clin Exp Allergy*. 2014;44(5):642-672. **3.** Venter C et al. *Clin Transl Allergy.* 2017;7:26. **4.** Koletzko S et al. *J Pediatr Gastroenterol Nutr.* 2012;55(2):221-229. **5.** Munblit D et al. *JAMA Pediatr.* 2020;174(6):599-608.

Formula Choices for Cow's Milk Allergy

Formula Tiers[1-3]

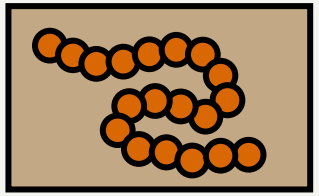
Cost

Allergenicity



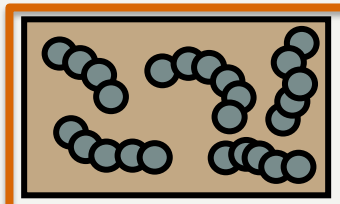
Standard, intact-protein cow's milk formulas are made of complete chains of CMP

Options for Infants With IgE-mediated CMPA

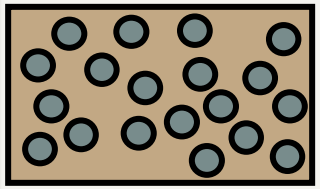


Plant-based protein formulas are made from intact plant protein chains (eg, soy)

Options for Infants With Non-IgE-mediated CMPA



Hydrolysate formulas are made from CMP that has been partially or extensively hydrolyzed (broken into) shorter casein and/or whey chains. Extensively hydrolyzed formulas are considered hypoallergenic



Amino acid–based (elemental) formulas are made with individual amino acids and are considered hypoallergenic

Formulas **not** recommended for CMPA:[2]

- Standard cow's milk formula
- Goat milk–based formula
- Other mammal milks and formulas
- A2 formula
- Soy formula (non-IgE-mediated CMPA)

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. **3.** AAP Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.

AAP-Recommended Substitutions for Cow's Milk Formula in Patients With IgE-mediated CMPA[1,2]

Allergy	Age	Formula type	
		First choice	Second choice
IgE-mediated CMPA	**<6 months**	Extensively hydrolyzed[a]	Amino acid–based
	>6 months	Extensively hydrolyzed[a] **OR** Soy	Amino acid–based
Non-IgE-mediated CMPA	**All ages**	Extensively hydrolyzed[a]	Amino acid–based

a. Guidelines are not specific, but extensively hydrolyzed formula is typically the first choice among hypoallergenic formula options.

1. AAP Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349. **2.** Barrera EL et al. *Open Nutr J.* 2021;15:1-9.

CMP Reintroduction & Tolerance Induction

- Most children with CMPA "outgrow" their allergy (ie, develop tolerance to CMP) **by age 5 years**[1]
  - Time to tolerance varies and may be more rapid with non-IgE– vs IgE-mediated CMPA
- Guidelines often recommend trialing reintroduction of baked milk in **6- to 12-month intervals** to evaluate for tolerance[1,2]
- Increasingly, there is a focus on various strategies for increasing tolerance by modulating the immune response through home reintroduction and/or immunotherapy[2]

~72%

Proportion of infants with OFC-confirmed CMPA who developed tolerance to baked milk by age 3 years[3]

1. Luyt D et al. *Clin Exp Allergy*. 2014;44(5):642-672. **2.** Nowak-Wegrzyn A et al. *Pediatr Allergy Immunol*. 2023;34 Suppl 28:162-167. **3.** de Jong NW et al. *Nutrients*. 2022;14(3):629.

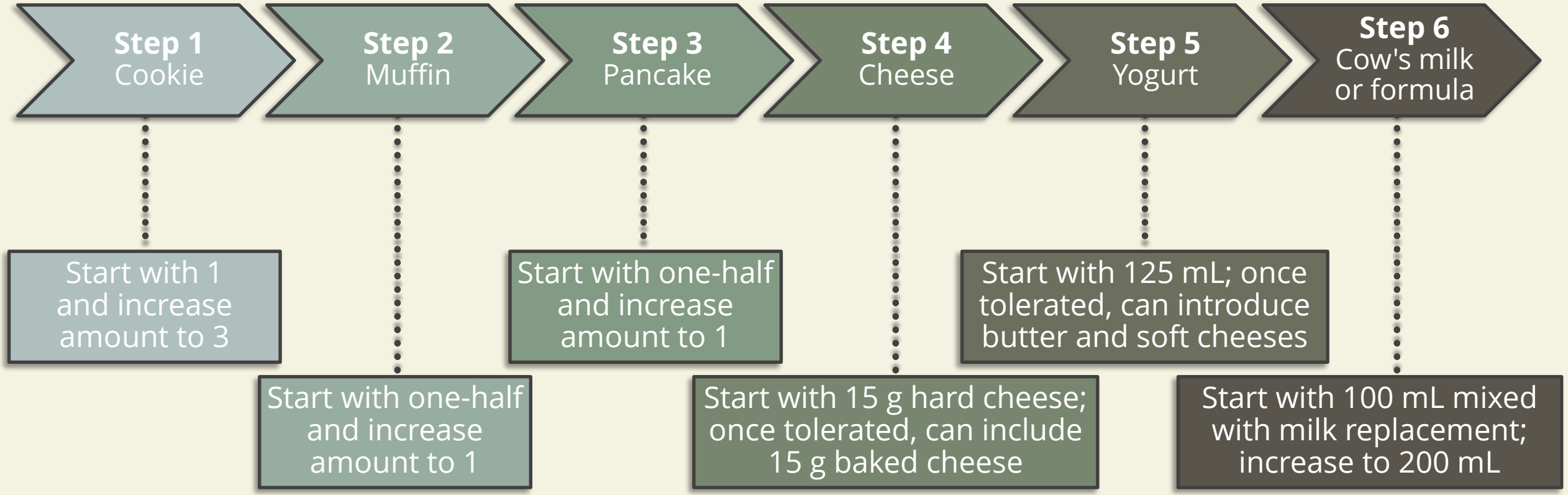
Reintroduction With "Food Ladders" to Induce CMP Tolerance[1]

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

- Begins with introduction of heavily heat-treated foods (eg, baked goods) and progresses through cooked foods (eg, pancakes) to less-processed products (eg, soft cheeses, cow's milk formula)[1]
- 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 CMP-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.

iMAP Milk Ladder for Infants With Mild or Moderate Non-IgE–Mediated CMPA[1,a]



a. Recommended for use under the supervision of a health care provider and according to homemade recipes (steps 1-3).

1. Venter C et al. *Clin Transl Allergy.* 2017;7:26.

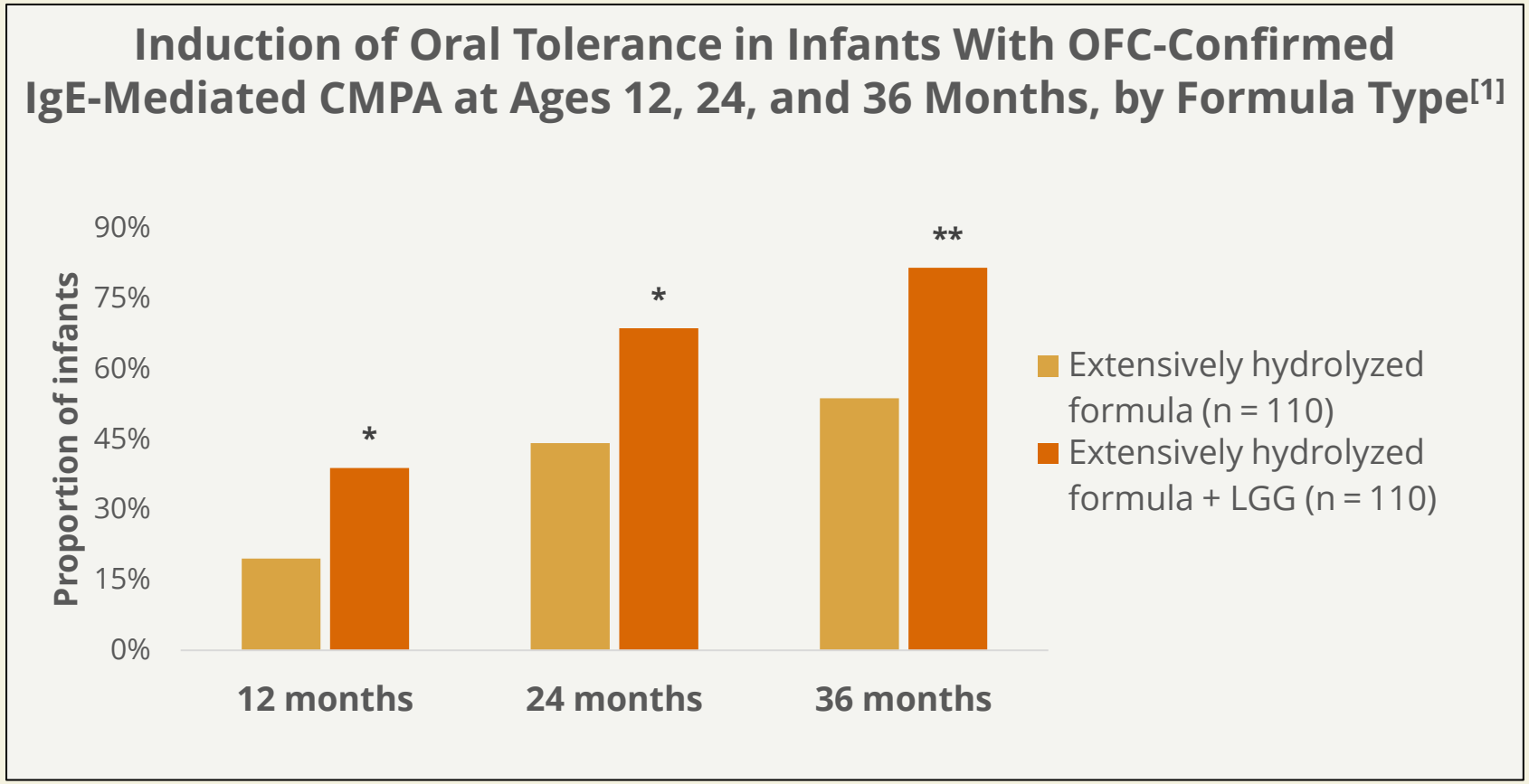
Probiotics & CMPA Management

Probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[1]

- Most commonly used genera in commercial products: *Lactobacillus* and *Bifidobacterium*[2,3]
  - Abundant in healthy breastfed infants
  - Associated with reduced intestinal permeability and improved immune modulation
- Infants with CMPA often have lower levels of these bacteria in their gut microbiomes[2]

1. Hill C et al. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506-514. **2.** Moriki D et al. *Nutrients*. 2022;14(21):4537. **3.** Li Y et al. *Nutrients*. 2022;14(24):5397.

CMP Tolerance With the Addition of *Lactobacillus rhamnosus* GG (LGG) to Formula[1]



In addition to improved CMP tolerance, **fewer allergic conditions** and **fewer functional GI disorders** developed in infants fed formula supplemented with LGG.[1,2]

* $P < .01$; ** $P < .001$

1. Berni Canani R et al. *J Allergy Clin Immunol.* 2017;139(6):1906-1913.e4. **2.** Nocerino R et al. *J Pediatr.* 2019;213:137-142.e2.

Oral Immunotherapy for IgE-Mediated CMPA

- **Oral immunotherapy (OIT)** can induce desensitization to CMP but does not typically "cure" CMPA (ie, sustained unresponsiveness)[1,2]
  - **Not** routinely recommended in patients with CMPA due to the risk for anaphylaxis and GI adverse effects
- **Recommendations for CMP OIT:**[1]
  - Consider for patients with confirmed IgE-mediated CMPA who value the ability to ingest controlled amounts of milk more than the potential risks
  - Consider use of omalizumab (anti-IgE antibody) when starting OIT
  - Avoid use in patients who cannot tolerate baked milk

OIT ≠ Food Ladder

Food ladders introduce allergens in forms that are likely to be tolerated by patients.[2]

OIT involves ingestion of allergens in forms known to cause allergic reactions.[2]

1. Brozek JL et al. *World Allergy Organ J.* 2022;15(4):100646. **2.** ASCIA. Position Paper - Oral Immunotherapy for Food Allergy. June 2023. https://www.allergy.org.au/hp/papers/ascia-oral-immunotherapy-for-food-allergy.

Key Takeaways

- The allergic march represents the natural history of allergic diseases, beginning with AD and potentially progressing to asthma.
- Gut dysbiosis, skin barrier dysfunction, and other genetic and environmental factors contribute to the progression of the allergic march.
- Extensively hydrolyzed formulas are typically the first-line approach for formula-fed infants with CMPA.
- CMPA has conventionally been managed through avoidance and periodic reintroduction to test for tolerance; food ladders and/or OIT can help to induce desensitization and/or tolerance.