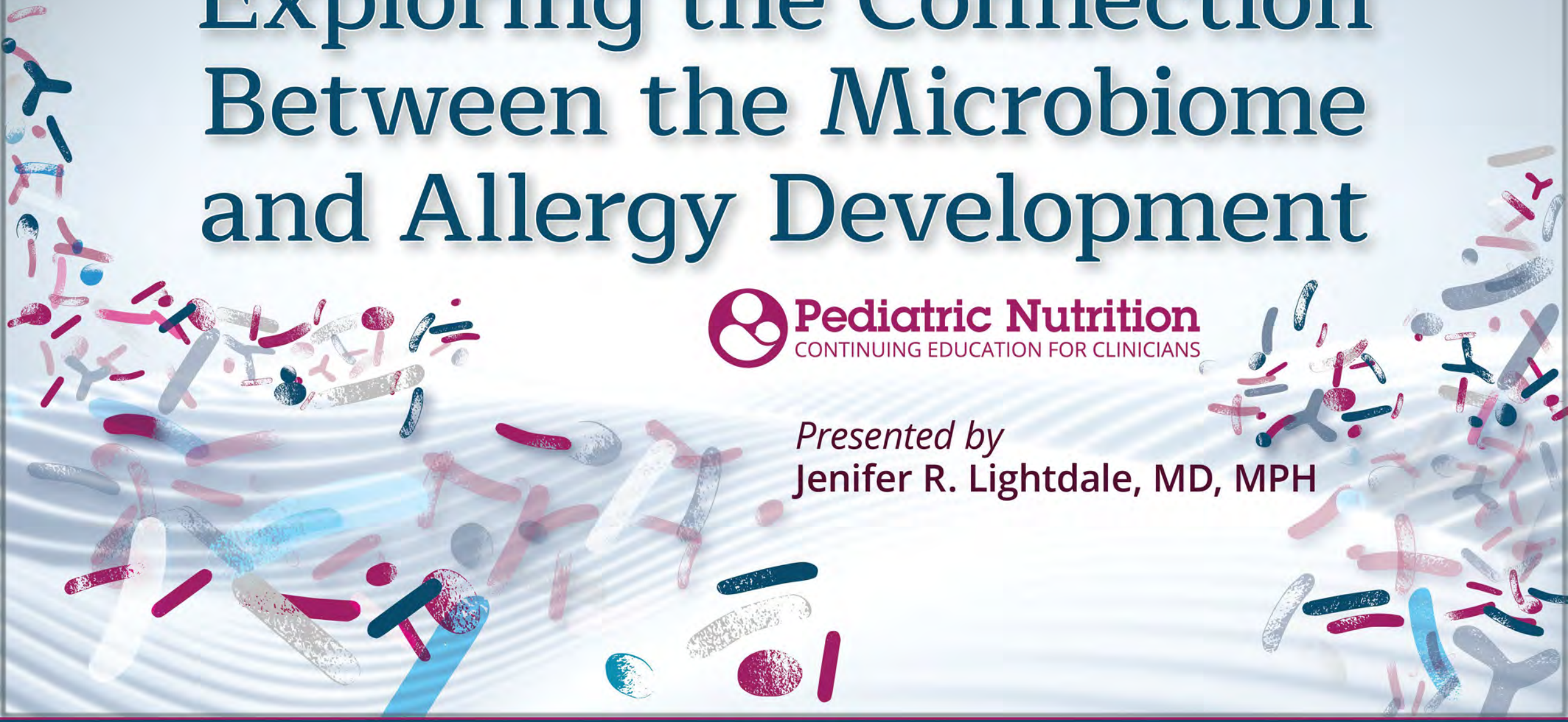
Exploring the Connection Between the Microbiome and Allergy Development



Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Presented by
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ANNENBERG CENTER FOR HEALTH SCIENCES
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This activity is supported by an educational grant from
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Learning Objectives

By participating in this education, you will better:

- Describe the diagnostic approach for CMPA, including clinical presentation, differential diagnosis, and diagnostic guidelines and criteria
- Recognize the role of the gut microbiome in immune system development and its subsequent impact on the risk of allergic disease
- Summarize the clinical and pharmacoeconomic impact of hypoallergenic formulas with probiotic LGG in the management of CMPA

Overview of Cow's Milk Protein Allergy

What Is Cow's Milk Protein Allergy (CMPA)?

- Adverse reaction involving an immune response to 1 or more protein fractions in mammalian milk[1],[2]
- Mammalian milk proteins:
  - Casein (~80%)
  - Whey (~20%)
    - » β-lactoglobulin and α-lactalbumin
- Can affect the gastrointestinal (GI) tract, skin, and respiratory tract, among multiple other systems[1],[2]
- Can cause systemic anaphylaxis[1],[2]

[1]. Flom JD, Sicherer SH. *Nutrients*. 2019;11(5):1051. [2]. Vandenplas Y. *Nutrients*. 2017;9(7):731.

Prevalence of CMPA in the United States

1.4 million

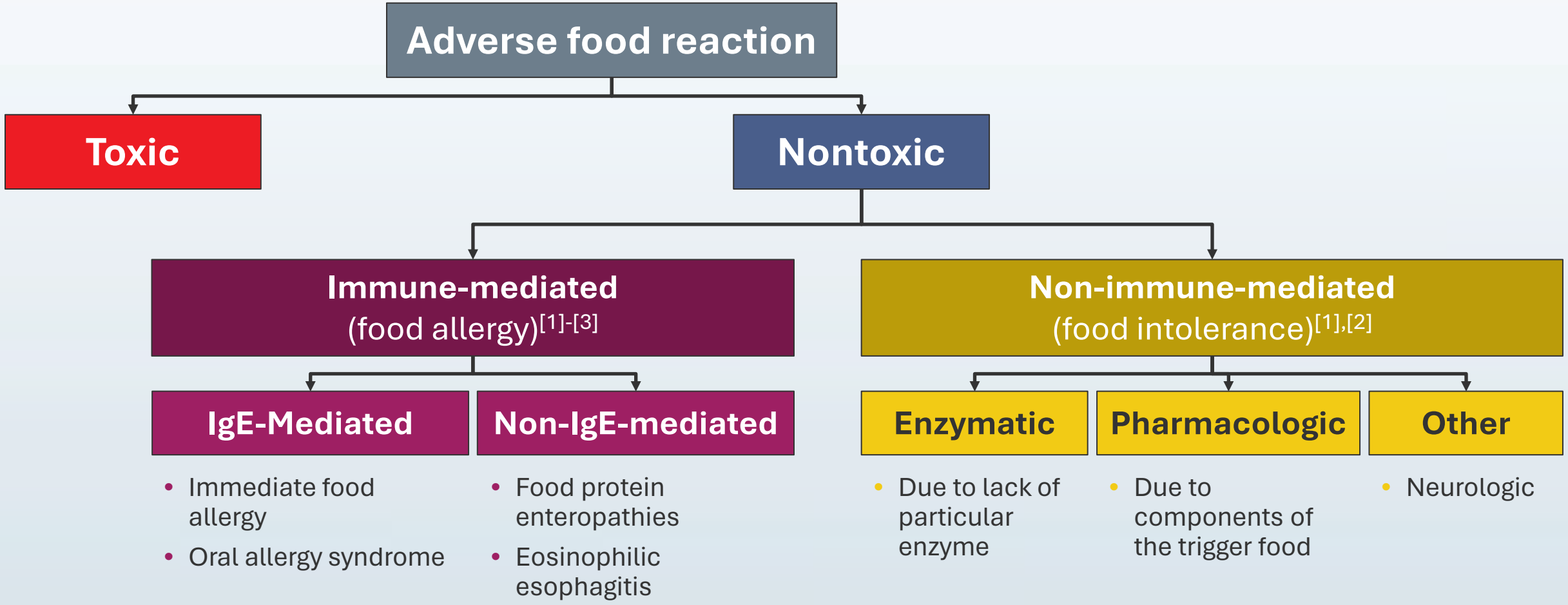
Estimated number of children with CMPA in the United States[1]

- **1.9% of US individuals** have cow's milk protein allergy (CMPA) with convincing symptoms by self-report or parent proxy-report[2]
- CMPA is the **most common** food allergy among infants and children 2 years and younger[a],[1]
  - Prevalence ranges from **1.5%** in infants younger than 1 year to **4.3%** in children aged 2–3 years

a. By parent-proxy responses and including only those with convincing symptoms of IgE-mediated food allergy.

[1]. Gupta RS et al. *Pediatrics*. 2018;142(6):e20181235. [2]. Warren CM et al. *World Allergy Organ J*. 2022;15(4):100644.

Classifying Adverse Reactions to Foods



[1]. Burks AW et al. *Pediatrics*. 2011;128(5):955-965. [2]. Burks AW et al. *J Allergy Clin Immunol*. 2012;129(4):906-920. [3]. Spergel JM. *Allergy Asthma Clin Immunol*. 2006;2(2):78-85.

Heterogeneous Clinical Presentation of CMPA

	IgE-mediated CMPA	Non-IgE-mediated CMPA
Onset of symptoms after exposure	Usually within minutes	Usually between 6–72 hours
General symptoms	• Anaphylaxis	• Colic/irritability • Failure to thrive • Iron deficiency anemia
Gastrointestinal symptoms	• Regurgitation/vomiting • Diarrhea	• Food refusal • Dysphagia • Regurgitation/vomiting • Diarrhea • Constipation • Anal fissures • Perianal rash • Blood loss
Respiratory symptoms	• Rhinitis • Conjunctivitis • Asthma • Mild dysphonia	• Rhinitis • Wheezing • Chronic cough
Cutaneous symptoms	• Atopic dermatitis • Oral allergy syndrome • Acute rash • Angioedema	• Atopic dermatitis

Most infants with CMPA have non-IgE-mediated allergy with mild-to-moderate symptoms.

Vandenplas et al. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413.

The Gut Microbiome, Immune System Development, and Food Sensitization

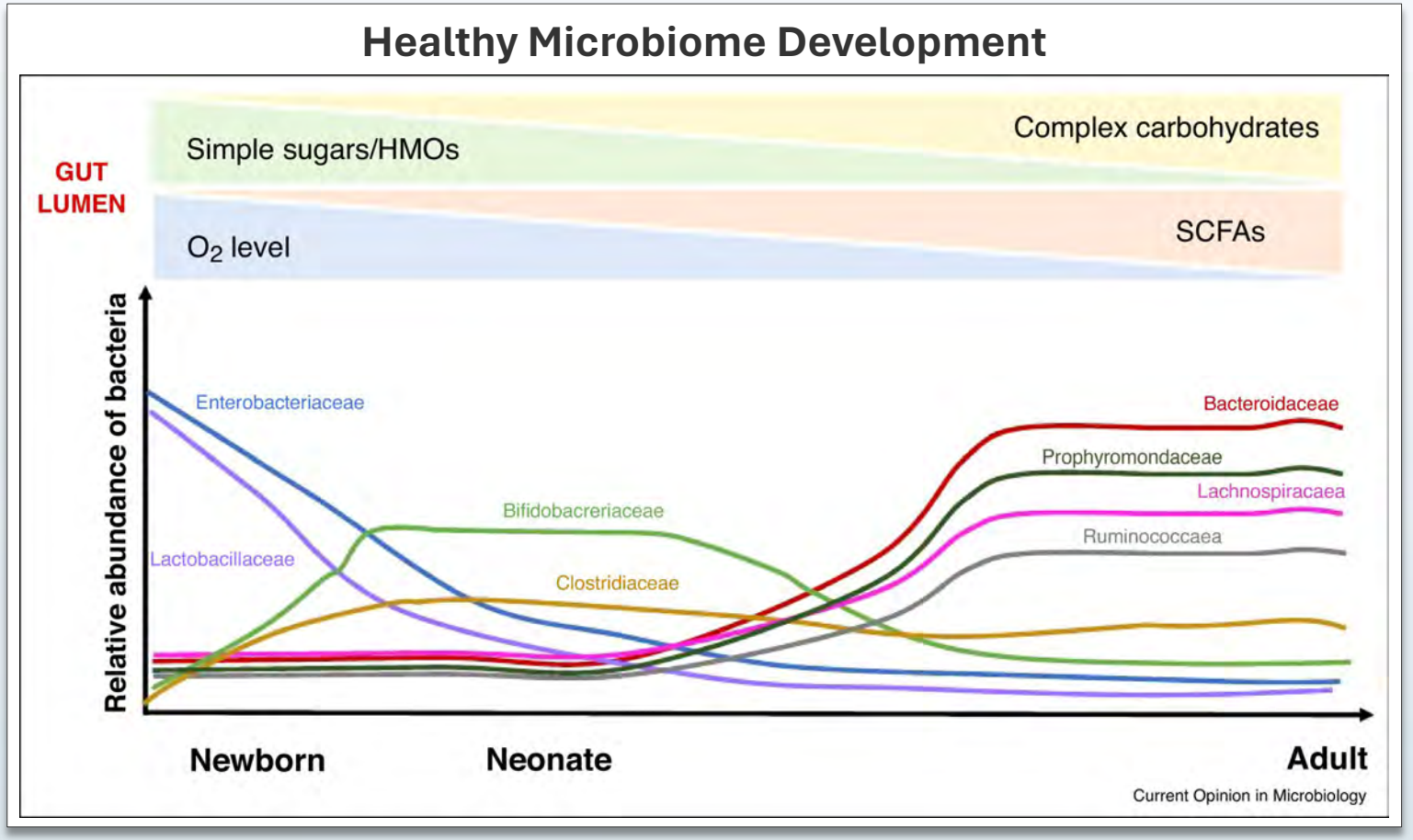
Relationship Between Human Immune System, Gut Epithelial Barrier and Microbiome

- **70%–80%** of the human immune system is located in the GI tract
- The **intestinal epithelium** separates the immune system and the microbiome
- There is emerging evidence of important **bidirectional interactions between the immune system** and the **gut microbiome**
  - Not fully understood yet
  - Involves interaction through and/or around the gut epithelium
  - Many examples of how dysbiosis may trigger immune dysfunction
  - May contribute to development of allergic and/or autoimmune diseases

Kinashi Y, Hase K. *Front Immunol*. 2021;12:673708.

The Dynamic Gut Microbiome During Infant Development

- Development of the gut microbiome is dynamic and responsive to external factors
- Predominated by *Enterobacteriaceae, Bifidobacteria,* and *Lactobacilli* early in infancy
- Over the first thousand days, relative abundance changes, and diversity increases



HMOs, human milk oligosaccharides; SCFAs, short-chain fatty acids.

Factors That Contribute to Dysbiosis in Infancy

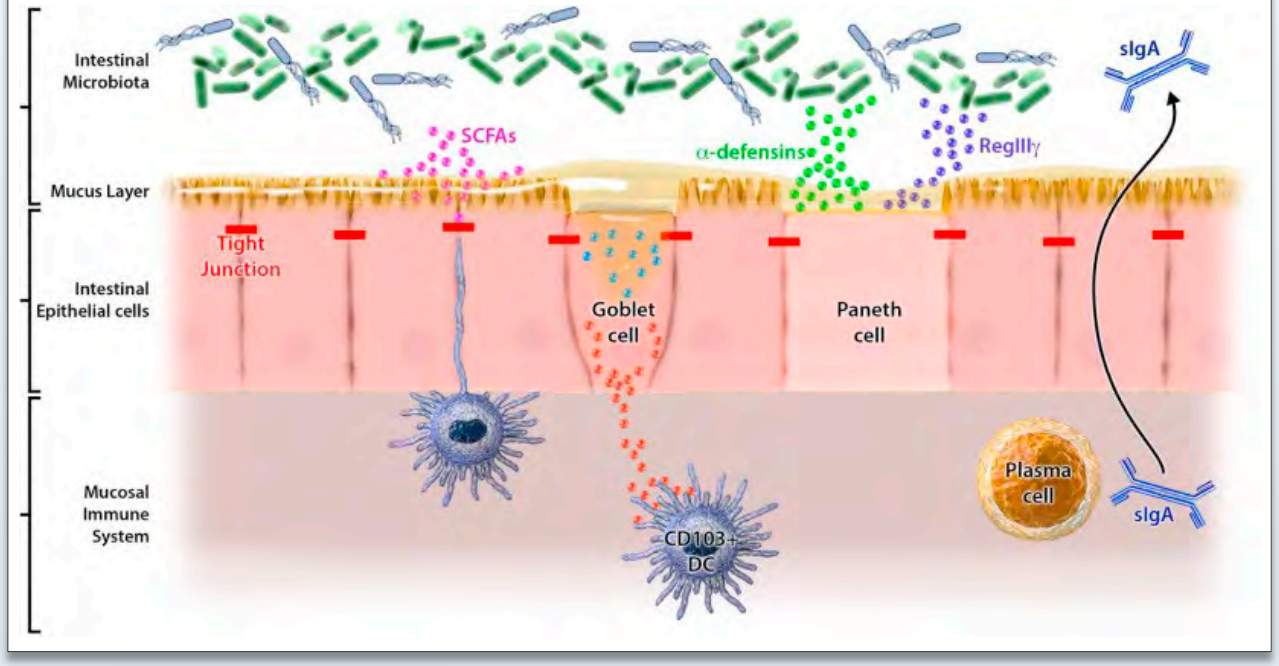
- Cesarean delivery (vs vaginal delivery)
- Earlier gestational age
- Antibiotic use
- Formula feeding (vs breastfeeding)
- Hospitalization in the NICU

Parkin K et al. *Microorganisms*. 2021;9(10):2066.

Gut Dysbiosis and Intestinal Barrier Permeability

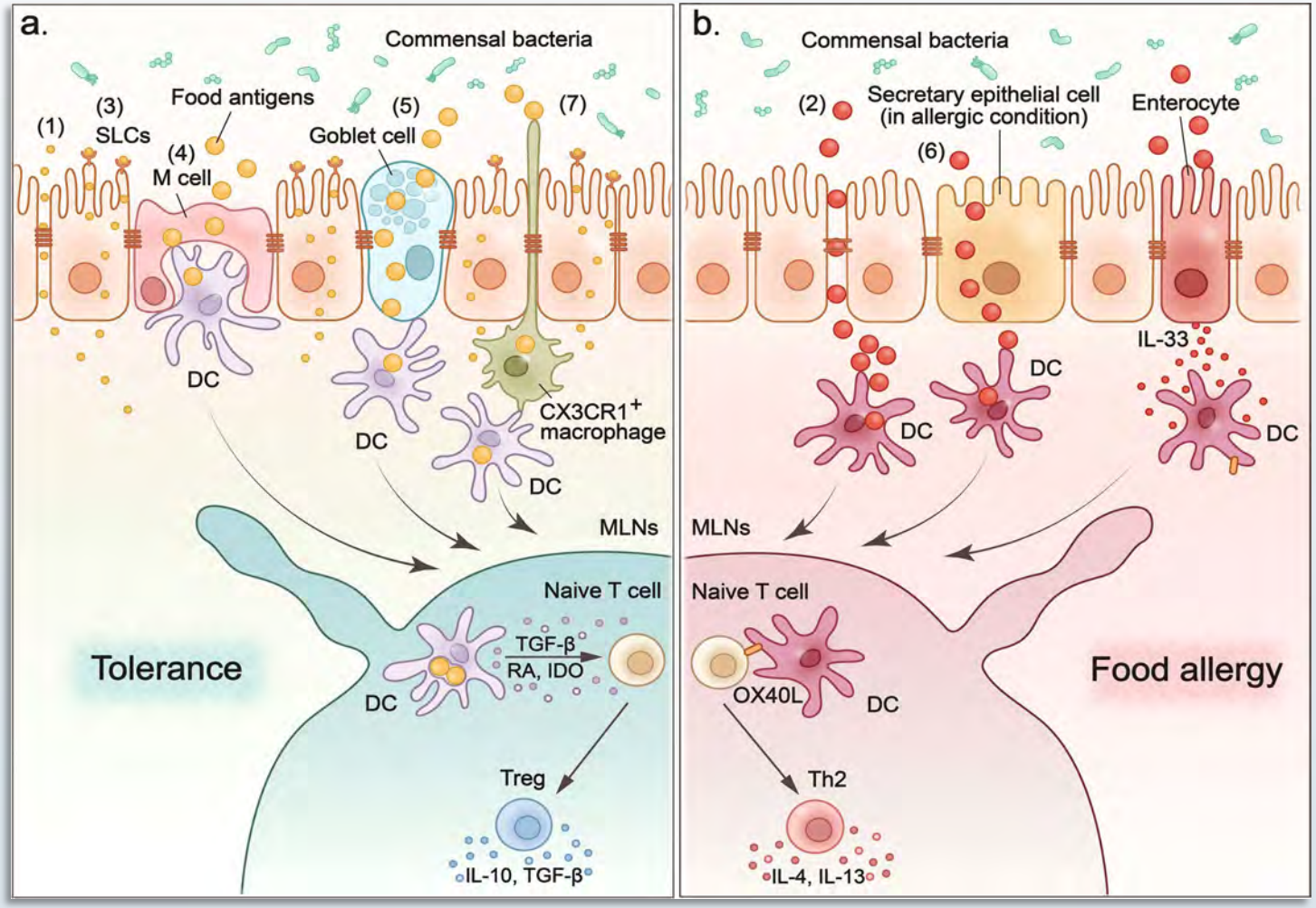
- A healthy intestinal barrier maintains selective permeability[1]
- Gut dysbiosis can lead to:[2]
  1. Pathologic toll-like receptor (TLR) activation
  2. Overexpression of proinflammatory mediators
  3. Epithelial damage
  4. Breakdown of the intestinal barrier

Layers of the Intestinal Barrier, Including Tight Junctions Within the Epithelial Layer[1]



Disruption of the intestinal barrier may be referred to as "**leaky gut.**"[2]

Intestinal Permeability and Atopic Diseases



Dysbiosis-mediated intestinal permeability can lead to uncontrolled entry of food antigens and contribute to the development of food allergy.

CMPA Management Practices

CMPA Diagnostic Challenges

- Both **over- and underdiagnosis** of CMPA occur, with overdiagnosis more common than underdiagnosis for non-IgE-mediated CMPA
  - Overdiagnosis associated with risk for growth faltering, micronutrient deficiencies, and worse familial quality of life
- Symptoms of CMPA make diagnosis a challenge because they are often…
  - **Common** in healthy infants (eg, colic, regurgitation)
  - **Nonspecific** and **overlapping** with other more common infant conditions (eg, functional gastrointestinal disorders)

Anaphylaxis is the only specific symptom of CMPA; all other symptoms are **nonspecific**, making accurate diagnosis a challenge.

Vandenplas et al. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413.

Recommendations for the Diagnosis of CMPA

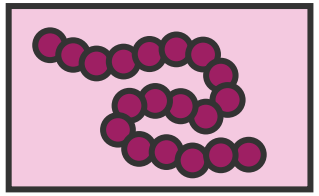
- The standard diagnostic procedure for CMPA is a **diagnostic elimination diet** followed by an **oral food challenge (OFC)**
- Diagnostic elimination diet for the formula-fed infant
  - 2–4 weeks
  - Extensively hydrolyzed cow's milk formula (eHF) with hypoallergenicity confirmed in RCTs—preferred diet
- If symptoms persist after 2–4 weeks of the diagnostic elimination diet, reevaluate for other food allergies and/or alternative diagnoses

Elevated serum IgE levels and positive skin prick test results show cow's milk sensitization but do not confirm CMPA.

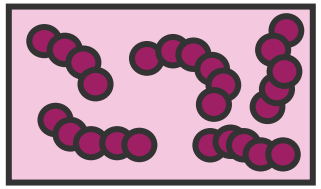
RCT, randomized controlled trial

CMPA Management: Therapeutic Elimination Diets for Formula-Fed Infants

Increasing hydrolysis level is associated with decreasing allergenicity



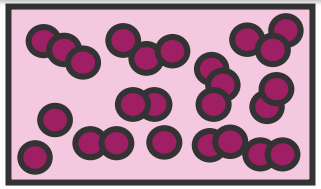
Intact cow's milk protein



Partial hydrolysis

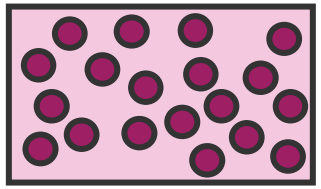
Not hypoallergenic; both large proteins and partially degraded peptides

Preferred for most therapeutic elimination diets



Extensive hydrolysis

Hypoallergenic; devoid of large intact proteins, but contain small peptides that may increase tolerance



Amino acids

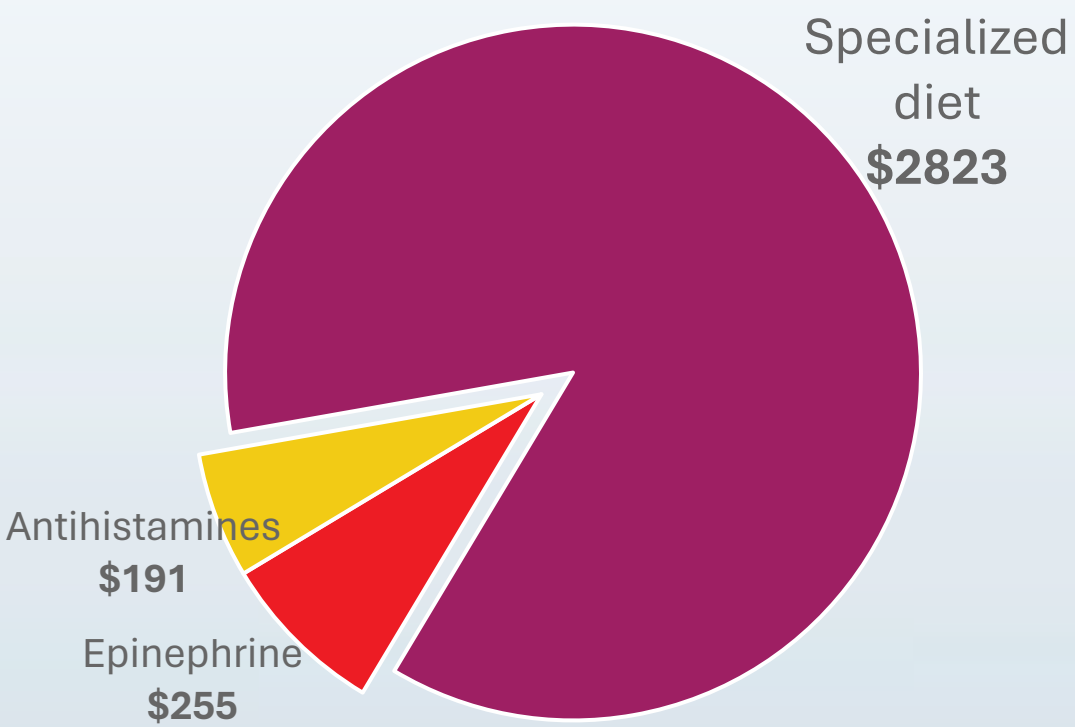
Hypoallergenic; individual amino acids, unlikely to increase tolerance acquisition

Decreasing allergenicity

Vandenplas et al. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413.

Specialized Formulas as Major Cost Burden for Families

Out-of-Pocket Costs for Families With Children With Food Allergies[1]



- Specialized formulas can be costly for families[2]
- Specialized formulas and foods are the major out-of-pocket costs for families of children with food allergies[1]
- eHF is generally more cost-effective than AAF[2]

[1]. Bilaver L et al. *J Allergy Clin Immunol*. 2023;151(2):AB186. [2]. Vandenplas et al. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413.

Probiotics in the Management of CMPA

Impact of the Gut Microbiome on CMPA Resolution

- Given the association between dysbiosis and food allergy development, interest in the effects of the microbiome on CMPA resolution has grown[1]
- In an observational study of 226 children with CMPA, researchers found that:[2]
  - **Gut microbiome composition** at 3 and 6 months was **predictive of CMPA resolution**
  - *Clostridia* and *Firmicutes* were enriched in the microbiome of infants whose CMPA resolved
- Therefore, microbiota manipulation through probiotics may influence the development of tolerance

[1]. Di Costanzo M et al. *Nutrients*. 2024;16(2):297. [2]. Bunyavanich S et al. *J Allergy Clin Immunol*. 2016;138(4):1122-1130.

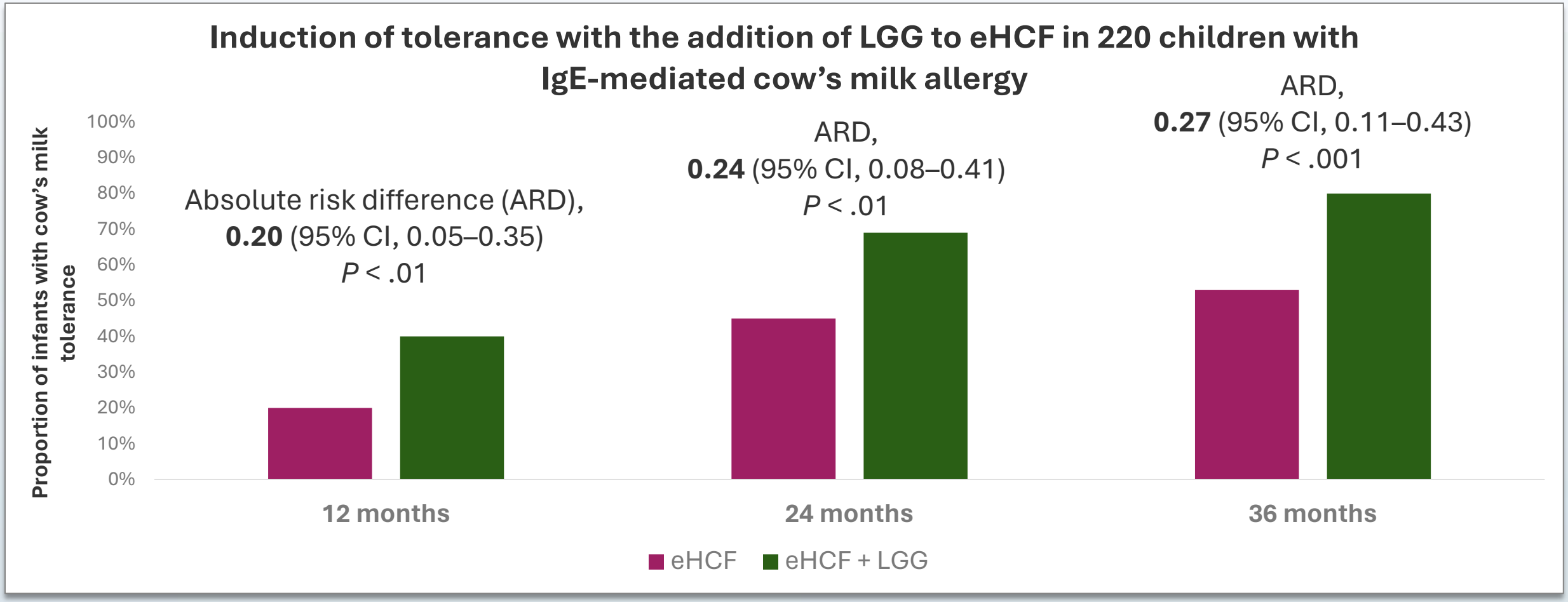
Probiotics Evaluated for CMPA: *Lactobacillus rhamnosus GG* (LGG)

- Benefits of probiotic supplementation depend on the bacterial strains used

- *L rhamnosus GG* (LGG) supplementation has been associated with several potential digestive and immune benefits in infants:
  - **Reduced allergy sensitization** and increased tolerance[1]
  - **Reduced diarrhea** duration and severity[2]
  - **Improved integrity** of the intestinal epithelial barrier
  - **Reduced risk** of respiratory infections[4]

[1]. Berni Canani R et al. *J Allergy Clin Immunol*. 2017;139(6):1906-1913.e1904. [2]. Nixon AF et al. *Pediatr Emerg Care*. 2012;28(10):1048-1051. [3]. Han X et al. *Gut Microbes*. 2019;10(1):59-76. [4]. Hojsak I et al. *Clin Nutr*. 2010;29(3):312-316.

Addition of LGG to eHCF for Tolerance Induction



eHCF, extensively hydrolyzed casein formula.

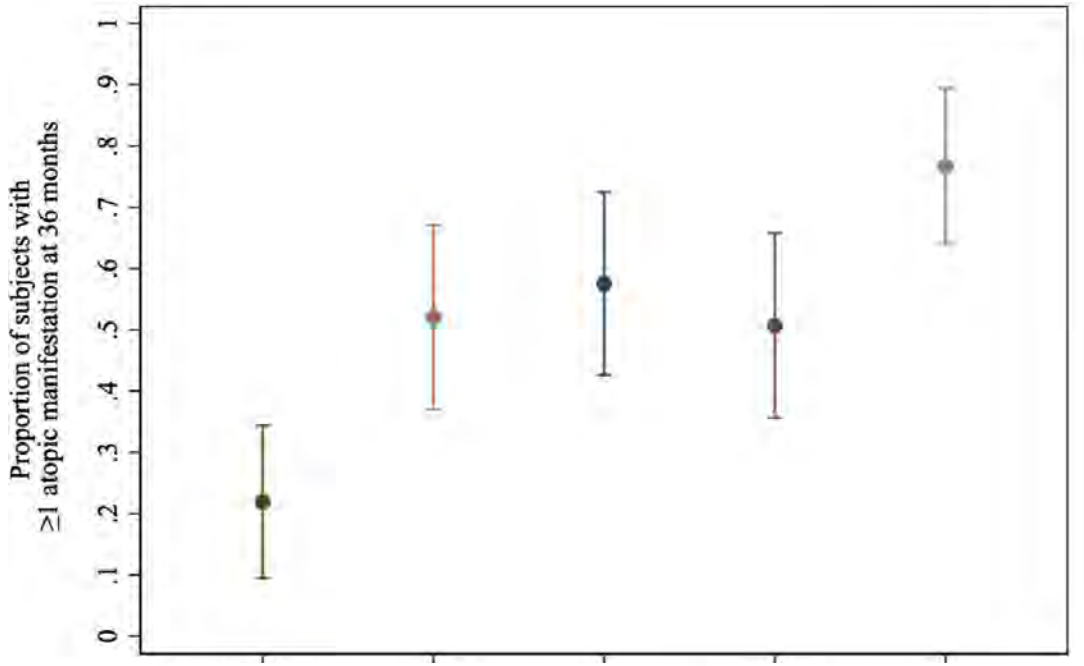
Berni Canani R et al. *J Allergy Clin Immunol*. 2017;139(6):1906-1913.e4.

Addition of LGG to eHCF and Time to Cow's Milk Protein Tolerance

Atopic March Cohort Study

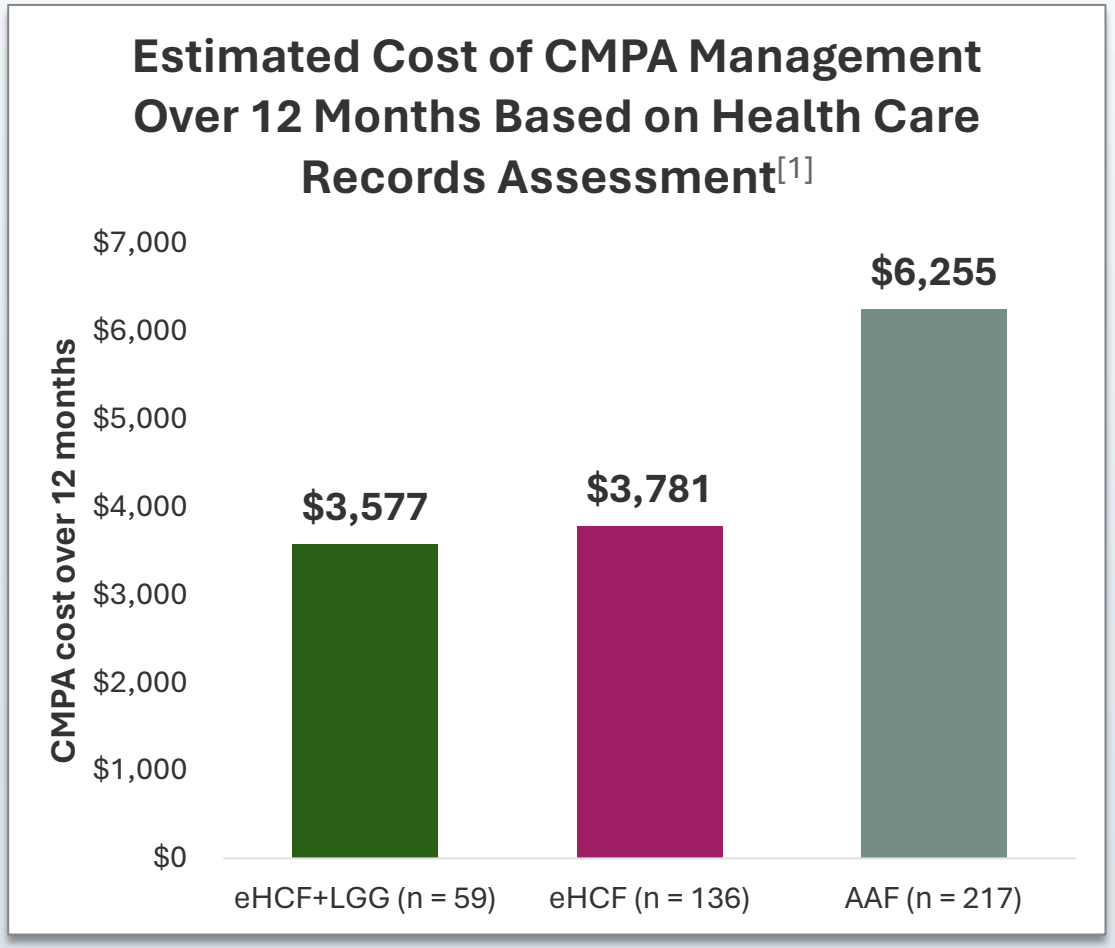
- Enrolled 365 infants with cow's milk allergy to different formula cohorts:
  - eHCF + LGG
  - Rice hydrolyzed formula (RHF)
  - Soy formula (SF)
  - eHWF
  - AAF
- Relative to other formula types, eHCF + LGG was associated with more rapid and durable tolerance

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



LGG Supplementation as a Cost-Effective Approach to CMPA Management

- eHCF+LGG has consistently been shown to be cost-effective relative to other therapeutic formulas including:[1]-[4]
  - eHCF alone
  - AAF
  - Soy formula
- Compared with AAF, eHCF+LGG is expected to save $6161 in CMPA management costs over 3 years[3]
- Cost benefits of eHCF+LGG are attributed to more rapid tolerance and shorter duration of specialized diet

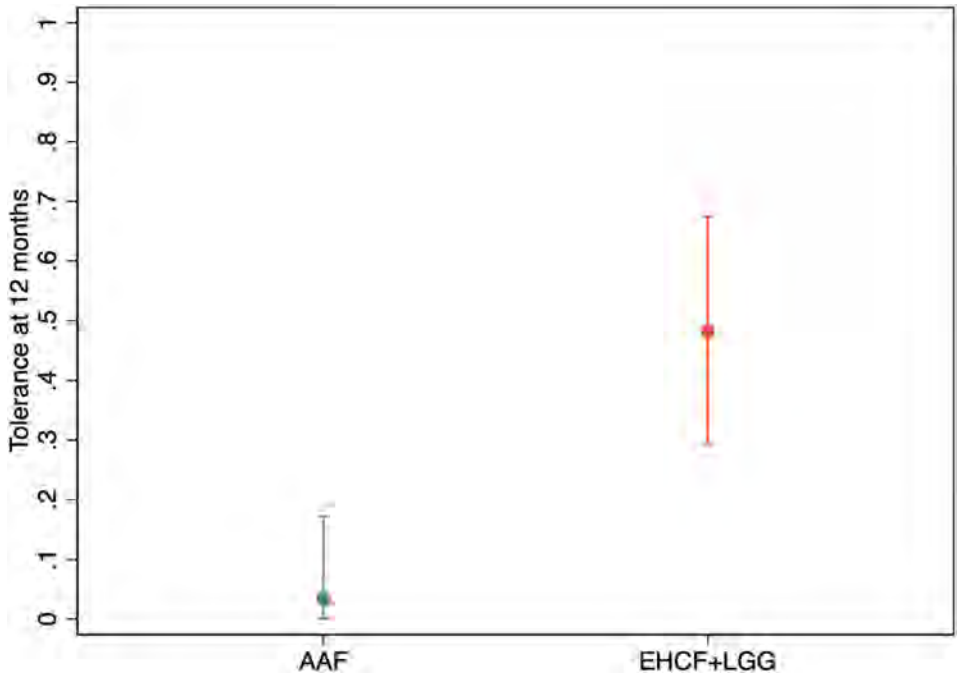


[1]. Ovcinnikova O et al. *Clinicoecon Outcomes Res*. 2015;7:145-152. [2]. Guest JF et al. *Curr Med Res Opin*. 2019;35(10):1677-1685. [3]. Suratannon N et al. *Front Nutr*. 2023;10:1099462. [4]. Guest JF et al. *Clinicoecon Outcomes Res*. 2015;7:325-336.

Considerations for Your Practice

Considerations for Your Practice: Stepping Down From AAF With eHCF + LGG

Tolerance to Cow's Milk Protein at 12 Months of Age, by Formula Choice



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 continue AAF or switch to eHCF+LGG
- Switching to eHCF+LGG was well tolerated and associated with more rapid tolerance acquisition

Most infants on AAF for CMPA can be safely transitioned to eHCF+LGG.

Nocerino R et al. *Allergy*. 2023;78(9):2477-2486.

Prognosis of CMPA: Development of Tolerance

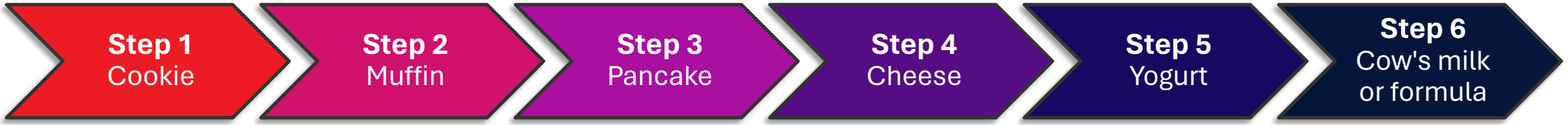
- CMPA is transient in most infants[1]
  - Most (but not all) will outgrow CMPA by 3–4 years of age[1]-[4]
- Rates of tolerance acquisition vary by study:
  - Caroccio et al (2000)[2]
    - » 30% at 1 year
    - » 54% at 2 years
    - » 70% at 3 years
  - Vanto et al (2004)[3]
    - » 96% of non-IgE-mediated CMPA at 3 years
    - » 63% of IgE-mediated CMPA at 3 years
  - Skripak et al (2007)[4]
    - » Median age IgE-mediated CMPA resolution of 10 years

[1]. Chatchatee P et al. *J Allergy Clin Immunol*. 2022;149(2):650-658.e5. [2]. Carroccio A et al. *Allergy*. 2000;55(6):574-579. [3]. Vanto T et al. *J Pediatr*. 2004;144(2):218-222. [4]. Skripak JM et al. *J Allergy Clin Immunol*. 2007;120(5):1172-1177.

Reintroduction of Milk Using Current Guidelines

- Reintroduction may be trialed **after 6 months** or **at age 1 year** (whichever comes first)[1]
- Consider at-home milk reintroduction trial[1]
  - Except for severe IgE-mediated CMPA and FPIES
- Use a standardized **"milk ladder"** approach[1],[2]
  - Begins with theoretically less antigenic foods at small doses (eg, bite of a baked muffin) and moves stepwise to more antigenic foods with higher doses of intact proteins (eg, yogurt)

Example Foods Used in a Milk Ladder[2]



FPIES, food protein-induced enterocolitis syndrome.

[1]. Vandenplas et al. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413. [2]. Venter C et al. *Clin Transl Allergy*. 2017;7:26.

Persistent Symptoms After Reintroduction: Next Steps

- May consider retrial every 6 months according to ESPGHAN guidelines[1]
- If symptoms persist at 12 months, check IgE levels (casein, whey, lactalbumin)
- In children with IgE-mediated CMPA, higher peak IgE levels are associated with longer duration of allergy[2]
  - May use skin prick tests to guide exposure timing

[1]. Vandenplas et al. *J Pediatr Gastroenterol Nutr*. 2024;78(2):386-413. [2]. Protudjer JLP et al. *Nutrients*. 2018;10(5):651.

Considerations for Your Practice: Counseling Caregivers & Managing CMPA

- Important to **rigorously diagnose** CMPA
  - Recognize it to be a clinical diagnosis that relies on patient reports
  - Counsel about risks of over-diagnosing and restricting cow's milk protein unnecessarily
  - Positively manage those patients who do have CMPA
- Follow infants with CMPA regularly to **monitor growth**
- Provide dietary counseling that **intentionally "steps up" milk protein exposure** via a ladder approach
- Develop resources for **accessing specialty formulas** and **determine back-up plans** in case of shortages

Key Takeaways

Key Takeaways: CMPA & the Microbiome

- CMPA is the most common immune-mediated adverse food reaction.
- The immune system is highly influenced by the microbiome; over the first 1000 days of life, the microbiome exhibits a dynamic nature reflective of a variety of influences, including the source of nutrients.
- Dysbiosis, or an imbalanced microbiome, may lead to food allergy, including CMPA, through intestinal barrier permeability.

Key Takeaways: CMPA Management

- Treat CMPA by prescribing a diet that is devoid of intact cow's milk proteins (eg, eHF), and consider the potential role of probiotics in addressing allergy.
- Recognize the economic impact of prescribing therapeutic formulas.
- Intentionally re-introduce intact proteins through a graduated approach (a "milk ladder").