

Exploring the Connection Between the Microbiome and Allergy Development



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Consultant


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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]}



Prevalence of CMPA in the United States



1.4 million

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

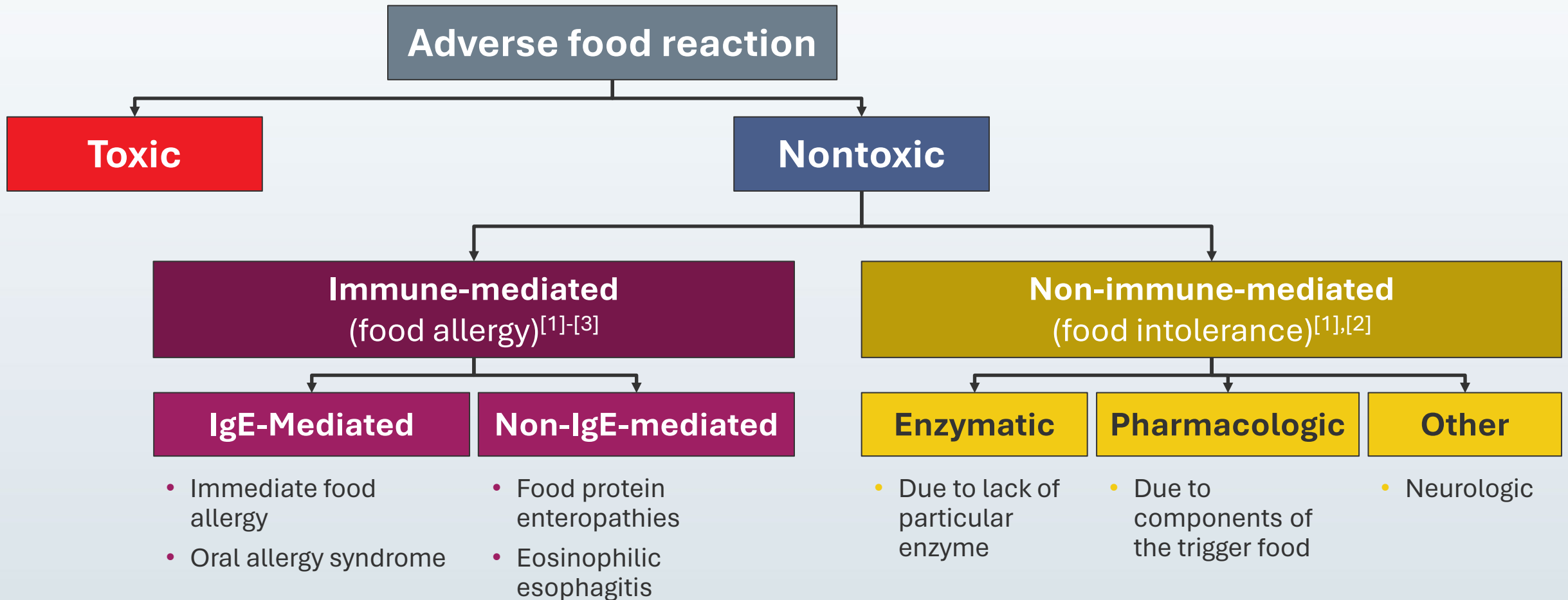
- **1.9% of US individuals** have cow's milk protein allergy (CMPA) with convincing symptoms by self-report or parent proxy-report^[2]
- CMPA is the **most common** food allergy among infants and children 2 years and younger^{[a],[1]}
 - Prevalence ranges from **1.5%** in infants younger than 1 year 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	<ul style="list-style-type: none"> • Anaphylaxis 	<ul style="list-style-type: none"> • Colic/irritability • Failure to thrive • Iron deficiency anemia
Gastrointestinal symptoms	<ul style="list-style-type: none"> • Regurgitation/vomiting • Diarrhea 	<ul style="list-style-type: none"> • Food refusal • Dysphagia • Regurgitation/vomiting • Diarrhea • Constipation • Anal fissures • Perianal rash • Blood loss
Respiratory symptoms	<ul style="list-style-type: none"> • Rhinitis • Conjunctivitis 	<ul style="list-style-type: none"> • Asthma • Mild dysphonia • Rhinitis • Wheezing
Cutaneous symptoms	<ul style="list-style-type: none"> • Atopic dermatitis • Oral allergy syndrome 	<ul style="list-style-type: none"> • Acute rash • Angioedema • Atopic dermatitis

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



The Gut Microbiome, Immune System Development, and Food Sensitization



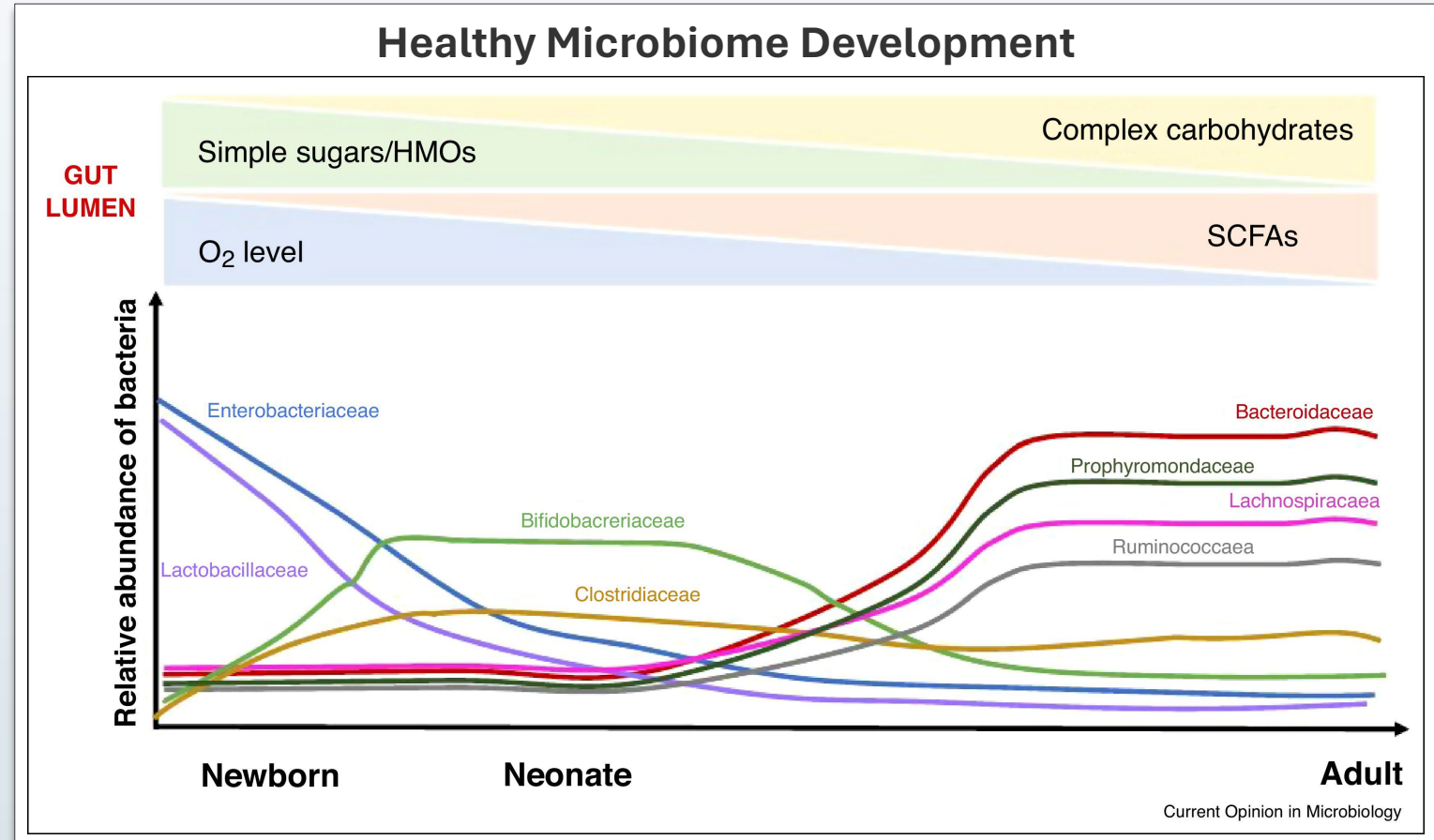
Relationship Between Human Immune System, Gut Epithelial Barrier and Microbiome

- **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



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)**

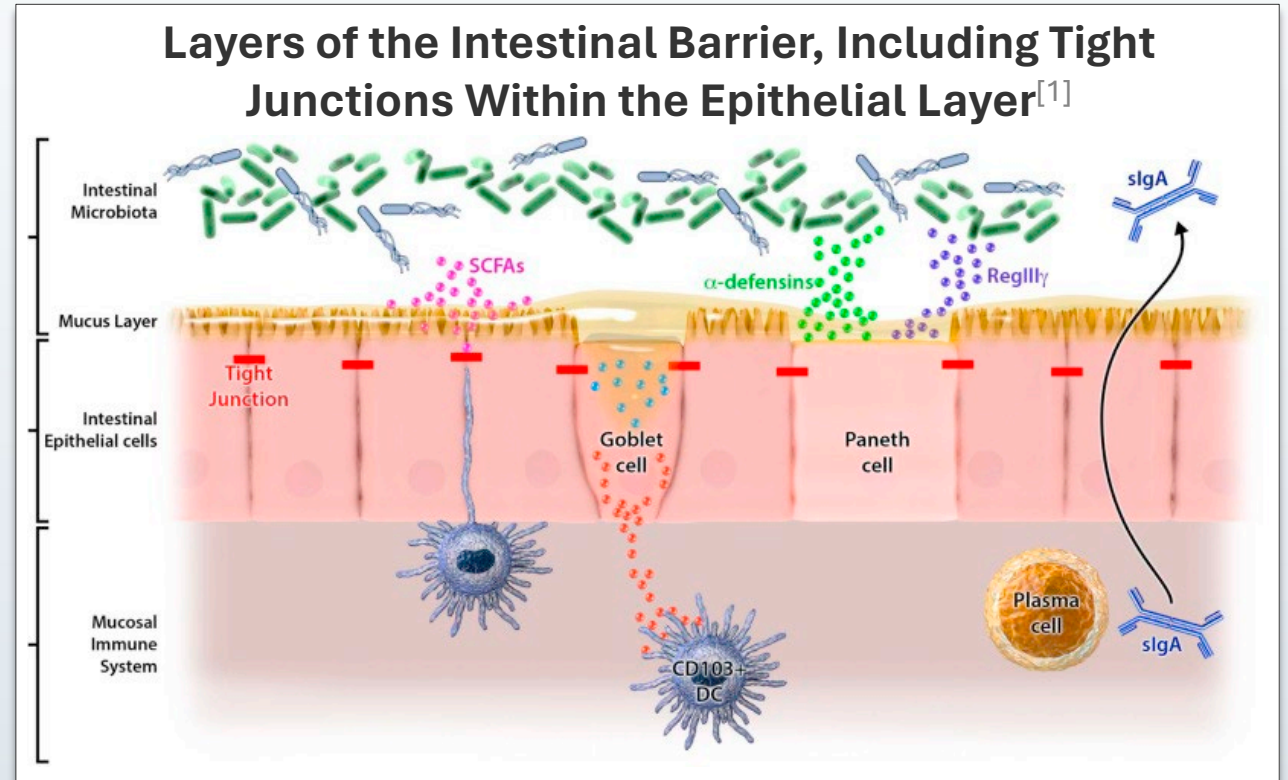


**Hospitalization in the
NICU**



Gut Dysbiosis and Intestinal Barrier Permeability

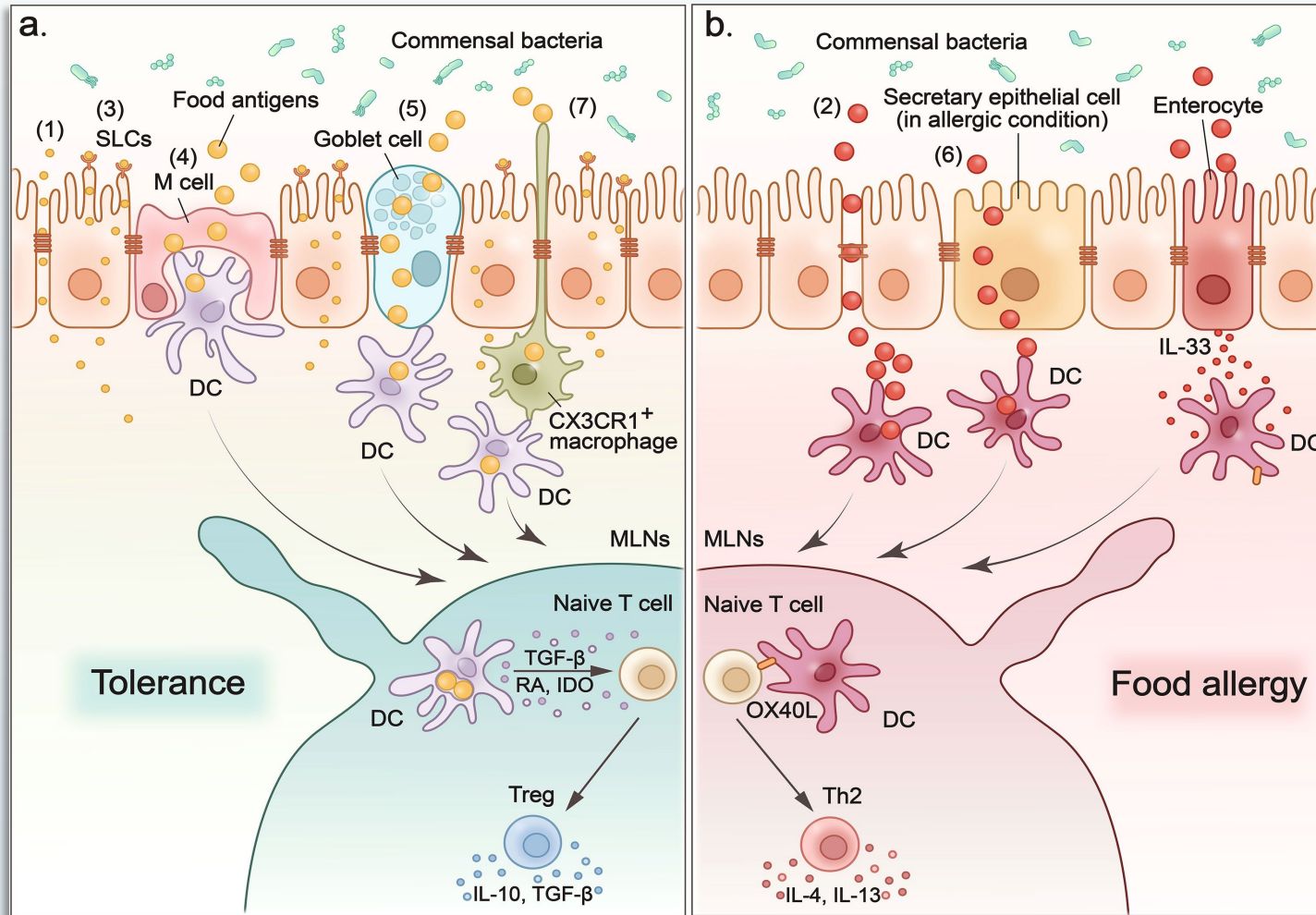
- A healthy intestinal barrier maintains selective permeability^[1]
- Gut dysbiosis can lead to:^[2]
 1. Pathologic toll-like receptor (TLR) activation
 2. Overexpression of proinflammatory mediators
 3. Epithelial damage
 4. Breakdown of the intestinal barrier



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.



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

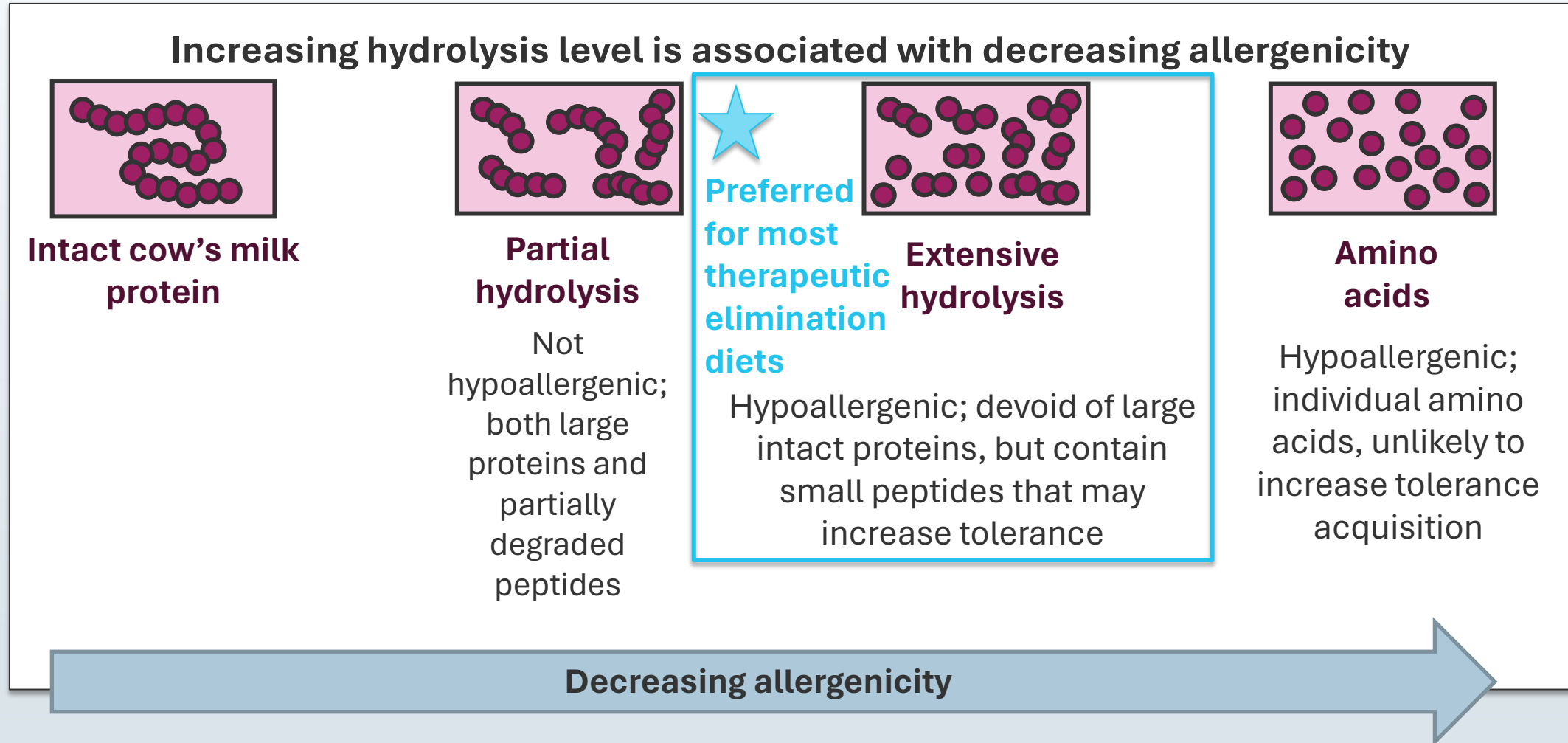


Elevated serum IgE levels and positive skin prick test results show cow’s milk sensitization but do not confirm CMPA.

RCT, randomized controlled trial

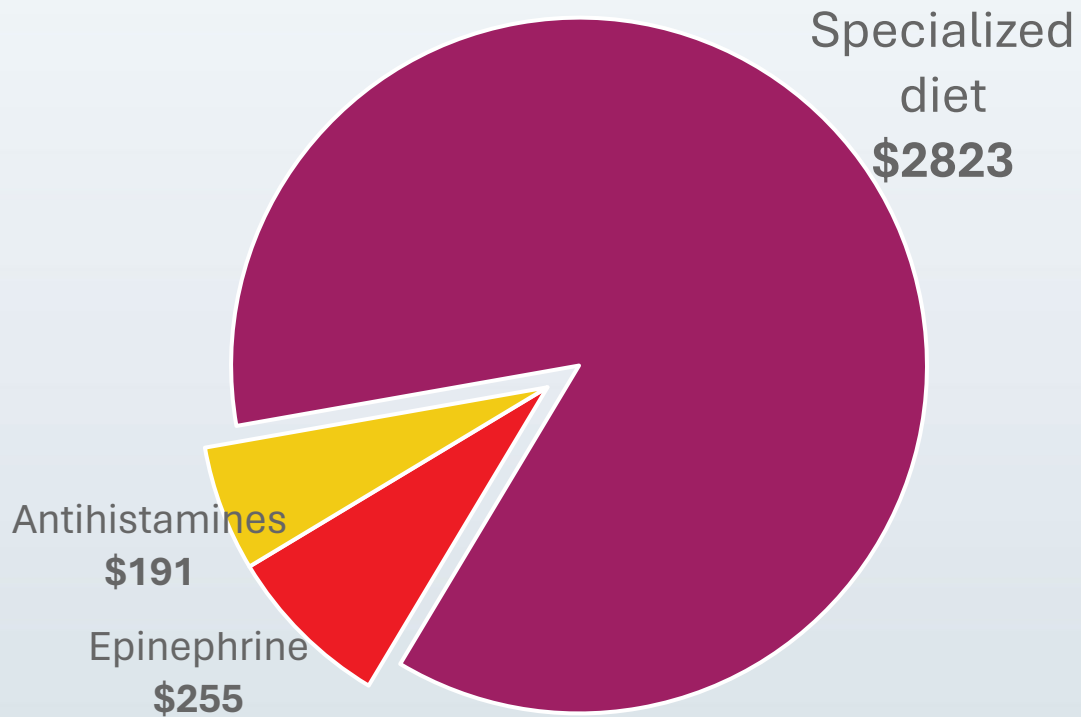


CMPA Management: Therapeutic Elimination Diets for Formula-Fed Infants



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 amino acid formula (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



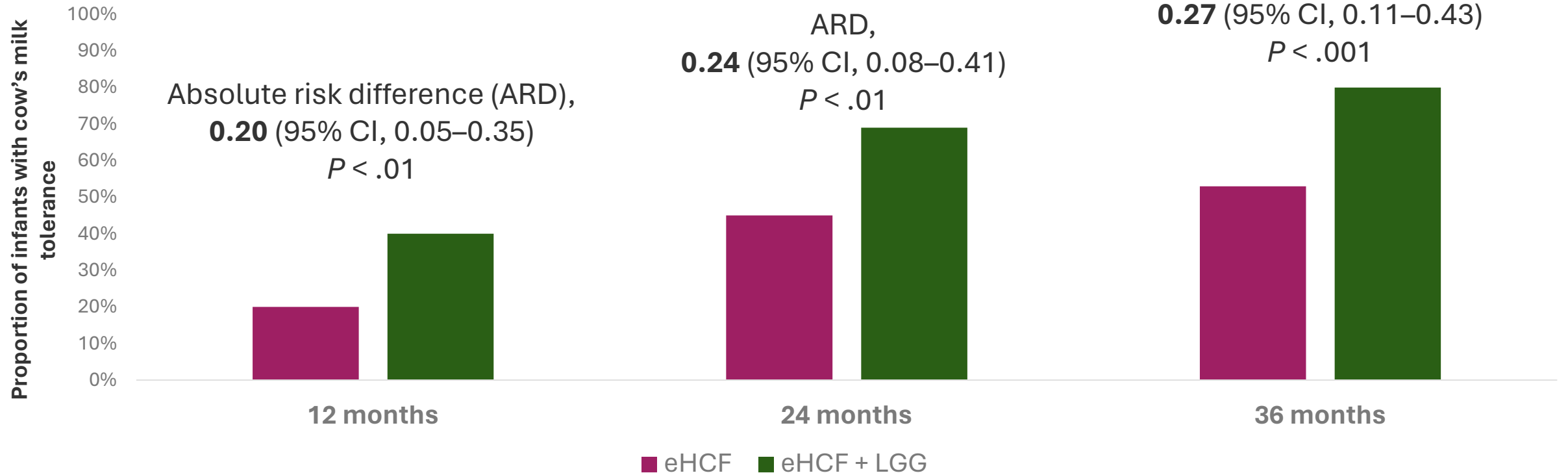
Probiotics Evaluated for CMPA: *Lactobacillus rhamnosus GG* (LGG)

- 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]



Addition of LGG to eHCF for Tolerance Induction

Induction of tolerance with the addition of LGG to eHCF in 220 children with IgE-mediated cow's milk allergy



eHCF, extensively hydrolyzed casein formula.

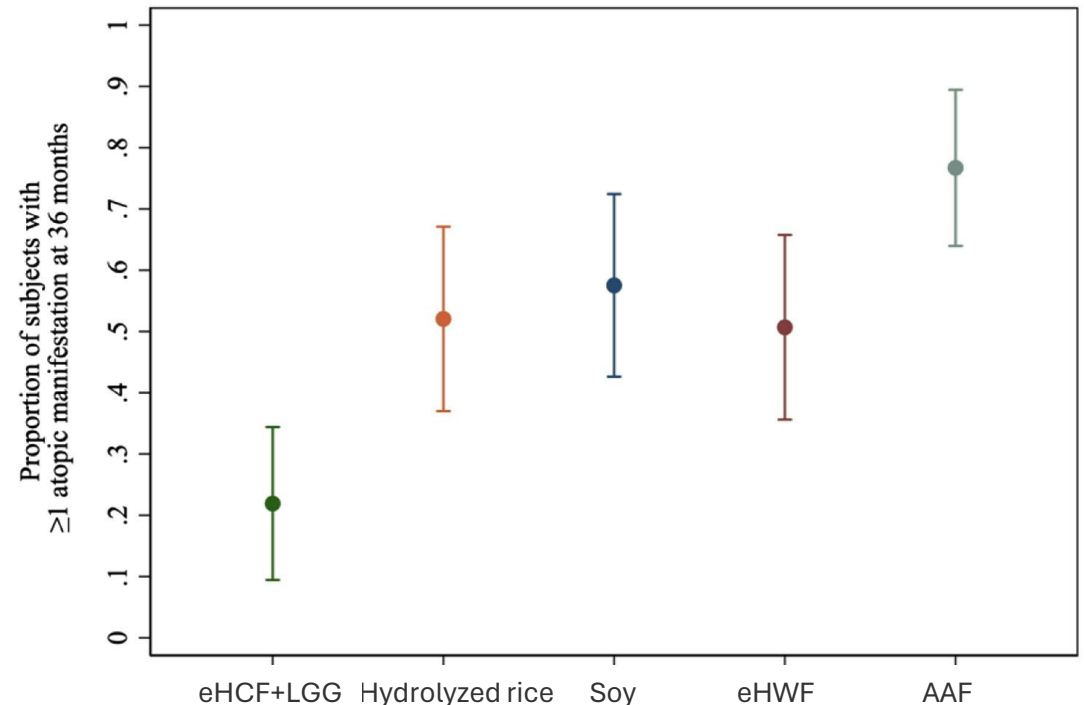


Addition of LGG to eHCF and Time to Cow's Milk Protein Tolerance

Atopic March Cohort Study

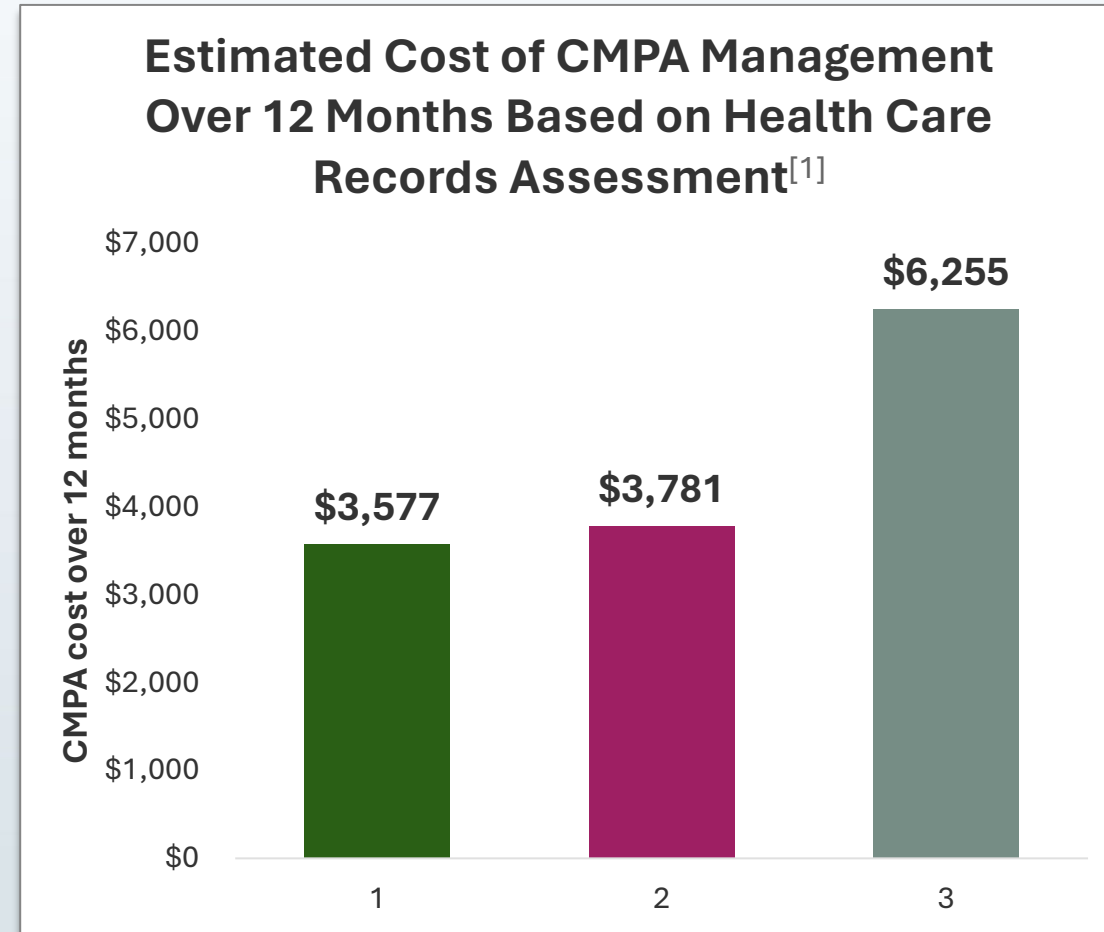
- Enrolled 365 infants with cow's milk allergy to different formula cohorts:
 - eHCF + LGG
 - Rice hydrolyzed formula (RHF)
 - Soy formula (SF)
 - eHWF
 - AAF
- Relative to other formula types, eHCF + LGG was associated with more rapid and durable tolerance

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.

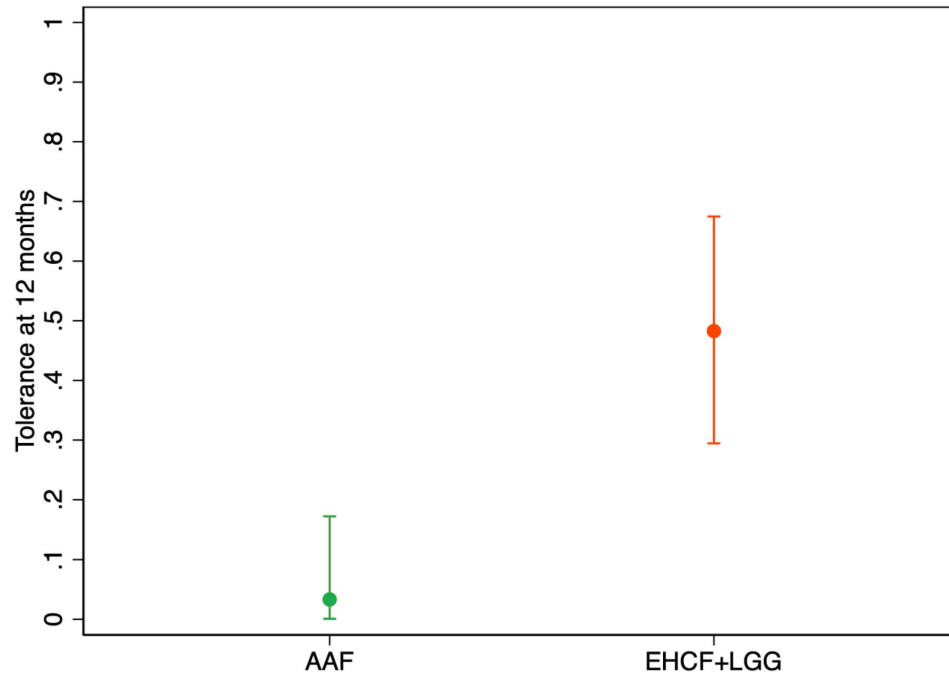


Considerations for Your Practice



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.



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:
 - Carroccio 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



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.



Persistent Symptoms After Reintroduction: Next Steps

- May consider retriial 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



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”).

