

Immunology in Infants and Food Allergy Management

Cow's Milk Allergy: Mechanisms, Diagnosis, and Treatment



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Additional Disclosures for Dr. Fleischer

During the past 2 years, I **have/had** an affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of my presentation(s).

Financial Interest/Affiliation	Name of Company(s)
Grant/research support	DBV Technologies Aimmune Therapeutics
Membership on an advisory panel, standing committee, or board of directors	NIAID Coordinating Committee and Expert Panel, Update to the Food Allergy Guidelines, Prevention of Peanut Allergy Medical Advisory Board for the Food Allergy & Anaphylaxis Connection Team (FAACT); Clinical Advisory Board for Food Allergy Research & Education (FARE); Medical Advisory Council for the National Peanut Board
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Learning Objectives



Apply current standard of care for the diagnosis and management of cow's milk allergy in infants



Link research targets to diagnosis and treatment of cow's milk allergy



Specify nutritional strategies to manage food allergy in infants



MODULE 1: DIAGNOSING AND MANAGING FOOD ALLERGIES IN INFANTS

- Define food allergy
- Diagnosis of food allergies in infants
 - Cow's milk allergy (CMA), specifically
- Prevalence food allergies
- Strategies for proper diagnosis
- Distinguish between IgE-mediated and non-IgE-mediated food reactions



Food Allergy Defined

- NIAID consensus definition: Adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food
- Food allergy develops as a lack of oral tolerance, which is a default immune response by the gut-associated lymphoid tissues to ingested antigens that is modified by the gut microbiota

NIAID, National Institute of Allergy and Infectious Diseases.

Boyce JA, et al. *J Allergy Clin Immunol*. 2010;126:S1-58; Nowak-Wegrzyn A, et al. *Nat Rev Gastroenterol Hepatol*. 2017;14:241.



Types of Adverse Reactions to Food

Food Aversion

Adverse Food Reaction

Immune Mediated
(food allergy)

Non-Immune Mediated
(food intolerance)

IgE
Mediated

Non-IgE
Mediated

Mixed IgE
and
Non-IgE
Mediated

Cell
Mediated

Toxic

Metabolic

Pharma-
cologic

Idio-
syncratic

Other

Adapted from *J Allergy Clin Immunol.* 2010;126:S1-S58.





Gastrointestinal Hypersensitivity Disorders

**Pollen-Food Allergy Syndrome
Immediate GI Hypersensitivity**

**Eosinophilic Esophagitis
Eosinophilic Gastritis
Eosinophilic Gastroenteritis**

**Dietary Protein Enterocolitis
Dietary Protein Proctitis
Dietary Protein Enteropathy
(Celiac Disease)**

Cutaneous Hypersensitivity Disorders

**Acute Urticaria & Angioedema
Acute Contact Urticaria**

Atopic Dermatitis

Dermatitis Herpetiformis

Respiratory Hypersensitivity Disorders

**Allergic Rhinitis
Acute Bronchospasm**

Asthma

**Food-induced Pulmonary Hemosiderosis
(Heiner's Syndrome)**

Systemic Hypersensitivity Disorders

**Generalized Anaphylaxis
Food-associated Exercise-induced Anaphylaxis**

Sampson HA. *J Allergy Clin Immunol.* 1999;103:721.



Food Allergy Prevalence in Infants and Toddlers

- Food allergy affects 4–8% of children <5 years in U.S.
 - ~5.9 million children under age 18
 - 38.7% have history of severe reactions
 - 30% have multiple food allergies
- Comparatively, 3–4% of the general population in developed countries
- Prevalence increasing
 - Peanut and tree nut allergies increased considerably over the past decade (more than tripled 1997–2008)
- **Our focus—cow's milk allergy (CMA)**
 - Prevalence of 2.5% <1 yr old in US



Major Food Allergy in Infants and Toddlers

Most Common Food Allergies

*Cow's milk allergy (CMA)

Egg

Wheat

Soybean

Peanut

Tree nuts

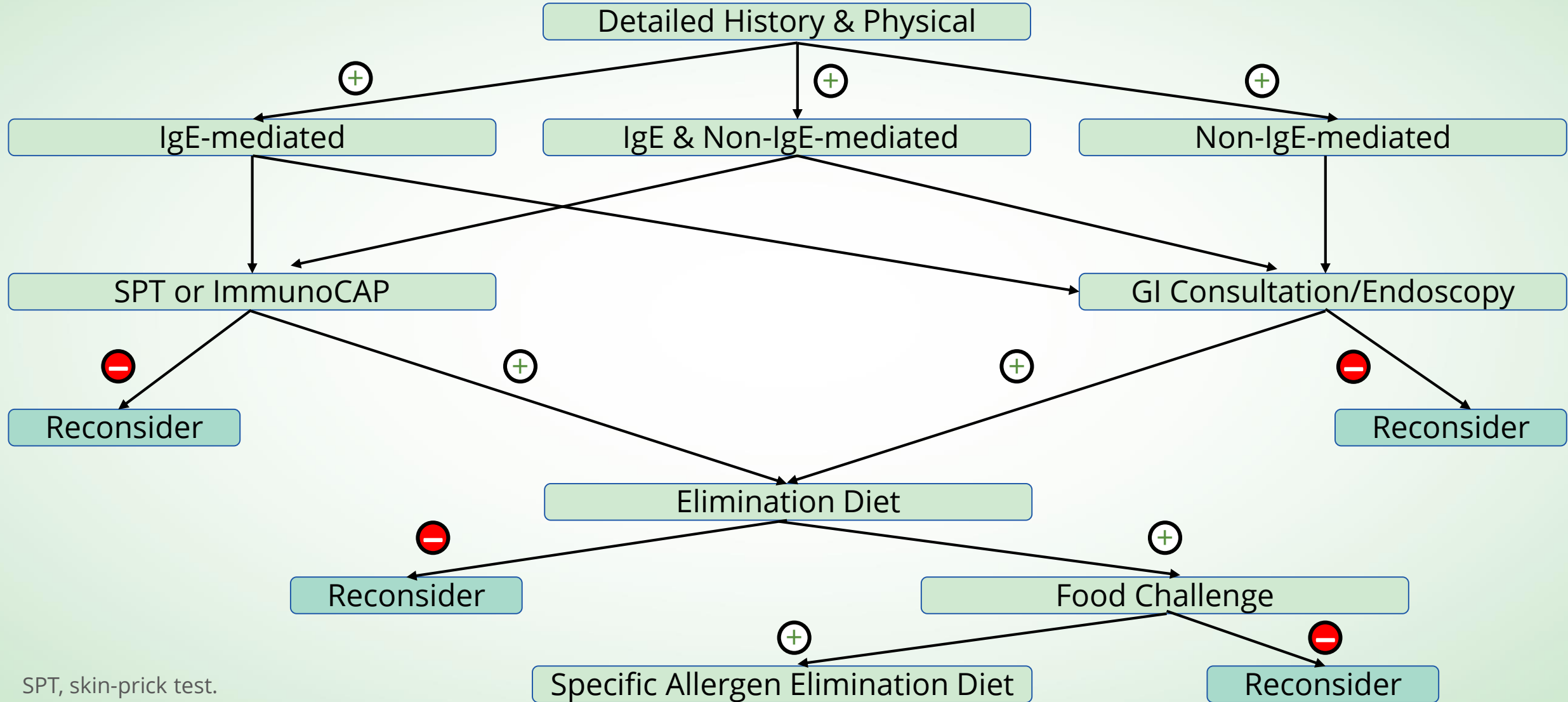
Shellfish

Fish

*Most common of food allergies, with prevalence in children ranging between 1.9% and 4.9%.



Diagnostic Approach to the Evaluation of Food Allergy



SPT, skin-prick test.

Sampson HA. *J Allergy Clin Immunol.* 1999;103:721.



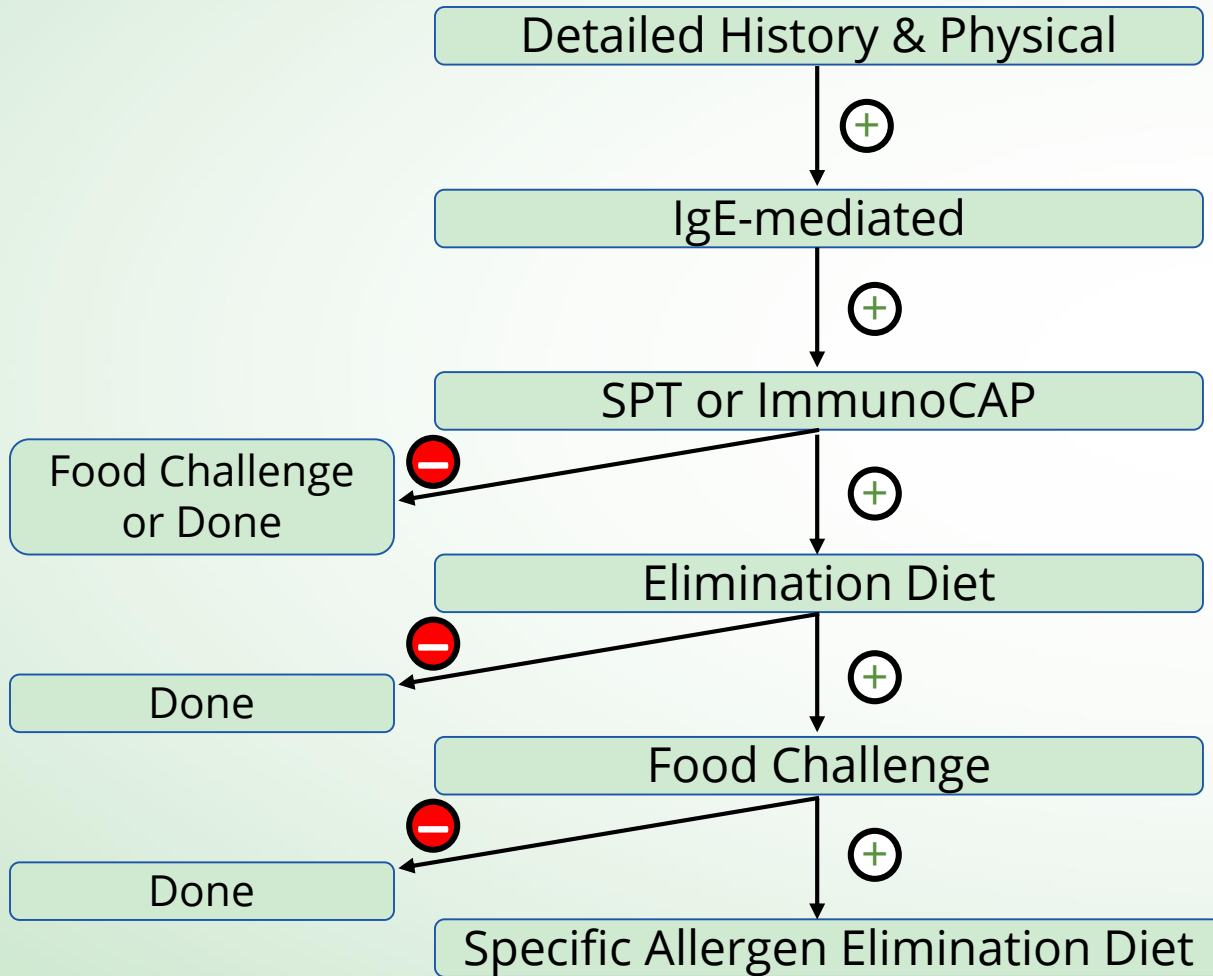
IgE-mediated vs non-IgE-mediated Reactions

Important to differentiate clinically between IgE-mediated and non-IgE-mediated characteristics.

Characteristic	IgE-mediated	Non-IgE-mediated
Time from exposure to reaction	Immediate onset—minutes to 2 hours	Delayed onset; usually ≥ 2 hours
Severity	Mild to anaphylaxis	Mild to moderate More severe presentations
Duration	Usually persist beyond 1 year of age	Often persist beyond 1 year of age
Diagnosis	Clinical history Specific serum IgE, skin-prick test Oral challenge	Clinical history Elimination diet Oral food challenge when indicated



Diagnostic Approach to the Evaluation of IgE-Mediated Food Allergy



- Family and personal history of allergic disease
- List of suspected foods
- Precise description of reactions

Symptoms

- **Cutaneous**
Flushing, hives, angioedema, eczema
- **Gastrointestinal**
Oropharyngeal pruritus and edema, abdominal cramping, nausea, vomiting, diarrhea
- **Pulmonary**
Rhinitis, laryngeal edema, wheezing, coughing & shortness of breath
- **Cardiovascular**
Hypotension, tachycardia, arrhythmias
- **Neurological**
Loss of consciousness
- **Behavioral**
Irritability (preceding or in combination with other symptoms)



Evaluation of Infant

Symptoms common with infant health issues may not be IgE-mediated CMA related

- Irritability (colic)
- Gastroesophageal reflux
 - Vomiting hours after a meal ('delayed gastric emptying') may be associated to allergy
- Atopic dermatitis
 - Environmental issues may be due to irritants, microbes, and allergens



Treatment: Patient Education

General Considerations:

- Establish an elimination diet
- Teach how to avoid the offending food
 - Teach label reading
 - Review likely sources of accidental exposure
- Provide reliable sources of information
 - Consultation with a registered dietician
 - Food Allergy Research and Education (foodallergy.org)
- Suggest purchasing an identification bracelet, necklace, card
- Develop an **ACTION PLAN** for treatment of accidental exposures
- Train how to administer epinephrine by injection
- **Encourage ALWAYS having rescue medications available**
- Educate extended family and caretakers



Long-Term Management

- Reinforce need to carry medications at all times and review use of medical devices (epinephrine auto-injector, inhaler if asthmatic)
- Food challenge indicated by history and/or lab results?
- Aid in interactions with school and community
- Answer questions
- Suggestions regarding impact on quality of life
- Is referral indicated
 - Allergist
 - Gastroenterologist
 - Dietician
 - Psychosocial clinician



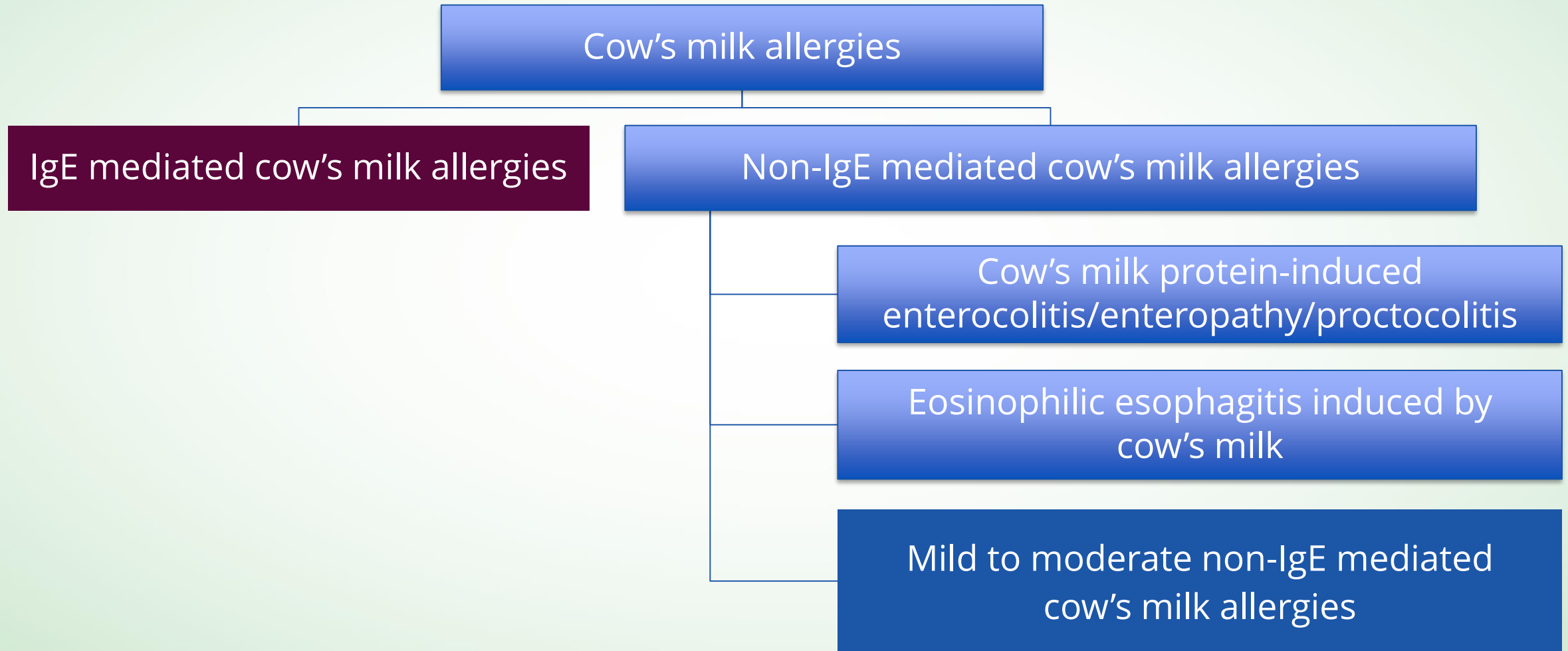
Clinical-Case Presentation of IgE-Mediated Infant: 6 ½ months

- Atopic parents: dad hay fever and mom asthma
- **Mild eczema in early infancy** (well controlled with emollients)
- Exclusively breast fed for 6 months
- Maintaining growth
- Developed **urticaria and angioedema** after first bottle of cow's milk formula at 6 months (within 10 min)
- Given goat's milk as an alternative but suffered same reaction

Diagnostic method	
History	✓
SPT	✓
Specific IgE test	✓
Oral food challenge – office setting	x/?
Cow's milk avoidance from maternal diet for around 4 weeks and reintroduction	NA



Mechanism: Type of cow's milk allergy?



Diagnosis

Diagnostic method	
History	✓
SPT	✓
Specific IgE test	✓
Oral food challenge – office setting	x/?
Cow's milk avoidance from maternal diet for around 4 weeks and reintroduction	NA

- Specific IgE to milk 40 kuA/L
- Milk skin-prick test 3 mm
- ? Food Challenge
- ? Specific IgE to casein
- ? Component testing



What Do the Guidelines Recommend Regarding Formula Choice?

Clinical Presentation	DRACMA	BSACI Guidelines	NIAID US Guidelines	ESPGHAN
Anaphylaxis	AAF	AAF	No specific recommendation	AAF
Acute urticaria or angioedema	EHF	EHF	No specific recommendation	EHF
Atopic eczema/dermatitis	EHF	EHF	No specific recommendation	EHF
Eosinophilic Esophagitis	AAF	AAF	The NIAID guidelines acknowledge that trials in EoE have shown symptom relief and endoscopic improvement in almost all children on AAF/elemental diet, though no specific recommendation on formula choice is made.	AAF (as specified by current ESPGHAN guidelines on EoE)
Gastroesophageal reflux disease	EHF	EHF	No specific recommendation	EHF
Cow's milk protein-induced enteropathy	EHF	EHF unless severe in which case AAF	No specific recommendation	EHF but AAF if complicated by faltering growth
FPIES	EHF	AAF	Hypoallergenic formulas are recommended	EHF
Proctocolitis	EHF	EHF	No specific recommendation	EHF
Breastfeeding with ongoing symptoms (already on maternal elimination diet) or requiring a top-up formula	No recommendation	AAF	No specific recommendation	With severe symptoms that are complicated by growth faltering, a hypoallergenic formula up to 2 weeks may be warranted. In many countries, AAF is used for diagnostic elimination in extremely sick exclusively breast-fed infants. Although this is not evidence based, it is aimed at stabilizing symptoms.

AAF, amino-acid formula; EHF, Extensively hydrolyzed formula; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition.



American Academy of Pediatrics. *Pediatrics*. 2000;106(2 Pt 1):346-9. Fiocchi A, et al. *J Allergy Clin Immunol*. 2010;126(6):1119-28 e12. Host A, et al. *Arch Dis Child*. 1999;81(1):80-4. Luyt D, et al. *Clin Exp Allergy*. 2014;44(5):642-72. Meyer R, Groetch M, Venter C. *J Allergy Clin Immunol Pract*. 2017.

MODULE 2: IMMUNOLOGIC RESEARCH

- Science behind infant food allergies
- Immune response and microbiome
- Pathophysiology of CMA
- Source of Intolerance



Immune Response

Microbiome

- Ensures integrity of the gut wall and regulation of the immune system
- Diverse microbiome associated with tolerance development
- The role of diet diversity in this is unclear



Allergy Research Targets

Additional research targets include

- Gut microbiome
 - What does an ideal gut microbiome look like?
- Prebiotics and probiotics
 - Their particular role on the microbiome and tolerance induction
- How to manipulate the microbiome to induce tolerance



Pathophysiology of Cow's Milk Allergy

- Triggers—Principal cow's milk allergens
 - Casein fraction of proteins (α s1-, α s2-, β -, and κ -casein)
 - Whey proteins (α -lactalbumin and β -lactoglobulin)
- Complex interplay
 - Epithelial barrier
 - Mucosal and systemic immune response
 - Route of exposure
 - Microbiome and other influences resulting in allergy or tolerance

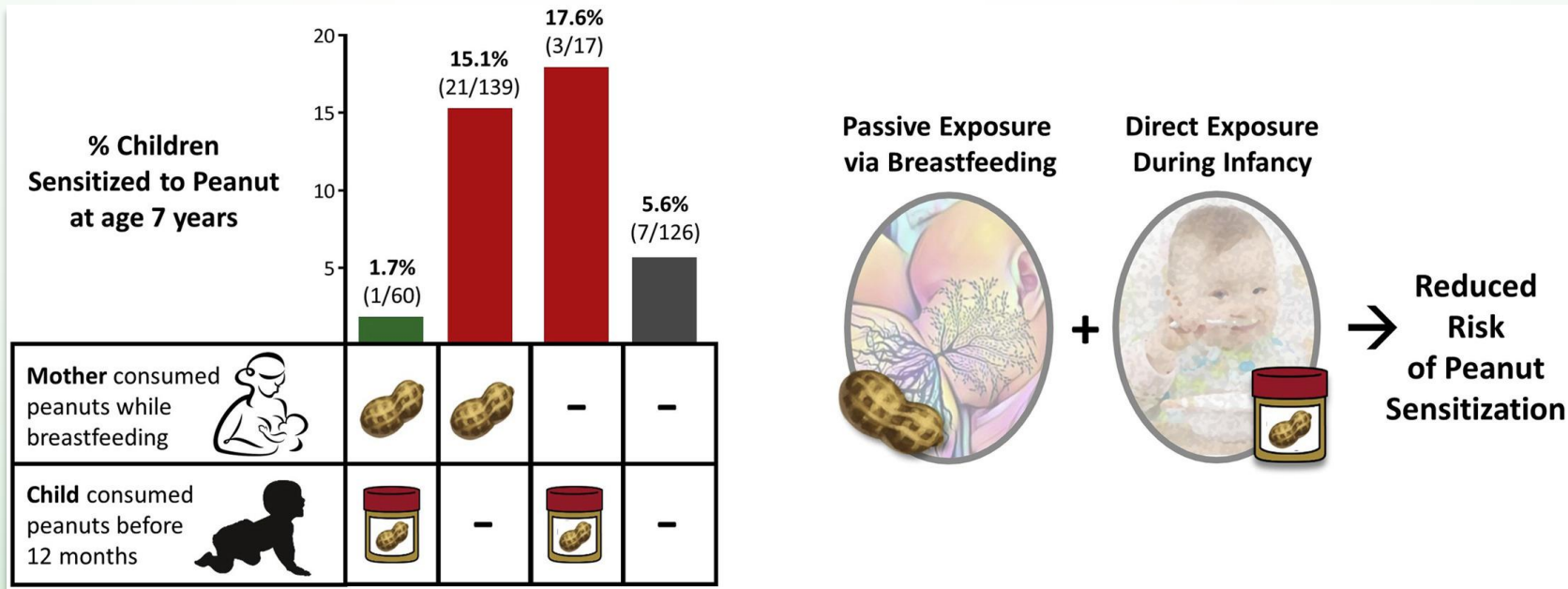


Breast Milk and What it Provides

Tolerance

- Support the infant's developing immune system
- Tolerance to potential food allergens?

Graphical abstract



Yu W, et al. *Nat Rev Immunol.* 2016;16(12):751-765.

Pitt TJ, et al. *J Allergy Clin Immunol.* 2018;141(2):620-625.e1. Used from *Journal of Allergy and Clinical Immunology* with permission from Elsevier.



MODULE 3: NUTRITIONAL TREATMENT STRATEGIES

- Current standards of care
- Clinical recommendations for severe food allergies
- Interventional therapies for treatment of food allergy
- Suitable infant formulas
- Mechanisms and triggers of allergy
 - New research targets for allergy treatments
 - Clinical trials underway

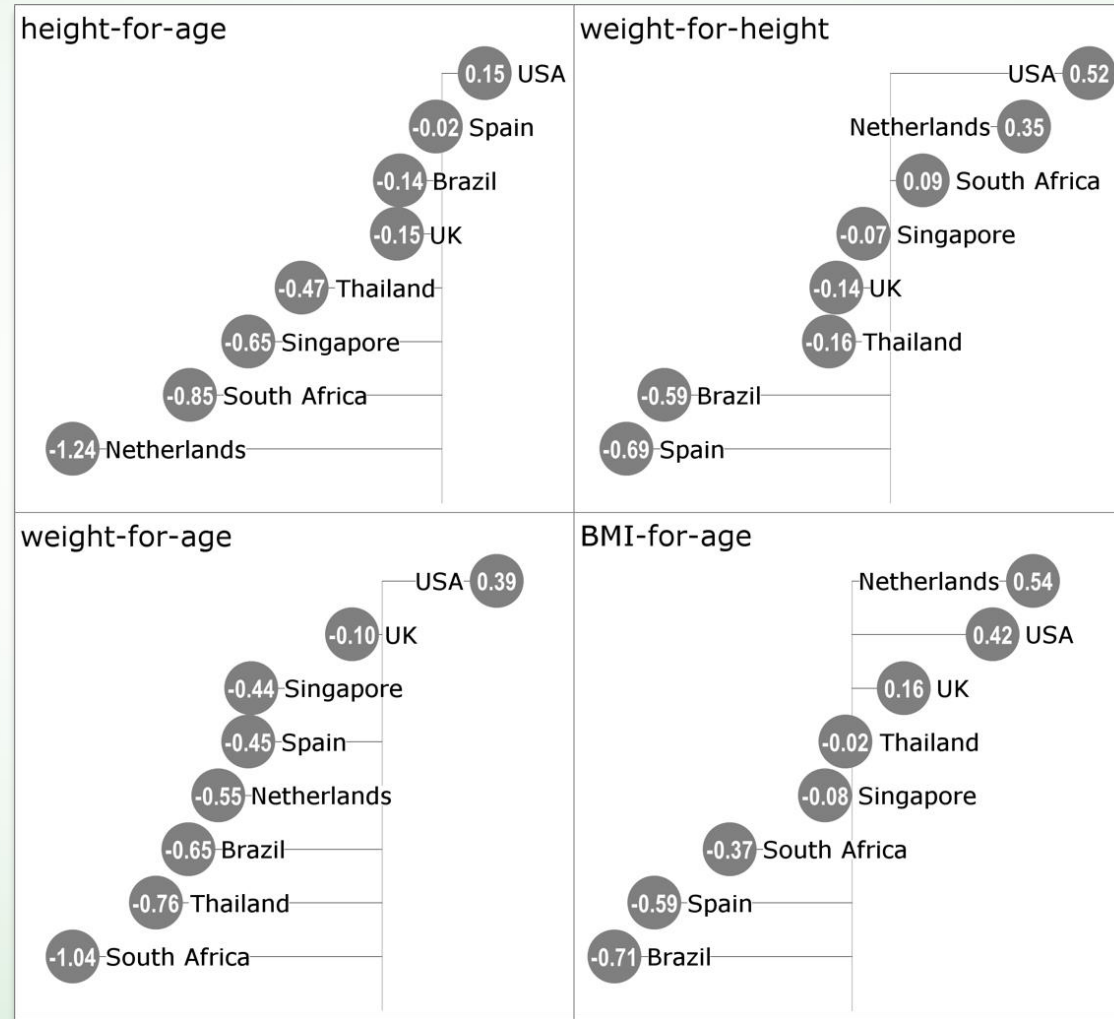


Current Standard of Care—IgE-Mediated Cow's Milk Allergy

- CMA elimination diet
- Monitor growth
 - Weight
 - Length
 - Head circumference



Growth and Food Allergy



Meyer R, et al. *J Hum Nutr Diet.* (forthcoming).



Recommended Treatment of CMA

- Breastfed infants
 - May need to consider avoidance of cow's milk protein from maternal diet
 - May take up to 72 hrs to clear breast milk antigens
- Infants ≤ 6 months
 - Formulas extensively hydrolyzed protein or amino acid-based formula
- Infants > 6 months
 - Soy formula may be appropriate in IgE-mediated cases
 - Country specific: Not to be used in infants with food allergy < 6 months of age



Clinical Recommendations: Suitable Infant Formulas

- Elemental/amino acid
- Extensively hydrolyzed casein
- Extensively hydrolyzed whey
- Soy formula



Hypoallergenic Formulas

- May be used in the absence of breast milk
- AAP/ESPGHAN define **hypoallergenic formula** as immunoreactive protein <1% of total nitrogen containing substance, which translates to the majority of peptides <1.5 kDa
- Tolerated by 90% of patients with CMP allergy
- **Hypoallergenic formula** include both EHF and AAF

AAF, Amino-acid formulas; AAP, American Academy of Pediatrics; CMP, cow's milk protein; EHF, extensively hydrolyzed formulas; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition.



Amino-Acid & Extensively Hydrolyzed Formulas

Amino-acid formulas (AAF)

- Provide protein only in free amino acids and no peptides
- High cost may be limiting factor

Extensively hydrolyzed formulas (EHF): whey or casein

- EHF casein first hypoallergenic formulas (>60 year history)
- EHF whey—newer additions to treatment of CMPA; some have lactose added

CMPA, cow's milk protein allergy.



Soy-Protein Formula

- Option for soy-negative (SPT/sIgE) CMPA infants >6 months of age who refuse a hypoallergenic formula
- IgE-mediated infants 2%–14% more likely to tolerate soy formula
- Useful in resource-poor environments
- Some nutritional disadvantages
 - Absorption of minerals and trace elements may be lower because of phytate content
 - Contain appreciable amounts of isoflavone that can lead to high serum concentrations in infants

sIgE, specific IgE.



Which Formula is Right for Your Patient?

- Degree of hydrolysis
- Fat source and content
- Presence or absence of lactose
- Nutritional status of child
- Nutrient profile:
 - Additional iron
 - Varying calcium and vitamin D
 - Contain pro/prebiotics
- Palatability/flavor
- Culture and religion
- Pre/Probiotics
- Cost



When to use Amino Acid-Based Formula?

Publications	Breastfeeding	Severe GI symptoms	Growth Faltering	Multiple Allergies	Atopic Dermatitis
Hill et al. 1995	+		+	+	
Sicherer et al. 2001		+		+	
Kaczmarewski et al. 2005		+			+
Isolauri et al. 1995			+	+	+
De Boissieu et al. 2002		+	+		+
De Boissieu et al. 1997		+		+	+
Vanderhoof et al. 1997	+	+			
Lucarelli et al. 2011	+	+		+	



Hill DJ, et al. *J Allergy Clin Immunol.* 1995;96:386-394. Sicherer SH, et al. *J Pediatr.* 2001;138:688-693. Kaczmarewski M, et al. *Annales Academiae Medicae Bialostocensis.* 2005;50:275-278. Isolauri E, et al. *J Pediatr.* 1995;127:550-557. de Boissieu D, et al. *J Pediatr.* 2000;136:119-20. de Boissieu D, et al. *J Pediatr.* 1997;131:744-747. Vanderhoof JA, et al. *J Pediatr.* 1997;131:741-744. Lucarelli S, et al. *BMC Gastroenterol.* 2011;11:82.

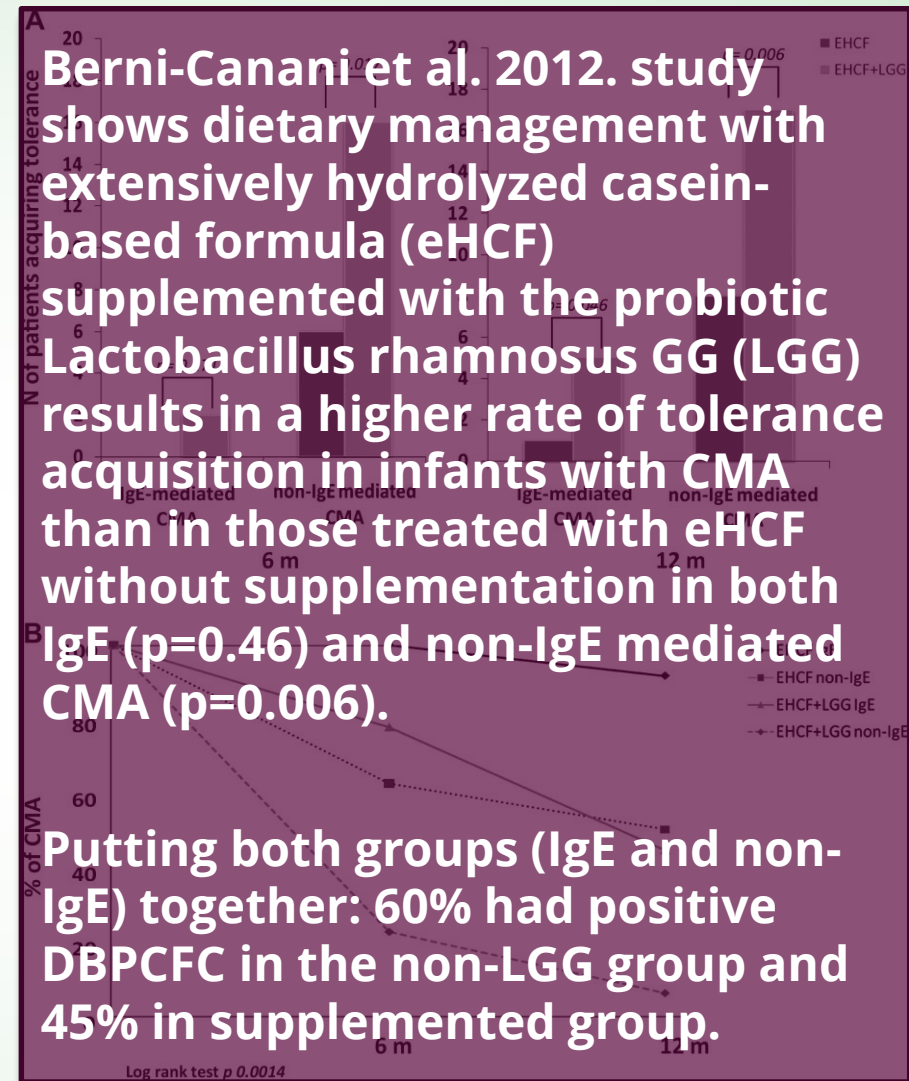
Allergy Management Strategies

- Introduction of solid food in CMA-baby diet
 - What to do when (re)introducing food in allergic baby
 - Ongoing management includes planned reintroduction of milk protein
- Use of extensively hydrolyzed protein formula + supplement



Management of Cow's Milk Allergy

- 2012 RCT: Effect of LGG on tolerance acquisition in infants with CMA
- 2017 RCT; n=220
- EHCF+LGG reduces incidence of other allergic manifestations and hastens development of oral tolerance in children with IgE-mediated CMA



DBPCFC, double-blind, placebo-controlled food challenge; EHCF, extensively hydrolyzed casein formula; LGG, *Lactobacillus rhamnosus* GG.



Interventional Therapies

- Food immunotherapies aim to desensitize patients to the food to which they are allergic
 - May result in a less severe or absence of allergic reaction with accidental ingestion by inducing desensitization
- Desensitization: a reversible state typically induced by short-term exposure to allergen; once administration of allergen is discontinued, the previous level of clinical reactivity returns.



Oral Immunotherapy

- Patients ingest small, but gradually increasing, allergen doses over every 2 weeks for several months until they reach a maintenance dose
 - Doses are given under medical supervision
- Has shown efficacy in phase 3 clinical trial for peanut
- Higher risk of systemic reactions compared to epicutaneous immunotherapy
- Risk of eosinophilic esophagitis (EoE)
- Not currently FDA-approved or under commercial investigation for FDA approval



Epicutaneous Immunotherapy



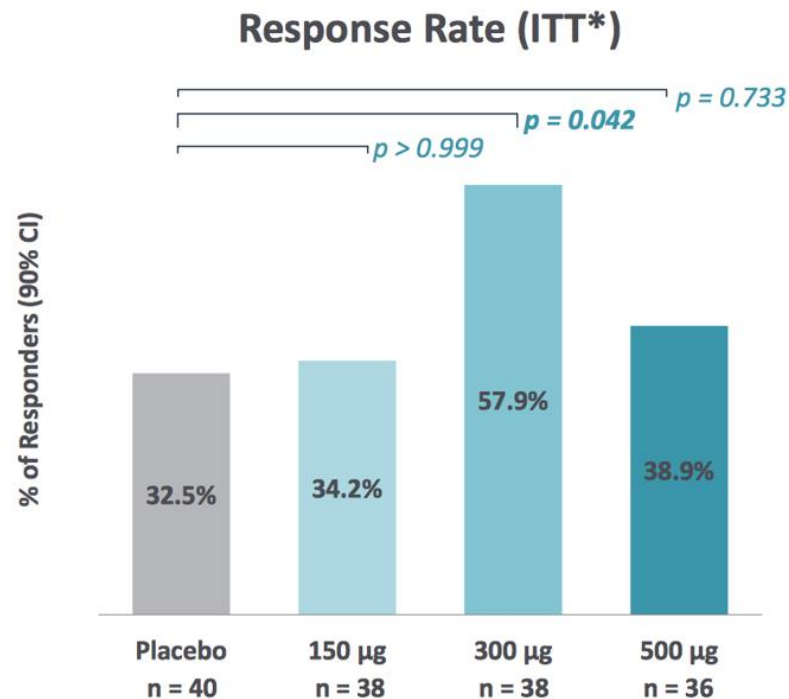
- Single, daily-dose patch
 - Applied to back in children
- First patch applied at study site
- Additional applications at home
- 2-week treatment initiation leading to 24-hour wear time
- No restrictions to daily activities required

EPIT peanut patch is under clinical investigation and has not been approved for marketing within or outside the European Union.



Future Care—Relevant Clinical Trials

MILES Results: Support Viaskin Milk 300µg as the Potential First Treatment for CMPA in Children 2-11



* Missing data: failure imputation (considered as non-responders) in ITT population
P-values obtained using exact logistic regression
ITT, Intent-to-Treat

Favorable safety, tolerability and compliance

- Overall discontinuation rate of 4.5%
 - 1.5% dropout due to AEs
- Most AEs related to application site (mild to moderate)
- No severe anaphylaxis
- No SAEs or epinephrine related to treatment
- Treatment adherence was high
 - Mean patient compliance > 95%



What the Future Holds

- Better understanding of mechanisms and triggers of allergy provide new research targets
- Better understanding of genetic, epigenetic, and environmental risk factors
- Future therapies
 - Milk patch for EoE
 - Phase 3 trial for EPIT for CMPA next year
 - Milk patch for diagnosis
 - Manipulation of the microbiome to develop tolerance
 - Development of milk peptides that can lead to tolerance development

EoE, eosinophilic esophagitis; EPIT, epicutaneous immunotherapy.



Key Takeaways

- ✓ No approved interventional treatments for CMA, to date
- ✓ Standard of care is advancing beyond food allergen avoidance and injectable epinephrine for acute allergic reactions
- ✓ CMA allergy generally has a favorable prognosis
- ✓ Majority of children will outgrow their food allergy
- ✓ Food allergy should be managed by individualized avoidance strategy, label reading and involvement of an RDN

