Trends in the Clinical Management of Food Allergy



Presented by Raquel Durban, MS, RD, LD/N



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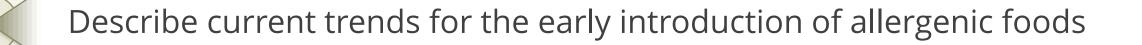
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Speakers BureauAbbott Nutrition, Mead Johnson Nutrition,Nutricia North America

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Learning Objectives





Apply food allergen exposure guidelines to clinical practice



Counsel parents and caregivers to safely and appropriately introduce foods with potential allergens to infants

Anticipate future trends for the introduction of allergenic foods



Current State of Food Allergy



Food Allergy vs Food Intolerance

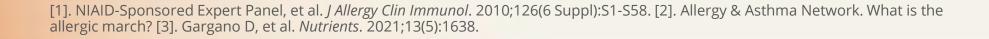
Food Allergy

Reproducible adverse health effect from an immune response on exposure to a food^[1]

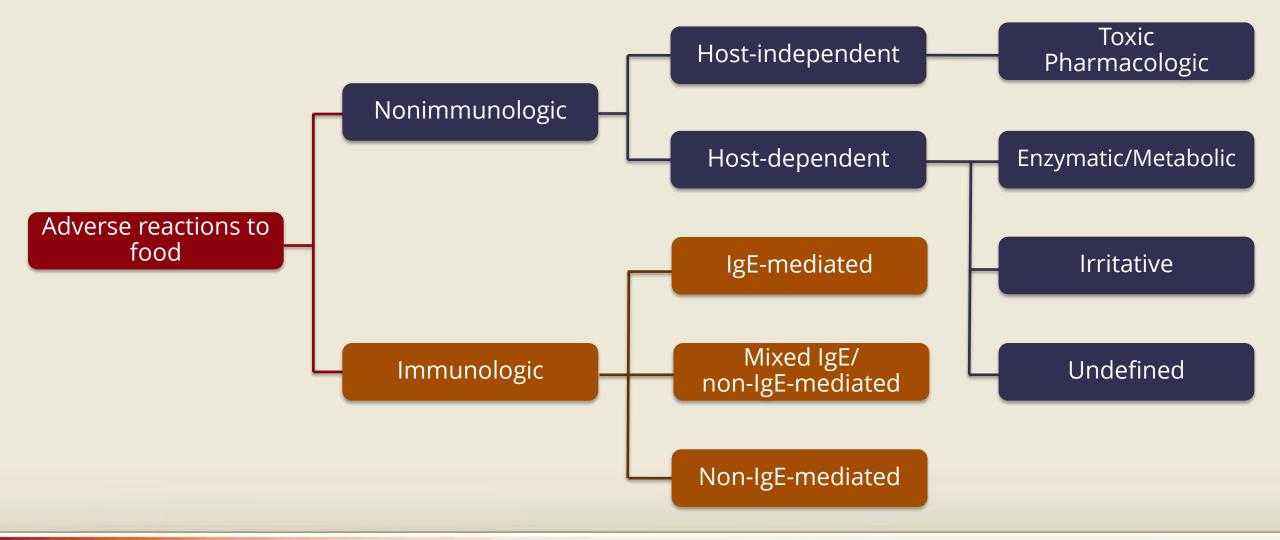
- IgE-mediated vs non-IgE-mediated
- Most common food allergies: Peanut, tree nut, cow's milk, egg, wheat, soy, fish, shellfish, sesame^[2]

Food Intolerance

Nonimmune reactions that include metabolic, toxic, pharmacologic, and undefined mechanisms^[3]

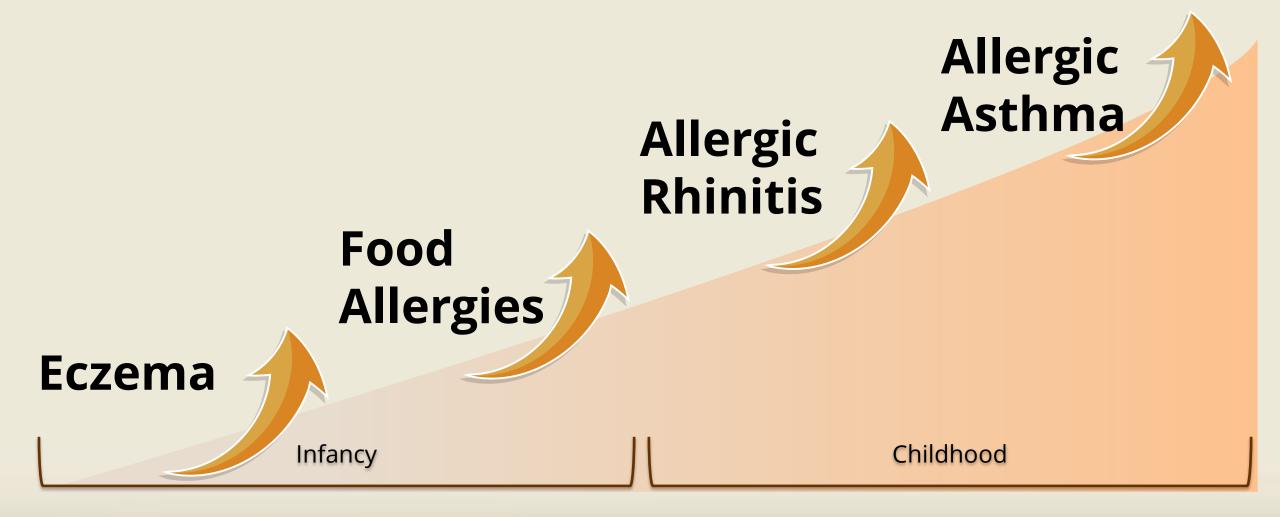


Food Allergy vs Food Intolerance^[1]





The Allergic March^[1]





[1]. Yang L, et al. *Front Immunol.* 2020;11:1907.

Prevalence of Food Allergy

Prevalence increasing over time^{[1],[2]}

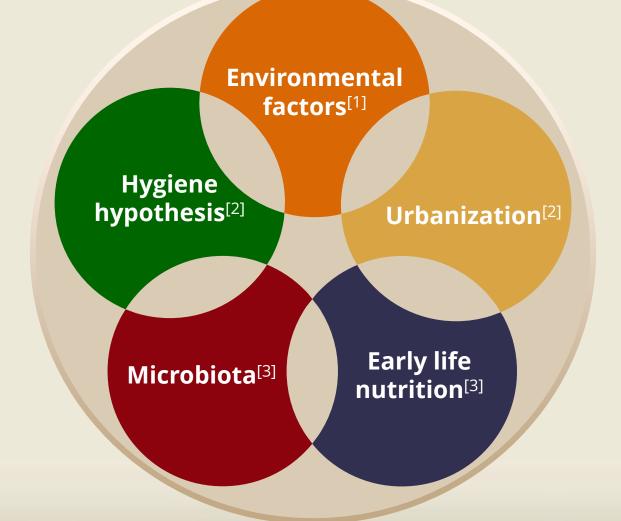
7.0% 8.0% 7.1% 5.9% 7.0% 6.0% 6.1% 5.1% 6.0% 5.0% 5.0% 4.4% 4.0% 3.4% 4.0% 3.0% 3.0% 2.0% 2.0% 1.0% 1.0% 0.0% 0.0% 2009-2011 2021 1997-1999 6–11 years 12–17 years 0–5 years



[1]. NCHStats. Food allergy action month. May 11, 2015. [2]. Zablotsky B, et al. NCHS data brief: diagnosed allergic conditions in children aged 0-17 years: United States, 2021. January 2023.

Prevalence increases with age^[2]

Why Is Food Allergy Prevalence Increasing?





[1]. Islam N, Chu DK. Front Allergy. 2022;3:1037596. [2]. Warren CM, et al. Curr Allergy Asthma Rep. 2020;20(2):6. [3]. Benedé S, et al. EBioMedicine. 2016;7:27-34.

Disparities in Food Allergies

• 2021 prevalence among racial and ethnic groups^[1]

- Non-Hispanic Black children = 7.6%
- Non-Hispanic White children = 5.3%
- Hispanic children = 5.0%

• Factors contributing to disparities^[2]

- Environmental exposures
- Food insecurity
- High cost of therapies
- Poor representation in clinical trials
- Food deserts

• Black children at higher risk for^[3]

- ED visits
- Anaphylaxis



So, what can we do with what we have learned?



2015 LEAP Study^[1]

- What peanut consumption strategy is most effective for preventing peanut allergy development in high-risk infants?
- Population
 - 640 infants between 4 and 11 months of age at high risk for peanut allergy based on existing severe eczema, egg allergy, or both

Randomization

- Randomly assigned to consume or avoid peanuts until 60 months of age
- Cohorts assigned based on pre-existing sensitivity to peanut extract on skin-prick test wheal measuring 1 to 4 mm in diameter

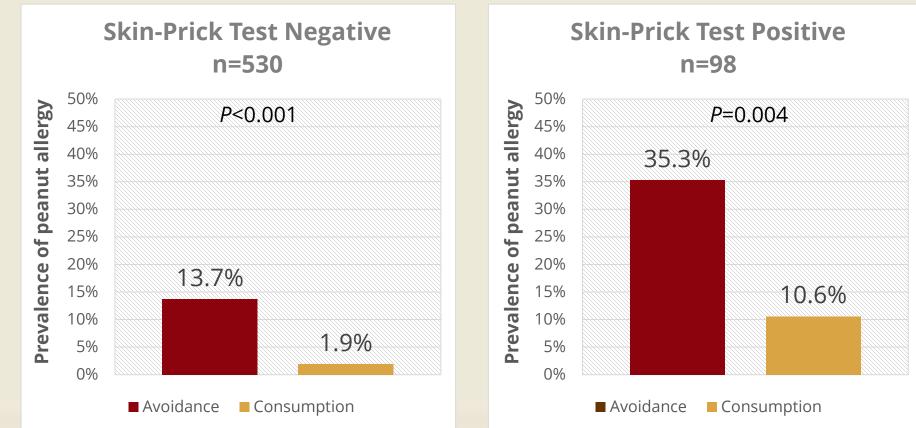
• Primary outcome

Presence of peanut allergy at 60 months of age



2015 LEAP Study^[1]

Results^[a]



[a]. Intent-to-Treat Analysis



[1]. Du Toit G, et al. [correction appears in *N Engl J Med*. 2016 Jul 28;375(4):398]. *N Engl J Med*. 2015;372(9):803-813.

2016 Enquiring About Tolerance (EAT) Study^[1]

- Does early introduction of allergenic foods affect breastfeeding performance?
- **Population**: 1303 infants in UK, any atopic status, breastfed only
- **Randomization**: Infants randomly assigned to 1 of 2 groups
 - No introduction of allergenic foods before 6 months of age
 - Introduction of 6 allergenic foods starting at 3 months of age
 » Cow's milk, peanut, hard-boiled hen's egg, sesame, whitefish (cod), and wheat
- Primary outcome
 - Rates of breastfeeding at 6 and 9 months of age compared to national average



2016 Enquiring About Tolerance (EAT) Study^[1]

• Results

- By 6 months of age, >95% of infants in early introduction group were consuming each of the allergenic foods
- At 6 and 9 months of age, breastfeeding rates in both groups significantly exceeded UK government data for equivalent infants



Timing of Introduction of Complementary Foods: Systematic Review from 2019^[1]

- What is the relationship between food introduction and allergy development?
- **Population**: Healthy infants/toddlers 0–24 months of age followed through age 18 years of age
- **Methods**: Literature search using 4 databases
- 31 observational studies from 1980 to 2017 reviewed



Timing of Introduction of Complementary Foods: Systematic Review from 2019^[1]

- **Finding #1**: <u>Moderate evidence</u> suggests that there is no relationship between the age at which complementary feeding first begins and risk of developing food allergy, atopic dermatitis/eczema, or asthma during childhood. **Grade:** Moderate
- **Finding #2**: There is <u>insufficient evidence</u> to determine the relationship between the age at which complementary foods or beverages are first introduced and risk of developing allergic rhinitis during childhood. **Grade**: Grade Not Assignable



Guidelines to Improve Allergy Management and Patient Care

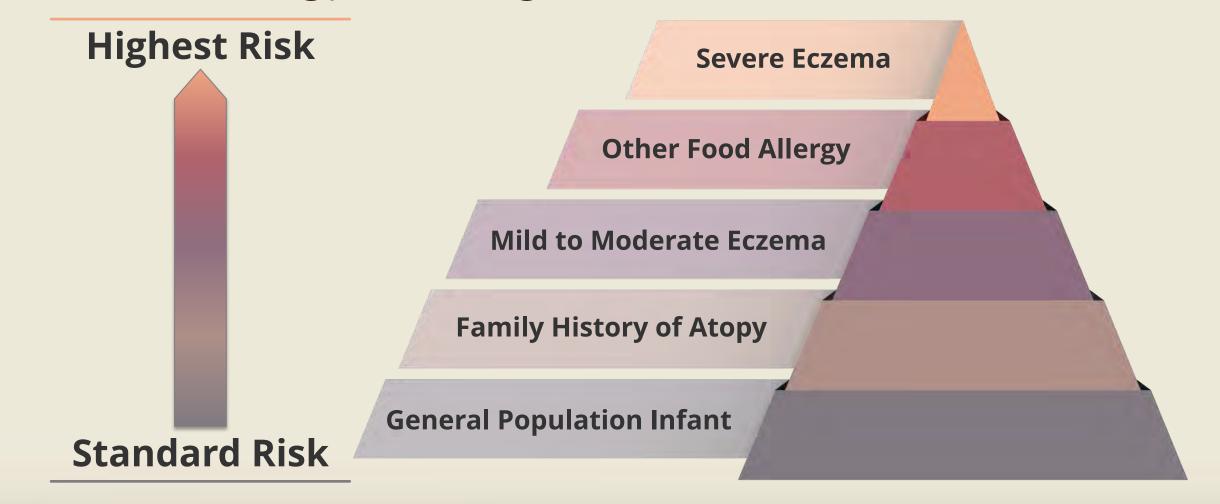


2017 Addendum Guidelines for the Prevention of Peanut Allergy in the United States^[1]

Infant Criteria	Recommendations	Earliest Age of Peanut Introduction
Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE and/or skin-prick test and, if necessary, an oral food challenge. Based on test results, introduce peanut containing foods	4 to 6 months of age
Mild-to-moderate eczema	Introduce peanut-containing foods	About 6 months of age
No eczema or any food allergy	Introduce peanut-containing foods	Age-appropriate and in accordance with family preferences and cultural practices

slgE, specific immunoglobulin E.

A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition^[1]



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[1]. Fleischer DM, et al. *J Allergy Clin Immunol Pract*. 2021;9(1):22-43.e4. Illustration adapted from Figure 2.

A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition^[1]

Peanut Introduction

Introduce peanut-containing products to all infants, irrespective of their relative risk of developing peanut allergy, starting around 6 months of life, though not before 4 months of life

Egg Introduction

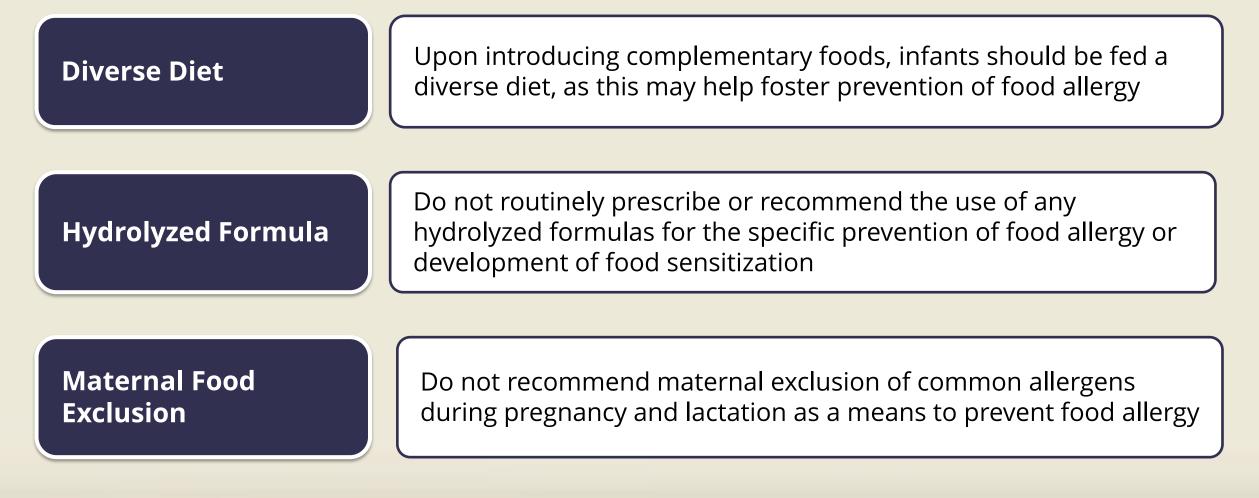
Introduce egg or egg-containing products to all infants, irrespective of their relative risk of developing allergy, around 6 months of life, though not before 4 months of life

Delayed Introduction

Do not deliberately delay the introduction of other potentially allergenic complementary foods once introduction of complementary foods has commenced at around 6 months of life but not before 4 months



A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition^[1]





Managing Food Allergy: GA²LEN Guideline 2022^[1]

• Dietary interventions

- Avoid the offending agent (Low certainty of evidence)
 - » Most breastfeeding mothers do not need to avoid source of infant allergy
- Infants with cow's milk allergy: hypoallergenic extensively hydrolyzed cow's milk formula or an amino-acid based formula (Moderate certainty of evidence)
 - » Suggest against partially hydrolyzed cow's milk formula, mammalian milks and, also for infants under 6 months of age, against soy-based formula.
- No recommendation for or against prebiotics, probiotics or synbiotics (Very low certainty of evidence)
- No recommendation for or against hydrolyzed plant-based formulas (Very low certainty of evidence)



Managing Food Allergy: GA²LEN Guideline 2022^[1]

- Allergen immunotherapy
 - <u>Peanut oral immunotherapy</u> for select children >4 years of age (*High certainty of evidence*)
 - <u>Peanut epicutaneous immunotherapy</u> (if it becomes available) for select children 4–11 years of age (*Moderate certainty of evidence*)
 - » No recommendation for or against for adolescents (Very low certainty of evidence)
 - <u>Oral immunotherapy</u> for select children >4 years of age with hen's egg or cow's milk allergy (Moderate certainty of evidence)



Managing Food Allergy: GA²LEN Guideline 2022^[1]

- Educational interventions
 - Good practice to offer structured education (Very low certainty of evidence)
- Biological therapies
 - No recommendation for or against etokimab or omalizumab (Very low certainty of evidence)
- Identification of those at risk of severe reaction

(Very low certainty of evidence)

- Adolescents and young adults at increased risk of severe reactions
- Good practice to optimize asthma control in people with food allergy
- Consider severity of previous symptoms and the likely triggering dose when evaluating the risk of anaphylaxis



Clinical Tools for Management of Food Allergy



Approach to Food Allergy Management^[1]





[1]. Durban R, et al. Immunol Allergy Clin North Am. 2021;41(2):233-270.

Avoidance and Exposure Prevention^[1]

Food label reading

- Laws vary by country
- Major allergens must be labeled
- Encourage caregivers to recheck food labels for changes
- Call the manufacturer for any uncertainty
- Provide information from patient and professional organizations
- Education on precautionary allergy labels^[2]
- Information on suitable substitutions
- Avoid cross contact

Avoidance and Exposure Prevention: Considerations

- Budget
 - Inflation
 - WIC/SNAP
- Access
 - Food desert, food pantries
 - Big box vs local grocer

• Culture

- Staple ingredients
- Religious food avoidances

• Schedule

- School
- Travel/dining out



Avoidance and Exposure Prevention: Milk Alternatives

Plant-Base	ed "Milk"	Beverag	e (PBM) S	ummary o	f Nutrient	Provision	Ranges in 1	Сир
Beverage	Calories	Protein (gm)	Fat (gm)	Added Sugar (tsp)	Calcium (mg)	Vitamin D (IU)	>10% DV vitamins ^[a]	>10% DV minerals ^[a]
Whole milk	150	8	8	0	275	124	B2, B12, D	Ca, Phos, Se
Soy PBM	70–150	6–9	3.5–5	0—4	10–350	80-200	A, D, E, B2, B12, Folate	Ca, Phos, Mg, K+
Oat PBM	45-160	1–4	0.5-9	0–4	17–350	0–160	A, D, B2, B12	Ca, Phos, Mg, K+
Coconut PBM	45-90	0	0–7	0–2.5	40-470	0–100	A, D, E, B12	Ca, Se
Pea PBM	80–140	4-8	4.5-8	0–4	320-455	184–240	A, D, B12	Ca, Iron, K+
Nut PBM	25–130	0–5	1.5–11	0–5	0–470	0–200	A, D, E, B12	Ca, K+
Hemp PBM	60–140	3–4	4.5-6	0–3	260–270	80	D	Ca, Iron, Mg
Flax PBM	25	0	2.5	0	270	90	A, D, B12	Ca, Phos

1 tsp. sugar = 4 g

[a]. Varies based on product and information provided on nutrition facts label



Growth and Feeding Issues^[1]

- Micronutrient deficiencies
- Feeding difficulties
- Insufficient growth (especially height)
- Role of registered dietitian
 - Regular assessment of anthropomorphic measurements
 - Intervene early for poor growth
 - Assess micronutrient intake
 - Offer feeding advice
 - Ensure medical management when needed



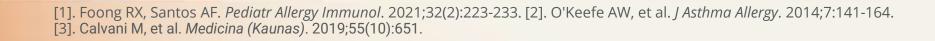
Growth and Feeding Issues: Nutrients

Food Group	Nutrients
Milk	Protein, calcium, magnesium, phosphorus, vitamins A, B6, B12, D, riboflavin, pantothenic acid
Eggs	Protein, calcium, phosphorus, magnesium, iron, zinc, thiamin, riboflavin, Vit B6, folate
Grain	Carbohydrate, zinc, selenium, thiamin, niacin, riboflavin, folic acid, iron, magnesium, fiber
Seafood	Protein, phosphorus, selenium, niacin, zinc. lodine. Fatty fish: vit A & D, omega-3 fatty acid
Seeds	Protein, iron, potassium, fiber, calcium, magnesium, phosphorus, zinc, vit E, B vitamins, selenium
Legumes	Protein, fiber, B vitamins, iron, folate, calcium, potassium, phosphorus, zinc



Food Reintroduction

- Oral food challenge^{[1]-[3]}
 - <u>Gold standard</u> to confirm food allergy diagnosis and resolution
 » For both IgE- and non-IgE-mediated
 - Incrementally increasing doses of the food are ingested
 - Very safe when performed in controlled environment
 - Often necessary due to low sensitivity/specificity of skin-prick or IgE testing » But, higher IgE levels and larger wheals associated with increased risk of reaction
 - Protocols vary by clinician
 - » Can be done blinded or open for IgE-mediated
 - » Should always be open for Food Protein Induced Enterocolitis Syndrome (FPIES)
 - Risk factors for reaction: peanut/tree nut, older age, concurrent asthma

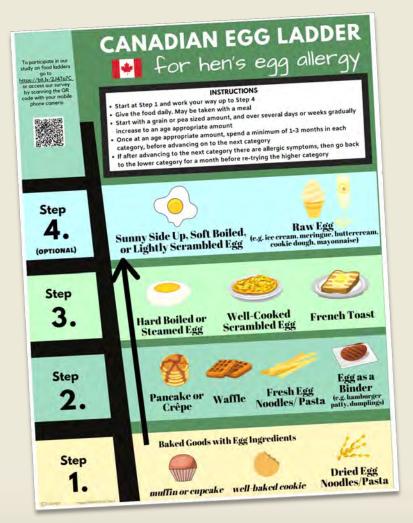


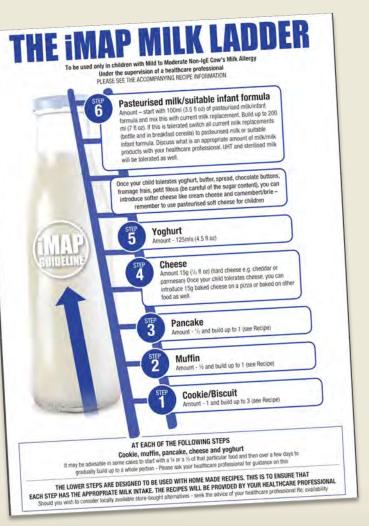
Food Ladders^{[1]-[2]}

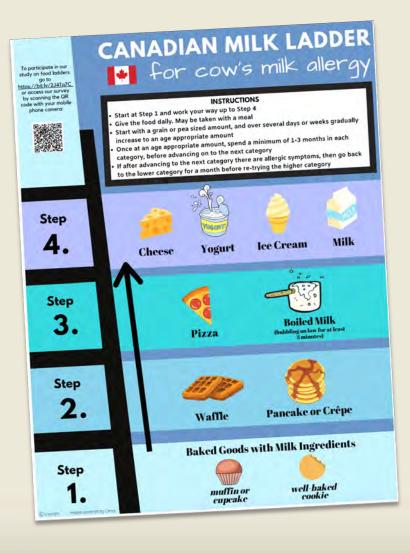
- What is a food ladder?
- Facilitates tolerance through gradual introduction
- Baked products → Well-cooked forms → Less processed forms
- Started with non-IgE-mediated allergies → IgE-mediated allergies
- Generally safe and effective



Food Ladders: So Many Options







Venter C, et al. Clin Transl Allergy. 2018;8:4. Chomyn A, et al. Allergy Asthma Clin Immunol. 2021;17(1):83.

Potential Benefits of Food Ladders^{[1]-[2]}

- Home-based = "demedicalization" of food
- Reduce healthcare utilization
- Increase food diversity and variety
- Reduce food costs and shopping difficulty for families
- Decrease anxiety about food allergy



[1]. Chua GT, et al. Allergy Asthma Clin Immunol. 2022;18(1):51. [2]. Venter C, et al. Pediatr Allergy Immunol. 2022;33(1):e13714.

Gaps in Current Food Ladders^[1]

- Lack of detail on dose of food and protein, time and temperature for baking, alternative foods
- Considerations for taste and texture of food and cultural appropriateness
- Lack of straightforward recipes to follow
- Consensus needed on appropriate candidates, number of days per step

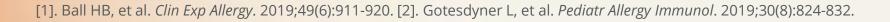


Studies of Food Ladders

- Ball et al. 2019^[1]
 - Retrospective chart review
 - 86 patients 8–33 months of age with IgE-mediated cow's milk allergy
 - 43% had allergic symptoms documented, 80% of these from milk ladder
 - No anaphylaxis
 - By 6 months of age, only 8 patients not tolerating almost all dairy products

• Gotesdyner et al. 2019^[2]

- Case-control study
- 39 patients 12–19 months of age with IgE-mediated egg allergy
- Treated with ladder approach until ~39 months of age
- Egg allergy resolved at ~24 months of age (78 months in avoidance group)





Resources for Families

- Food Allergy Research & Education (FARE) www.foodallergy.org
- Kids with Food Allergies (KFA)

www.kidswithfoodallergies.org

- Asthma and Allergy Foundation of America (AAFA)
 www.aafa.org
- American Academy of Asthma, Allergy & Immunology (AAAAI)
 www.aaaai.org
- American College of Allergy, Asthma, & Immunology (ACAAI)
 www.acaai.org



Where Are We With Immunotherapy?



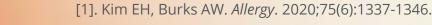
What Is Immunotherapy?^{[1]-[2]}

- Preventive treatment for allergic reactions
- Historically used for triggers of allergic rhinitis (pollen, dust mites)
- Exposure to incrementally increasing doses of allergen
- Can prevent march from allergic rhinitis to allergic asthma



Types of Immunotherapy for Food Allergy^[1]

- Subcutaneous immunotherapy (SCIT)
 - Side effects and safety make this a currently nonviable option
- Sublingual immunotherapy (SLIT)
- Oral immunotherapy (OIT)
 - Regular ingestion of food allergen in mg to gram quantities
 - Usually, food allergen in flour form mixed with vehicle food
- Epicutaneous immunotherapy (EPIT)
 - Cutaneous exposure to mcg quantities
 - Allergen adhered to a medicinal patch



Oral Immunotherapy (OIT)

Initial dose escalation

- Multiple increasing doses of allergens ingested over several hours in clinic
- Highest tolerated dose becomes starting dose for next phase

• Dose escalation phase

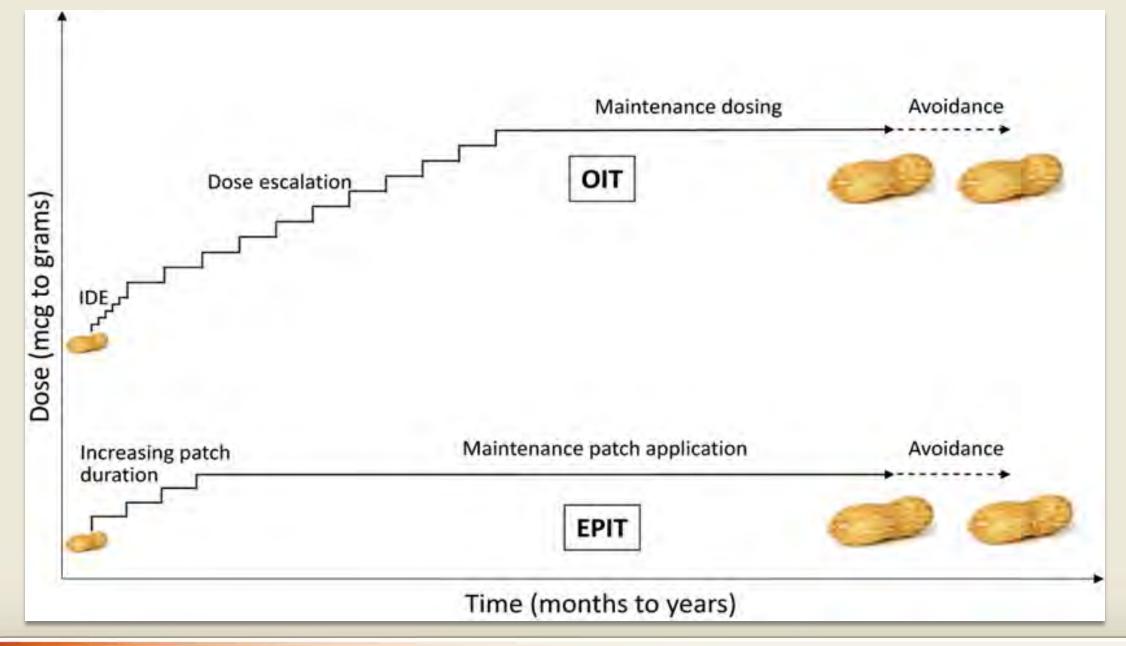
- Initial dose administered in clinic
- If tolerated, this dose repeated at home daily for 1–2 weeks
- Pattern repeated until maintenance dose achieved
- Maintenance phase
 - Home daily dosing continues with intermittent clinic visits for safety



Epicutaneous Immunotherapy (EPIT)

- Allergen content of patch remains unchanged
- Exposure varied by duration of application
- Initial dose escalation is not used
- Increase in duration usually accomplished in a few weeks
- Maintenance dose is 24-hour application





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Kim EH, Burks AW. *Allergy*. 2020;75(6):1337-1346. Illustration appears as Figure 1; used with permission from John Wiley and Sons Ltd. [© 2020 John Wiley & Sons A/S]

Allergen Immunotherapy and/or Biologicals for IgE-mediated Food Allergy: A Systematic Review and Meta-analysis (2022)^[1]

- Task force of allergy specialists, patient representatives, primary care doctors, psychologists, other clinicians, teachers and methodologists from 19 countries
- 6 databases searched
- 36 trials of immunotherapy
- 2126 participants (mainly children)



Allergen Immunotherapy and/or Biologicals for IgE-mediated Food Allergy: A Systematic Review and Meta-analysis (2022)^[1]

Peanut allergy

Oral immunotherapy

- » Large increase in proportion able to tolerate peanut during therapy
 - 6X more likely than controls to tolerate 300mg of peanut
 - 17X more likely than controls to tolerate 1000mg of peanut
- » May increase proportion of children able to tolerate peanut after stopping therapy

Epicutaneous immunotherapy

- » Probably increased proportion able to tolerate peanut during therapy
- » 2X more likely than controls to tolerate 300 mg peanut

Sublingual immunotherapy

» May result in large increase in proportion able to tolerate peanut

• No statistically significant increase in adverse reactions

Allergen Immunotherapy and/or Biologicals for IgE-mediated Food Allergy: A Systematic Review and Meta-analysis (2022)^[1]

Cow's milk allergy

- Oral immunotherapy
 - » Probably increased proportion able to tolerate cow's milk protein during therapy
 - » An increased proportion may have experienced adverse reactions

Hen's egg allergy

Oral immunotherapy

- » Probably increased proportion able to tolerate hen's egg during therapy
- » May increase proportion of children able to tolerate hen's egg after stopping therapy
- » Probably resulted in a large increase in the proportion of children experiencing adverse reactions



Ongoing Studies on Food Allergy Prevention and Management



The PEBBLES Study: Testing a Strategy for Preventing Eczema and Food Allergy in High-Risk Infants^[1]

- Phase 3, single blind, randomized controlled, multicenter trial
- Objective
 - Demonstrate that twice daily application of a ceramide dominant emollient reduces the risk of eczema and food allergy, when compared to standard skin management

• Participants

• 760 infants with first degree family history of allergic disease

• Methods

- Treat from birth to 6 months of age with 6 week, 6 and 12 month follow-up
- Primary outcomes to be assessed at 12 month follow-up



Early Peanut Introduction: Translation to Clinical Practice (EPI)^[1]

- Prospective observational study
- Objective
 - Determine who should be screened prior to early introduction for peanut allergy, how screening should be done, and what quantity of peanut is needed to prevent allergy
- Participants
 - 400 infants 4 to 11 months of age from 3 high-risk groups

• Methods

- Baseline oral food challenge with subsequent peanut introduction based on results
- Participants followed until 30 months of age



The Food Allergies Superheroes Training (FAST) Program (FAST Program)^[1]

- Prospective, randomized, single blind study
- Objective
 - Test the efficacy of a 5-session intervention designed to increase adherence to food allergy safety guidelines among low-income children ages 6 to 8 years of age with food allergies
- Participants
 - 55 children ages 6 to 8 years of age
- Methods
 - Multiphase study consisting of content development followed by comparison of FAST program to FA knowledge in study groups



Natural History and Genetics of Food Allergy and Related Conditions $\ensuremath{^{[1]}}$

- Prospective, observational, case-control study
- Objective
 - To learn more about the causes and effects
- Participants
 - 1800 people 2 to 99 years of age with food allergy and/or a related genetic or other and unaffected relatives or healthy controls

• Methods

 Samples of blood, skin, saliva, stool, gastrointestinal biopsies, and other samples will be collected over a 2-year period and used to explore the immunologic, biochemical, microbial, and genetic basis of food allergy



The TreEat Study: Can Early Introduction of Tree Nuts Prevent Tree Nut Allergy in Infants with Peanut Allergy^[1]

- Phase 3, randomized, open-label clinical trial
- Objective
 - Assess the safety and efficacy of a supervised, hospital-based multi-tree nut oral food challenge followed by home introduction of remaining tree nuts

• Participants

200 infants with peanut allergy

• Methods

- Infants in experimental group will undergo 4-nut butter graded and supervised oral food challenge
- Comparison group will follow standard of care, graded introduction of tree nuts individually at home



Introduction to Reduce Early (Peanut) Allergy in Children (iREACH)

- Prospective, randomized, open label trial
- Objective
 - Assess and improve pediatric clinician adherence to 2017 NIAID Prevention of Peanut Allergy Guidelines
- Participants
 - Minimum of 30 pediatric practice sites
- Methods
 - Pediatric practices will use iREACH, an EMR clinical decision support tool with educational modules to assist in implementing guidelines

EMR, electronic medical record.



Key Takeaways



Food allergies are becoming more prevalent, and management recommendations are evolving based on abundant research.



Introduction of allergenic foods should not be delayed. In some circumstances, early introduction may prevent food allergies.



Avoidance and education are key to food allergy management, and families require significant support from clinicians for success.

