Clinical Recommendations for Reducing and Preventing Food Allergies

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER Imparting knowledge. Improving patient care.

Presented by

Hugh A. Sampson, MD Kurt Hirschhorn Professor of Pediatrics Department of Pediatrics Icahn School of Medicine at Mount Sinai

Marion Groetch, MS, RDN Director of Nutrition Services Jaffe Food Allergy Institute Division of Allergy & Immunology Icahn School of Medicine at Mount Sinai



This activity is supported by an educational grant from **Mead Johnson Nutrition.**

Faculty Presenters

Hugh A. Sampson, MD

Kurt Hirschhorn Professor of Pediatrics Department of Pediatrics Icahn School of Medicine at Mount Sinai New York, New York

Marion Groetch, MS, RDN

Director of Nutrition Services Jaffe Food Allergy Institute Division of Allergy and Immunology Icahn School of Medicine at Mount Sinai New York, New York



Faculty Disclosures

Hugh A. Sampson, MD

Research Support	National Institutes of Health
Consultant	N-Fold Therapeutics
Shareholder	DBV Technologies, N-Fold Therapeutics
	clinical area for above: food allergy

Marion Groetch, MS, RDN

Speakers Bureau Abbott, Nutricia, Mead Johnson Nutrition

clinical area for above: food allergy



Learning Objectives



Develop management strategies to optimize nutrition in the allergic child and prevent allergic progression



Interpret the latest evidence for introducing allergenic food in the first years



INTRODUCTION

- Food allergy prevalence
- The link between food allergies and poor growth



Most Common Allergens



Eight food groups account for 90% of all food allergies in the United States.



 \mathbf{O}

NIAID-Sponsored Expert Panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–S58.

Food Allergies Limit Growth

 Food allergies can negatively affect growth and food intake¹⁻³

Height-for-Age by Allergy Status¹

Height-for-age percentile

- Growth limitations are likely attributable to elimination diets and inadequate nutrient intake¹
- Below-average weight and height persists into childhood for those with food allergies, particularly for milk allergies⁴

Participants	<25th	25th – 75th	>75th
Healthy controls (n = 96)	17%	56%	27%
Children with food allergy (n = 95)	28%	52%	20%
Allergic to 1 food (n = 32)	16%	50%	34%
Allergic to ≥ 2 foods (n = 63)	35%	52%	13%



- 1. Christie L, et al. J Am Diet Assoc. 2002;102(11):1648-1651.
- 2. Hobbs CB, et al. J Allergy Clin Immunol Pract. 2015;3(1):133–134.e1.
- 3. Robbins KA, et al. J Allergy Clin Immunol. 2014;134(6):1466-1468.e6.

4. Mehta H, et al. J Pediatr. 2014;165(4):842-848.

Milk Avoidance Compared With Other Food Avoidance[†]



[†]In a retrospective medical records review of children from a single center, with avoidance on the basis of real or perceived food allergies. WFL/BMI, weight for length for participants less than 2 years of age and body mass index for participants 2 years or older.





International Survey on Growth in Children With Food Allergy[†]

- Cow's milk elimination led to lower weight-for-height Z scores than elimination of other foods
- Mixed IgE and non-IgE-mediated allergy had lower height-for-age Z scores than IgE-mediated allergy.
- Overall, the data indicated:
 - 9% were stunted
 - 6% were underweight
 - 5% were undernourished
 - 8% were overweight

Children particularly at risk of poor growth are those with non-IgE- and mixed IgE/non-IgE-mediated allergies, as well as those with cow's milk allergy.

[†]In a study of 430 children from 12 centers.

Meyer R, et al. J Hum Nutr Diet. 2019 Apr;32(2):175-184.



OPTIMIZING NUTRITION FOR THE ALLERGIC CHILD



Avoid Unnecessary Elimination Diets

Elimination Diets in Children With AD⁺



Elimination diets can place children at risk for poor growth and nutritional deficiency.^{1,2}

[†]Necessary elimination diet was one in which cow's milk allergy was confirmed with a double-blind placebo-controlled food challenge. Unnecessary elimination diet was one in which a double-blind placebo-controlled trial confirmed tolerance of cow's milk and cow's milk was successfully reintroduced. AD, atopic dermatitis.



1. Sinagra JL, et al. Pediatr Dermatol. 2007;24(1):1-6.

2. Dambacher WM, et al. *Nutr J.* 2013;12:22.

Diagnosing Food Allergy: When Elimination Diets Are Necessary

- Long-term elimination diets should only be recommended by specialists for documented food allergy
- Skin prick testing results may be positive in cases where the food can be tolerated

For more information, see *Diagnosing Food Allergies in Infants and Children* with Jonathan Spergel, MD, PhD.



NIAID-Sponsored Expert Panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–S58.

A Patient-Specific Approach to Develop an Exclusion Diet to Manage Food Allergy in Infants and Children

Foods to avoid and degree of avoidance

Suitable substitutes

Self-management skills

Co-existing and cross-reacting allergens

Novel allergens



- Travelling and immigration
- Food and nutrition literacy
- Threshold levels and cross-contact or cross-contamination

Nutrition

- Promote optimal growth
- Prevent nutrient deficiencies
- Development of normal feeding skills
- Optimal nutrition for long-term health

Future

The role of nutrients, dietary patterns, and other food factors regarding:

- Gut microbiome
- Immune system
- Allergy prevention and tolerance development



Venter C, et al. *Clin Exp Allergy*. 2018;48(2):121-137.



Food Substitutions

Allergen	Lost nutrients	Suggested alternatives (if not allergic)
Milk	Protein, fat, calcium, riboflavin, phosphorous, vitamins A, D, B12	Meat, fish, poultry, legumes, eggs, fortified milk substitutes, calcium-fortified foods or drinks
Eggs	Protein, iron, biotin, folacin, riboflavin, vitamins A, D, E, B12, selenium	Meats, fish, poultry, legumes, dairy, leafy greens, enriched grains
Soy	Protein, thiamin, riboflavin, iron, calcium, zinc, vitamin B6	Meats, fish, poultry, legumes, eggs, dairy, fruit, vegetables, leafy greens, enriched grains
Wheat	Thiamin, niacin, riboflavin, folate, iron, fiber	Meats (iron), whole and fortified alternate grain products (oats, buckwheat, amaranth, millet, quinoa, teff, sorghum), seeds, legumes
Peanuts and tree nuts	Protein, vitamins, minerals	Meats, fish, poultry, eggs, dairy, fruit, vegetables, enriched grains, seeds
Fish and shellfish	Protein, PUFA (fatty fish) iodine, B12, A, E	Meats, poultry, eggs, fruit, vegetables, enriched grains, seeds, marine algae and seaweed

Modified from: Asthma and Allergy Foundation of America. https://www.kidswithfoodallergies.org/page/replacing-lost-nutrients.aspx. Reviewed March 2013.

Nutrients in Cow's Milk and Substitutes

Cow's milk or enriched substitute	kCal per 8 oz	Protein (g)	Fat (g)	Calcium (mg)/ Vitamin D (IU)
Cow's Milk	150	8	8	
Реа	100	8	4.5	
Soy	100	7	4	
Oat	120	4	3	Varies based on fortification!
Rice	120		2.5	
Coconut	80		4.5	
Almond	50		2.5	

(!) Milk substitutes are not nutritionally equivalent.



Encourage Breastfeeding and Ensure Adequate Maternal Nutrition

- Fatty acid composition of breast milk reflects maternal diet
- Secretion into milk is rapidly and substantially reduced by maternal depletion of the following nutrients:
 - •
- Thiamin Retinol
 - Riboflavin Vitamin A
 - Vitamin B-6 Vitamin D
 - Vitamin B-12 Selenium
 - Choline

- Iodine
- Maternal supplementation with these nutrients can increase breast milk concentrations and improve infant health



Hypoallergenic Formulas

- **Extensively hydrolyzed formulas** (eHF)
- **Amino acid-based formulas** (peptide-free)
- **Not Hypoallergenic**
 - Partially hydrolyzed formulas are not hypoallergenic.¹
 - European formulas labeled "HA" are typically partially hydrolyzed.²
 - Soy formula is also not hypoallergenic but may be tolerated by those with cow's milk allergy—especially those with IgE-mediated allergy—and may be used after 6 months of age.¹



American Academy of Pediatrics. Committee on Nutrition. *Pediatrics*. 2000;106(2 Pt 1):346-349. DiMaggio DM, et al. *J Pediatr Gastroenterol Nutr*. Published online May 9, 2019. doi:10.1097/MPG.00000000002395

The Importance of Feeding in Infancy

- Complementary feeding should be aligned with physiological, oral and motor skills beginning around 6 months of age (and not sooner than 4 months)
- Infants will generally accept a new flavor on the first presentation¹
- In contrast children 2–5 years need multiple exposures to a new food¹
- Early introduction of a variety of flavors and textures can impact long-term food acceptance
- Children introduced to lumpy solids after 9 months ate less of many food groups at 7 years of age including fruits and vegetables (P < .05) and were significantly more likely to have feeding problems at 7 years (P < .05)²

There is no reason to delay introduction of complementary foods beyond 6 months, including those complementary foods thought to be highly allergenic.³



1. Birch LL, et al. Appetite. 1998;30:283-95.

- 2. Arlinghaus KR, et al. Am J Clin Nutr. 2018;108:730-6.
- 3. Greer FR, et al. *Pediatrics*. 2019;143(4). pii:e20190281.

Ensure That the Diet Is Balanced!

USDA MyPlate www.choosemyplate.gov

United States Department of Agriculture

Typical needs of a 1 year old

Choose MyPlate.gov

MyPlate Daily Checklist Find your Healthy Eating Style

Everything you eat and drink matters. Find your healthy eating style that reflects your preferences, culture, traditions, and budget—and maintain it for a lifetime! The right mix can help you be healthier now and into the future. The key is choosing a variety of foods and beverages from each food group—and making sure that each choice is limited in saturated fat, sodium, and added sugars. Start with small changes—"MyWins"—to make healthier choices you can enjoy.





Dietary and Nutritional Counseling Improves Nutritional Status[†]

	Healthy children at	Patients with food allergy		
Median nutrient intake	baseline (n = 66)	At baseline (n = 91)	6 months after counseling (n = 85)	
Energy intake (kcal/kg/d)	96	91*	97.3 [‡]	
Macronutrients				
Carbohydrate (g/kg/d)	4.9	5.1	6.0*,‡	
Fat (g/kg/d)	4.2	3.8	3.6*	
Protein (g/kg/d)	4.6	2.2*	3.6*,‡	
Micronutrients				
Fiber (g/d)	7.2	5.8	11.2*,‡	
Calcium (mg/d)	848.3	314.4*	600*,‡	
Iron (mg/d)	7.0	6.1	8.0*,‡	
Zinc (mg/d)	4.1	3.0*	4.5*	

**P* < .01 vs healthy children at baseline. P < .01 vs patients with allergy at baseline.

[†]In a prospective, interventional study of children aged 6–36 months with food allergies.

Berni Canani R, et al. J Acad Nutr Diet. 2014;114(9):1432-1439.

Vitamin and Mineral Supplementation

- May be appropriate if adequate vitamin and mineral intake cannot be obtained with food substitutes
- Common supplementation needs:
 - **Cow's milk allergy:** calcium and vitamin D
 - Multiple allergies: individualized approach to supplementing

Recommended Dietary Intake

Age	Calcium (mg/day)	Vitamin D (IU/day)
0 to 6 months	210	400
7 to 12 months	270	400
1 to 3 years	500	600
4 to 8 years	800	600
9 to 18 years	1300	600

Dietary reference intake calculator for health care professionals: https://fnic.nal.usda.gov/fnic/dri-calculator/



Dietary Effects of Elimination Diet

	Without eliminations	Eliminations	With substitutions
Breakfast	Waffles with syrup Strawberries Milk	Waffles with syrup Strawberries Milk	Gluten-free, milk-free, egg-free waffles made with buckwheat Strawberries Elemental formula (8 oz)
Lunch	Turkey on whole wheat with cheese, lettuce, and mayonnaise Carrots with ranch dressing Pudding Juice	Turkey on whole wheat with cheese, lettuce, and mayonnaise Carrots with ranch dressing Pudding Juice	Turkey on teff tortilla with lettuce and canola oil-based mayonnaise or cranberry sauce Carrots with hummus Alternative yogurt smoothie with frozen peaches
Snack	Corn chips with guacamole	Corn chips with guacamole	Corn chips with guacamole
Dinner	Hamburger Helper (ground beef, macaroni, cheese, tomato sauce) Spinach salad with lettuce, tomato, peppers, cheese, ranch dressing Milk	Hamburger Helper (ground beef, macaroni , cheese , tomato sauce) Spinach salad with lettuce, tomato, peppers, cheese , ranch dressing Milk	Lean ground beef with marinara on chick pea noodles Spinach salad with lettuce, tomato, peppers, Italian dressing Elemental formula (8 oz)
Snack	lce cream	lce cream	Coconut ice cream



Key Takeaways

- 1. Encourage breastfeeding exclusively to 4–6 months of age and continuing breastfeeding while introducing complementary foods.
- 2. Consider breast milk, optimal hypoallergenic formula, or beverage choice and appropriate volumes and/or vitamin/mineral supplementation as needed.
- **3**. Encourage a healthy diet rich in fruits, vegetables, fibers in particular digestible fibers, and long chain PUFA.
- 4. Do not delay introduction of complementary foods.
- 5. Provide an otherwise individualized approach to meet nutritional needs within the context of the allergen elimination diet.



Online Patient Resources





www.foodallergy.org



REDUCING THE RISK OF ALLERGY

- Milestone LEAP, EAT, and PETIT studies
- Solid food introduction and allergies
- Skin barrier maintenance and allergies



180-Degree Change in Prevention Rationale

American Academy of Pediatrics Guidelines on Preventing Food Allergy

2000¹

Wait to introduce allergenic foods:



Milk: 1 year



Eggs: 2 years



Nuts and fish: 3 years

2008²

No evidence for delaying introduction of allergenic foods:



Milk, eggs, nuts, and fish: 4-6 months

2019³

No evidence for delaying introduction of allergenic foods:



Milk, eggs, tree nuts, and fish: 4-6 months

Early introduction of peanuts may be beneficial for infants at high risk for allergy:



Peanuts: 4-6 months



Zeiger RS. *Pediatrics*. 2003;111(6 Pt 3):1662-1671.
 Greer FR, et al. *Pediatrics*. 2008;121(1):183-191.
 Greer FR, et al. *Pediatrics*. 2019;143(4). pii:e20190281.

180-Degree Change in Prevention Rationale

American Academy of Pediatrics Guidelines on Preventing Food Allergy

2000 ¹	2008 ²	2015	2019 ³
Wait to introduce allergenic foods:	No evidence for delaying introduction of allergenic foods:		No evidence for delaying introduction of allergenic foods:
Milk: 1 year	Milk, eggs, nuts, and fish: 4-6 months		Milk, eggs, tree nuts, and fish: 4-6 months
Eggs: 2 years	LEAP st	udy	Early introduction of peanu may be beneficial for infant at high risk for allergy:
Nuts and fish: 3 years		E	Peanuts: 4-6 months



- Zeiger RS. *Pediatrics*. 2003;111(6 Pt 3):1662-1671.
 Greer FR, et al. *Pediatrics*. 2008;121(1):183-191.
- 3. Greer FR, et al. *Pediatrics*. 2008, 121(1), 185-191.

LEAP Study Design



SPT, skin prick test.

Du Toit G, et al. N Engl J Med. 2015;372(9):803-813.



Primary and Secondary Prevention of Allergies at 60 Months[†]



[†]In the intention-to-treat analysis, as determined by an oral food challenge (96.4%) or diagnostic algorithm (1.7%).

Image adapted from Du Toit G, et al. N Engl J Med. 2015;372(9):803-813.

LEAP-ON Follow-up Study

LEAP Study LEAP-ON Follow-up Study Avoidance n = 270 Consumption Oral Clinic visits All participants in ITT n = 272peanut at baseline, population were 12 months challenge 12, 30, 60, eligible at 72 Avoidance of dietary and 72 n = 556 of 628 eligible months of **Avoidance** consumption of peanuts participants months n = 51 age Consumption n = 47

3

Persistence of Peanut Tolerance After Avoidance at 72 Months[†]



[†]In the enrolled participants in the follow-up study who had a peanut-allergy outcome that could be evaluated.

Image adapted from Du Toit G, et al. N Engl J Med. 2016;374(15):1435-1443.

2017 NIAID Addendum Guideline Recommendations



NIAID-Sponsored Expert Panel. https://www.niaid.nih.gov/sites/default/files/addendum-peanut-allergy-prevention-guidelines.pdf. Published 2017.

EAT Study Design



SPT, skin prick test.



Prevalence of Allergy Between 1 and 3 Years

- No significant difference in food allergy between groups by intentionto-treat analysis
- Adherence was lower for early feeding group (42.8%) than for standard feeding group (92.9%)







Early Introduction of Egg and Egg Allergy: Systematic Review and Meta-analysis

- Of 416 articles identified and screened, 6 randomized controlled trials met eligibility criteria for data extraction
- Allergic outcomes evaluated in a total of 3032 participants
- A low to moderate level of evidence showed a benefit of early introduction of egg
- Consumption of less than 4 g/week of egg protein had greater preventive effect than a higher dose



Al-Saud B, Sigurdardóttir ST. Int Arch Allergy Immunol. 2018;177(4):350-359.

PETIT Study Design



exacerbations




Prevalence of Egg Allergy at 12 Months[†]



[†]In the primary analysis population. Sensitization cut-off was 0.35 kU_A/L of egg-white specific lgE at baseline.

Image adapted from Natsume O, et al. Lancet. 2017;389(10066):276-286.



Early Introduction of Cow's Milk: Observational Study

- A total of 5276 12-month-old infants were recruited from the HealthNuts longitudinal population-based food allergy study
- SPT to cow's milk allergy was performed on 2715 participants
 - Sensitization: wheal <u>></u>2 mm
- Early exposure to cow's milk protein was determined by parental questionnaire at 1 year of age





Dietary Measures With No Proven Benefit or Insufficient Evidence

- Supplementation with vitamins A, D, E, and C; zinc; or selenium^{1,2}
- Supplementation with probiotics³
- Introduction of hypoallergenic formulas⁴
- Exclusive breastfeeding⁵
- Maternal PUFA supplementation during pregnancy or lactation⁶

PUFA, long chain polyunsaturated fatty acids.



 Nurmatov U, et al. J Allergy Clin Immunol. 2011; 127(3):724-733.e1-30.
 di Mauro G, et al. World Allergy Organ J. 2016;9:28.

3. Fiocchi A, et al. World Allergy Organ J. 2015;8(1):4.

- 4. Osborn DA, et al. Cochrane Database Syst Rev. 2018;10:CD003664.
- 5. Lodge CJ, et al. Acta Paediatr. 2015;104(467):38-53.
- 6. Gunarathe AW, et al. *Cochrane Database Syst Rev.* 2015;(7):CD010085.

Rising Prevalence of Food and Skin Allergies





Image adapted from Jackson KD, et al. NCHS Data Brief. 2013;(121):1-8.

Eczema Is Associated With Development of Food Allergy

- Eczema increases the odds of developing food allergy, multiple food allergy, and specific types of food allergy
- Earlier onset eczema increases odds of food allergy
- More severe eczema increases odds of food allergy





Skin Barrier Disruption Can Influence the Development of Allergies





Mixed results on whether emollient therapy improves skin barrier enough to prevent allergy development

Image adapted from: Lowe AJ, et al. *Ann Allergy Asthma Immunol.* 2018;120(2):145-151. Image components courtesy of Servier Medical Art by Servier (CC BY 3.0).

Food Allergy and Skin Barrier Disruption

Supporting evidence for allergic sensitization through skin:

- Allergic reactions to foods can occur without prior oral exposure
- Oral exposures in infancy generally lead to tolerance
- Atopic dermatitis and food allergy are highly comorbid
- Peanut allergy correlates with household peanut consumption and not individual peanut intake

Proposed Model

Skin barrier disruption

Environmental exposure to allergen and
epicutaneous absorption

Systemic sensitization

Development of food allergy



Izadi N, et al. Children (Basel). 2015;2(3):382–402.

Enhancement of Skin Barrier to Prevent Atopic Dermatitis

- Protection of the skin barrier from dryness and irritation along with aggressive treatment of inflammation may prevent sensitization
- Decrease use of bathing, soaps, and anti-microbials
- Apply emollients
- Limit allergen contact exposure
- Treat inflammation aggressively



Application of Emollient to Prevent Atopic Dermatitis

- Randomized controlled trial of daily emollient application beginning by 3 weeks of age in infants at risk of atopic dermatitis[†] in the United Kingdom and United States
- Infants were randomly assigned to daily emollient treatment (n = 64) and no emollient treatment (n = 60)
- At 6 months, the risk of atopic dermatitis was decreased by 50% with emollient treatment relative to no treatment

(20% vs 43%; *P* = .017)

Did not evaluate sensitization to allergens

[†]At risk for atopic dermatitis defined as biologic parent or sibling with disease.



Application of Moisturizer to Prevent Atopic Dermatitis

- Enrolled neonates with one biologic parent or sibling with atopic dermatitis
- Participants were randomly assigned to receive emulsion-type moisturizer daily during the first 32 weeks of life (n = 59) or to control (n = 59)
 - All participants were prescribed petrolatum at the request of the institutional review board
- Intervention was associated with significantly lower risk of developing AD (P = .012)
- No significant difference in sensitization to egg
 - 38% vs 45% for treated vs control
 - 56% of infants who developed AD had IgE to egg (>0.7 kU_A/L)



 \mathbf{O}

Image adapted from Horimukai K, et al. J Allergy Clin Immunol. 2014;134(4):824-830.e6.

Recently Released Negative Results Regarding Skin Interventions and Atopic Dermatitis

- PreventADALL study of 2172 infants revealed no benefit to skin or food interventions initiated at birth (and possibly risks)
 - Rates of atopic dermatitis at 12 months (P = .003):
 - 11.1% in skin intervention group (oil baths and Ceridal cream applied to the face)
 - 9.0% in food intervention group (introduction of peanut, milk, wheat, and egg between 3 and 6 months)
 - 5.3% in food and skin intervention group
 - 8.1% in no intervention group
- BEEP study of 693 high-risk babies revealed no benefit to skin intervention initiated at birth
 - Rates of eczema at 2 years (*P* = .61):
 - 23% in skin intervention group (application of double-based gel or cream emollient for 12 months)
 - 25% in no intervention group



Anticipated Randomized Controlled Trial: PEBBLES

- A total of 760 infants with a family history of allergic disease will be recruited from maternity hospitals in Melbourne
- Intervention: Application of a ceramide-dominant emollient 2 times per day from birth to 6 months
- **Primary outcomes:** Presence of AD and food allergy in the first 12 months of life
- Phase 3 trial is underway, with results expected in 2021





Key Takeaways: Measures to Prevent Development of Food Allergy Through Environmental Exposure

- Reduce/eliminate environmental exposure to foods
- Have to address environmental exposure and skin barrier in high-risk children
- Parental education programs (bathing and eczema care)
- Daily use of petrolatum for barrier protection
- Treat eczema or atopic dermatitis aggressively



Key Takeaways

- There is no evidence for delaying the introduction of common allergenic foods beyond 4 to 6 months
 - For infants at high risk for peanut allergy, may be beneficial to introduce peanuts at 4 to 6 months
 - Additional evidence may support early feeding of other allergenic foods
- Skin barrier dysfunction may precede development of allergies
- Evidence for reducing allergies by addressing skin barrier integrity is conflicting
 - Further studies are needed

