



Clinical Recommendations for Reducing and Preventing Food Allergies

Overview

Hugh Sampson, MD, and Marion Groetch, MS, RDN, examine the importance of optimal nutrition in allergic children, as well as the latest evidence for introducing allergenic foods. The faculty discuss the link between food allergies and poor nutrition and growth; communicating strategies for nutritionally complete elimination diets; assessing and mitigating nutritional risk; the LEAP, EAT, and PETIT studies; solid food introduction and allergies; and the role of skin barrier maintenance in preventing allergies.

Target Audience

This activity was developed for pediatric physicians, advanced practice clinicians, nurses, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- 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.

Faculty

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The estimated time to complete the activity is 1.0 hour.

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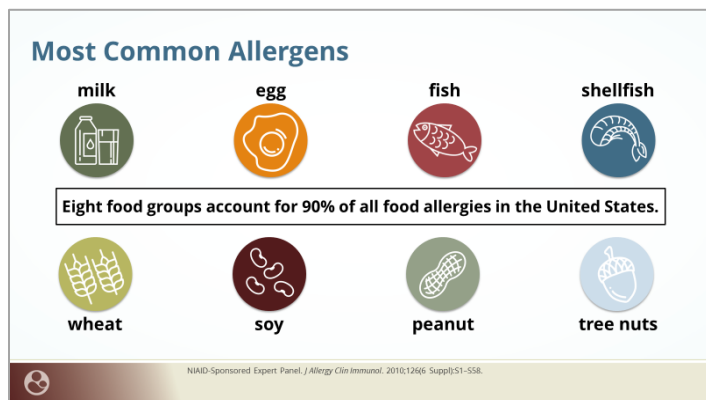
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Editor's Note: This is a transcript of an audio webcast presented on July 19, 2019. It has been edited and condensed for clarity.



Marion Groetch: We're going to start by looking at food allergy prevalence, and the link between food allergies and poor growth. Extensive data suggest that food allergies have been increasing in prevalence, and rates as high as approximately 10% have been reported. These 8 foods, milk, egg, fish, shellfish, wheat, soy, peanut, and tree nut, account for about 90% of all food allergies in the United States.¹



Slide 1 – Most Common Allergens

We know that growth impairment and nutritional deficiencies have been reported in children with elimination diets. Lynn Christie was one of the first to look at growth in children with food allergies. She and her colleagues found that children with 2 or more food allergies were shorter, based on height-for-age percentile, than those with 1 food allergy. They also found that children who had cow's milk allergy were more capable of meeting their nutritional needs when they had seen a dietitian or when they had an adequate milk substitute in their diets.²

Food Allergies Limit Growth

- Food allergies can negatively affect growth and food intake¹⁻³
- 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

Height-for-Age by Allergy Status¹

Participants	Height-for-age percentile		
	<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.

Slide 2 – Food Allergies Limit Growth

Then, consistent with previous reports, the specific food avoided can also play a role. In 2014, Mehta and colleagues at Mount Sinai conducted an electronic medical record review of close to 10,000 children, and found below average weight and height persisted into childhood for those with food allergies, particularly those with milk allergy.³

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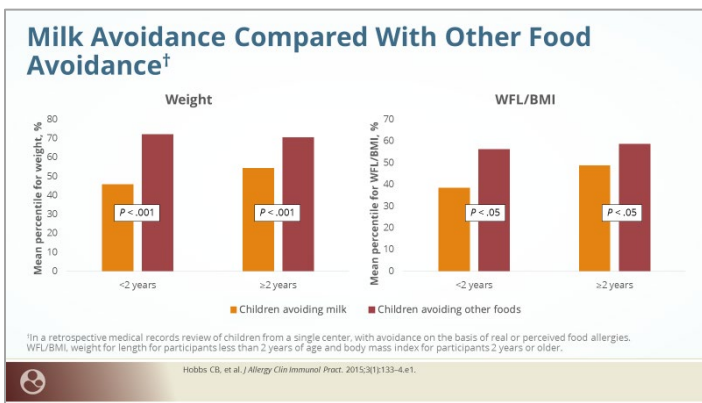
1. Christie L, et al. *J Am Diet Assoc*. 2002;102(11):1648-1651.
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3. Robbins KA, et al. *J Allergy Clin Immunol*. 2014;134(6):1466-1468.e6.
4. Mehta H, et al. *J Pediatr*. 2014;165(4):842-848.

Slide 3 – Food Allergies Limit Growth

Other studies have also noted an impact from cow's milk allergy. Hobbs and colleagues investigated the degree to which elimination diets, due to real or perceived food allergies, were associated with

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impaired growth [slide 4]. The children who were avoiding milk, and those are the orange bars, had significantly lower mean percentiles for weight and weight-for-length (ie, BMI) than children who were avoiding other foods. Those are indicated by the red bars. The impact of milk avoidance was more pronounced in children who were younger than 2 years.⁴ We think that's likely due to the fact that milk and dairy products play a larger role in meeting nutritional needs in children under 2 years of age.



Slide 4 – Milk Avoidance Compared With Other Food Avoidance

This year we published an international survey on growth in children with food allergy. This was a study led by Rosan Meyer. We prospectively enrolled 430 children with confirmed food allergy from 12 centers worldwide. We found cow's milk allergy led to lower weight-for-height Z scores than elimination of other foods. Those children with non-IgE-mediated allergies or mixed IgE- and non-IgE-mediated allergy had lower height-for-age Z scores than children with IgE-mediated allergy alone.⁵

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.

Slide 5 – International Survey on Growth in Children With Food Allergy

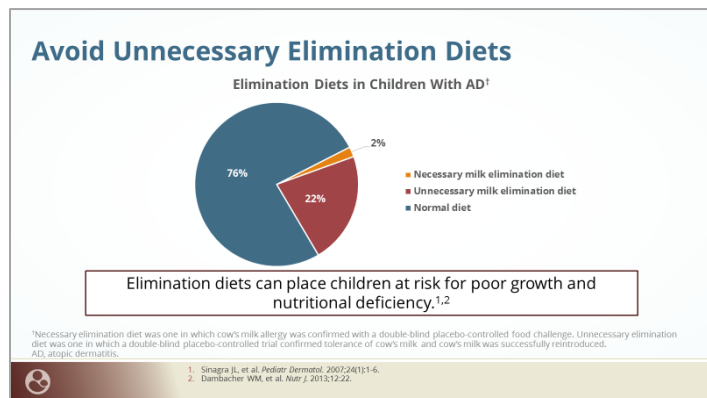
Overall stunting was more common than underweight in our combined populations. We had 9% of our population who were stunted, meaning they had a height-for-age Z score of less than -2. A total of 6% were underweight; 5% were undernourished; and 8% were overweight. It's interesting to note that overweight was also reported in the food allergic population, but at a much lower rate than what's generally seen in the general pediatric population. Overall in this study, we found children particularly at risk for poor growth when they had non-IgE-mediated allergy or mixed IgE- and non-IgE-mediated allergy, as well as those with cow's milk allergy. Of course, we've seen previously that multiple food allergies can also impact growth.

Optimizing Nutrition for the Allergic Child

Now that we know that children with food allergies are at risk of inadequate nutrient intake and poor growth, how do we optimize nutrition for the allergic child? The first step is avoiding unnecessary elimination diets. In this study, 186 children with atopic dermatitis were evaluated, and 24% were on a milk elimination diet. However, after an oral food challenge, only 4 of these patients, or 2%, were found to be allergic. All the others were able to introduce milk during the oral food challenge and maintain milk in the diet after the oral food challenge without worsening their eczema.⁶ The

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elimination diets were unnecessary. The first step is ensuring that we have a correct diagnosis.



Slide 6 – Avoid Unnecessary Elimination Diets

Long-term elimination diets should only be recommended by specialists for a documented food allergy. Our National Institute of Allergy and Infectious Disease food allergy guidelines recommend against using panels of tests when evaluating for food allergy, as food-specific serum IgE test and skin prick test results may still be positive in cases where the food can be tolerated.¹ The first step in an allergy assessment is typically an allergy-focused dietary history. For more on diagnosis I'd like to refer you to Jonathan Spergel's lecture in this series, *Diagnosing Food Allergies in Infants and Children*.

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;125(6 Suppl):S1-S58.

Slide 7 – Diagnosing Food Allergy: When Elimination Diets Are Necessary

When elimination diets are necessary, we need to consider how to apply them. This figure summarizes

factors to consider to ensure that the patient-specific approach is utilized [Slide 8]. First, we cover foods to avoid, and the degree of avoidance. We should think about how we need to individualize that. For instance, what ingredient needs to be avoided based on the allergenic food? Patients who are avoiding soy, for instance, typically don't need to avoid soy oil or soy lecithin. That would be an example of over-avoidance.

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

Foods to avoid and degree of avoidance	Industry and environment
Suitable substitutes	<ul style="list-style-type: none"> • Traveling and immigration • Food and nutrition literacy • Threshold levels and cross-contact or cross-contamination
Self-management skills	Nutrition
Co-existing and cross-reacting allergens	<ul style="list-style-type: none"> • Promote optimal growth • Prevent nutrient deficiencies • Development of normal feeding skills • Optimal nutrition for long-term health
Novel allergens	Future
	The role of nutrients, dietary patterns, and other food factors regarding: <ul style="list-style-type: none"> • Gut microbiome • Immune system • Allergy prevention and tolerance development

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

Slide 8 – A Patient-Specific Approach to Develop an Exclusion Diet to Manage Food Allergy in Infants and Children

We have new international guidelines for the diagnosis and management of food protein induced enterocolitis syndrome, or FPIES.⁷ These guidelines don't recommend routine avoidance of products with "may contain" precautionary allergy labels for patients with FPIES. These patients seem, for the most part, to have higher thresholds for reacting. For a patient with FPIES, you might not say, "Avoid products with precautionary allergen labels," but for those patients with IgE-mediated allergies, you might be advising your patients to a higher degree of avoidance. Thinking about how you can individualize your approach to avoiding foods in an exclusion diet.

We have to consider suitable substitutes. These are important for nutrition, for growth, and also long-term health. We should teach families how to manage the food allergy across all activities of daily living. Self-management skills are important. Then,

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we have to think about what to do about potential cross-reacting allergens.

Think about a time in food allergy management when we would see a patient with peanut allergy and advise them to avoid all peanuts and tree nuts, because of the risk of cross-reacting allergens as well as cross-contact in manufacturing. Now it's much more common for us to include all tolerated nuts in the diet, and there are many tree nuts that are now manufactured in dedicated facilities. Our families really enjoy eating these nuts and reaping the benefits of plant-based protein foods and including these healthy fats in the diet.

Lastly, we have to consider novel allergens, such as insect powders. These are being added to high-protein bars, pastas, and other foods. These are potential allergens. New ingredients are being added on a monthly basis to our food supply. We have to consider their allergenic potential. The insect powders actually cross-react with shellfish, so that is something that we have to think about.

As dietitians, we think not only about adequate nutrition but also optimal nutrition for long-term health. Even though there aren't very strong data at this point indicating that specific nutrients or dietary powders can impact allergy prevention or tolerance development, we do know that encouraging a healthy diet is beneficial, in any case, for the long term. In the future, we may find some data turning up that suggest a preventative effect.

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.

Slide 9 – Food Substitutions

When prescribing an elimination diet, it's important to know what nutrients will be eliminated as a result. Starting at the bottom [Slide 9], we see that fish and shellfish provide important macronutrients, such as protein, but also fats, and in particular, the long-chain polyunsaturated fatty acids, like EPA and DHA. These are essential in a human diet, meaning that we have to get them from the diet because we can't make them.

Again, there are limited data to support fish consumption for allergy prevention. Mostly the data relate to the maternal diet. However the American Academy of Pediatrics and the World Health Organization recommend that fish should play a larger role in the diets of children. They're important in development during early childhood.

What do we do if fish cannot be tolerated? I think the first step, again, is thinking about what I just said, about peanuts and tree nuts. If you have a patient that's come in and they have reacted to 1 fish species, do they need to avoid all fish species? You might want to consider evaluating them or referring for evaluation, to see whether they can tolerate some fish species. If they can't, you might have to consider seeds and some of the nuts that might provide some of the omega-3 fatty acids that would be beneficial for those families.

We know that wheat is a nutrient-dense food, and it provides a large percentage of daily dietary intake.

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When we eliminate wheat in the diet, we want to ensure that we're providing nutritionally dense alternatives. Gluten-free oats, buckwheat, amaranth, millet, quinoa, teff, and sorghum are all very nutritionally dense. If you are substituting only those gluten-free products that have predominantly rice, corn, and potato starch, then you're not going to be meeting the nutritional needs of the child. Those nutrients that are lost to the wheat elimination diet will not be replaced.

Soy and eggs are extremely nutritionally dense. They do not provide the same large percentage of daily dietary intake, so unless you're seeing a child who is also a vegetarian, it will be easier to substitute for those nutrients. But milk, on the other hand, provides a large percentage of daily dietary intake, about 30% in a typical 1-year-old. It's a major source of protein, fat, calcium, and vitamin D in the diets of young children. The quality of the milk substitute that we choose has to be carefully evaluated.

Let's take a look at these milk substitutes. You can see that the protein content is not there. In many of these, there is very little protein. They're all very low in fat as well. This would be inappropriate for a very young child, between 1 and 2 years of age. Typically, we would recommend a full-fat milk for that child. The soy and pea protein milks actually have a higher protein content, but they still tend to be very low in fat. That child would have to be able to meet their fat needs through the solid-food diet.

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	Varies based on fortification!
Pea	100	8	4.5	
Soy	100	7	4	
Oat	120	4	3	
Rice	120	1	2.5	
Coconut	80	0	4.5	
Almond	50	1	2.5	

! Milk substitutes are not nutritionally equivalent.

Slide 10 – Nutrients in Cow's Milk and Substitutes

Fortification will vary based on the brand, and based on the products within the brand, so you have to be careful. These milk substitutes are not nutritionally equivalent to cow's milk and they're not nutritionally equivalent to each other. The World Allergy Organization Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines recommend a cow's milk substitute of adequate nutritional value until 2 years of age. That's either breast milk or a substitute formula, to meet nutritional needs.⁸

I just want to pause here for a moment to talk about breastfeeding, because it's universally encouraged for all of the nutritional benefits, and also because of the potential benefits from an allergy perspective, even if there's no evidence of protection against food allergies in particular. There is some evidence of a protective effect of exclusive breastfeeding through 3–4 months in the cumulative incidence of eczema, and any duration of breastfeeding—meaning not exclusive but continuing to breastfeed beyond 3–4 months of age—may protect against wheezing in the first 2 years of life. The longer duration of breastfeeding protects against asthma even after 5 years of age.

With that in mind, we want to encourage breastfeeding, and we want to ensure that mothers are healthy when we do that. The fatty acid composition of breast milk reflects the maternal

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diet. Again, we have to think about the nutritional content of the maternal diet. If you have a mom who is avoiding fish, shellfish, nuts, and seeds, then the long-chain polyunsaturated fatty acid content of the breast milk will be affected.

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
 - Riboflavin
 - Vitamin B-6
 - Vitamin B-12
 - Choline
 - Retinol
 - Vitamin A
 - Vitamin D
 - Selenium
 - Iodine
- Maternal supplementation with these nutrients can increase breast milk concentrations and **improve infant health**

Allen L. Adv Nutr. 2012;3:362-369.

Slide 11 – Encourage Breastfeeding and Ensure Adequate Maternal Nutrition

The first step is to determine whether she needs to avoid those foods in her diet. Is it because the infant is allergic? Is the infant having symptoms? In that case, she might need to avoid those. Then you would be considering supplementing, but at this point, evidence and studies have not supported maternal exclusion diets for the prevention of atopic disease. If mom is excluding those foods from her diet because she thinks it's going to prevent her infant from having food allergy, that is not a good step. It might impact the quality of her milk.

In addition, secretion into milk is rapidly and substantially reduced by maternal depletion of many of these nutrients that are listed on your screen [Slide 11]. These are nutrients that are common in some of the more allergenic foods like egg, fish, milk, and grains. Again, consider the maternal diet and ensure that it's nutritionally complete. Maternal supplementation with nutrients can increase breast milk concentrations very rapidly, and it can improve the infant health as well.

For those infants who are not being breastfed, we have to consider a substitute formula. For substitute formulas, we have hypoallergenic formulas. There are two classes of hypoallergenic formulas that we have available in this country, extensively hydrolyzed formulas, and for those infants who continue to have symptoms on extensively hydrolyzed formula, we have to go on to an amino acid-based formula. These are peptide free.

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

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.0000000000002395

Slide 12 – Hypoallergenic Formulas

Soy formula is not hypoallergenic, but it can be an adequate substitute, especially for infants who have IgE-mediated allergies. For those with non-IgE-mediated allergies, there is a greater risk of co-allergy to soy, so they may react to those. It's maybe as high as about 30%. The American Academy of Pediatrics says we can use soy formula in infants after 6 months of age⁹; however, it's typically not the first formula that we recommend for our patients with cow's milk allergy.

The formulas that are not considered hypoallergenic are partially hydrolyzed formulas. These are not appropriate for the treatment of cow's milk allergy, and European formulas that are labeled HA are typically partially hydrolyzed formulas. In general, in most European countries in order to get a truly hypoallergenic formula you would need a script.¹⁰

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The formulas that are labeled HA are formulas that have reduced allergenicity, so they are hydrolyzed. They are marketed in Europe actually for allergy prevention, but in the United States, the 2019 American Academy of Pediatrics clinical report on the early nutritional interventions for the development of atopic disease found a lack of any evidence that partially hydrolyzed formulas prevent atopic disease, even in infants and children who are considered high risk.¹¹ This is a change from the 2008 clinical report, so just keep that in mind, that we don't use hydrolyzed formulas for prevention.

Teaching children how to eat and enjoy a wide variety of foods is important for long-term health. When we begin complementary feeding, it should be aligned with physiologic, oral, and motor skills, beginning around 6 months of age, and no sooner than 4 months of age. Infants at this age will generally accept a new flavor on the very first presentation. Usually between 4 and 9–10 months of age this is true. This is in contrast to children 2–5 years of age who need multiple exposures to a new food before they really start to consume any volume of that food.

vegetables. They were significantly more likely to have feeding problems at 7 years of age.¹² These are issues that could lead to poor nutritional quality long term.

Remember, there's no reason to delay introduction of complementary foods beyond 6 months of age, including those complementary foods thought to be highly allergenic. Dr. Sampson is going to be covering those. There's definitely no benefit from a prevention perspective, and there may actually be some harm.

Annotation added August 2021

Looking at the studies that Dr. Sampson will review with you in a few minutes, and also the nutritional guidelines for the prevention of food allergy from the American Academy of Pediatrics, the National Institute of Allergy and Infectious Diseases, and the joint North American allergy societies, we created this table to help families with early introduction of potentially allergenic foods. When the recommendations were not clear, we simply provided guidance based on early infant feeding for a healthy diet.

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. Coulthard H, Harris G, Emmett P. *Matern Child Nutr*. 2009;5(1):75-85.
3. Greer FR, et al. *Pediatrics*. 2019;143(4): pii:20190281.

Slide 13 – The Importance of Feeding in Infancy

Early introduction of a variety of flavors can impact long-term food acceptance, and also textures, which we've seen from [Coulthard] where they found children who were introduced to lumpy solids after 9 months of age, ate less of many food groups at 7 years of age, including fruits and

Food	Choose healthy infant foods*	How much/how often as part of the infant's complementary diet
BENEFICIAL for prevention When developmentally ready** around 6 months of age or between 4-6 months of age if advised by your doctor due to high risk of allergy (severe eczema or egg allergy)**		
Peanut†	Choose peanut flour or thinned peanut butter that has no added ingredients (salt, sugar, oils) for healthier options! Peanut butter should be thinned with breastmilk, water or formula or mixed into a pureed food, eg, 2 teaspoons of peanut butter mixed with 2-3 teaspoons liquid.	About 1-2 teaspoons peanut butter/powder per serving, served 2-3 times per week as tolerated
BENEFICIAL for prevention but effective dose requires further research When developmentally ready after 4-6 months of age**		
Egg	Serve well-cooked egg mashed with pureed foods or chopped and served as finger food.	About 1/3 of a well-cooked egg, 2-3 times per week
HAVE NOT BEEN STUDIED SUFFICIENTLY to know if early introduction decreases risk of allergy, therefore doses are based on healthy feeding†† There is currently no evidence of benefit to delay introduction of highly allergenic foods after 4-6 months of age and developmentally ready**		
Wheat	Infant wheat cereals (iron-fortified for the breastfed infant); whole wheat toast, pasta or crackers for older infants	1/1-1 oz total grains per day.
Milk	Plain, full-fat yogurt can be mixed into pureed fruit or vegetable; cow's milk should not substitute for breast milk or infant formula	2-4 fl oz per day
Sesame†	Tahini is sesame paste typically served as an ingredient in hummus or as tahini dipping sauce for finger foods like vegetables	> or = 3 teaspoons seeds/any nuts per week
Seafood	Low mercury finfish https://www.fda.gov/media/102331/download	1 oz per serving, 3 times per week (See FDA link for frequency and type of fish)
HAVE NOT BEEN STUDIED to know if early introduction decreases allergy risk, therefore doses are based on healthy feeding†† There is currently no evidence of benefit to delay introduction of highly allergenic foods after 4-6 months of age and developmentally ready**		
Tree nuts†	Smooth, thinned nut butters, eg, almond, cashew, hazelnut, pistachio, walnut	> or = 3 teaspoons seeds/any nut per week
Soft	Soft tofu	2 tablespoons per serving

Slide 14 – Choose Healthy Infant Foods

For peanut, we suggested introduction around 6 months of age or 4-6 months of age if advised by the physician due to higher risk of peanut allergy. Ongoing peanut intake is recommended for all and these amounts here are based on EAT and LEAP studies. For infants with high risk of peanut allergy

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the recommendation from the NIAID is to continue eating 2 g peanut protein or 2 tsp diluted peanut butter, 3 times per week.

Evidence is less strong for egg, and not all guidelines are in agreement. There is agreement however that there is no benefit to delay introduction of any potentially allergenic food past 6 months of age, so the amounts we recommend here for the other common allergens are based on healthy infant feeding patterns.

When considering feeding in infancy, one needs always to consider the overall healthy diet. Choosing whole foods as opposed to processed foods, higher fiber intake from vegetables, fruit, whole grains, and a high diet diversity are all beneficial for the health of the infant. Balance and proportionality are always important to meet nutritional needs and optimize the diet for developing healthy eating habits and preventing chronic diseases.

We want to ensure that the diet is balanced, and the need for good nutrition does not end after infancy. A diverse and balanced diet of healthy whole foods can increase microbial diversity, and it can increase exposure to nutrients that are being studied for their preventative impact, such as omega-3 fatty acids and fiber from fruits and vegetables. We also want to encourage exposure to foods that are more commonly allergenic, as Dr. Sampson's going to discuss. There are no randomized controlled studies recommending a diverse diet, but this is balanced by no known harm in introducing a diverse range of healthy foods.

What you're seeing on your screen here is a checklist from the choosemyplate.gov website [Slide 15]. You can download a checklist for any age group, including adults.¹³ This is one for a 1-year-old. It's very useful for parents. It's a very useful handout because it gives them specific food groups and goals for food groups that they should be aiming for, for their children. Parents are frequently

surprised to see how many servings of fruits and vegetables their children should be eating on a daily basis, so this is a great resource.

Ensure That the Diet Is Balanced!

USDA MyPlate
www.choosemyplate.gov

Typical needs of a 1 year old

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 matches it to a balanced diet. The right mix can help you to maintain your weight and health. The key is choosing a variety of foods and beverages from each food group—and making sure that each choice is limited to saturated fat, sodium, and added sugars. That's why our goal is "MyPlate"—to make healthier choices you can enjoy.

Food Group Amounts for 1200 Calories a Day

Food Group	Amount
Fruits	1 cup
Vegetables	1 cup
Grains	1/2 cup
Protein	2 ounces
Dairy	2 cups

Focus on whole fruits and have frozen, canned, or dried.

Choose a variety of colorful fruits, berries, and citrus.

Make half your grains whole grains.

Find whole grain foods by looking for the fiber label and transferring the label and transferring the label.

Very your protein regularly.

Use up your protein foods to include natural cheese, eggs, beans, lentils, tofu, and fish. Protein is important for building strong muscles.

Move to lower fat or fat-free milk or yogurt. Choose fat-free milk, yogurt, and ice cream. Try milk to cut back on your saturated fat.

Drink and eat less sodium, saturated fat, and added sugars. Limit:

- Sodium to 1,000 milligrams a day.
- Saturated fat to 16 grams a day.
- Added sugars to 25 grams a day.

USDA MyPlate. www.choosemyplate.gov. Accessed June 17, 2019.

Slide 15 – Ensure That the Diet Is Balanced!

When things go poorly, a consultation with a registered dietitian can help. What you're seeing here is a study by Berni Canani and colleagues. They measured the impact of dietary counseling on children with food allergies in a prospective interventional study of children aged 6–36 months. They compared healthy children at baseline with children with food allergies at baseline.¹⁴

Dietary and Nutritional Counseling Improves Nutritional Status[†]

Median nutrient intake	Healthy children at baseline (n = 66)	Patients with food allergy
		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.

Slide 16 – Dietary and Nutritional Counseling Improves Nutritional Status

They found that energy intakes, protein intakes, and calcium and zinc intakes were significantly different in children with food allergies and children without food allergies. Then, after 6 months of counseling, they found that there was significant improvement in intake of energy, all macronutrients, and all

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micronutrients—fiber, calcium, iron, and zinc. Nutrition counseling can actually have an impact.

There are times when we cannot meet nutritional needs through the diet alone, and vitamin/mineral supplementation may be appropriate. It may be appropriate to supplement for calories as well, so we might need a substitute formula to help us supplement energy. It's very individualized. We would have to look at that patient's diet, we'd look at the foods that they're avoiding, we look at what is actually in their diet, and determine whether we can meet their needs through dietary sources. If not, we would think about supplementing with maybe some micronutrient supplements.

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/>

Somers L. *Pediatr Ann*. 2008 Aug;37(8):559-568.

Slide 17 – Vitamin and Mineral Supplementation

I wanted to point out a resource here, on the lower right-hand corner of your screen [Slide 17]. This is the dietary reference intake calculator for health care professionals.¹⁵ You can just search “dietary reference intake calculator” and this will pop up. You can put in your patient's age, weight, height, and date of birth, and it will give you exactly what that patient needs in terms of calories, protein, and each micronutrient so you would know how to supplement that patient.

I'm just going to end by showing you a diet without elimination and a diet with elimination, and what that would look like. If you look at the center column, we've eliminated the major allergens [Slide 18]: milk, egg, wheat, soy, peanut, tree nut, fish, and

shellfish. You can see that this diet really is not going to meet nutritional needs. It's low in carbohydrates, it's low in fibers, it's low in calcium, vitamin D, and other nutrients.

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 or chick pea noodles Spinach salad with lettuce, tomato, peppers, Italian dressing Elemental formula (8 oz)
Snack	Ice cream	Ice cream	Coconut ice cream

Groetch M, et al. *J Allergy Clin Immunol Pract*. 2013;1(4):323-331.

Slide 18 – Dietary Effects of Elimination Diet

With substitutions, a healthy and delicious diet can be provided. We can provide optimal nutrition when we focus on balance, proportionality, and appropriate substitutes in the diet.

Our key takeaways today are to encourage breastfeeding exclusively to 4–6 months of age, and to continue breastfeeding while introducing complementary foods, and beyond.

The American Academy of Pediatrics says that we should continue breastfeeding while introducing these foods, until 12 months of age or longer, as long as it's mutually desired by both parent and child. Remember, for that patient with cow's milk allergy, we may want to continue breastfeeding, at least partially, through that second year of life. We will also want to consider an optimal hypoallergenic formula or beverage choice. Appropriate volumes and vitamin/mineral supplementation as needed.

Don't think just because there is a formula in the diet that micronutrients are being met. It really depends on the volume of the formula, the age of the child, and the composition of the solid food diet. We want to encourage a healthy diet rich in fruits, vegetables, fibers, and long chain polyunsaturated fatty acids. We don't want to delay introduction of

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complementary foods, including those foods that are thought to be highly allergenic. Then lastly, we want to provide an otherwise individualized approach to meet nutritional needs within the context of the allergen elimination diet.

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.

Slide 19 – Key Takeaways

Lastly, through the Consortium for Food Allergy Research, we have developed a food allergy education program. You can just go to this website and click on food allergy education program. The handouts have been validated, and they're ready for your patients. FARE (Food Allergy Research & Education) has excellent patient education materials that you can download and use in your practice for your patients. With that I'm going to turn over the virtual podium to Dr. Hugh Sampson, who's going to be discussing reducing the risk of allergy.

Online Patient Resources



Slide 20 – Online Patient Resources

Reducing the Risk of Allergy

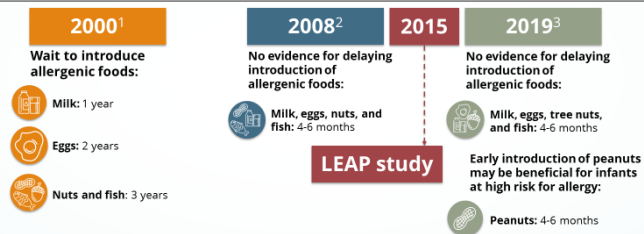


Dr. Hugh Sampson: I'd also like to thank you for joining us today. I am going to be discussing some of the more recent findings on the reduction of or the attempts to reduce food allergy.

For those of you who have been in practice since 2000, you see on this slide [Slide 21], there's really been a 180-degree change in our food allergy prevention rationale.

180-Degree Change in Prevention Rationale

American Academy of Pediatrics Guidelines on Preventing Food Allergy



1. Zeiger RS. Pediatrics. 2003;111(6): Pt 3:1162-1671.
 2. Greer FR, et al. Pediatrics. 2008;121(1):183-191.
 3. Greer FR, et al. Pediatrics. 2019;143(4): pii:e20190281.

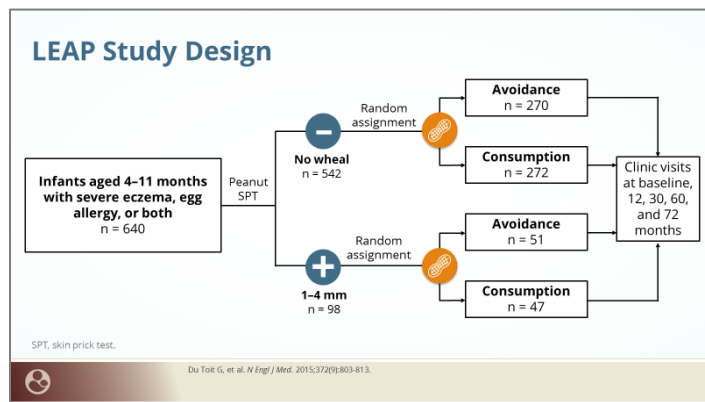
Slide 21 – 180-Degree Change in Prevention Rationale

Back in 2000, the recommendation was that we wait on introduction of some of these major allergenic foods, such as milk, egg, peanuts, and tree nuts.¹⁶ But this was actually questioned around 2008. At that time, the Academy of Pediatrics re-looked at the data and decided that there really was not strong evidence for delaying the introduction of these allergenic foods.¹⁷

However, in 2015 a real landmark study was done by Gideon Lack's group in the United Kingdom.¹⁸ This study really changed our paradigm on how we think about preventing food allergy. No longer are we just saying that there's no evidence that adding things such as milk, egg, and other major allergens are not harmful, there's actually evidence now to suggest that the addition of peanuts early is really important for the prevention of peanut allergy.

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Now, the study that was done that showed this very convincingly was the Learning Early About Peanut Allergy (LEAP) study. In this trial, the investigators recruited 640 infants who were considered to be at high risk for developing food allergy. This was based on the fact that they either had severe eczema, egg allergy, or both. This group of infants was skin tested, and then those infants that had no evidence of IgE antibody, or a negative prick skin test, were randomized to be in the avoidance group or the early consumption group.

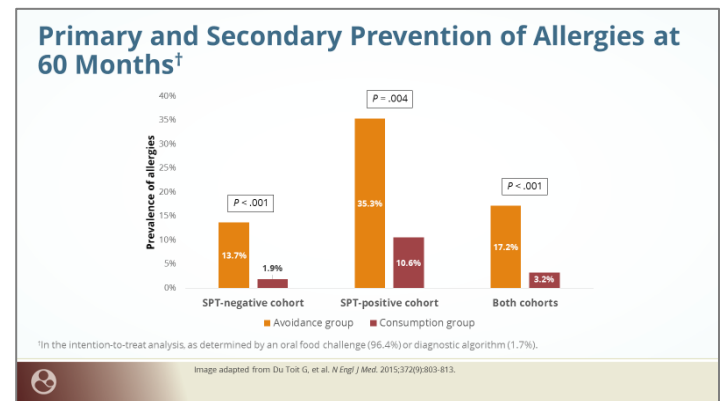


Slide 22 – LEAP Study Design

In that early consumption group, these infants were fed about 2 g of peanut protein 3 times a week, up through the age of 5 years. They also looked at a group that was considered to be minimally sensitized, or those that had a positive skin prick test of 1-4 mm, and they were also randomized to the avoidance or consumption group. These children were followed through age 5 years, and then challenged at that point to determine the prevalence of peanut allergy.

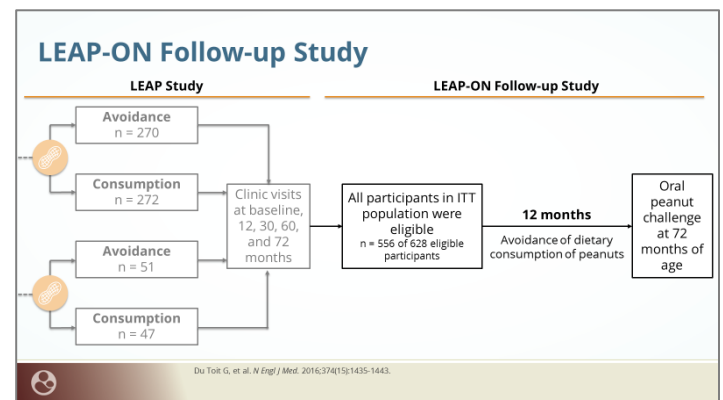
As you see on this next slide, there really was a major difference in the outcomes of these groups [Slide 23]. As you can see here, in the group that were skin test-negative (ie, those that didn't have evidence of IgE antibody to peanut) 13.7% of the individuals in the avoidance group actually ended up with peanut allergy at age 5 years, compared with just under 2% of those infants that received

peanut early. Looking at the skin test-positive group, there was an even more dramatic difference, with over a third of the babies who were in the avoidance group developing peanut allergy by 5 years of age, compared with 10% of those that had early consumption.



Slide 23 – Primary and Secondary Prevention of Allergies at 60 Months

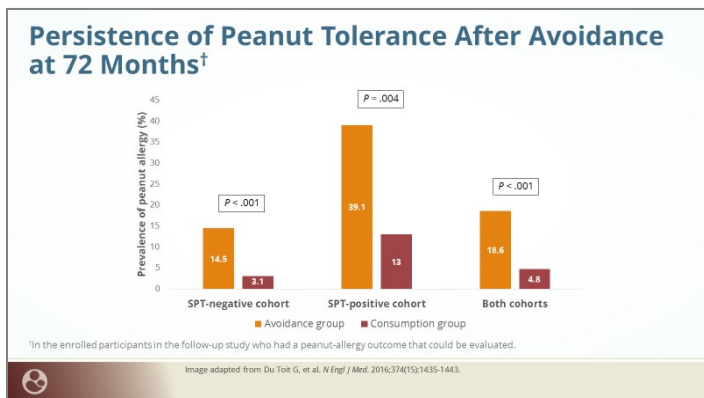
Now, the question then was, if these children were to go off peanuts for a period of a year, would they sustain their tolerance to peanut? The reason this question comes up is because we know when we do oral immunotherapy that children have to be maintained on peanut in order to maintain protection. In the follow-up study, the researchers were able to enroll most of the patients from the LEAP trial to go on to what's called the LEAP-ON trial, where they had all children eliminate peanut for a year, and then go through another challenge.¹⁹



Slide 24 – LEAP-ON Follow-up Study

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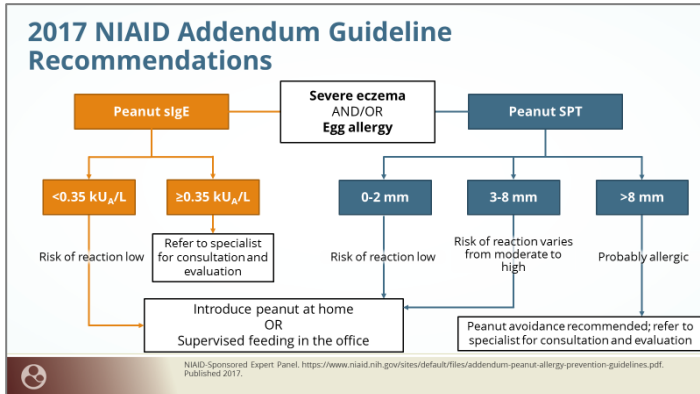
As you can see on this next slide [Slide 25], there was really no evidence of loss of their tolerance to peanut among those individuals that went off peanuts for a year.



Slide 25 – Persistence of Peanut Tolerance After Avoidance at 72 Months

This truly showed that those individuals who were given peanut early did develop permanent tolerance to peanut, and that this early introduction of peanut was protective for the prevention of peanut allergy.

Based on this, the National Institute of Health put together an expert panel that came out with recommendations on how we should deal with children who are considered at risk for peanut allergy.²⁰ These are infants with severe eczema and/or egg allergy. There are 2 ways to look at it. First, their physician can obtain serum IgE levels to peanut. If the level is less than 0.35, peanut can be introduced into the child's diet at home, or under supervision if the parents are nervous about adding peanut at home.



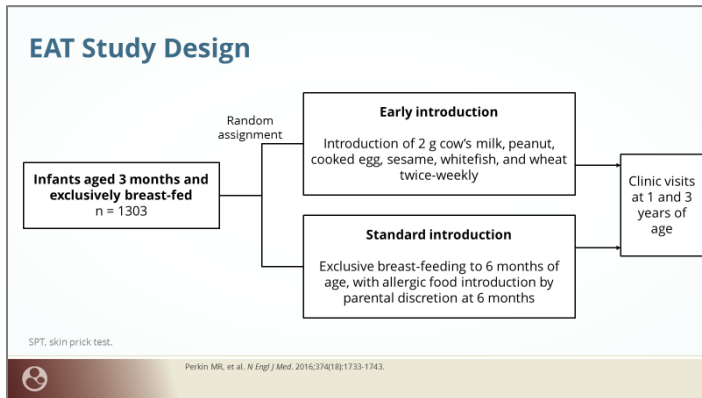
Slide 26 – 2017 NIAID Addendum Guideline Recommendations

In those infants who have evidence of IgE, or a level greater than 0.35, it was recommended that they be referred to a specialist for further evaluation. The specialist would then likely do a skin prick test. If the skin test wheal was quite small, 0–2 mm, then the child could have peanut introduced at home, or under a supervised office setting if the parents were nervous about doing it, with little risk of that patient having a reaction.

If the child had a skin test wheal in the range of 3–8 mm, then the risk of reaction is slightly increased, and it may be desirable to have the challenge done in the physician's office. If the skin test was greater than 8 mm, the panel felt that that was fairly confirmative of the fact that the patient *did* have peanut allergy, and peanut should be avoided.

Now, other questions that then came up were whether or not early introduction of allergenic foods would be beneficial for other kinds of foods. This is what led to the so-called EAT trial, in which the investigators in Dr. Gideon Lack's group in London did a trial where they enrolled over 1300 infants from the general population who had no evidence of food allergy. They then divided the group up into early introduction or standard introduction of the various foods.²¹

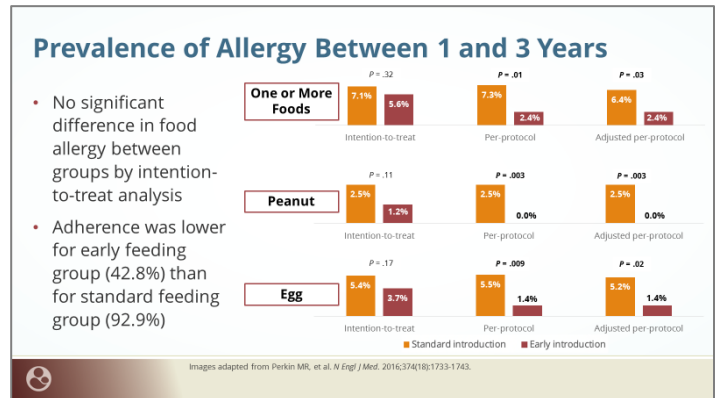
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Slide 27 – EAT Study Design

In the early introduction group, all infants were given up to 2 g of cow's milk on a weekly basis, as well as peanut, cooked egg, sesame, white fish, and wheat twice weekly. In this situation, milk was always the first food given, and wheat was the last, and the others were randomized. In the standardized introduction, patients were exclusively breastfed until 6 months of age, and then introduced according to the British standards, which are very similar to those in the US. Then, clinic visits took place at 1 year and 3 years of age. At 3 years of age, they evaluated the prevalence of allergy to various foods.

Looking then at the outcome of this study, the results were not quite as satisfactory as what we had seen in the LEAP trial. Here what you see is that up in the upper left-hand corner [Slide 29], when you look at the intention-to-treat results, there was no significant difference in the rate of allergy or the prevalence of allergy in any of the groups. This was shown to be largely due to the fact that the adherence was much lower in this study than in the LEAP trial. However, when you look at the per-protocol analysis, which is the center column, you can still see the fact that those children that actually adhered to the particular diet had a significant decrease in the prevalence of both peanut and egg allergy.



Slide 28 – Prevalence of Allergy Between 1 and 3 Years

Now, there have been a number of studies done looking at early introduction of egg into the diet. In fact, from this systematic review and meta analysis, there were 416 articles that were identified, 6 of which were appropriately randomized and met the criteria for evaluation. Allergic outcomes were evaluated in over 3000 infants. The bottom line was that there did appear to be a protective effect from the early introduction of egg.²²

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

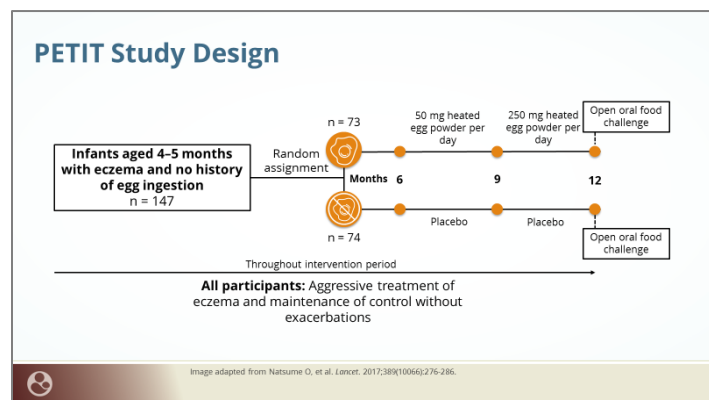
Al-Saud B, Sigurdardóttir ST. *Int Arch Allergy Immunol*. 2018;171(4):350-359.

Slide 29 – Early Introduction of Egg and Egg Allergy: Systematic Review and Meta-analysis

One of the studies looking at this was the PETIT study, which was done by a group in Japan, where they identified infants at 4–5 months of age with eczema and no history of egg ingestion. The children were randomized to receive no intervention or up to 50 mg of heated egg powder per day, through the first 9 months of life, and then 250 mg of heated egg up to 12 months of age. The

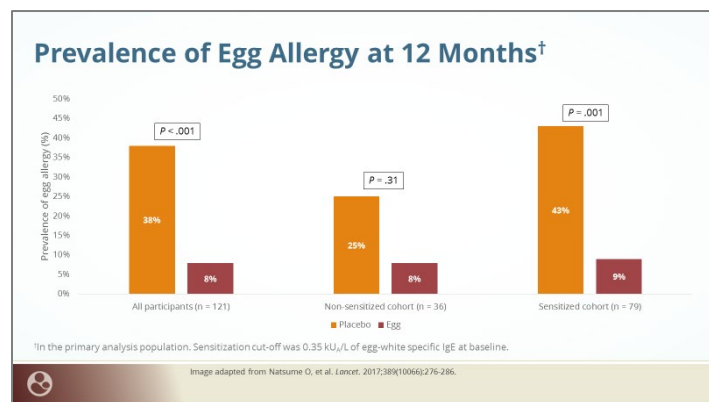
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children then went through an open food challenge, and the groups were compared.²³



Slide 30 – PETIT Study Design

What they found in this particular study was a significant decrease in the prevalence of egg allergy at 12 months in those infants who had received the early egg introduction. The one caveat to this is the fact that in the group that received egg early, 6 of the 60 in that group actually ended up being hospitalized for an allergic reaction to egg.



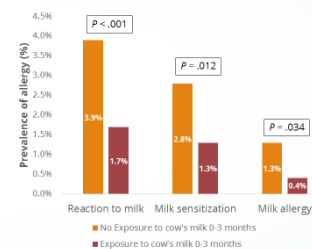
Slide 31 – Prevalence of Egg Allergy at 12 Months

Now, the other area that's been looked at is early introduction to cow's milk. This is from an associate study done with the HealthNuts cohort from Melbourne, Australia. In the full cohort, there were over 5000 infants that were evaluated at 12 months of age, but for the milk study, about half of these children were evaluated, going through skin prick testing for allergy to milk.²⁴

What they found in looking at this was that early exposure to milk protein did appear to lead to a decreased prevalence of milk allergy in the children who were sensitized to milk, and also that there were less reactions to milk, not necessarily considered allergic. One of the points here is that while this does certainly suggest that early introduction of milk can be protective, the authors do note that this is an association study, and an appropriate prospective study, similar to what was done in the LEAP trial, is really necessary to show that this is an effective way to prevent milk allergy.

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 ≥ 2 mm
- Early exposure to cow's milk protein was determined by parental questionnaire at 1 year of age



Slide 32 – Early Introduction of Cow's Milk: Observational Study

Through the years, a number of different measures have been looked at with the idea that they may in fact decrease the prevalence of food allergy. Things such as supplementation with various vitamins and minerals have been evaluated, with no proven benefit for the prevention of food allergy. There's a great deal of interest now in probiotic supplementations, but again the evidence is really insufficient to suggest that these are effective ways to prevent food allergy.

Clinical Recommendations for Reducing and Preventing Food Allergies

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.

1. Nurmatov U, et al. *J Allergy Clin Immunol*. 2011; 127(2):226-231.e1-30.
2. Di Mauro G, et al. *World Allergy Organ J*. 2016;9:23.
3. Flórcia 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 G, et al. *Acta Paediatr*. 2015;104(6):730-33.
6. Guaratone AW, et al. *Cochrane Database Syst Rev*. 2015;(7):CD010085.

Rising Prevalence of Food and Skin Allergies

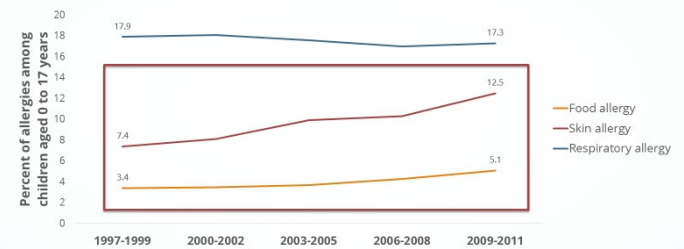


Image adapted from Jackson KD, et al. *NCHS Data Brief*. 2013;(121):1-8.

Slide 33 – Dietary Measures With No Proven Benefit or Insufficient Evidence

As Marion has just mentioned, introduction of hypoallergenic formulas has been thought to be useful in prevention of food allergy, but this has not been borne out in further studies. While we certainly promote exclusive breastfeeding, again there is no evidence that this is a way to prevent food allergy; however, as Marion pointed out, there are many other reasons why this is a good form of nutrition. Then there's also been the idea that adding polyunsaturated fatty acids to the diet of the mother, either during pregnancy or lactation, may be useful. But again, the data is lacking to support this as a preventative measure.

One of the things that's become clear as we look at changes in the prevalence of food allergy over the last decade or so, is that while in the lower orange line [Slide 34], you see about a 50% increase in the prevalence of food allergy, in the upper line that represents atopic dermatitis, you actually are seeing about a 75% increase in the prevalence.²⁵ We now are aware of the fact that it's highly likely that many of these children are being sensitized to food from contact through the skin.

Slide 34 – Rising Prevalence of Food and Skin Allergies

There's a building body of evidence to support that. For example, it's been shown that in children with eczema, there's definitely increased odds of developing food allergy, multiple food allergy, and even specific types of food allergies. For example, it's been shown that any food allergy is 6 times more likely in a child with significant atopic dermatitis or eczema. Peanut allergy is about 11 times more likely, and something like sesame allergy is 41 times more likely. The other thing that's been noted here is that the earlier the onset of eczema and the more severe the eczema, the more likely that child will develop food allergy.²⁶

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

Increased Odds of Allergy in Infants With Eczema

- 6X Any food allergy
- 11X Peanut
- 41X Sesame

Martin PE, et al. *Clin Exp Allergy*. 2015;45(1):255-264.

Slide 35 – Eczema Is Associated With Development of Food Allergy

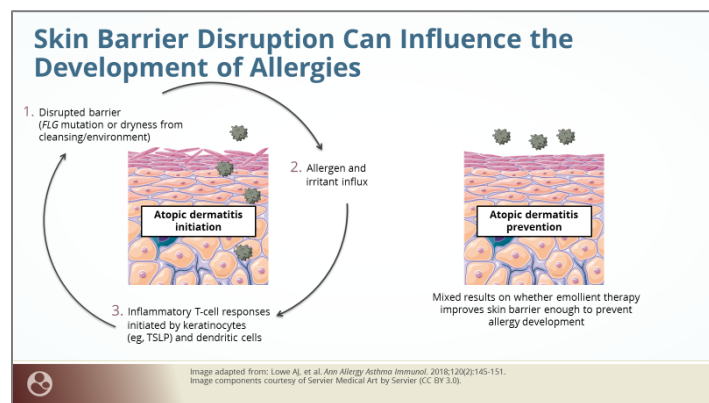
The question is, why is that? What's going on here that is leading to this higher rate of sensitization? Well, we're now very much aware of the fact that the skin is a very potent immune organ, and that keratinocytes, which make up a large proportion of

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the epidermis, are actually very important players in the innate immune system. These cells are able to express most of the toll-like receptors that are used in innate immunity.

They're capable of secreting a number of cytokines, including things such as IL-33, IL-25, and TSLP, which are cytokines which promote the development of hypersensitivity or IgE antibody production. They also are very active in secreting antimicrobial peptides for protection against various organisms.

However, when the skin is inflamed, such as in atopic dermatitis, these keratinocytes tend to secrete what we call alarmins, or the IL-33, IL-25, and TSLP, which then cause the immune system to develop IgE antibodies to various foods that are in contact with the skin. Much interest and emphasis has been placed on trying to protect the skin barrier.



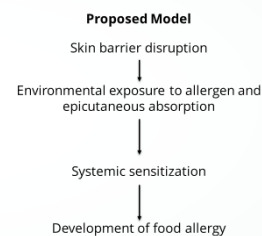
Slide 36 – Skin Barrier Disruption Can Influence the Development of Allergies

When we look at what information is out there to support this idea, one of the things that's been noted over the years is that allergic reactions to food often occur without prior obvious oral exposure. Normally, oral exposure to a food in infancy will lead to tolerance, not to hypersensitivity. We also know, and I'm sure you're all aware, that those infants with atopic dermatitis often have food allergy as a comorbidity.²⁷

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



Isadi N, et al. *Children (Basel)*. 2015;3(3):382-402.

Slide 37 – Food Allergy and Skin Barrier Disruption

The group from London has shown that peanut allergy really correlates with household peanut consumption, or peanut in the environment, and not the individual or the infant's peanut intake.²⁸ There's really developing strong evidence that contact with the skin from these really significant amounts of food proteins—peanut, egg, and milk—in house dust and on the hands of caregivers and siblings, may be leading to this sensitization, especially in those children with atopic dermatitis.

There's been a new move now to try to protect the skin barrier from dryness and irritation through aggressive treatment of the inflammation brought about by atopic dermatitis, in the hopes that we might prevent desensitization. There's also been a lot of interest in frequent bathing and the use of soaps—especially antimicrobial soaps—and their effects on the skin barrier, making it more permeable to some of these allergens. Many investigators are now looking at the application of emollients in an attempt to maintain a much more substantial skin barrier.

Clinical Recommendations for Reducing and Preventing Food Allergies

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.

Simpson EL, et al. *J Allergy Clin Immunol*. 2014;134(4):818-823.

Slide 38 – Enhancement of Skin Barrier to Prevent Atopic Dermatitis

Also, there's been discussion about trying to limit allergen contact exposure in the environment, as well as treating inflammation of the skin very aggressively. Now, there have been some studies that are ongoing, that support the idea that protecting or enhancing the skin barrier may be protective from allergies.

This is one study that was carried out both in the UK and the United States in infants who were randomly assigned to a daily emollient treatment or no emollient treatment at the first 3 weeks of age.²⁹ Then at 6 months of age, the investigators evaluated the prevalence of atopic dermatitis in each group. What they saw was that those infants who had been treated with emollient had a 50% decrease in the prevalence of atopic dermatitis compared with those who had not received the emollient. Here though, they did not look at sensitization to allergens.

Slide 39 – Application of Emollient to Prevent Atopic Dermatitis

In this trial, which was done in Japan, there was, again, early use of the skin emollients in an attempt to fortify the skin barrier and look at differences in the outcome of atopic dermatitis, as well as sensitization to egg protein. Here, as you see, on the right, in that Kaplan–Meier curve, the darker line indicating those children who were in the control group had a greater incidence of atopic dermatitis [Slide 40], whereas the intervention group in the upper line in orange had a significantly decreased prevalence of atopic dermatitis.³⁰

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)

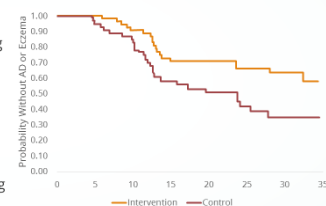


Image adapted from Horimukai K, et al. *J Allergy Clin Immunol*. 2014;134(4):824-830.e6.

Slide 40 – Application of Moisturizer to Prevent Atopic Dermatitis

Now, in this study there was no significant difference in sensitization to egg between the 2 groups; although, in fairness, the study was probably not sufficiently powered to look at that. The investigators did note that over half of the children who developed atopic dermatitis did, in fact, have evidence of IgE sensitization to egg.

Clinical Recommendations for Reducing and Preventing Food Allergies

These studies really support that idea that fortification of that skin barrier may be very important. However, as [with] many things in medicine, it's never quite that clear. At the European Academy meeting that took place this June in Lisbon, there were reports on 2 large prospective studies that were done, one in Norway and one in the UK.³¹

In the PreventADALL study, over 2000 infants were evaluated and divided into 4 groups, those who received emollients for their skin only (about 575 children), 642 who had appropriate dietary applications, 642 who had both, and 597 infants who received no treatments. As you can see on the slide [Slide 41], those who were in the skin intervention alone or the food intervention alone groups actually had a slightly higher prevalence of atopic dermatitis than both the control group and those who had both the food and skin intervention. This was somewhat discouraging.

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 Ceridol 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

Hein I. Emollient Fail to Protect Against Eczema. <https://www.medscape.com/viewarticle/914051>. Published June 6, 2019. Accessed June 17, 2019.

Slide 41 – Recently Released Negative Results Regarding Skin Interventions and Atopic Dermatitis

Immediately after that, the second trial, which was done in the UK, evaluated 693 high-risk babies that had emollients started in the first several weeks of life. The prevalence of eczema or atopic dermatitis was evaluated at 2 years of age. This trial was equally disappointing, showing that there was no difference in the prevalence of atopic dermatitis in the 2 groups receiving the emollient therapy or no intervention.

However, there were some issues related to those studies. There are other studies that are underway. For example, this PEBBLES study that's being done in Melbourne, Australia, where they're looking at 760 infants with a family history of allergic disease who have been recruited. Here, they're evaluating both the presence of atopic dermatitis and food allergy in the first 12 months of life. This is a phase 3 trial that's underway, and we do expect to see results in 2021. In addition, there are a number of other trials that are going on around the world that should help us answer this question more directly.

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

NCT03667651. <https://clinicaltrials.gov/ct2/show/NCT03667651>. Updated October 2, 2018.

Slide 42 – Anticipated Randomized Controlled Trial: PEBBLES

What are the key takeaways, then, with the prevention in the development of food allergies through environmental exposure? Many investigators at this point would agree that we should try to reduce or eliminate environmental exposure to foods if possible. We need to address this environmental exposure and the skin barrier more thoroughly in these high-risk children, and the use of things such as emollients to fortify that skin barrier.

Clinical Recommendations for Reducing and Preventing Food Allergies

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

Slide 43 – Key Takeaways: Measures to Prevent Development of Food Allergy Through Environmental Exposure

We also need to educate the parents on the outcome of frequent bathing and what effect that can have on drying and irritating the skin. Also, in those parents that have children with eczema, we should really aggressively treat that disorder because it's really the eczematous skin—or the number of lesions of eczema—that seems to correlate best with the prevalence of food allergy. Then, most investigators would agree there's probably some advantage to daily use of petrolatum as barrier protection, and as mentioned, really treating eczema or atopic dermatitis aggressively.

Looking at the area in general, at this point we really have no evidence to support the delay of introduction of the common allergenic foods beyond 4-6 months of life. There is very solid evidence to show that early introduction of peanut will prevent food allergy in high-risk children. There is growing evidence that this may be true for other allergenic foods as well.

Slide 44 – Key Takeaways

There's certainly strong circumstantial evidence that barrier dysfunction precedes the development of allergies, and food allergies in particular, and that this is something that needs to be addressed. The evidence is also mounting that reducing allergen exposure on the skin barrier may be useful, but as I mentioned, the data supporting the integrity of the skin barrier is still somewhat conflicting. However, further studies are underway and we should have answers to that within the next year or so. At this point I'm happy to open it up for questions from the floor.

Question & Answer

Editor's Note: This is a transcript of audience questions together with Ms. Groetch's and Dr. Sampson's responses from the July 19 and August 1, 2019, audio webcasts.

What is the role of a dietitian in managing food allergies? Do all children with milk or multiple food allergies need referral to a dietitian?

Ms. Groetch: I think if you look at most of the guidelines, almost every guideline—those for FPIES, eosinophilic esophagitis, even our National Food Allergy Guidelines—do recommend a referral to a dietitian. However, it doesn't happen frequently just because of the way our health system works. Dietitians aren't always covered.

Clinical Recommendations for Reducing and Preventing Food Allergies

But I would say that the role of the dietitian is actually really quite important. We work with the families to teach about avoidance. We individualize the approach, like I mentioned earlier. When I have a patient with multiple food allergies, I'm working with the physician so that we can get as many foods into the diet as possible, because we want that child to be able to eat all tolerated foods. Thinking about the foods that are probably more nutritionally needed at that time, we want to try to introduce those first. There are many ways that the dietitian can actually be involved, but I think an individualized approach is really very important.

How should peanuts be fed to infants? For example, should they eat peanut butter, cooked peanuts, or another option?

Dr. Sampson: I think probably the best way to address that is that in the report put out by the NIH expert panel, on the NIAID webpage,²⁰ there's a very good description of ways to feed peanuts to children, depending on their particular age. For example, if we want to try to get 2 g of peanut protein into the diet 3 times a week, one of the ways to do that is essentially taking 2 teaspoons of peanut butter, and watering that down into a mixture that would be acceptable to a young infant, either in a liquid or in something like applesauce.

What I would encourage people to do is to go to that website. There is an instruction sheet that can be printed out. This is probably also available on the FARE website, and allows you to give age-appropriate foods. When children get a little bit older many of them do like Bamba, which was one of the foods used in the LEAP trial. This is something that looks like a Cheez Doodle, except it has peanut instead of the milk protein. This also can be a very successful way to get peanuts into young children.

Ms. Groetch: I would just like to add that obviously we shouldn't be feeding whole nuts to infants or

children under 4 years of age. Typically, we just thin peanut butter out a little bit. Sometimes infants even like to eat it straight up, but we don't want to give them chunks or spoonfuls of peanut butter because that also can be a choking hazard. We just thin it 1:1, so 2 teaspoons of peanut butter with 2 teaspoons of water or breast milk.

Is there any literature or guidelines on how to introduce solids to an infant who has been on elemental formula due to a suspected food allergy, such as mucous and blood in the stool, after a failed 6 month food elimination diet by the breastfeeding mom?

Ms. Groetch: This is a child who sounds like they have allergic proctocolitis. Typically for allergic proctocolitis, with blood in the stool, this is the type of food allergic disorder that typically resolves within the first year of life. We would start thinking about nutritional needs, but also about teaching that child how to eat and enjoy a variety of foods.

We would start with fruits and vegetables. The foods that are more commonly implicated in proctocolitis are milk and soy, which are more commonly implicated in those non-IgE mediated allergies. We would start there. We would probably delay milk and soy, maybe egg, a little bit longer, but start with the fruits and vegetables.

Dr. Sampson can probably speak to this more, but if you're not seeing visible blood in the stool, we would probably say to continue to feed them, because delaying introduction of foods is probably more harmful than invisible amounts of blood in the stool.

Dr. Sampson: Just to add to that, many of the children with allergic proctocolitis thrive beautifully. Again, if you don't see any significant amounts of blood, many gastroenterologists nowadays feel that

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you can just go ahead and continue with the particular food.

Has it been postulated that society-wide changes to children's skin barriers over recent years have been contributing to the rise in food allergy prevalence? For example, the use of antimicrobial soaps or even the widespread increase in the use of sunblock.

Dr. Sampson: Yeah, that's a great question. That's an area that's really under significant research at the moment. There is a strong feeling that because of the types of soaps we use now, which often have high quantities of surfactants that are known to cause some irritation and activation of the skin, [they] may be having some effect on the increased allergy that we're seeing, given sensitization through the skin.

We also know that, with the use of these antimicrobials, there's a significant change in the microbiome of the skin. Just as in the gut, the skin has a microbiome that is very important for the development of tolerance vs sensitization. There are lots of reasons to think that use of many of these antimicrobial soaps, and other stringent soaps that we have today, could be having some effect on the increase in allergy prevalence.

Regarding the early introduction of eggs, peanut butter, etc, would you follow the same recommendations for a child with parents having multiple food allergies?

Ms. Groetch: Absolutely, yes. We would follow the same recommendations.

How do you determine baked milk tolerance in someone with milk allergy?

Dr. Sampson: One of the things that we noted a number of years ago was that about [70%] of children with milk and egg allergy do tolerate the milk or egg if it's in the baked form.^{32,33} We can get a clue by looking at the level of IgE to some of the component proteins. For example, in egg, we often will look at ovomucoid along with egg white protein. If we see levels of IgE antibody to ovomucoid that exceed 5 kU/L, we know that that child point is going to be less likely to tolerate the baked egg.

However, the only really true indicator of whether they tolerate it or not is by doing what we call a baked egg or baked milk challenge. We typically do that with a muffin that's been baked appropriately in the oven. The other advantage to doing this is we have found that by introducing the baked product into the diet of a milk or egg allergic child who will tolerate the baked form, you can often accelerate the development of tolerance to all forms of the milk or egg. Not to mention the fact that it makes the diet for the family much more acceptable.

Can incorporating baked milk or egg into the diet of a patient with allergies to fresh milk or eggs increase the likelihood of tolerance?

Dr. Sampson: Yes. That's what we see. We've done studies looking at the development of full tolerance for both egg and milk. We do see that with both, looking at 5 years for example, it's 15–16 times more likely that a child that's been placed on the baked egg or baked milk will tolerate all forms of egg or milk compared with the child who's been held on a strict milk or egg avoidance diet.³⁴ Again, it's something that is beneficial for the more rapid development of full tolerance, and also makes life for the child and the family much easier because of the decreased stringency of the diet.

Clinical Recommendations for Reducing and Preventing Food Allergies

In addition to extensively hydrolyzed and amino acid-based formulas, are there additional nutritional strategies that you recommend for managing food allergies in infants?

Ms. Groetch: Yeah. Formulas are not always part of the plan. I mean, ideally you want the patient to be breastfed, making sure that we're introducing complementary foods at an appropriate time. We know that breast milk beyond 6 months of age is not nutritionally complete. We want to make sure that we are getting complementary foods in at that time. The nutritional strategies are making sure that we have the right balance and proportionality, especially as the child ages, of breast milk or formula with their solid foods.

We don't want to see, for instance, a 1-year-old drinking 40 oz of formula and having very little solid food in their diet. That's something that we would be looking at. It's looking at the overall diet, and again a very individualized approach, but ideally you just want to make sure that you're progressing the diet in an age-appropriate and skill-appropriate manner.

Can aggressive treatment of atopic dermatitis, after it's been diagnosed, prevent food allergies?

Dr. Sampson: The feeling today is that being aggressive with the treatment of atopic dermatitis would be beneficial. Right now, we don't have a prospective study proving that, but what we do know is that when we look at the number of eczematous lesions or the severity of the eczema, there's a direct correlation between the number of lesions, the severity of lesions, and the likelihood of developing food allergy.

We think that by minimizing the amount of inflamed skin, which is really the site where you would expect sensitization to occur, the likelihood of developing a food allergy would be decreased. Until we actually

have the prospective studies to prove that, and there are many of those studies now ongoing, this is still in the hypothesis range, but likely something that would be beneficial.

What are your thoughts about using products that are comprised of foundational foods such as peanuts, milk, shellfish, etc, that are specifically designed as part of a food allergy protection plan?

Dr. Sampson: There are several sources now where you're able to purchase combinations of the various major allergens. However, I do need to point out that the amount of allergens that are typically present in these various substances is very low. To date, none of these have been tested in any kind of formal trial to determine whether or not they're effective.

The only data that we have at this point is really related to the LEAP trial. In the LEAP trial, peanut was administered in the quantity of 3 g 3 times a week. This is much higher than the amounts that are being used in these other preparations. Also, there is no evidence, at this point in time, that taking an early approach to all these different foods is going to be successful. As pointed out in the EAT trial, where the investigators added up to 6 foods into the diet, they did not see any benefit in the intention-to-treat analysis. Even in the per-protocol analysis, they only saw benefit for peanut and egg. At this time, I think the evidence is not there. This is something that should be studied really in formalized prospective trials.

Do you have any hypothesis as to why there is a sudden increase in the prevalence of sesame allergies?

Dr. Sampson: I don't know of any hypothesis out there. What we could speculate on is that, as we believe is happening with things like peanuts, there



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is contact with the skin, and children are being sensitized through the skin. My only speculation might be that sesame products seem to have become much more common in the food supply, which may be leading to this higher rate. There has been some attempt to look at the problems of sesame. At this point in time, even as an allergist and seeing patients in clinic, it certainly feels like there's much more sesame allergy around. The studies that have been done to date really haven't documented that. At any rate, I would suggest that, possibly, the more frequent use of sesame in our food supply is, like with peanut and other foods, leading to this apparently higher prevalence of sesame allergy.

For children on an elimination diet, how is delayed growth or weight loss evaluated to ensure that there is not a secondary cause outside of the food allergy and elimination diet?

Ms. Groetch: First of all, I would say that it's not the dietitian's role to diagnosis any medical condition. It's the dietitian's role to diagnose nutritional issues. The first thing the dietitian is going to be doing is looking at the patient as a whole. They'll look at their medical history and their food allergy history, but also the dietary history. They'll be looking at the labs. They'll be looking at the growth chart, not just the one point that is going to be comparing that child to a referenced population, but how has that child been growing all along? These are all clues that help us in our nutrition diagnosis. Then, of course, we look at the diet. In order to know whether there's something else going on, we have to first see is there really a growth problem? If a patient has been growing at the fifth percentile all along, and the parent is unhappy with the fifth percentile but that just happens to be where the patient should be, then I would say that there probably isn't a growth issue.

If we do see that this patient has suddenly dropped across 2 percentile lines (ie, 2 standard deviations) or they are showing signs of malnutrition, then it's the job of the dietitian to figure out is this a dietary issue? That is, I think, the biggest clue. If I'm looking at the diet, and I'm seeing the child is really eating well and shouldn't be having poor growth, then I'll be having a discussion with the physician. The physician might think that this is a good patient to refer to a gastroenterologist, for instance. Again, the medical diagnosis is not the job of the dietitian. The dietitian needs to evaluate the diet as part of looking at the whole patient to determine whether the diet is contributing to poor growth, or whether there might be another issue. Then that patient would have to be referred on.

Should the LEAP study be applied to adults?

Dr. Sampson: To adults? The LEAP study really addressed the introduction of peanut early in young infants, 4–6 months of age. Basically, the findings there, as we discussed, were overwhelmingly positive that early introduction in a high-risk population was very effective in reducing the prevalence of peanut allergy. It did not address in the general population. However, many people do feel that this would be applicable to children who are not at as high of a risk. The other question that arises is, should this be done with all foods? This is where the EAT trial was meant to provide information. In the EAT trial, there certainly is a suggestion with egg, as well as peanut, that if the introduction is maintained on a regular basis with the compliance, then it may be effective there as well. There's still a great deal of work that needs to be done on this early introduction and who will benefit in the long run.

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Are you able to expand more about the usage of soy-based formulas after 6 month of age?

Ms. Groetch: The American Academy of Pediatrics has recommended that we don't use soy prior to 6 months. Actually, I would say that it's not even as strong as that. What they say is that soy formula can be used as a substitute for cow's formula, especially after 6 months of age. There are no very strong recommendations against using it earlier. I know in the European Union, they have now stated that soy formula shouldn't be used in very young children. I think there is some concern about the phytoestrogens in soy, especially as soy might be the only food in the infant's diet prior to 6 months of age. Children who are premature don't seem to grow as well on soy.

In general, children after 6 months of age grow just as well on soy or with soy in a mixed diet. It doesn't seem to have any long-term impact. The phytoestrogen impact is really insignificant and doesn't seem to have any negative consequence for children. Soy is—especially for older children who are transitioning from breast milk or formula to cow's milk substitutes—soy is actually a substitute that provides pretty comparable nutrition to cow's milk. We aren't really that concerned about the phytoestrogens. The American Academy of Pediatrics does look at that data. At this point they don't recommend it as the first choice substitute formula, especially for children under 6 months of age.

Where do we stand on oral desensitization for peanuts and other foods?

Dr. Sampson: At the present time, there have been 2 phase 3 trials that have been completed for treatments for peanut allergy. One is oral immunotherapy, which had a positive outcome and

is going to be reviewed by the FDA Advisory Committee this fall. Depending on the outcome of that, there could be an oral immunotherapy product available within the next year. There also was another phase 3 trial that was performed using epicutaneous immunotherapy. That also will be filed to the FDA, and will eventually go to an Advisory Committee, I'm sure, for review. It's possible that we'll have 2 different methods that may be available for treatment of peanut allergy. However, this all is pending FDA review and approval. There are many other therapies that are in the pipeline, but these are all a number of years away.

How do I encourage families to offer age- and skill-appropriate textures to prevent development of food difficulties?

Ms Groetch: I would say that education is the most important thing. I mean, when we're working with families with food allergies, the most important thing is that we are empowering those families to treat their child like they would treat a child that doesn't have food allergies. They can participate in every activity and do everything that the nonallergic child is doing except eat those foods to which they are allergic. Sometimes, they don't know how to progress the diet and how to feed during infancy. There's some educational component to it. Really, what we want to do is provide the best education so that they know how to avoid the food, but can include all the foods that don't need to be avoided. That's the individualized approach, looking at each of those patients, and knowing why they're avoiding foods, and what foods might be at risk, and working with the allergist to make sure that we can include as many foods in the diet as possible.

Abbreviations

BMI body mass index

FPIES food protein-induced enterocolitis syndrome

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DHA	docosahexaenoic acid	IgE	immunoglobulin E
EPA	eicosapentaenoic acid	NIH	National Institutes of Health
FARE	Food Allergy Research & Education	NIAID	National Institute of Allergy and Infectious Diseases

1. Boyce JA, Assa'ad A, Burks AW et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1–S58. doi:10.1016/j.jaci.2010.10.007

2. Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc*. 2002;102(11):1648-1651.

3. Mehta H, Ramesh M, Feuille E, Groetch M, Wang J. Growth comparison in children with and without food allergies in 2 different demographic populations. *J Pediatr*. 2014;165(4):842-848. doi:10.1016/j.jpeds.2014.06.003

4. Hobbs CB, Skinner AC, Burks AW, Vickery BP. Food allergies affect growth in children. *J Allergy Clin Immunol Pract*. 2015;3(1):133–4.e1.

5. Meyer R, Wright K, Vieira MC, et al. International survey on growth indices and impacting factors in children with food allergies. *J Hum Nutr Diet*. 2019;32(2):175-184. doi:10.1111/jhn.12610

6. Sinagra JL, Bordignon V, Ferraro C, et al. Unnecessary milk elimination diets in children with atopic dermatitis. *Pediatr Dermatol*. 2007;24(1):1-6.

7. Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111-1126.e4. doi:10.1016/j.jaci.2016.12.966

8. Fiocchi A, Brozek J, Schünemann H, et al; World Allergy Organization (WAO) Special Committee on Food Allergy. World Allergy Organization (WAO) Diagnosis and

Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. *Pediatr Allergy Immunol*. 2010;21 Suppl 21:1-125. doi:10.1111/j.1399-3038.2010.01068.x

9. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.

10. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics*. 2000;106(2 Pt 1):346-349.

11. Greer FR, Sicherer SH, Burks AW; Committee on Nutrition; Section on Allergy and Immunology. The Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Hydrolyzed Formulas, and Timing of Introduction of Allergenic Complementary Foods. *Pediatrics*. 2019;143(4). pii: e20190281. doi:10.1542/peds.2019-0281

12. Coulthard H, Harris G, Emmett P. Delayed introduction of lumpy foods to children during the complementary feeding period affects child's food acceptance and feeding at 7 years of age. *Matern Child Nutr*. 2009;5(1):75-85. doi:10.1111/j.1740-8709.2008.00153.x

13. USDA MyPlate. www.choosemyplate.gov. Accessed August 12, 2019.

14. Berni Canani R, Leone L, D'Auria E, et al. The effects of dietary counseling on children with food allergy: a prospective, multicenter intervention study. *J Acad Nutr Diet*. 2014;114(9):1432-1439. doi:10.1016/j.jand.2014.03.018

15. DRI Calculator for Healthcare Professionals. National Agricultural Library. <https://fnic.nal.usda.gov/fnic/dri-calculator/>. Accessed August 12, 2019.



Clinical Recommendations for Reducing and Preventing Food Allergies

16. Zeiger RS. Food allergen avoidance in the prevention of food allergy in infants and children. *Pediatrics*. 2003;111(6 Pt 3):1662-71.
17. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Timing of Introduction of Complementary Foods, and Hydrolyzed Formulas. *Pediatrics*. 2008;121(1):183-191.
18. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy [published correction appears in *N Engl J Med*. 2016;375(4):398]. *N Engl J Med*. 2015;372(9):803-813. doi:10.1056/NEJMoa1414850
19. Du Toit G, Sayre PH, Roberts G, et al; Immune Tolerance Network LEAP-On Study Team. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435-1443. doi:10.1056/NEJMoa1514209
20. NIAID-Sponsored Expert Panel. <https://www.niaid.nih.gov/sites/default/files/addendum-peanut-allergy-prevention-guidelines.pdf>. Published 2017. Accessed August 12, 2019.
21. Perkin MR, Logan K, Tseng A, et al; EAT Study Team. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733-1743. doi:10.1056/NEJMoa1514210
22. Al-Saud B, Sigurdardóttir ST. Early introduction of egg and the development of egg allergy in children: A systematic review and meta-analysis. *Int Arch Allergy Immunol*. 2018;177(4):350-359. doi:10.1159/000492131
23. Natsume O, Kabashima S, Nakazato J, et al; PETIT Study Team. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10066):276-286. doi:10.1016/S0140-6736(16)31418-0
24. Peters RL, Koplin JJ, Dharmage SC, et al. Early exposure to cow's milk protein is associated with a reduced risk of cow's milk allergic outcomes. *J Allergy Clin Immunol Pract*. 2019;7(2):462-470.e1. doi:10.1016/j.jaip.2018.08.038
25. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief*. 2013;(121):1-8.
26. Martin PE, Eckert JK, Koplin JJ, et al; HealthNuts Study Investigators. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy*. 2015;45(1):255-264. doi:10.1111/cea.12406
27. Izadi N, Luu M, Ong PY, Tam JS. The role of skin barrier in the pathogenesis of food allergy. *Children (Basel)*. 2015 Sep 2;2(3):382-402. doi:10.3390/children2030382
28. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol*. 2009;123(2):417-23. doi:10.1016/j.jaci.2008.12.014
29. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818-823. doi:10.1016/j.jaci.2014.08.005
30. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824-830.e6. doi:10.1016/j.jaci.2014.07.060
31. Hein I. Emollients fail to protect against eczema. <https://www.medscape.com/viewarticle/914051>. Published June 6, 2019. Accessed August 12, 2019.
32. Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Węgrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol*. 2008;122(5):977-983.e1. doi:10.1016/j.jaci.2008.09.007
33. Nowak-Węgrzyn A, Bloom KA, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol*. 2008;122(2):342-7, 347.e1-2. doi:10.1016/j.jaci.2008.05.043
34. Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in



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children. *J Allergy Clin Immunol.* 2011;128(1):125-131.e2.
doi:10.1016/j.jaci.2011.04.036