



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, nurses, nurse practitioners, 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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Marion Groetch, MS, RDN

Speakers Bureau Nutricia North America – clinical area: food allergies
Abbot Nutritional – clinical area: food allergies
Mead Johnson – clinical area: food allergies

Hugh A. Sampson, MD

Employee DBV Technologies – clinical area: novel therapies for treating food allergy

Consultant N-Fold Therapeutics, LLC – clinical area: novel therapies for treating food allergy

Significant Shareholder

DBV Technologies – clinical area: novel therapies for treating food allergy
N-Fold Therapeutics, LLC – clinical area: novel therapies for treating food allergy

Other

Royalties from various textbooks

The faculty for this activity have disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners

Stephanie Leonard, MD (peer reviewer)

Consultant LabCorp – clinical area: food allergy diagnostics

The following have no significant relationship to disclose:

Heather Marie Jimenez, FNP (nurse reviewer)

Jessica Martin, PhD (medial writer)

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

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The estimated time to complete the activity is 1.0 hour.

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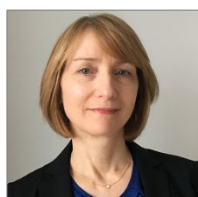
This activity was released on August 2, 2019 and is eligible for credit through August 2, 2021.

Contact Information

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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

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;155(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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Slide 3 – Food Allergies Limit Growth

Most Common Allergens

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

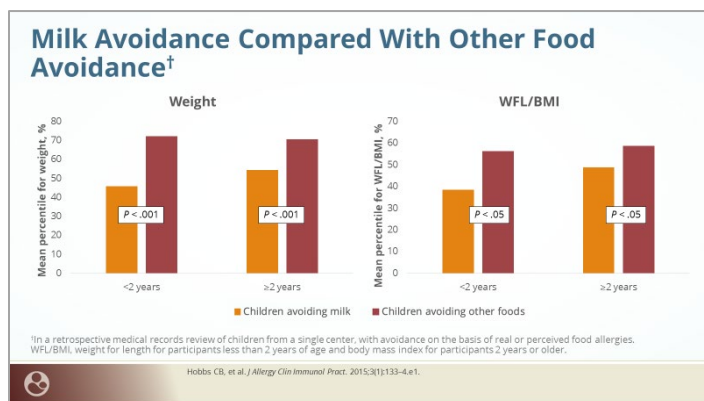
NIADD-Sponsored Expert Panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-S58.

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

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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 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

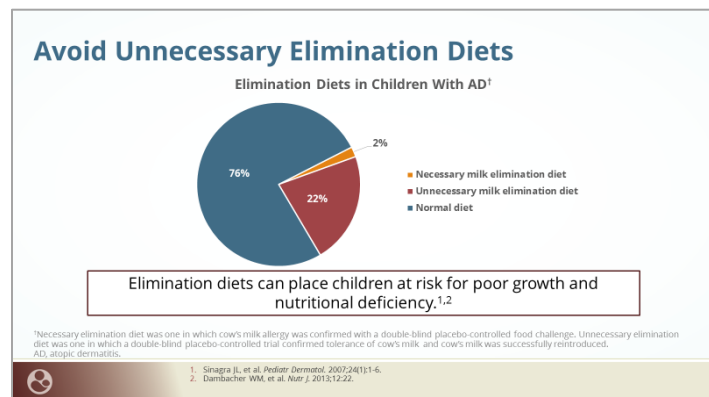
Overall stunting was more common than underweight in our combined populations. We had 9% of our population who were stunted, meaning they had a height-for-age Z score of less than -2. A total of 6% were underweight; 5% were undernourished; and 8% were overweight. It's interesting to note that overweight 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.

NIAD-Sponsored Expert Panel. *J Allergy Clin Immunol*. 2010;126(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 Suitable substitutes Self-management skills Co-existing and cross-reacting allergens Novel allergens	 Industry and environment <ul style="list-style-type: none"> Travelling and immigration Food and nutrition literacy Threshold levels and cross-contact or cross-contamination Nutrition <ul style="list-style-type: none"> Promote optimal growth Prevent nutrient deficiencies Development of normal feeding skills Optimal nutrition for long-term health Future <p>The role of nutrients, dietary patterns, and other food factors regarding:</p> <ul style="list-style-type: none"> Gut microbiome Immune system Allergy prevention and tolerance development
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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/NPG.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.

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 K, Harris G, Emmett P. *Matern Child Nutr*. 2009;5(1):75-85.
3. Greer FR, et al. *Pediatrics*. 2019;143(4):e20190281.

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 a study 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

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.

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](https://www.choosemyplate.gov) website [Slide 14]. 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.

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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 makes it fun to follow! The right mix can help you be healthier now and into the future. The key is choosing a variety of foods and beverages from each food group—and making sure that each choice is limited or substituted fat, sodium and added sugars. Start with small changes—“MyPlate” can make healthier choices you can enjoy.

Food Group Amounts for 1,000 Calories a Day

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

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

Slide 14 – 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 15 – 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 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 16 – Vitamin and Mineral Supplementation

I wanted to point out a resource here, on the lower right-hand corner of your screen [Slide 16]. 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 17]: 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,

Clinical Recommendations for Reducing and Preventing Food Allergies

it's low in fibers, it's low in calcium, vitamin D, and other nutrients.

Dietary Effects of Elimination Diet		
	Without eliminations	Eliminations
Breakfast	Waffles with syrup Strawberries Milk	Waffles with syrup Strawberries Milk
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
Snack	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
Snack	Ice cream	Ice cream

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

Slide 17 – 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 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 18 – 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 19 – Online Patient Resources

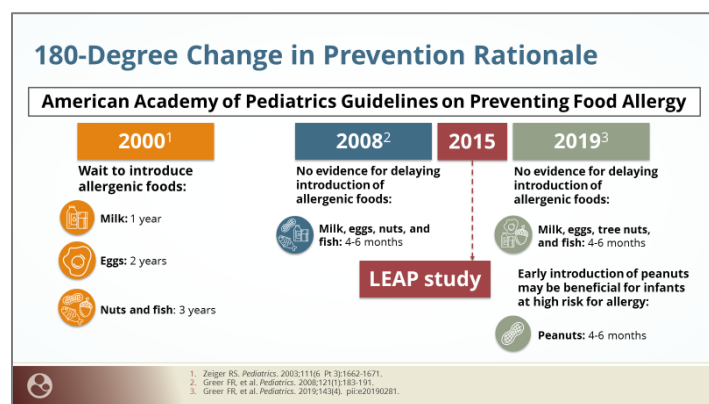
Clinical Recommendations for Reducing and Preventing Food Allergies

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 20], there's really been a 180-degree change in our food allergy prevention rationale.

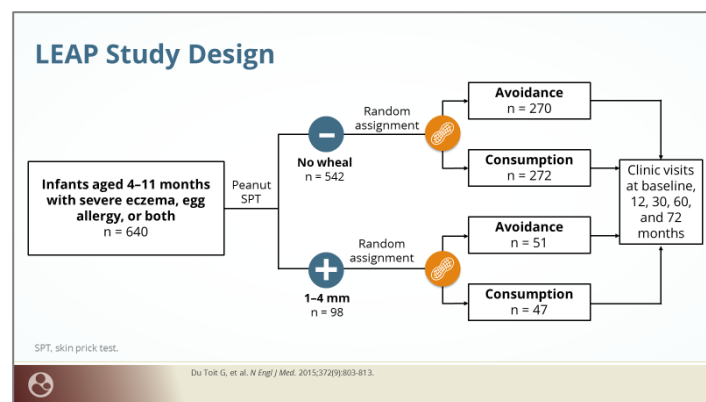


Slide 20 – 180-Degree Change in Prevention Rationale

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.

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.



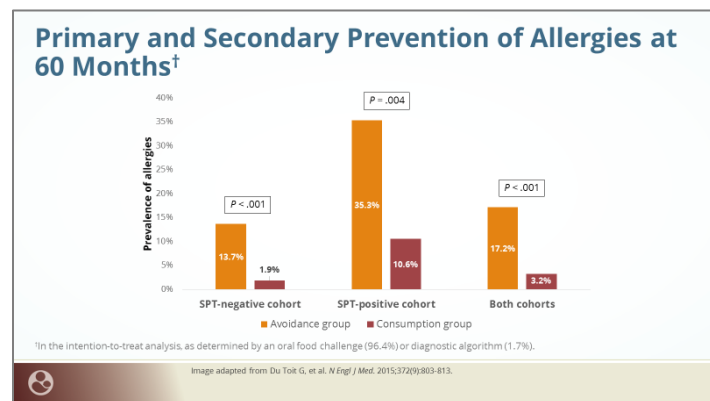
Slide 21 – LEAP Study Design

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 22]. 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

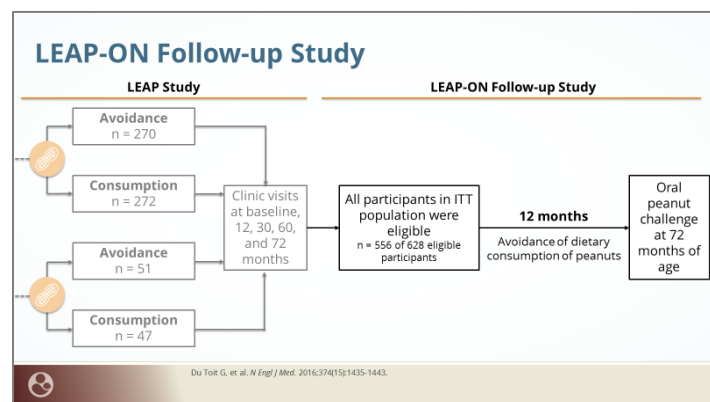
Clinical Recommendations for Reducing and Preventing Food Allergies

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.



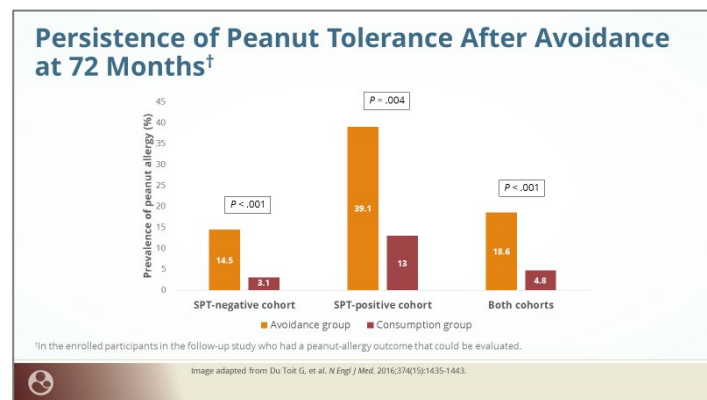
Slide 22 – Primary and Secondary Prevention of Allergies at 60 Months

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 23 – LEAP-ON Follow-up Study

As you can see on this next slide [Slide 24], there was really no evidence of loss of their tolerance to peanut among those individuals that went off peanuts for a year.

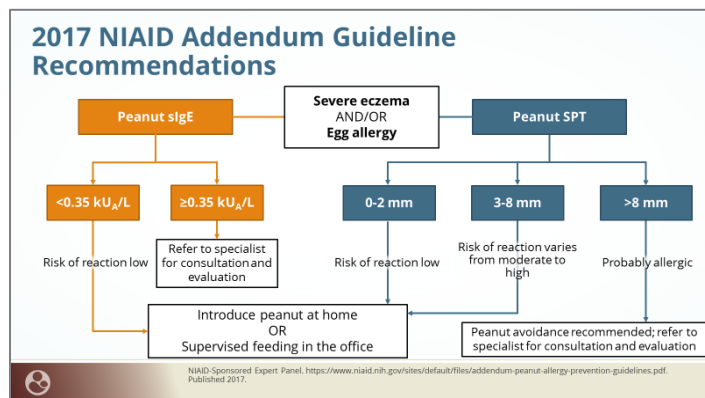


Slide 24 – Persistence of Peanut Tolerance After Avoidance at 72 Months

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.

Clinical Recommendations for Reducing and Preventing Food Allergies

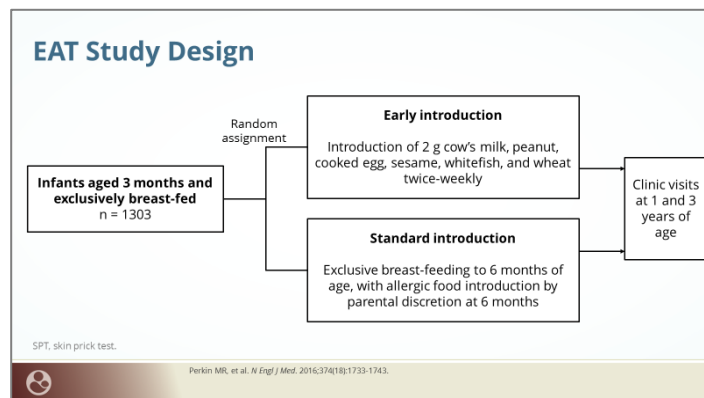


Slide 25 – 2017 NIAID Addendum Guideline Recommendations

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



Slide 26 – EAT Study Design

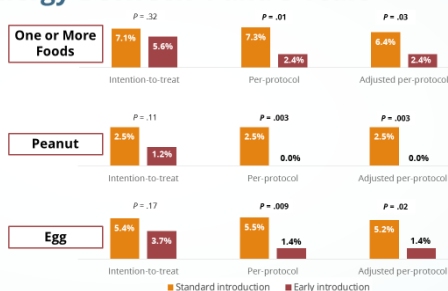
In the early introduction group, all infants were given up to 2 g of cow's milk on a weekly basis, as well as peanut, cooked egg, sesame, white fish, and wheat twice weekly. In this situation, milk was always the first food given, and wheat was the last, and the others were randomized. In the standardized 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 27], 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.

Clinical Recommendations for Reducing and Preventing Food Allergies

Prevalence of Allergy Between 1 and 3 Years

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



Images adapted from Perkin MR, et al. *N Engl J Med*. 2016;374(18):1733-1743.

Slide 27 – 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-Saudi B, Sigurdardottir ST. *Int Arch Allergy Immunol*. 2018;177(4):350-359.

Slide 28 – 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

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

PETIT Study Design

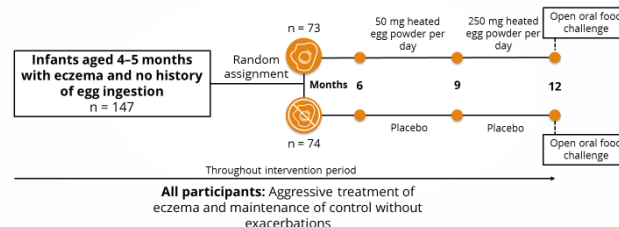
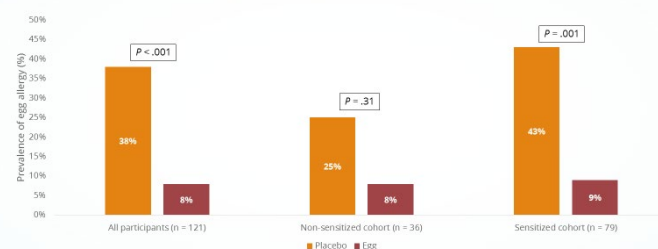


Image adapted from Natsume O, et al. *Lancet*. 2017;389(10066):276-286.

Slide 29 – 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.

Prevalence of Egg Allergy at 12 Months[†]



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

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

Slide 30 – 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

Clinical Recommendations for Reducing and Preventing Food Allergies

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.

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(3):726-733.e1-30.
2. di Mauro G, et al. *World Allergy Organ J*. 2016;9:28.
3. Focchia A, et al. *World Allergy Organ J*. 2015;8(1):4.
4. Osborn DA, et al. *Cochrane Database Syst Rev*. 2018;10:CD003664.
5. Lodge CJ, et al. *Acta Paediatr*. 2015;104(6):738-53.
6. Gounalakis M, et al. *Cochrane Database Syst Rev*. 2015(7):CD010085.

Slide 32 – 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 33], 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.

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

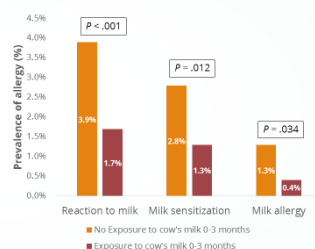
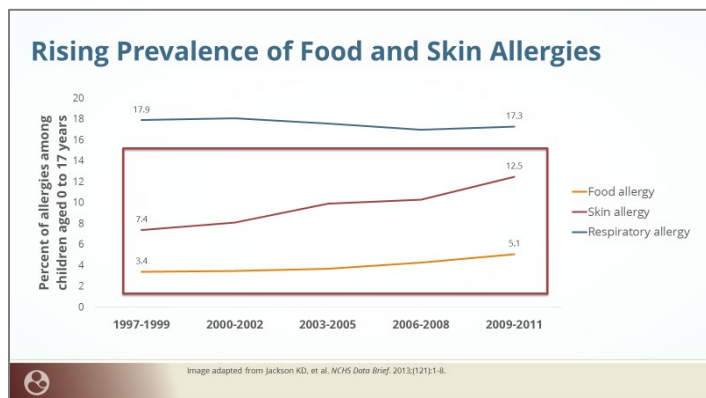


Image adapted from Peters RL, et al. *J Allergy Clin Immunol Pract*. 2019;7(2):462-470.e1.

Slide 31 – Early Introduction of Cow's Milk: Observational Study

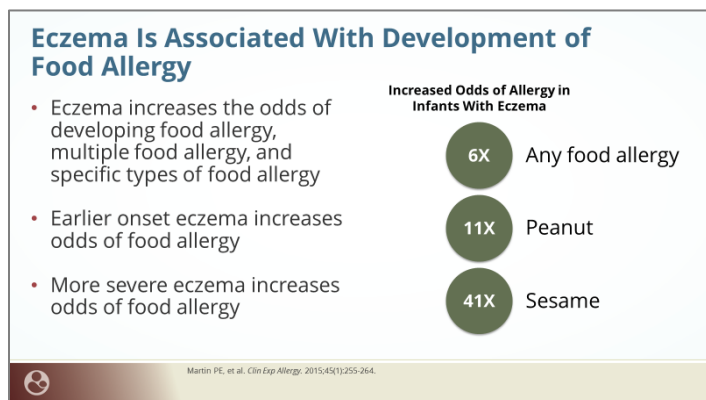
Through the years, a number of different measures have been looked at with the idea that they may in fact decrease the prevalence of food allergy. Things such as supplementation with various vitamins and minerals have been evaluated, with no proven benefit for the prevention of food allergy. There's 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



Slide 33 – 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



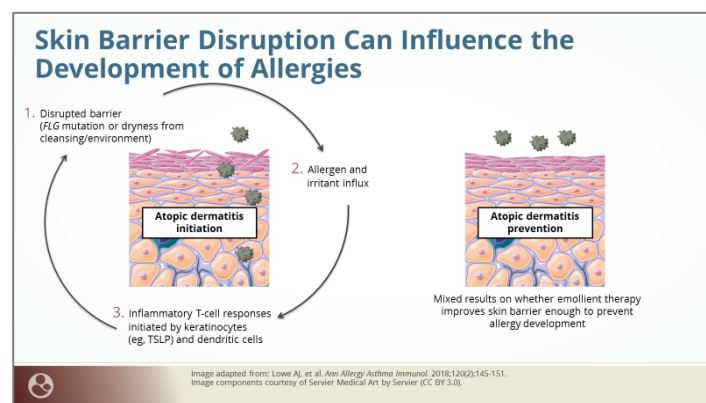
Slide 34 – Eczema Is Associated With Development of Food Allergy

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

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 35 – Skin Barrier Disruption Can Influence the Development of Allergies

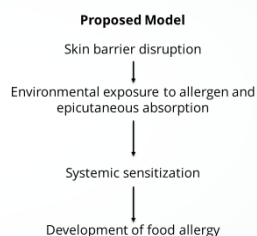
When we look at what information is out there to support this idea, one of the things that's been noted over the years is that allergic reactions to food often occur without prior obvious oral exposure. Normally, oral exposure to a food in infancy will lead to tolerance, not to hypersensitivity. We also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

Clinical Recommendations for Reducing and Preventing Food Allergies

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



Isaacs N, et al. *Children (Basel)*. 2015;2(3):382-402.

Enhancement of Skin Barrier to Prevent Atopic Dermatitis

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

Slide 36 – 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.

Slide 37 – 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.

Clinical Recommendations for Reducing and Preventing Food Allergies

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 – 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 39], 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)

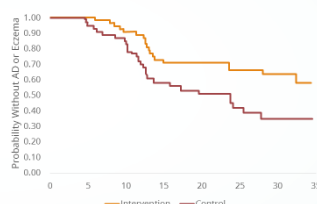


Image adapted from Horimukai K, et al. *J Allergy Clin Immunol*. 2014;134(4):824-830.e6.

Slide 39 – 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.

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 40], 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 40 – 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.

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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 41 – 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.

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

Slide 42 – 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.

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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

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.

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

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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

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.

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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.

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

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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

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 if there really is 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.

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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.

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

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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
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

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