Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Diagnosing Food Allergies in Infants and Children

Overview

Jonathan Spergel, MD, PhD, reviews the diagnosis of food allergies and the role of the primary care clinician within the process. Dr. Spergel discusses the importance of a clinical history and physical exam; diagnostic strategies for IgE-mediated food allergies, including skin prick tests, serum IgE testing, and food challenges; strategies and indications for referral to an allergist; unproven or disproven food allergy tests; and future diagnostic tools.

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:

- Evaluate test methods for detection and diagnosis of food allergy
- Incorporate diagnostic test results to manage food allergies.

Faculty

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Jonathan Spergel, MD, PhD

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Stephanie Leonard, MD (peer reviewer)

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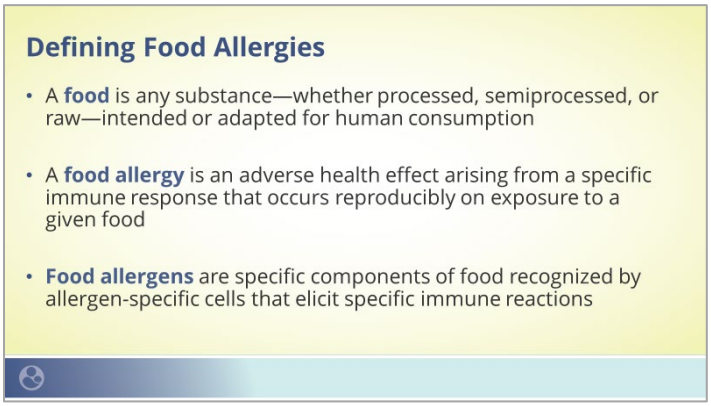
Diagnosing Food Allergies in Infants and Children

Editor's Note: This is a transcript of an audio webcast presented on July 9, 2019. It has been edited and condensed for clarity.

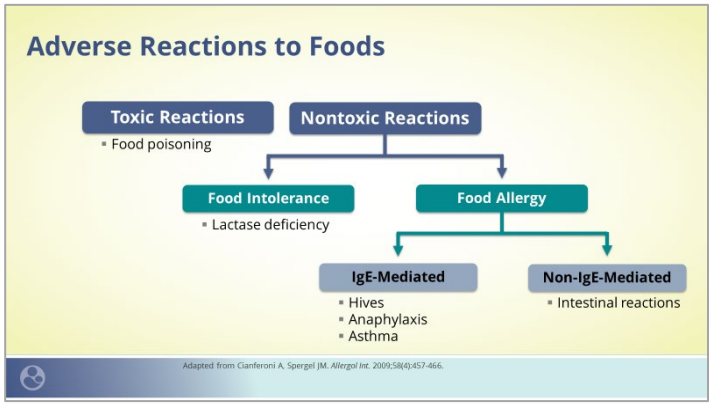
Dr. Jonathan Spergel: It's my honor to do this presentation. We'll go over what food allergies are before going over various diagnostics. We will also discuss what role the pediatrician or nurse practitioner may have during diagnosis.

First, we need to define what food allergies are. Let's start at the beginning: What is food? Food is basically anything that you eat. A food allergy is an adverse health event to a food, and a food allergen is a specific food that causes that immune-mediated reaction.



Slide 1 – Defining Food Allergies

When we think about food reactions, we break them down into different types. There is food poisoning, which is not really an allergic reaction. Instead, that is an adverse reaction. If everyone at the table has the same reaction to a food, it's unlikely that everyone is allergic to the food. That's an important distinction as we go through the patient's history to figure out whether the reaction is food poisoning or an allergy.



Slide 2 – Adverse Reactions to Foods

Then there are the nontoxic reactions, such as food intolerance. The classic food intolerance is lactose intolerance, where a glass of milk causes bloating, gas, or diarrhea. There are also nontoxic reactions to pharmacologic agents. My favorite is caffeine causing a stimulant effect. That is a reaction to a food. It's not an allergic reaction, but it is a food reaction.

Then there's food allergy, and food allergy gets broken down into 2 broad categories, which we'll discuss in greater detail as we go along. These are IgE-mediated reactions and non-IgE–mediated reactions.

We'll start with IgE-mediated reactions, which are the most common, and this is the one that gets the most press. It is the primary cause of anaphylaxis (severe allergic reaction) in children. As with most atopic diseases, the incidence of IgE-mediated reactions has increased over the last 20–40 years and is probably still increasing at this point.[1,2,3] We used to think food allergies were about 1% of the population, but now we know they occur in [about 3%–6%] of the population, depending on how you define food allergy.[4]

The symptoms of IgE-mediated food reactions are typically rapid onset, so that could mean seconds to

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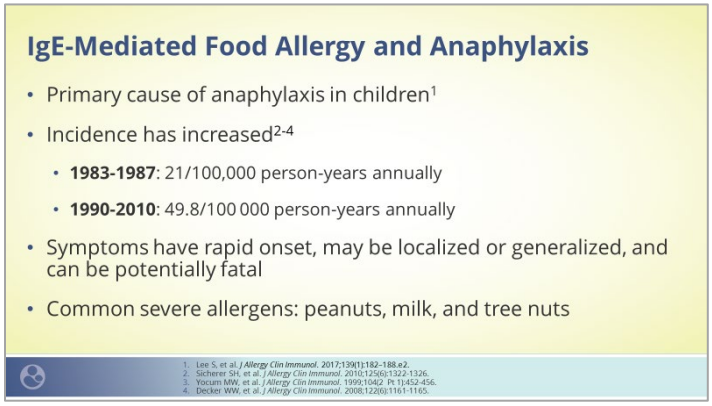
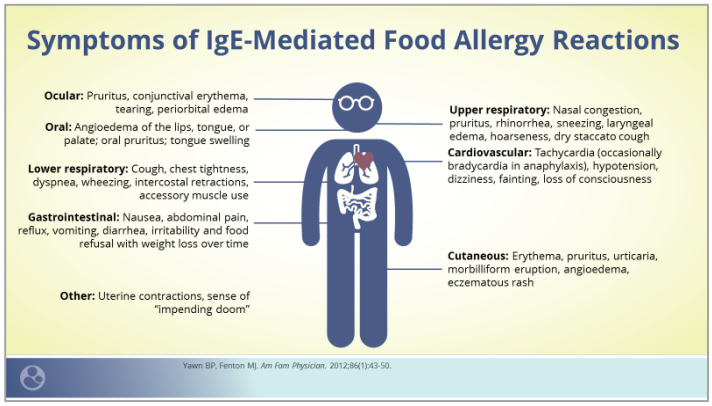
about 2 hours after eating the food. If the symptoms occur more than 2 hours after eating the food, it's not an IgE-mediated reaction. IgE-mediated symptoms can be local or generalized, and we'll go over that in more detail in a few slides. Overall, the most common allergenic foods are milk, egg, peanuts, and tree nuts.



Slide 3 – IgE-Mediated Food Allergy and Anaphylaxis

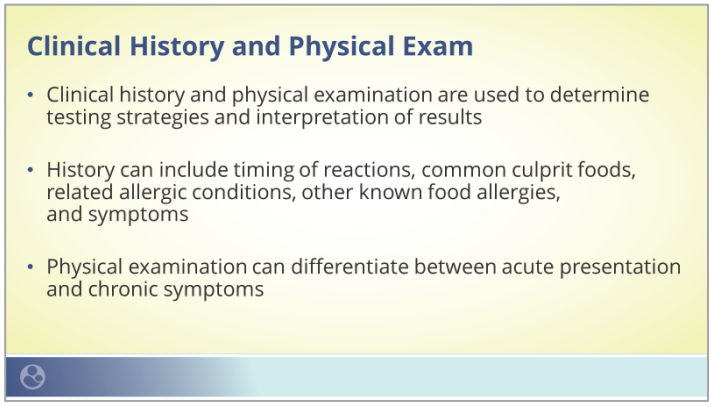
When we think about IgE-mediated food reactions, reactions can be localized, like hives or itching, or they can be more generalized. Examples include coughing, wheezing, and shortness of breath. There are 2 signs of anaphylaxis, which are hypotension and difficulty breathing. Patients may also have a "sense of doom." When someone has an allergic reaction, they may feel like something terrible is going to happen.

Associated [symptoms], like nasal congestion and sneezing, can occur during food allergy, but in the absence of other symptoms, that is probably not a food reaction. It may be an environmental allergy—for example, to a cat or pollen. Furthermore, despite what people might read on the web, food allergies do not cause ear infections.



Slide 4 – Symptoms of IgE-Mediated Food Allergy Reactions

When we do a history and physical exam, we discuss the timing of the reaction, the type of food, and other symptoms. [For example], Suzie went to the diner and ate an ice cream sundae. Two minutes later, she was sneezing, coughing, wheezing, and vomited. If only Suzie had a reaction, that's probably an allergic reaction. In contrast, if Bobby went to a sushi restaurant, and everyone got sick and has abdominal pain, that's probably bad sushi, right?



Slide 5 – Clinical History and Physical Exam

On a physical exam, unless you were present at the time, you're not going to see the reaction. Most IgE-mediated reactions resolve before presentation to the clinic. For a non-IgE–mediated reaction, symptoms can be more delayed and may be chronic. Occasionally, you may see signs and symptoms of non-IgE–mediated reactions during an exam.

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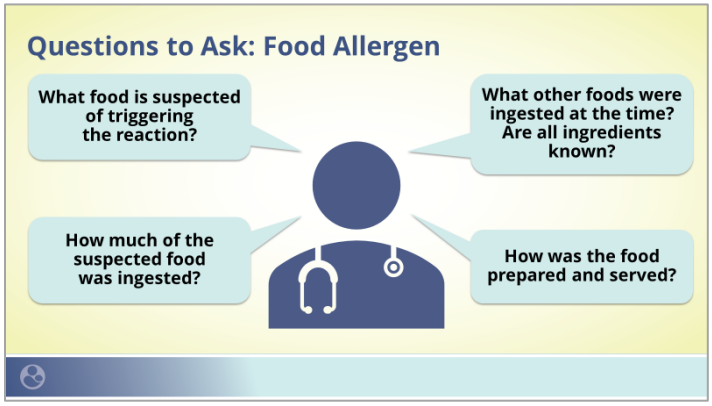
When diagnosing allergies, obtaining a good clinical history is critical. It will influence what to test, how to test, and when to test. Those are all really critical considerations. There are several questions to consider. What food was it? Going back to the example of Bobby, was it that sushi? Did only 1 person get sick, or did everyone get sick?



Slide 6 – Questions to Ask: Food Allergen

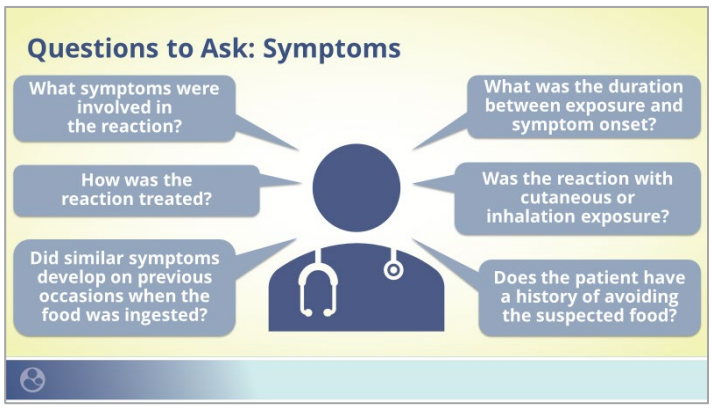
Another important question to ask is "how much food was eaten?" For example, I told a patient that he's not allergic to milk. He went home and ate a half-gallon of ice cream to celebrate. Then he called us back the next day and said he got sick. But, of course, after eating that much ice cream, anyone would be sick. Typically, patients who are allergic to food usually react after exposure to a small dose. They're not eating a half-gallon of ice cream. They're taking a few licks of that ice cream or eating a bite of that peanut butter cookie.

Additionally, we have to know what other foods were ingested at the time. For example, an ice cream sundae—is it the milk and the egg in the ice cream? Is it the nuts in that sundae? Or is it the cookie in the sundae?

You also have to ask, has the patient eaten the food before? Because if they've eaten the food before without reaction, they're probably not allergic to it. Typically, once you've eaten a food more than 1 or 2 times, it's considered a safe food.

Another question to ask is, how was the food prepared? Again, thinking about an ice cream sundae, was that ice cream scooper used for peanut ice cream before it was used for your sundae? Or did a patient react to a food at a large buffet, where foods were not separated?

We then want to know what symptoms were happening in the reaction? This helps us figure out whether the reaction is a food allergy or not. As I mentioned before, if someone is only sneezing, that's probably not a food reaction; however, if they get hives everywhere and are coughing and wheezing, that's probably an allergic reaction to something. But then you need to consider, could it have been the food? Yes. But also, could it have been a drug allergy or an insect bite?



Slide 7 – Questions to Ask: Symptoms

You also want to know how the reaction was treated. If a patient had 1 hive that got better by itself, it may not be a true food allergy. A lot of foods have a high amount of histamines in them. The classic example is that many people think they are allergic to strawberries. That's because strawberries have histamines in them, and little kids are messy eaters. When they eat the food, they wear it, and they have irritant reactions along their mouths. Typically, when we see reactions just around the mouth or in areas of contact and nothing else, we don't consider those allergic reactions. Those are

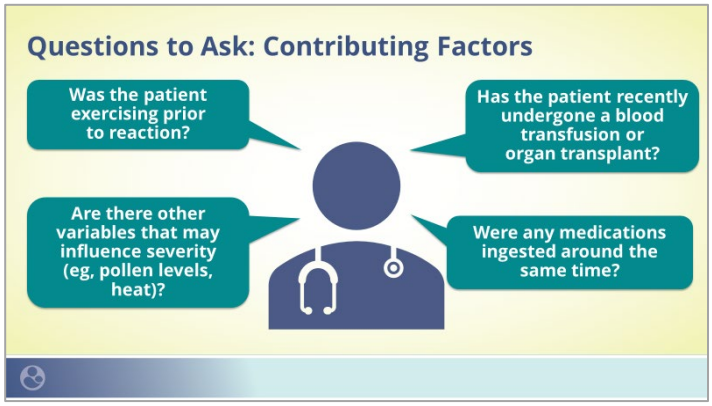
more likely to be contact reactions. We don't typically worry about it.

We talked about the timing of exposure. If the reaction occurs within seconds to about 2 hours, that's possibly an allergic reaction. If the symptoms occur after that, it's probably not an IgE-mediated reaction. Food protein-induced enterocolitis (FPIES) can lead to symptoms occurring anywhere from 2–4 hours, and eosinophilic esophagitis is more of a chronic condition, and it's really almost impossible to correlate with timing of food ingestion.

Most food allergies are due to ingestion. Cutaneous reactions can occur, but usually it's just a contact reaction. Inhalation reactions are almost unheard of. There are a few exceptions. For example, if you're allergic to milk, and you go to a coffee shop, inhaling the steam of the milk can cause an allergic reaction. For inhalation reactions to occur, the protein has to be aerosolized and cooked. It happens with milk, egg, and fish. Rarely, there are inhalation reactions to peanuts. You actually have to soak up the peanut protein in the air. Unless someone is roasting peanuts, you do not commonly see inhalation reactions to peanuts.

Interestingly, most children who are allergic to a food will avoid the food. For example, a kid who is allergic to egg, may refuse to eat the eggs, cookies, and cakes. Kids have a good amount of self-preservation and will avoid the foods that they are allergic to.

We also ask patients about contributing factors. There are a few things that will make allergic reactions worse, and some food allergies only occur in conjunction with certain conditions. The big one is exercise. There's something called food-induced exercise anaphylaxis that can happen with wheat and celery. People with this condition will be able to eat wheat without exercising, or exercise without eating wheat, but the combination can cause a reaction.



Slide 8 – Questions to Ask: Contributing Factors

Other things that can make allergies worse include NSAIDs or menses will make people more sensitive. If patients have a minor sensitivity to the food, but they're sick, menstruating, or using NSAIDs, that can exacerbate allergies. Similarly, if there are high pollen levels and high heat, allergies can get worse. The effect of high heat or exercise is related to core body temperature, which will make patients who have had minor reactions in the past, more sensitive.

For the rare patients who've gone under organ transplant, that can actually induce a new food allergy. Patients might be nonallergic to something and become allergic, or a bone marrow transplant can actually cure food allergies. It's a little extreme, but there have been case reports of curing a food allergy.

We're going to be focusing most of this talk on IgE-mediated reactions. We'll briefly mention the 2 non-IgE–mediated reactions. There have been separate webinars that went over those in much greater detail. But we'll go over those just to be complete.

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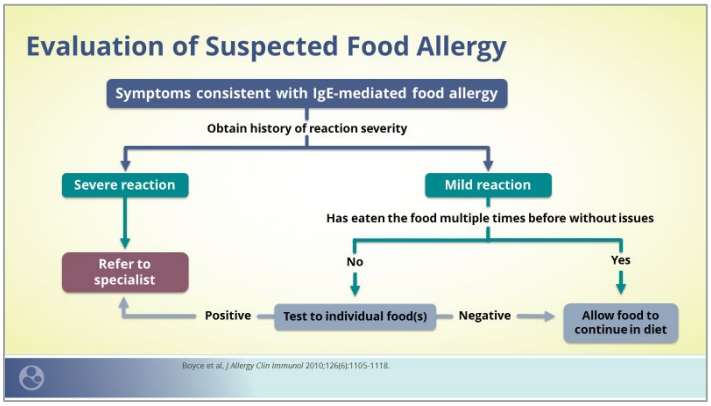


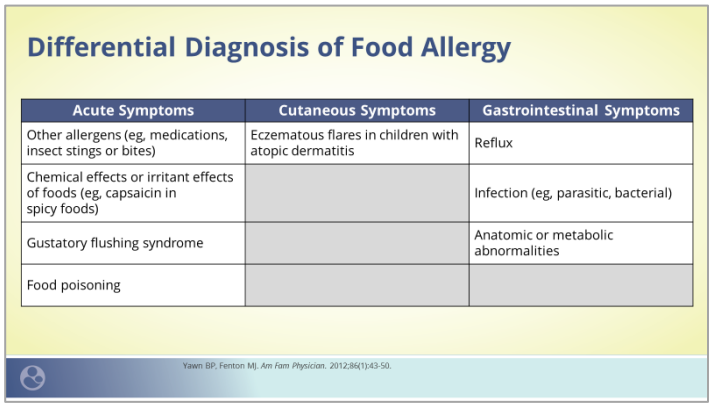
Slide 9 – Evaluation of Suspected Food Allergy

When we think someone has a food allergy, we obviously begin with a history. These are the guidelines that were written by the NIAID [National Institute of Allergy and Infectious Diseases] on food allergy guidelines about 10 years ago now.[4] If someone had a severe reaction (anaphylaxis), you should probably just refer them to a specialist to make an evaluation.

If someone had a mild reaction but has eaten the food multiple times before, it's probably okay to recommend allowing the food to continue in the diet. For example, if someone said, "I've eaten bread multiple times, but the last time, my stomach felt a little funny," it's probably okay to continue eating wheat. However, if it's the first time a person has eaten the food, and the signs and symptoms are characteristic of food allergy, then you probably need to test for allergies.

At that point, you want to test for allergies to individual foods. We don't like people ordering the panels. The panels, as we will go over in a few minutes, create a lot of business for us as allergists, but they also create a lot of unnecessary avoidance, which is not good for the families.

For differential diagnosis, we have to think about a few other things that could be causing the symptoms. I mentioned that insect stings can cause anaphylactic reactions, as well as medications. Some foods with high histamine levels may cause reactions. Or some people get a flushing reaction from spiciness in foods, but that's not really an allergic reaction. We also have to consider food poisoning.



Slide 10 – Differential Diagnosis of Food Allergy

If someone presents with vomiting, there are two GI diseases that can cause that, which we'll talk about soon. But, most commonly, this is just plain reflux or viral gastroenteritis. You need to rule these things out.

Atopic dermatitis is another consideration. Many parents show up at my clinic and think that eczema was due to a food, but most eczema is not caused by food. It can be, but that's a rare occasion. When we think about eczema, 90% of the time it's just due to improper skincare. That 10% can be due to a food allergy. That percentage increases as your eczema is more severe. Someone with severe eczema, maybe it's [20% to 30%].[5] Typically, testing is only recommended when a patient is not controlled with good skincare, such as proper bathing and moisturizing, intermittent use of topical steroids, or the new topical PDE4 inhibitors. If someone is not well controlled with these interventions, then it's probably worth being evaluated by a specialist for allergies. I probably would not recommend pediatricians, nurse practitioners, or family practice folks doing that because there is a high rate of false positives due to a high IgE baseline in atopic dermatitis.

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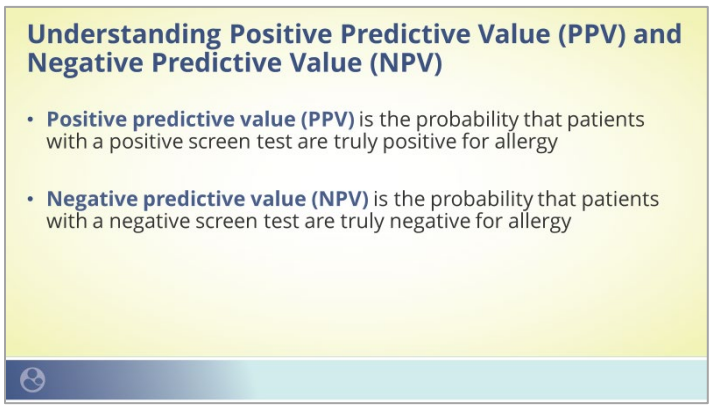
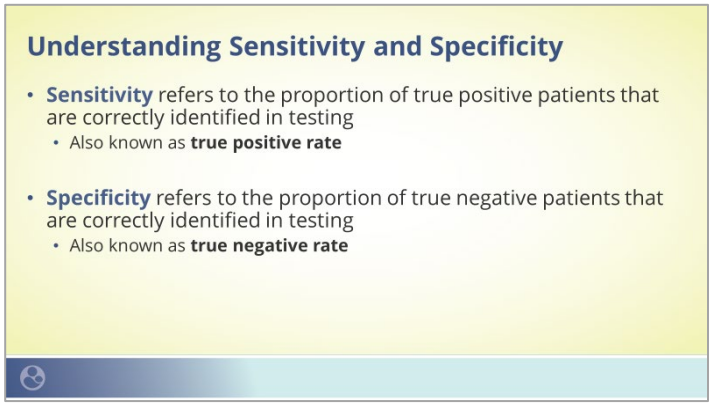
If you do not have a specialist nearby, which is true in parts of the United States and elsewhere in the world, then you can think about screening by specific IgE, but I would only test for a few foods that are in the diet, and typically, it's most likely milk, egg, and wheat. I would not screen for anything else—only the most common foods in their diet.

We worry about over-testing because of the issue of positive predictive value, negative predictive value, sensitivity, and specificity. I'm just going to do a brief overview, going back to basic statistics. Positive predictive value is the probability that a patient with a positive screen test is really allergic. And negative predictive value is the probability that a patient with a negative test is truly negative. Basically, is a negative truly a negative, and is a positive truly a positive?



Slide 11 – Understanding Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

Sensitivity is the rate at which true positive patients are positive on testing. Do you miss people? Specificity is looking at the proportion of true negative tests. Are you missing negative tests?



Slide 12 – Understanding Sensitivity and Specificity

When we think about allergy testing, specifically for IgE-mediated food allergy, we think about skin prick testing. The skin prick test, as you can see in this photo here [Slide 13], is the little mosquito bite in the picture. The positive control is a histamine, and the negative control is saline. [If] some patients are so sensitive that the saline is positive, then you know the testing is not useful. Or, patients forgot to stop their antihistamines, and everything is negative. You need a good positive and negative control.

Slide 13 – Testing for IgE-Mediated Food Allergy: Skin Prick Testing

Typically, we measure the wheal size. The wheal is the little white bump that you see that looks like a mosquito bite. The redness is the flare, which we measure, but it really has not been useful as a predictive value. There are other allergy testing options, such as intradermal testing, which is used

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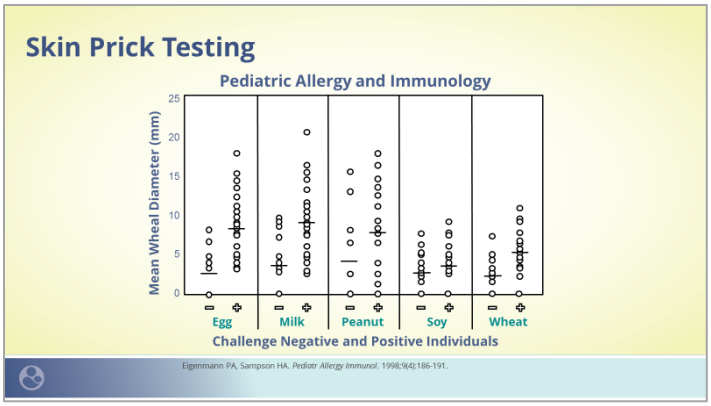
primarily for pollens. No one does intradermal testing for food. It is not a validated test. There are too many false positives.

There's also atopy patch testing, which is really used more for non-IgE–mediated food allergy, and we'll go over that in a few slides. But again, it's not as accurate a test.

This is the data validating skin prick testing [Slide 14], which is almost 20 years old, and, interestingly, hasn't changed in 20 years. This is a study that was published by [Philippe] Eigenmann and Hugh Sampson many years ago when they were at Hopkins.[6] We've been doing skin prick tests for allergies for the last 100 years or so, and the data's been pretty consistent.

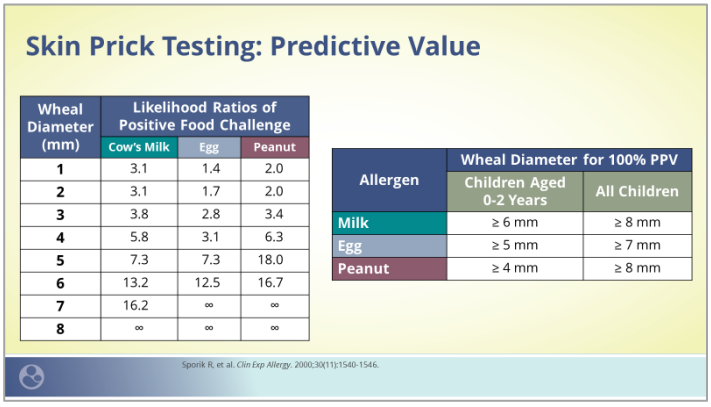


Slide 14 – Skin Prick Testing

The wheal size is on the y-axis, and on the x-axis, we have the positive patients who are allergic to the food and the negative patients who are not. As you can see, we consider a 3-mm wheal a positive result. Many of the patients with negative food challenge, who are not allergic to the food, have positive skin tests by that criteria.

The main point is that very few of the positive patients have skin prick test results less than 3 mm. Particularly for egg and milk, there are zero positive patients with wheal sizes less than 3 mm. There was 1 patient each for [peanut], soy, and wheat who had a negative skin prick test and still reacted to the food. But if you look at soy and wheat, the negatives and positives are almost identical. There's almost no way to differentiate skin prick test results for those 2 foods. For milk, egg, and peanut, the skin prick test is pretty reliable, and usually we say that when the wheal's greater than 8 mm, the patient is probably allergic to the food.

We've come up with these criteria [Slide 15], to determine the likelihood that a patient is allergic to a food. It varies from food to food and by age. Typically, we say that 8 mm or more, the patient is probably allergic to the food. But note that this is not screening the general population. These criteria are for screening in patients who we think have had an allergic reaction. For example, this can be used in patients who ate a sundae, and they don't eat much milk or egg. So, without testing, we can't tell which food is causing the allergy. However, this is not a general screening test for any patient from the street. This is specifically for patients who we think had an allergic reaction, or for patients who have atopic dermatitis, and we're screening to see if they have food allergies. And as you can see, as the millimeter wheal increases, the likelihood they're going to have an allergic reaction does increase.



Slide 15 – Skin Prick Testing: Predictive Value

Again, when the wheal is greater than 8 mm, the risk for allergic reaction is probably real. In patients who present with a typical clinical history, most allergists will not recommend a food challenge wheal greater than 8 mm because the patient is probably going to

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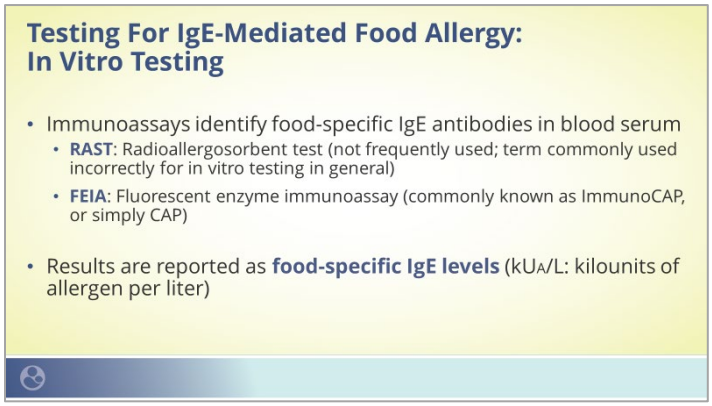
react. Our goal when we do food challenge is not to make people sick but to see what they truly are allergic to.

The other way to test for allergies is with in vitro testing. This is looking for specific IgE in the blood. The advantage of the in vitro test is that you can use it in a patient when they're on antihistamines. People used to call them RAST tests. No one really does RAST tests anymore. The RAST test was the original assay, and it's a radioactivity-based assay, which no one really does anymore. Most people do what's [known as] ImmunoCAP (CAP) testing, or FEIA testing, or Immulite, which are very similar assays, which is an amino-based test looking for specific IgE.

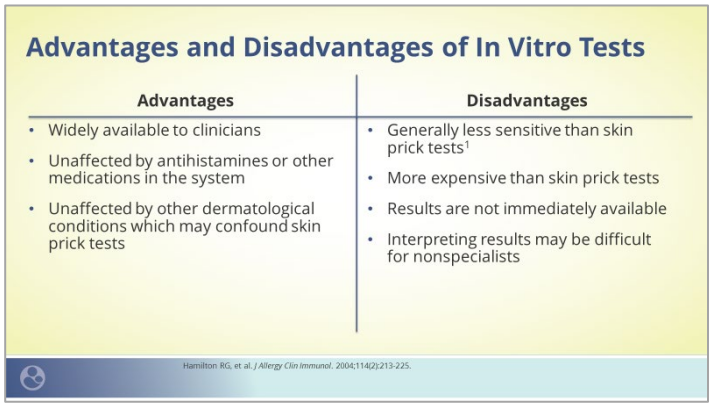


Slide 16 – Testing For IgE-Mediated Food Allergy: In Vitro Testing

It's done with an isoplate, like a plate or a mesh, depending on exactly what test you're doing, and the lab looks for changes in color. The test results are reported as specific IgE levels in kU_A/L for these tests.

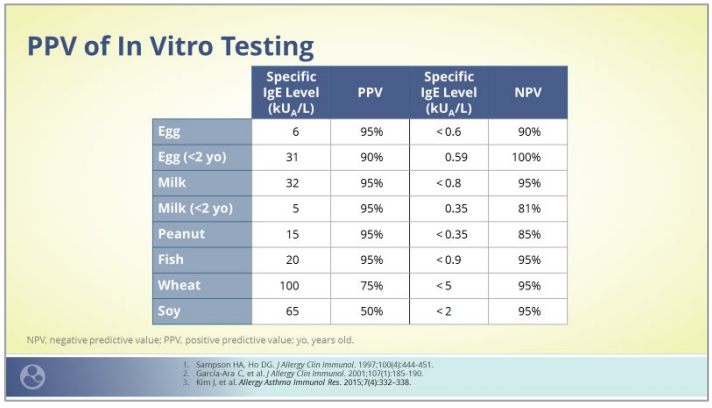
The main advantage of in vitro testing is that it's widely available, and anyone can do it. It's just ordering a test in a lab. Again, it's not affected by antihistamines, and you can do it on patients who have bad atopic dermatitis who you can't skin test.

The issue is that they're more expensive. I know in our institution, specific IgE tests run about $80 per test, and skin testing runs about $20 per test. Every place is a little bit different, but the skin prick test is cheaper, and you get results within 10–15 minutes, whereas blood tests take at least a day to run in the lab. That depends where you get the results. Additionally, in vitro tests tend to be less sensitive than skin prick tests, and interpreting the results can be difficult, and we'll go over that in a second to show you why.



Slide 17 – Advantages and Disadvantages of In Vitro Tests

This is data looking at the positive predictive value of in vitro tests for different foods [Slide 18]. These were a bunch of studies done in patients who we thought had food allergies. This was work primarily done by Hugh Sampson and his colleagues, and completed by groups out of Spain and elsewhere, looking at patients who had food allergy, looking at different levels.[7,8,9]



Slide 18 – PPV of In Vitro Testing

As you can see, the 95% predictive value varies from food to food. For egg, it's as low as 6 kU_A/L, but for wheat, we never get a 95% predictive value. Same

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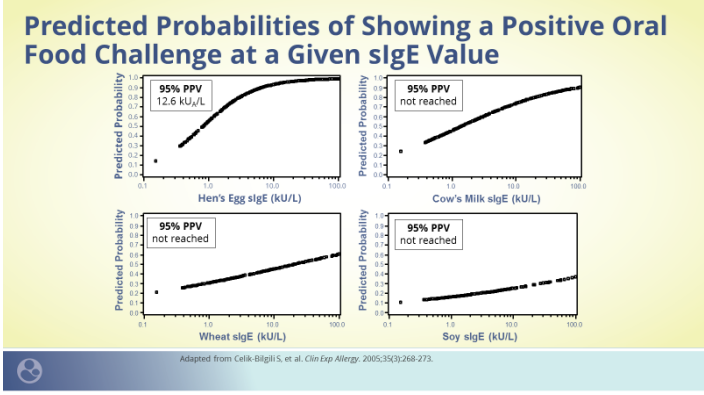
with soy. Specific IgE levels range from just 0.35 up to 100 kUA/L. At that point, they usually stop and say greater than 100 kU_A/L. For someone who has a wheat-specific IgE of 100 kU_A/L or a soy-specific IgE of 100 kUA/L, the predictive value is just above 50%—not much better than flipping a coin.

And there's also a variation by age. For milk, the younger you are, it's more predictive. Egg happens to be the opposite, which is an odd thing, but you really have to look [at] each individual food. And the numbers only really exist for these few major allergens. You can't get specific IgE to everything. The implications of specific IgE levels for chicken, or tomato, or banana—it's really unknown. No one really knows what those values mean because no one's compared the results with the outcomes of challenges to all these foods. We have done many challenges, as well as groups from Sinai, Hopkins, and Denver, and we find that the patients who pass food challenges—outside the top 8 foods, it's about 95% pass—most of those patients are probably not allergic to the food. The top 8 food allergens are milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish. Those are the main allergens. When you go outside of that, you have to wonder if someone is really allergic.

But the good thing about these foods with negative predictive value is that if you're negative on either the skin test or blood test, you're probably not allergic to it. They're pretty good for that, with the exception of milk in little kids and peanut for all ages. There is about a 10% to 15% false negative rates in those foods.

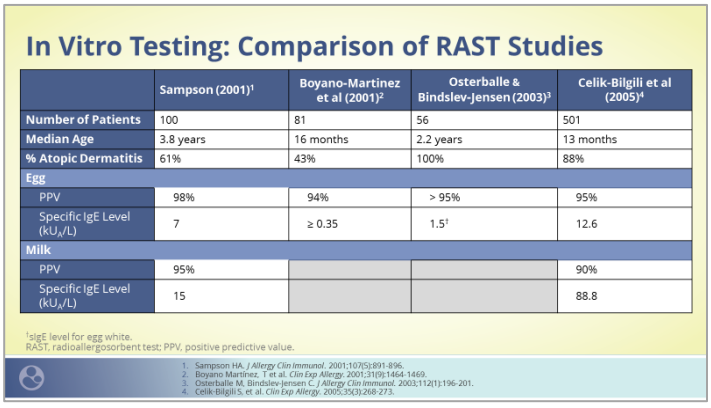
Now, if we were to screen a general population, the numbers get really bad. This is just screening a general population [Slide 19]. This was a huge study, and you can see, for egg, instead of being 6 kU_A/L, now it's up to 12 kU_A/L. You get a negative predictive value of 95%. For wheat, they never even got to the 95% positive predictive value. At 100 kU_A/L, the predictive value was about 60%. Soy, at 100 kU_A/L, the positive predictive value was 40%. Less than half the people with soy-specific IgE of 100 kU_A/L are allergic to the food. You've got a huge number of false positives. Even for milk, you get about 90% predictive value at 100 kU_A/L. To reach 50% predictive value, you need about 10 to 20 kU_A/L.



Slide 19 – Predicted Probabilities of Showing a Positive Oral Food Challenge at a Given sIgE Value

They're not a great screening tool. A lot of patients are carrying specific IgE to a food that's currently not significant. I really want to emphasize not doing screening tests, because it creates problems.

Here [we have] a bunch of different studies that look at in vitro tests [Slide 20]. It's important to look at this because you see some differences. The original Sampson study, which enrolled patients with atopic dermatitis and a history of food allergy. For egg and milk, they reported a 95% predictive value of 7 and 15 kU_A/L, respectively.[10]



	Sampson (2001)[1]	Boyano-Martinez et al (2001)[2]	Osterballe & Bindslev-Jensen (2003)[3]	Celik-Bilgili et al (2005)[4]
Number of Patients	100	81	56	501
Median Age	3.8 years	16 months	2.2 years	13 months
% Atopic Dermatitis	61%	43%	100%	88%
Egg				
PPV	98%	94%	> 95%	95%
Specific IgE Level (kU_A/L)	7	≥ 0.35	1.5[†]	12.6
Milk				
PPV	95%			90%
Specific IgE Level (kU_A/L)	15			88.8

[†]sIgE level for egg white.
RAST, radioallergosorbent test; PPV, positive predictive value.

1. Sampson HA. *J Allergy Clin Immunol*. 2001;107(5):891-896.
2. Boyano-Martinez T, et al. *Clin Exp Allergy*. 2001;31(9):1464-1469.
3. Osterballe M, Bindslev-Jensen C. *J Allergy Clin Immunol*. 2003;112(1):196-201.
4. Celik-Bilgili S, et al. *Clin Exp Allergy*. 2005;35(3):268-273.

Slide 20 – In Vitro Testing: Comparison of RAST Studies

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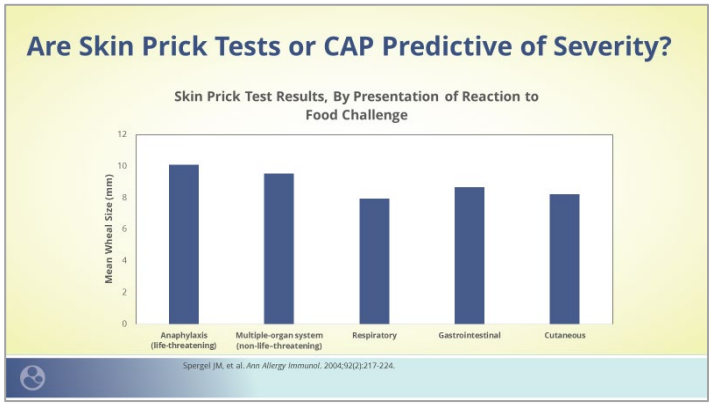
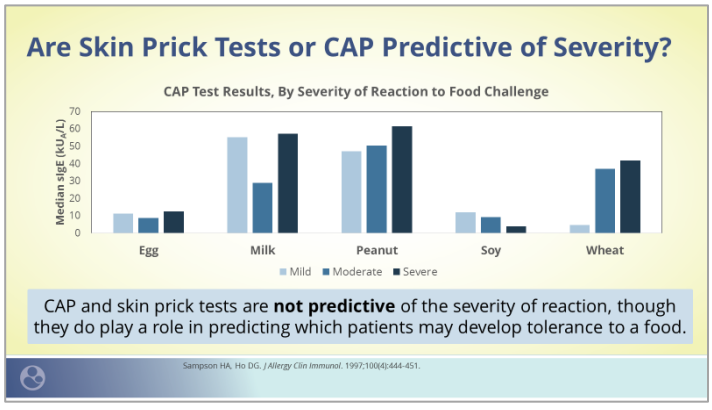
The Boyano-Martinez study looked at infants, and they found a predictive value of just 0.35 kU_A/L for egg.[11] This was the same in the Osterballe and Bindslev-Jensen study.[12] Again, it was much lower. But when you look at the general population, which was that large population of 501 patients in the same age group, the predictive value was much higher.[13] It really goes all over the place, so you have to be careful when you use these tools because there is a slight difference between the Immulite assay, ImmunoCAP assay, and others. You need to be very aware what test you order and why.

The other thing people always ask is, "I have a specific IgE of 100 kU_A/L. On my skin test, I have a wheal of 20 mm. Does that mean my reaction will be fatal or more severe?" Unfortunately, we have no way to predict who's at risk for severe reaction and who's at risk for a mild reaction. And there have been several studies that looked at this. We evaluated skin prick test results in patients when we've done food challenges. And we compare the results of patients who have different reactions—those who had severe reactions and needed multiple doses of epinephrine, patients who had hives and vomiting, patients with just wheezing, those with skin reactions, and those with GI reactions. As you can see [Slide 21], the wheal size is about the same in all of them.[14] It's nonpredictive. Patients with small wheal sizes can have bad reactions. Patients with large wheal sizes can pass or just have mild reactions. Wheal size is not predictive of severity.



Slide 21 – Are Skin Prick Tests or CAP Predictive of Severity?

And that's the exact same thing for ImmunoCAP, as shown in this Sampson study published over 20 years ago.[7] Every study since then has found the exact same results. This has been done multiple times. This is one of the big things in the allergy world, who do we really worry about? We can't tell at this time. In this study, they rated reactions as mild, moderate, severe. As you can see [Slide 22], for egg, there's really no difference based on specific IgE levels. Peanut specific IgE levels rose a little as severity increased. For soy, the more severe reactions had lower specific IgE levels. Wheat specific IgE levels did go up with severity. For milk, it goes up and down.



Slide 22 – Are Skin Prick Tests or CAP Predictive of Severity?

Again, it's completely nonpredictive. We cannot predict who is at risk or who is not, so we tell patients, if you are allergic to the food, you need to avoid it. If we're not sure based on your history, skin

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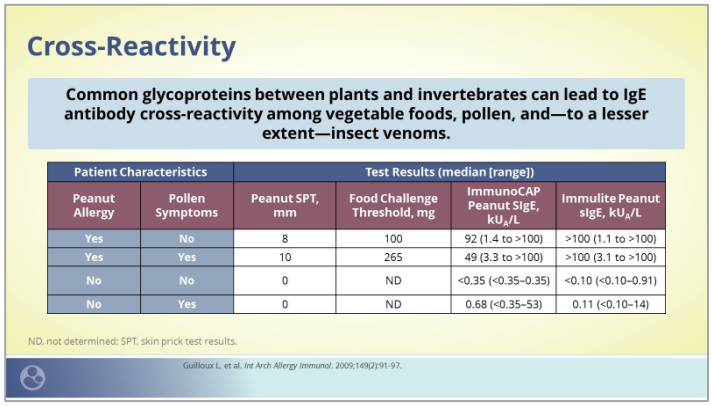
test results, or specific IgE levels, we do a food challenge to find out whether you're allergic or not.

A positive skin test or ImmunoCAP just indicates the presence of IgE to the food. It doesn't indicate that you're allergic to it. There's a very high false positive rate depending on the age and the food, anywhere from 20%–60% or more, depending on the exact test, the allergen, and the age.[10]

Negative skin prick test results or ImmunoCAP results basically means you don't have IgE to the food. And the false negative rate is less than [5%] for most of the foods. The highest is about 15%.[7-9] Most of the time, if you're negative on specific IgE to a food, you're not going to react. There are a couple exceptions. Sometimes, patients react only to the fresh food. The classic one is shrimp. Patients can be negative to the commercial shrimp extract, but when they eat shrimp, they react. The protein can be a little labile, meaning it breaks down when you eat it. That is a case when we will do testing to fresh foods to confirm the allergy in many of our patients.

The other big issue about testing is the issue of cross-reactivity, and this is why there's a high false positive rate. An example of cross-reactivity that's been worked out well is cross-reaction between peanut and birch. Birch pollen cross-reacts with peanut. Another common example is grass pollen, right? Grass pollen cross-reacts with wheat. A lot of patients who appear wheat allergic on skin tests are really allergic to wheat pollen, not to wheat as food. They may have seasonal allergies to grass pollen.



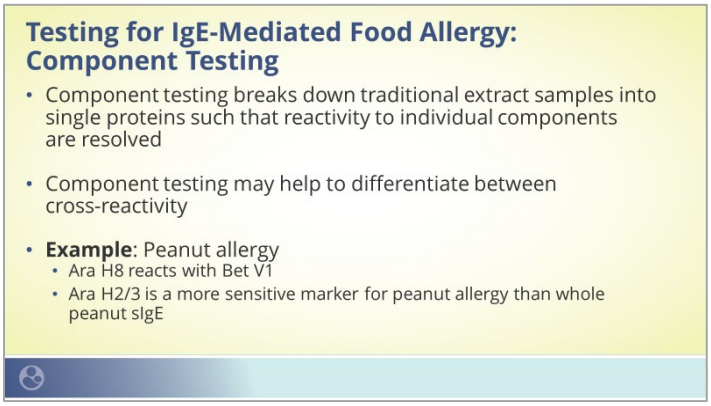
Slide 23 – Cross-Reactivity

But again, the example that's been worked out the best is this issue with peanut and pollen. This is a study that looked at 2 different tests, the ImmunoCAP and the Immulite, as well as skin prick test results in patients who were allergic to pollen or not allergic to pollen. As you can see [Slide 23], there were some differences in the 2 tests. The Immulite test tends to run a little bit higher for the pollen-allergic patients.

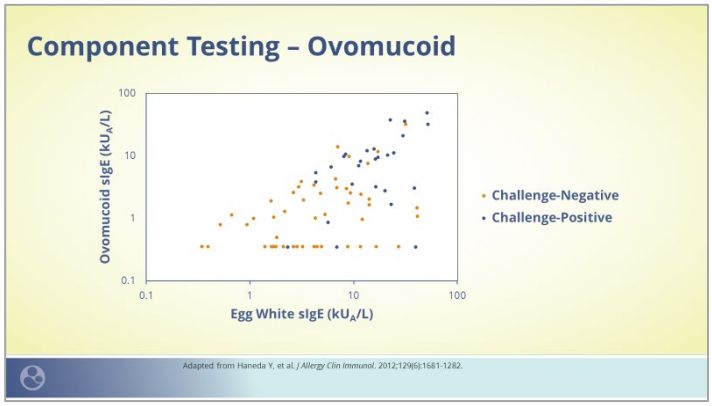
Patients who are not allergic, they all tend to be negative. Patients who are pollen allergic, but not peanut allergic, don't react to peanut on a skin prick test. However, as you can see, some of the ImmunoCAP patients were all the way up to 53 kU_A/L here, which is pretty high.

Cross-reactivity between peanut and birch is caused by the Bet V1 protein, which is a major birch pollen allergen that cross-reacts with the protein Ara H8, which is part of the peanut protein. Ara is the Latin name for peanut, and the letter H was used for all the allergens. Ara H8 is one of the allergens that cross-reacts with birch. This is why we now use component testing. You can order component testing for lots of foods, but peanut is probably the best characterized at this point.

Diagnosing Food Allergies in Infants and Children



Slide 24 – Testing for IgE-Mediated Food Allergy: Component Testing



Slide 25 – Component Testing – Ovomucoid

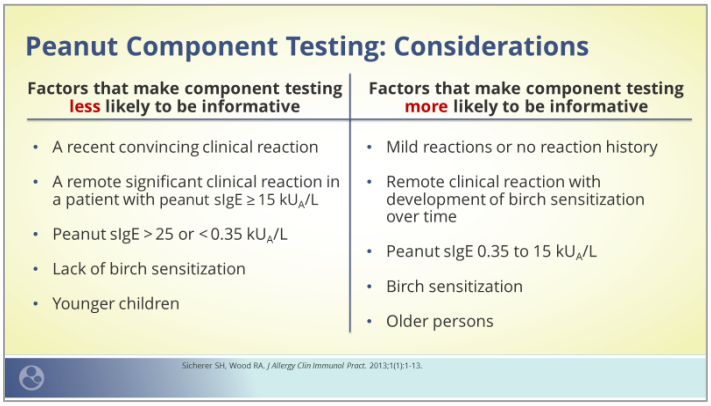
You can split things out and say, "Hey, my patient who I thought was allergic to peanuts, is really more birch allergic, so he doesn't have to worry about peanuts." Or a patient can be allergic to both peanut and birch. In that case, test results for both components would be positive. The component test that tends to be a little more sensitive is for Ara H2 and Ara H3, which tend to be a better marker of peanut allergy, compared with testing for whole peanut- specific IgE.[15]

For egg, we can look at egg white and egg ovomucoid, which is one of the proteins in egg. Unfortunately for that one, it doesn't work as well as it does with peanut. In this one, you can see the orange dots for the patients who were negative, and the blue dots are the patients who were positive [Slide 25]. There's a pretty large overlap if you're positive to both. In the upper right-hand corner, you're allergic to both things. And if you're negative, you're negative to both. There are a few patients who are egg white positive but ovomucoid negative who react to a food challenge—it's that line at the bottom. But there are almost no patients who are ovomucoid negative who react.[16] Some people are trying to figure out whether this is useful or not.

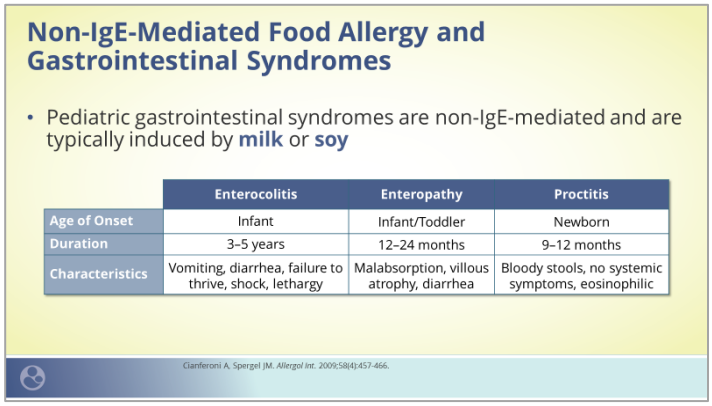
There is also some work now trying to figure out the issue of baked egg. This is true for milk and egg: when you cook the food, the food breaks down, so a lot of patients who are allergic to milk and egg react to scrambled eggs but can eat egg in a cake, or react to milk or ice cream, but can eat a cookie that's been baked with a cup of milk in it. When you bake a food, you denature the protein. For some patients who are less sensitive to the food, they can tolerate baked food, and this is something you can't right now figure out by any blood test or a skin test; you have to figure it out by challenge.

When we think about component testing in the future, peanut is the one that we really like the best at this point, and it tends to be more informative for patients who have birch pollen sensitization, those who had smaller skin prick test results, or those who had a mild reaction. But if someone ate a peanut and went into anaphylaxis, the component testing is probably not necessary. That's pretty clear. You probably don't need any other tests.

Diagnosing Food Allergies in Infants and Children



Slide 26 – Peanut Component Testing: Considerations



Slide 27 – Non-IgE-Mediated Food Allergy and Gastrointestinal Syndromes

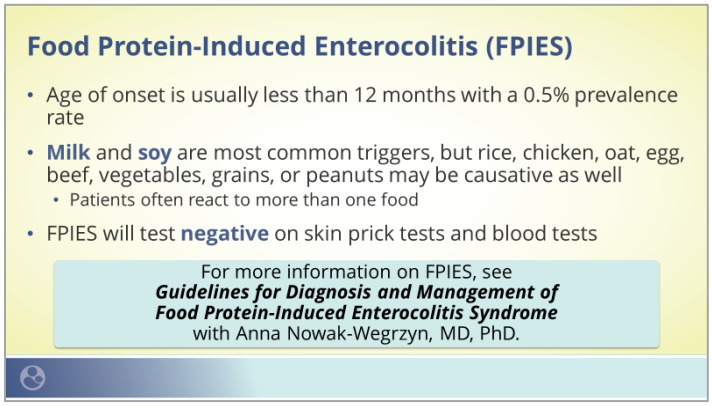
High specific IgE levels are probably not as informative in someone who doesn't have birch pollen sensitization. It's probably not necessary to do component testing in those patients. Pollen sensitization tends to occur in older patients, so component testing is probably less useful in infants, toddlers, and young children.

I've been talking the whole time about IgE-mediated reactions. What about non-IgE–mediated reactions? These are the reactions that tend to occur more than 2 hours after eating the food. They're much more delayed. And these are typically associated with GI symptoms, and they're most commonly allergic to milk and soy. In people with enterocolitis, which typically presents in infancy, ingestion of milk or rice may lead to vomiting, diarrhea, and a shock-like state. They tend to outgrow it anywhere from 1 to 5 years, depending on the study and what food you looked at.[17]

Enteropathy can lead to malabsorption and villous atrophy. Patients with enteropathy tend to be very young, and they outgrow it quickly. And then, proctocolitis, these are the patients that have bloody stools due to food or breast milk, and they tend to be relatively benign. They usually have no other symptoms whatsoever.

Food protein–induced enterocolitis is the infant one, and there's been an excellent webinar on that by Dr. Anna Nowak-Wegrzyn on diagnosis and management of food protein–induced enterocolitis. Again, milk and soy the most common allergens, but several grains can cause reactions as well. Since this is non-IgE–mediates, almost all of these patients are negative on skin prick tests and specific IgE tests, because IgE doesn't play a role at all in these patients' pathologies. Typically, we do not screen for this condition.

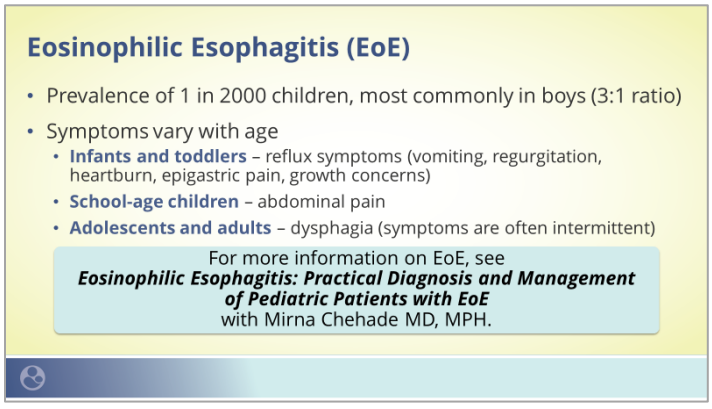
Diagnosing Food Allergies in Infants and Children



Slide 28 – Food Protein-Induced Enterocolitis (FPIES)

Some of these patients will have IgE reactions in addition to their food protein–induced enterocolitis reactions. In those scenarios, you can test. I recommend going to this webinar if you want more information.

Eosinophilic esophagitis is another GI disease. The symptoms vary with age. You get inflammation in the esophagus, esophageal dysfunction, and more problems. Infants present with failure to thrive because it hurts to eat, and they present with reflux. Slightly older children will present with abdominal pain and vomiting, and teenagers present with dysphagia or trouble swallowing because the esophagus is more rigid at that point. Allergy testing does not work in this disease because, again, this is a non-IgE-mediated disease.

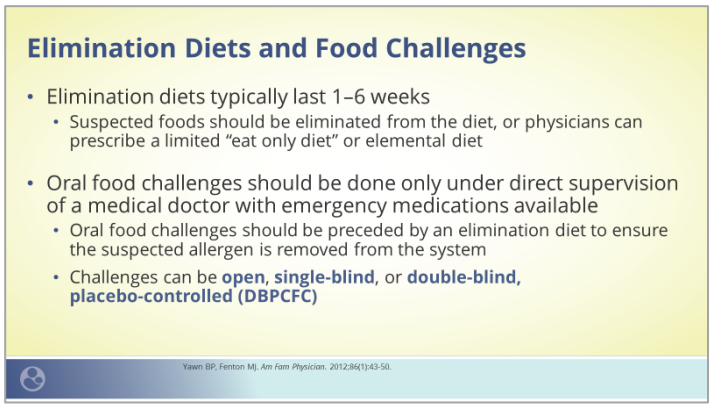


Slide 29 – Eosinophilic Esophagitis (EoE)

For these things, allergy testing by skin prick test or in vitro testing is not recommended. Patients with these conditions usually need to work with a gastroenterologist because you really need to diagnose these things by endoscopy, colonoscopy, or biopsy. You may not need to do any biopsies or endoscopies for someone with food protein–induced enterocolitis, but you do for eosinophilic esophagitis.

Slide 30 – Testing for Non-IgE-Mediated Food Allergy

What about elimination diets? Can we do those? Elimination diets are for patients when you're not sure exactly what's going on. You can take the food away for 1–6 weeks, and you slowly add things back in at that time. Occasionally, people do this for atopic dermatitis. I would not do this for patients who with major food allergies because they can have a severe reaction when the food is added back in.



Slide 31 – Elimination Diets and Food Challenges

Diagnosing Food Allergies in Infants and Children

Oral food challenge is the gold standard, so we diagnose patients with IgE-mediated allergies using a food challenge. During a food challenge, you give the patients back the food. We typically do an open food challenge, but for research studies or when the history is unclear, or if we are worried about psychological stuff, we recommend a double-blind or single-blind food challenge. Typically, you give doses every 20 minutes or so, slowly increasing the size, beginning with a small size, and then going up to a serving size. Then you observe for a reaction.

These need to be done in a place where you are prepared to treat anaphylaxis, because it can definitely happen. Depending on your center and how you organize it, the risk can vary a lot, but you need to prepare for a severe allergic reaction. It's not recommended to do a food challenge in a place without the ability to react quickly and treat a severe life-threatening reaction.

When do we do a food challenge? We do a food challenge with patients who ate that ice cream sundae with milk and egg, and we can't figure out which food caused the reaction. For example, both foods may have small skin prick test results, and the patient has never eaten either food before. In that case, we need to do a challenge. Or another example would be that the patient ate a casserole with lots of ingredients, and we don't know which one caused the reaction. When the history is unconvincing and we have a positive skin test or atopic dermatitis, and the skin did not improve when they did the elimination diet, we have to figure out which food is the right one to add back, which is done by food challenges.

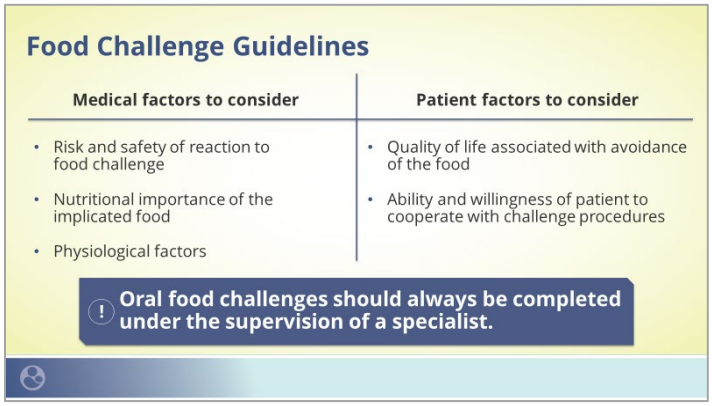
Slide 32 – Indications for Food Challenge

We also use food challenges to figure out whether patients have outgrown the food reaction. Most patients outgrow milk, egg, and wheat allergies, and even 20% can outgrow peanut [reactions].[4] You do food challenges when the wheal sizes or the specific IgE levels are now below that magical cutoff, and you wonder, "Hey, have they outgrown the food allergy?"

And on occasion you can do food challenges to determine level of reactivity—seeing how sensitive they are. That one's a little more controversial. Some think this may be the way of the future. In patients with mild reactions, you may be able to induce some tolerance.

When we think about food challenges, we've got to make sure we're safe; we've got to see how important the food is. For example, doing a food challenge with tomato is not that important. Most people aren't allergic to tomatoes; it's a really easy food to test, but for nutritional purposes, it's not that important. You always, again, have to be able to treat severe allergic reactions, so they're almost always done by specialists. I do not know any general practitioners, pediatricians, or nurse practitioners that do food challenges.

Diagnosing Food Allergies in Infants and Children

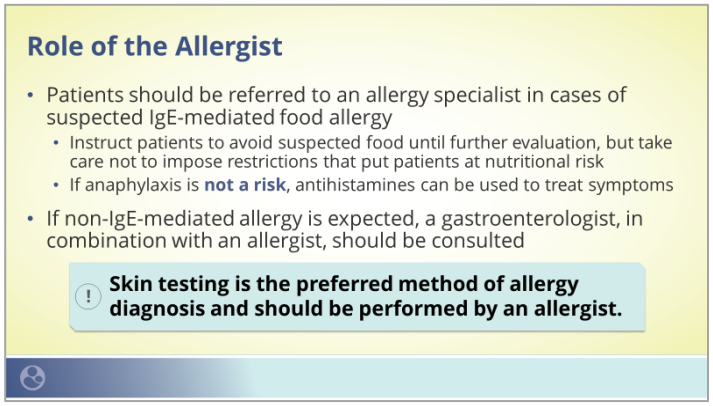


Slide 33 – Food Challenge Guidelines

Again, a negative food challenge just means you can eat the food; a positive food challenge means you're allergic and you need to avoid the food.

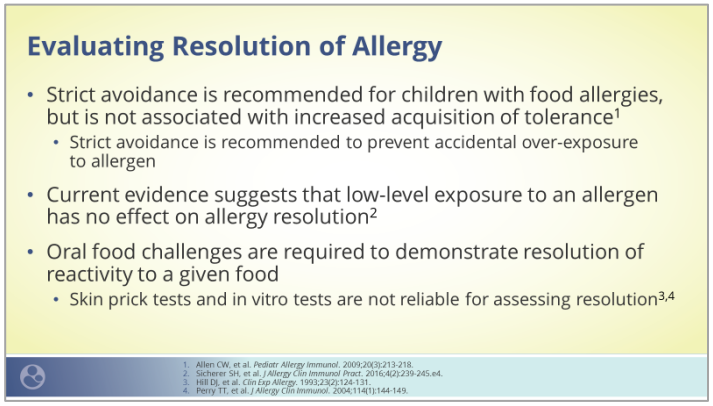
Slide 34 – Outcomes of Food Challenge

What does the allergist do? An allergist is the person who diagnoses food allergies. And then we consider how to treat and when to treat. With the non-IgE–mediated food allergies, you can work with a gastroenterologist to figure out treatment. Typically, allergists do skin testing because we can really help with the diagnosis and treatment of patients' food allergies.



Slide 35 – Role of the Allergist

We talked briefly about evaluating resolution of food allergy. We typically recommend avoidance until we test for tolerance. Interestingly, low levels of exposure to allergenic foods doesn't make patients outgrow allergies faster. We use skin tests to help figure out when we might be able to do food challenge to test for tolerance. As I said before, skin tests and in vitro tests are not really useful for assessing resolution of symptoms. We need food challenges to identify tolerance.



Slide 36 – Evaluating Resolution of Allergy

I'm briefly going to go over the unproven tests and future diagnostics and this will be pretty quick. Unproven tests: do not do these; do not order these. They're a waste of time. Provocation-neutralizing testing is when food is injected intradermally to induce symptoms. It doesn't work. You get systemic reactions, and they simply don't work.

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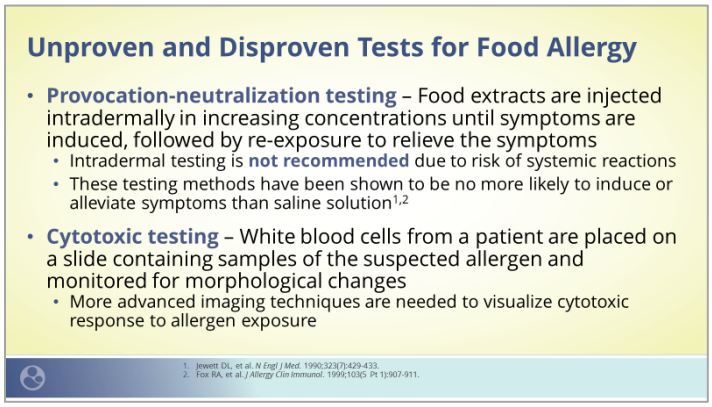
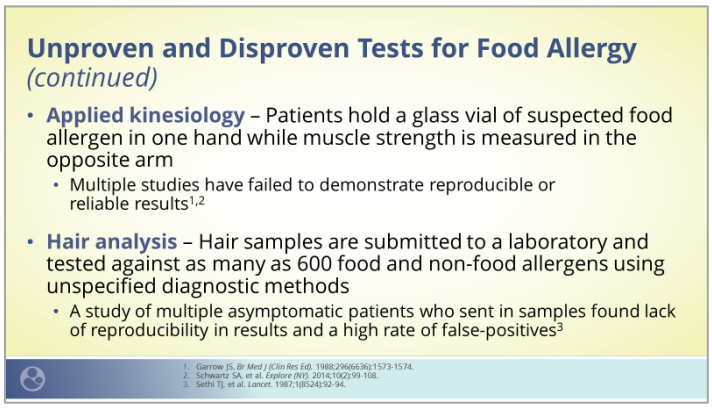
Cytotoxic testing is collecting a blood sample, adding the allergen, and looking for changes in cell morphology. It doesn't work. Maybe in the future, some basic histamine testing may have a role in diagnosis, but again, this doesn't work at all.



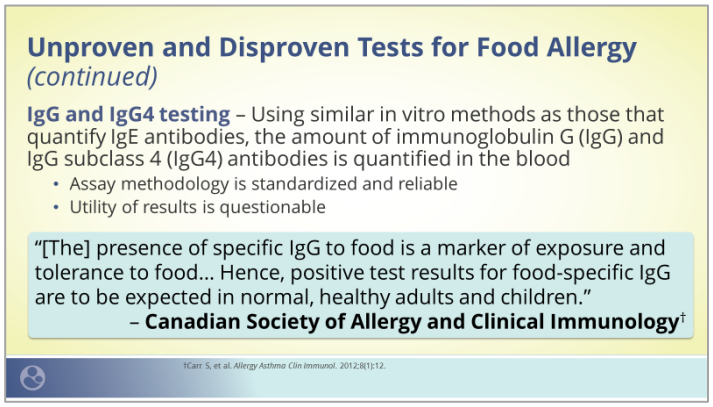
Slide 37 – Unproven and Disproven Tests for Food Allergy

Applied kinesiology, which was one of my favorite tests. You ask the patient to hold the food and you look how much the hand shakes while holding the food. It doesn't work and has never been shown to work for diagnosing anything. Hair analysis, where you cut people's hair and see what they're allergic to, doesn't work. Lots of studies have shown that there's a high rate of false positives. It really doesn't diagnose anything whatsoever.



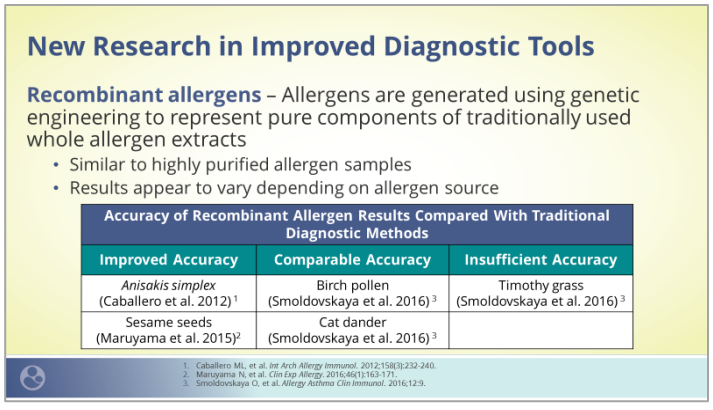
Slide 38 – Unproven and Disproven Tests for Food Allergy (continued)

IgG testing is really useful to find out what a patient is not allergic to. We all make IgG to foods. The presence of IgG tells you there's a normal reaction to foods. Patients that do IgG testing think they need to avoid foods with high IgG levels, but it's the complete opposite. The higher the IgG levels are, the better they are. So we do not recommend that at all. It's useful to help look at tolerance.



Slide 39 – Unproven and Disproven Tests for Food Allergy (continued)

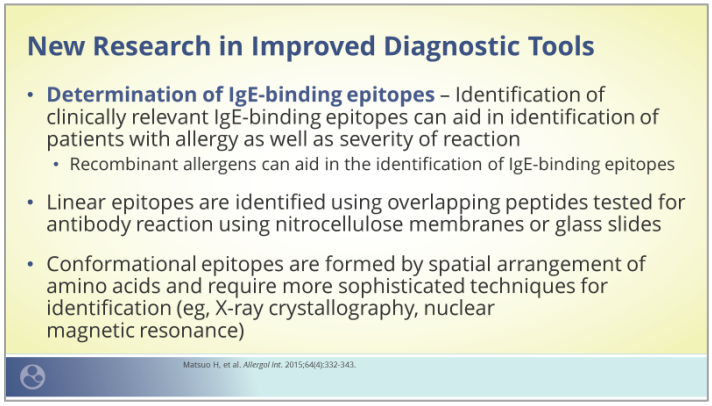
The future is these 3 [Slides 40-42]. Recombinant allergens are similar to component testing, which I mentioned before. These are being developed. Peanut looks pretty good. There are several other recombinant allergen tests that are coming out in the future. We talked about milk, and we talked about egg. There are other ones for sesame that look optimistic. Some recombinant allergens seem to work better, and some seem to work a little bit worse. As you can see, the pollen ones are a little less sensitive compared with the whole allergen.



Slide 40 – New Research in Improved Diagnostic Tools

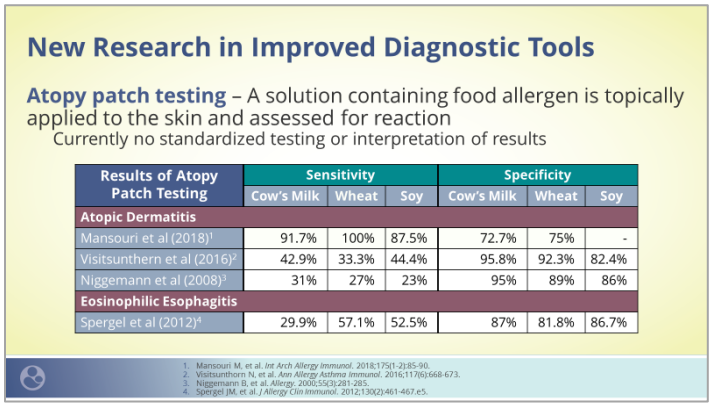
Diagnosing Food Allergies in Infants and Children

Epitope testing, which is looking at different parts of the allergen, may be helpful for testing for reactions to baked vs unbaked foods. You can look at linear epitopes vs overlapping epitopes. They may have some special role in the future. Again, this is probably out in the future. This test does not exist today.



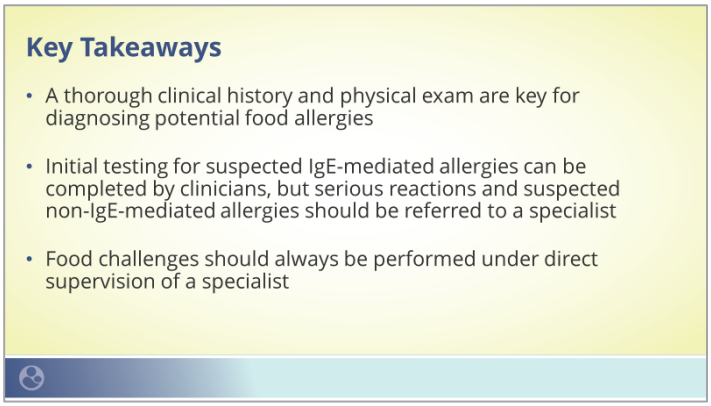
Slide 41 – New Research in Improved Diagnostic Tools

Atopy patch testing is sort of what I was famous for. It helps for testing for non-IgE-mediated food allergies. It helps a little, but the sensitivity is not great. Specificity is not bad, so if you're negative, it probably works really well, but you have a fair amount of missed positives, particularly for milk in eosinophilic esophagitis. For atopic dermatitis, the tests were all over the place. The issue is we have no validated testing at all for any of these patients.[18,19,20,21,22]



Slide 42 – New Research in Improved Diagnostic Tools

Our key takeaways: again, clinical history is critical, and the most important thing is that we need to figure out when they reacted and what they reacted to. We need to figure out the best test. IgE testing can be used, but you really need to test for the food they reacted to instead of doing panel testing. When we do food challenges, we need it to be under supervision of a specialist because patients can react to the food. We need to figure out what they're truly allergic to.



Slide 43 – Key Takeaways

Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Spergel's responses from the July 9 and July 25, 2019, audio webcasts.

For a baby who consumed egg and only sustained a rash around the mouth, it sounds like that may not be true food allergy and just a topical reaction. How would you advise on next steps?

Dr. Spergel: If they had a local reaction just around the mouth and nothing else, I would tell them to try to eat it again, see what happens, and be careful. If it's just reactions on areas of contact, I would tell them to try it at home. But if symptoms occur in areas of noncontact, then I would test for allergies.

Diagnosing Food Allergies in Infants and Children

Do you recommend preemptive allergy testing for younger siblings of children with multiple food allergies?

Dr. Spergel: In general, I do not. This is important in medicine because parents say, "This is my third kid, and my first 2 are allergic to milk and egg. I'm sure this one is allergic too." My answer is that every kid is different. So we typically do not, but if the kid is highly atopic, like the other siblings, occasionally we might test beforehand. However, if this kid is nonatopic while the first 2 kids had eczema, coughing, and wheezing, I'd say that kids are different. We typically do not recommend preemptive screening for patients with siblings with multiple food allergies because I think you get unnecessary avoidance.

When you have divergent test results, such as a negative skin prick test and positive immunoassay test, or vice versa, which test results do you trust more? Does one indicate a need for an oral food challenge more than the other?

Dr. Spergel: I believe the skin prick test results more than I believe specific IgE levels, especially for negative results. If you're negative in a skin prick test, the odds they're going to react are probably less than 2%–3%. If you're negative, I know you're probably fine.

We can also have patients with small skin prick test results and high specific IgE levels. These are the ones we challenge because we don't know what the right answer is. If the results are divergent, we tend to challenge, but I usually believe my skin prick tests more than specific IgE tests. But it ultimately depends on the patient's results and lots of other factors.

How do you determine whether a baked milk or baked egg challenge is appropriate after a child has tested positive for milk or egg allergies?

Dr. Spergel: That is a great question, because it's a moving target. There are some studies that suggest component testing is helpful for determining baked food reactions, and some studies suggest that it's not. I think that we don't have the exact answer. If someone is not eating baked milk or egg and has a relatively smaller wheal size—so just below the cutoff—I'll start off with a baked milk and baked egg challenge.

If the skin prick test or specific IgE results are completely negative, I'll go straight to a native challenge, so basically scrambled eggs and a glass of milk. It depends on the test results. The more negative you are, the more likely I'll challenge with native food. But if you're on the positive side, I'll start with baked goods.

How do you determine whether an oral food challenge should be done in an office setting or a hospital setting?

Dr. Spergel: That depends on your personal experience and whether you're able to treat a severe allergic reaction. Food challenges can be done in offices, but you need to be prepared to treat a severe allergic reaction. If your office is not able to treat anaphylaxis with epinephrine, IV fluids, and all those things, then the challenge should probably be done in a hospital setting, where you have the ability to do all those things.

If you have those things in your office, then it's probably okay to do. At our institution, all of our challenges are done in a hospital setting, just because that's where our challenge unit is, and that's true in a couple of other places. But many other major academic institutions do it in their offices. Either answer is fine, but you need to be prepared to treat a severe allergic reaction.

How do you handle testing in patients who have a low likelihood of allergies based on clinical history and nonspecific symptoms, but their parents believe that food allergies are responsible?

Dr. Spergel: You may want to try to educate patients on the false positive and false negative

rates. However, there'll be sometimes when they won't leave the office until you test them. You can test them, but you have to give the caveat that if the test is negative, you can go home and eat the food. If the test is positive, we're going to have you do food challenge with everything that's positive to see if you're really allergic. Often, those patients truly believe they're allergic, we have to do blinded challenges where one day, they eat something they're not allergic to, and then the next day, you'll do something that they're potentially allergic to.

We do try to convince them not to test, but sometimes, we're stuck, and they say, "I'm going to avoid it no matter what, so you need to prove it to me."

Will the epicutaneous immunotherapy patch work for most pediatric food allergies?

Dr. Spergel: Right now, epicutaneous immunotherapy has only looked at peanut and milk allergies. The data have been published for peanut in extract form and for milk. It is encouraging for those 2 foods but has not been evaluated for other foods at the current time. It doesn't work for every patient. It works for some patients, and it depends on what you define on as working.

If you want patients with peanut allergy to go home and eat a bag of peanuts, it's working on very few patients. If you want them to be able to eat a single peanut, then it's probably effective. Depending on the age and other criteria, epicutaneous immunotherapy is effective in anywhere from 40% to 70% of patients.[23,24]

In a theoretical sense, it's going to work for any food, but we have a long way to go from just the one published clinical trial with peanut to exposure to every food.

At what point should foods be reintroduced after a trial elimination diet?

Dr. Spergel: When you do a trial elimination, the timing is based on the reason for doing the trial, so we go backwards. If you're doing a trial elimination to test whether food is causing eczema, the symptoms haven't improved within 2 weeks, it's probably safe to add the food back in. If you eliminated a food because it's caused lots of hives, you probably don't want to add it back in. That patient probably needs to be seen by a specialist.

Is there a specific order for reentry?

Dr. Spergel: When we reintroduce foods, there is no specific order. It really depends on history and the exact clinical situation. Typically, there are 2 ways you can add foods back in: add the least allergenic foods in first, like fruits and vegetables (because you know those tend to be safe), or add some of the main staples like milk, egg, or wheat. You might do the latter because adding asparagus into the diet doesn't really add much nutritional value. You may want to add something that's going to make a difference.

Most food allergies are typically milk, egg, peanuts, tree nuts, fish, and shellfish. That probably counts for 80% to 90% of food allergies. So those are the ones that, if you're particularly worried, you might be a little more careful adding them back in.

Does family history play a role in food allergy. What about multiple siblings with food allergies?

Dr. Spergel: There are some genetics behind food allergies, it does run in families and not specific foods. If a parent or a sibling is allergic to the food, you might wonder whether you should be worried that the child is going to be allergic to the same food. It varies among studies. There is probably a slight increase in risk, but it's not huge. There's more of a risk that the child will have some allergies, but that could mean food allergy, asthma, or atopic dermatitis. If you have allergies, your children are more likely to have allergies.

The answer to the question about the multiple siblings is tricky. Say 2 kids in the family have milk allergy, what do you do about the third? In theory, it's not really more of a risk, but as a physician, I'm

always a little bit nervous. In those cases, sometimes I actually will screen before reintroducing those foods into the family or into the child.

I have heard that once tolerance to a previously allergic food is established, the child should eat the food multiple times a week to continue the tolerance. Is this true, and what is the frequency you recommend to encourage continued tolerance?

Dr. Spergel: If you were allergic to a food and you have now outgrown it, there's a few case reports of people who stopped eating the food and became allergic again. The general recommendation is to eat the food. For milk and egg, that's pretty easy because they are ingredients in many foods. But generally, we would recommend that they eat the food 3–5 times a week. For some of our peanut-allergic patients who really don't eat peanuts, we tell them to have a peanut M&M a day—have it as your vitamin in the morning.

Abbreviations

CAP	ImmunoCAP	**NIAID**	National Institute of Allergy and Infectious Diseases
FEIA	fluorescence enzyme immunoassay	**NSAIDs**	nonsteroidal anti-inflammatory drugs
GI	gastrointestinal	**PDE4**	phosphodiesterase 4
IgE	immunoglobulin E	**PPV**	positive predictive value
IV	intravenous	**RAST**	radioallergosorbent test
kU_A/L	kilounits of allergen-specific IgE per liter		

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